Analytic synthesis of the effect of foot orthoses on gait biomechanics and pain in patients with rheumatoid arthritis

an explorative experimental and clinical approach

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BY
MORTEN BILDE SIMONSEN

DISSERTATION SUBMITTED 2020

AALBORG UNIVERSITY
DENMARK

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CV

In 2013, Morten Bilde Simonsen (MBS) received a Bachelor in Sports Science from Aalborg University, Denmark. He received his master's degree in Sports Technology from the same university, which included an exchange semester at Technical University of Munich.

With a grant from TrygFonden, MBS was enrolled as a PhD-student at the doctoral school of the Faculty of Medicine at Aalborg University. The PhD project is a collaboration between Aalborg University, North Denmark Regional Hospital and Danish Hospital for Rheumatic Diseases. The supervisors are Rogerio Pessoto Hirata, Associate Professor and Michael Skipper Andersen, Associate Professor Peter Derek Christian Leutscher, Professor and Kim Hørslev-Petersen, Professor emeritus.

During his PhD, MBS have given presentations at the 42th and 43th International Society of Biomechanics meeting (ISB), the 8th World Congress of Biomechanics (WCB), the 18th European League Against Rheumatism (EULAR) Congress and the World Congress of the 16th International Society for Prosthetics and Orthotics (ISPO). Additionally, MBS won the student award for best presentation at the 10th Danish Society of Biomechanics. He is also a reviewer at Gait & Posture and invited speaker for 12th Nordic Congress of Prosthetics and Orthotics in 2021.

PREFACE

This PhD dissertation encompasses research conducted in the period from November 2017 to November 2020 at Department of Health Science and Technology, Aalborg University and Centre for Clinical Research at North Denmark Regional Hospital. During the PhD study, MBS stayed (January to March 2020) with Professor James Woodburn's research group at Glasgow Caledonian University (GCU) in Scotland. Data analysis and manuscript editorial work in relation to studies III and IV were performed during this stay. Furthermore, data collection on a supplementary project related to this PhD was started. Unfortunately, the stay was terminated earlier than planned due to the Covid-19 pandemic.

This PhD project funded by TrygFonden (124714), The Danish Rheumatism Association (R161-A5276) and Centre for Clinical Research at North Denmark Regional Hospital, combines biomechanics and pain assessment, investigating adaptations to experimentally induced pain in healthy individuals and the effect of foot orthoses in patients with rheumatoid arthritis.

The PhD dissertation is presented in six chapters. The first chapter is an introduction to the dissertation where the background, motivation, gaps in the current literature and outline of the included studies are presented. The second chapter describes the study design of the experimental and clinical studies. The third chapter presents key results of the included studies. The fourth chapter aims to combine and discuss the findings of the included studies and shows how they related to each other. Furthermore, a brief comparison is included of the patients who responded well to the custom-made foot orthoses with those who did not. The fifth chapter offers suggestions for future research in this area. Finally, the dissertation is completed with a summary of findings in all of the included studies.

LIST OF STUDIES

This dissertation is based on four original articles; two have been published in international peer-reviewed journals and two are submitted.

Study I: Simonsen, M.B., Yurtsever, A., Næsborg-Andersen, K., Leutscher, P.D.C., Hørslev-Petersen, K., Andersen, M.S., Hirata, R.P. *Tibialis posterior muscle pain effects on hip, knee and ankle gait mechanics*. Human Movement Science 66, 98–108. 2019

Study II: Simonsen, M.B., Yurtsever, A., Næsborg-andersen, K., Leutscher, P.D.C., Hørslev-petersen, K., Hirata, R.P., Andersen, M.S. *A parametric study of effect of experimental tibialis posterior muscle pain on joint loading and muscle forces — Implications for patients with rheumatoid arthritis?* Gait & Posture 72, 102–108. 2019

Study III: Simonsen, M.B., Hirata, R.P., Næsborg-andersen, K., Leutscher, P.D.C., Hørslev-Petersen, K., Woodburn, J., Andersen, M.S.,. *Different types of foot orthoses effect on gait mechanics in patients with rheumatoid arthritis.* Journal of biomechanics, under review

Study IV: Simonsen, M.B., Næsborg-andersen, K., Leutscher, P.D.C., Hørslev-Petersen, K., Woodburn J,. Andersen, M.S., Hirata, R.P., *Relief of pain in the ankle and the foot in conjunction with altered joint moments in patients with rheumatoid arthritis – outcome of a four-week trial with use of custom-made foot orthoses*. Arthrithis Care & Reseach, under review

The dissertation has been submitted for assessment in partial fulfilment of the PhD degree.

ENGLISH SUMMARY

Rheumatoid arthritis (RA) is a chronic autoimmune and inflammatory disease often causing foot pain in association with decreased ability to perform daily physical activities. Weakening of the muscle and tendon apparatus, synovitis, effusion and eventually erosive arthritis may cause clinically recognizable valgus heel or pes planovalgus deformity. These manifestations cause changes in the locomotion of the patient. With the intention to reduce pain, stabilization and alignment of the foot by a foot orthoses (FO) is often recommended in patients with RA.

The current PhD project aimed to quantify FO induced changes in biomechanics and pain perception in patients with RA and explore the effect of experimentally induced tibialis posterior (TP) muscle pain in healthy subjects during gait. Four studies (I-IV) were conducted using an experimental design to induce pain in the TP muscle in healthy subjects and a clinical intervention design to test the effect of FO in patients with RA.

Results from Study I demonstrated that experimentally induced pain in the TP muscle caused reduced knee and hip joint moments in the healthy subjects. Study II showed that flexor digitorum longus and flexor hallucis longus can compensate for the TP if the strength of the muscle is reduced due to pain. The study highlights the potential importance of the plantar flexor and inverter muscles of the foot among individuals with TP pain, which is often seen in patients with RA. Study III investigated the immediate effect of a custom-made FO for patients with RA compared with a sham insole. The study showed that the custom-made FO was the most efficient in reducing the following gait mechanics: the ankle planter flexion and eversion moment, the planter pressure in the forefoot and the ankle dorsiflexion. The altered mechanics lead to offloading of the plantar flexors and inverter muscles. Study IV demonstrated that four weeks custom-made FO therapy reduced foot and ankle pain intensity while maintaining the initial biomechanical effects. Furthermore, the custom-made FO also reduced the area of perceived pain of the foot, legs, arms and hands.

In summary, the first two studies showed how experimental pain models can be used to study alterations of gait mechanics as a response to pain stimuli. These potential alterations are important to understand to identify compensation strategies which are caused by pain or deformities. Study III showed that a custom-made FO reduced the ankle plantar flexion and eversion joint moments in patients with RA. Furthermore, Study IV showed that patients with RA benefit from custom-made FO in relation to foot pain, and possibly also in relation to pain in other parts of the body.

DANSK RESUME

Reumatoid artrit (RA) er en kronisk autoimmun og inflammatorisk sygdom, der ofte forårsager fodsmerter i forbindelse med nedsat evne til at udføre daglige fysiske aktiviteter. Svækkelse af muskler, sener, effusion og til sidst erosioner kan forårsage platfods og andre fod deformiteter. Disse manifestationer kan forårsage ændringer i patientens bevægelse. Med intensionen om at reducerer fodsmerter anbefales fodortoser (FO) ofte til patienter med RA.

Dette Ph.d. projekt sigtede mod at kvantificere de ændringer en FO har på gang biomekanik og smerter hos patienter med RA, samt udforske effekten af eksperimentelle smerter i tibialis posterior (TP) musklen hos raske forsøgspersoner. Fire studier (I-IV) blev udført, to eksperimentelle hvor smerter blev induceret i TP-musklen hos raske forsøgspersoner og to kliniske interventionsstudier som undersøgte effekten af FO hos patienter med RA.

Resultaterne fra Studie I viste at eksperimentelle smerter i TP musklen forsager reducerede knæ og hofte ledmomenter. Studie II viste at musklerne flexor digitorum longus og flexor hallucis longus kam kompensere for TP musklen. Studierne fremhæver vigtigheden af de muskler som udfører plantar fleksion og eversion-musklerne af foden hos personer med TP pain, som ofte observeres hos patienter med RA. Studie III undersøgte den øjeblikkelige biomekaniske effekt af et specialtilpasset FO for patienter med RA sammenlignede med et snyde (kontrol) indlæg. Studiet viste at det specialtilpassede indlæg reducerede ankel plantar fleksion og eversion momenterne, trykket under forfoden samt ankel dorsifleksion. Disse ændringer vil fører til aflastning af de muskler som udfører planter fleksion og eversion af foden. Studie IV viste at fire ugers anvendelse af det specialtilpassede FO reducerede fod og ankel smerter mens de biomekaniske ændringer fundet i studie III blev fastholdt. Yderligere reducerede det specialtilpassede FO også det areal patienterne oplever smerter fra benene, arme og hænder.

Sammenfattende viste de to første studier, hvordan eksperimentelle smertemodeller kan bruges til at undersøge ændringer i gangmekanik grundet smerte stimuli. Disse potentielle ændringer er vigtige at forstå, for at identificere kompensationsstrategier, der er forårsaget af smerte eller deformiteter. Studie III viste, at en specialtilpasset FO reducerede ankel plantarfleksionmomentet og eversionsmoment hos patienter med RA. Desuden viste undersøgelse IV, at patienter med RA drager fordel af specialtilpassede FO i forhold til fodsmerter og muligvis også i forhold til smerter i andre dele af kroppen.

ACKNOWLEDGEMENTS

The present dissertation could not have been completed without the generous financial support from TrygFonden and the Danish Rheumatism Association. Recruitment of patients took place at Department of Rheumatology, Hjørring and Danish Hospital for Rheumatic Diseases, and I thank both staff and the lovely people who volunteered to participate.

I would like to thank my supervisor Michael Skipper Andersen for providing overwhelming support and believing in me, not just during the PhD project but also during the two-year period where we tried to raise funding for the project. Without your guidance, this project would never have been possible. Thank you also to my supervisor Rogerio Pessoto Hirata for keeping me on my toes and constantly challenging my understanding of pain; Kim Hørslev-Petersen for your guidance in the field of rheumatology and for believing in me as a researcher; Peter Derek Christian Leutscher for your attention to detail, for your never-failing optimism and for helping me to develop a future career within research; Ketill Næsborg-Andersen for sharing your expertise and driving across the country for making insoles for the participants. It has been a privilege to work with you all, I have learned so much and hope to have great collaborations with all of you in the future.

Thank you to James Woodburn and his team at Glasgow Caledonian University for letting me visit your laboratory. Unfortunately, we did not manage to finish what we started due to the COVID-19 pandemic, but I hope it will be possible to continue our collaboration in the future.

Thank you to my colleagues at Centre for Clinical Research and Sports Sciences for creating a positive and motivational work environment. A special thanks goes to my colleagues Aysun, Dorthe, Julie, Anders, Caspar Kent, Mikkel, Ning and Rune.

Thank you to Carsten Demant Sørensen from my triathlon club for introducing me to Kim Hørslev-Petersen; this turned out to be the starting point for this whole process.

Thank you to my family and friends for your support even though you did not always understood my work. Last but not least, I would like to thank my girlfriend Merethe for your endless support and for being a source of inspiration.

Morten, October 2020

LIST OF ABBREVIATIONS

2D	Two-dimensional
3D	Three-dimensional
BW	Body weight
CNS	Central nervous system
CT	Computed tomography
COM	Centre of mass
DMARDs	Disease-modifying anti-rheumatic drugs
FO	Foot orthoses
GRF	Ground reaction force
MTX	Methotrexate
OA	Osteoarthritis
RA	Rheumatoid arthritis
SFE	Short foot exercise
TP	Tibialis posterior
VAS	Visual analogue scale

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CHAPTER 1. INTRODUCTION

Foot pain is a common musculoskeletal disorder in the general population (Hill et al., 2008). Besides affecting quality of life, foot pain is associated with decreased daily physical activities and increased risk for falling (Bowling and Grundy, 1997; Menz et al., 2006, 2005).

1.1 RHEUMATOID ARTHRITHIS

Rheumatoid arthritis (RA) is an systemic inflammatory disease causing substantial pain, disability and other morbidities (Klareskog et al., 2009). The first mentions of RA in written text appeared very early around year 1500 BC, when Ebers Papyrus described a condition similar to RA (Joshi, 2012). However, there is much speculation about early RA descriptions; Ebers Papyrus is controversial and many believe it referred to gout. But the first certain discovery of RA is attributed to Dr. Augustin Jacob Landré-Beauvais (1772–1840) in 1800. (Halberg, 1995). RA is commonly considered to be a joint disease, but substantial evidence shows that the condition also may affect other organ systems such as the eyes, lungs, skin, heart, blood vessels and almost all other organs (Cobb et al., 1953; Gulati et al., 2018; Kitas and Erb, 2003). In Denmark, it is estimated that 40,000 persons live with RA (Bech et al., 2002; K. Pedersen, 2011; Pedersen et al., 2007) and RA is three times more prevalent among women than men (Fishman and Bar-yehuda, 2010; K. Pedersen, 2011). The disease usually develops with onset between 35 and 50 years (Fishman and Bar-yehuda, 2010) and despite intensive research, the causes of RA remain unknown (Fishman and Bar-yehuda, 2010).

The initial symptoms of RA are pain, joint stiffness and joint swelling, often initially occurring in the hands and feet. RA is an autoimmune disease, which means the immune system by mistake attacks the tissue sounding the joints. The immune system destroys the joints by sending out antibodies which causes inflammation in the synovial of the joints (Song and Kang, 2009). The synovial inflammation in RA is followed by cartilage destruction, bone erosion, subsequent joint deformities and

malalignment (Klareskog et al., 2009). One of the main characteristics of RA is that joint involvement is bilateral (Fishman and Bar-yehuda, 2010).

RA often causes distinctive foot pain. The complexity of the foot and the disease challenges pain treatment. The joints, tendons and muscles slowly degenerate over time and synovitis, effusion and eventually erosive arthritis are thought to cause valgus heel or pes planovalgus deformity (Banks and McGlamry, 1987).

1.2 FOOT AND ANKLE PAIN IN RHEUMATOID ARTHRITHIS

More than 85% of patients with RA experience pain in the feet and ankles during the course of the disease, and 57% already within the first year of the diagnosis (van der Leeden et al., 2008). Otter et al. (2010) have shown that pain during the course of RA was most common in the forefoot (63.9 %) followed by the toes (45.9 %) ankle (42.7 %), hindfoot (21.8 %) and midfoot (17 %) (Otter et al., 2010). Foot and ankle pain is also the main reason for walking incapacity among patients with RA (Grondal et al., 2008). Walking difficulty due to foot and ankle pain has been reported by 71% of the patients with RA. This physical limitation has an impact on patients' quality of life, but it also poses a potential socio-economic challenge due to reduced physical work capacity.

RA can affect the anatomy and function of the foot in different ways. The smaller joints, tendons and tendon sheaths at the foot are commonly involved in the earlier stages of RA, especially the tibialis posterior tendon and muscle is frequently involved and increases the risk of developing pes planus deformity and thus additional pain severity (Banks and McGlamry, 1987; Göksel Karatepe et al., 2010; Gulati et al., 2018; Michelson et al., 1995; van der Leeden et al., 2008). Hallux valgus and claw toes deformities are also commonly observed in patients with RA and the metatarsophalangeal joints are also at increased risk of developing deformity due to synovitis and high load-bearing (Göksel Karatepe et al., 2010; Gulati et al., 2018; Methods et al., 1963).

1.3 TREATING RHUMATOID ARTHRITHIS

There is currently no curative therapy of RA. Therefore, the goal of treatment is to decrease the autoimmune inflammation to prevent development of permanent joint pathology and to reduce pain, leading to improvement of the patient's overall function (Tanaka, 2013). The first attempts to treat RA focused on very specific regions and included alternative medicine such as bloodletting, leeching, acupuncture and moxibustion. These treatments were not effective in improving conditions (Hart, 1976). Instead, the use of disease-modifying anti-rheumatic drugs (DMARDs), especially methotrexate (MTX) dramatically improved treatment outcome in patients with RA (Black et al., 1964; Sneader, 2005; Weinblatt, 2013). Initially, MTX was used to treat leukemia (Farber et al., 1948; Sneader, 2005) but later it was shown to also have a beneficial effect on patients with arthritis (Black et al., 1964; Gubner et al., 1951). By the early 1990's, low dosing of MTX was established as the standard treatment for RA (Weinblatt, 2013). MTX is an immunosuppressant drug, which reduces activity of the immune system and is often combined with other treatment strategies. Biological DMARDs have also been included as standard treatments if MTX is insufficient (Smolen et al., 2016). Biological medicine is a more targeted pharmacological approach, which has made clinical remission achievable for a larger proportion of patients with chronic autoimmune diseases (Burmester et al., 2017). Despite the good effect of biological DMARD, there is still a persistent biomechanical problem for several of these patients, relating to specifically foot and ankle pain, but also to other joints in the body (Gulati et al., 2018; Heijde et al., 2006; van der Leeden et al., 2008). Therefore, overall care including pharmacological treatment should also include other supplementary therapeutic measures (Hennessy et al., 2016). Foot Orthoses (FO) is one of the initiatives that has been gaining increasing attention in recent years, realizing that biological DMARD is not always sufficient (Hennessy et al., 2016). Therefore, FO still remains a commonly used supplementary therapy for patients with RA and foot pain (Woodburn et al., 2010). Even though a FO reduces foot pain and changing the gait pattern, the interaction between these two things is not well understood (Barn et al., 2014; Hodge et al., 1999; Jackson et al., 2004; Kavlak et al., 2003; MacSween, 1999; Mejjad et al., 2004; Woodburn et al., 2003). This makes

it difficult to improve the design of FO, since it is uncertain which gait features should be altered to provide optimal pain relief.

1.3.1 FOOT ORTHOSES

Dorland's Medical Dictionary defines FO as a therapeutic in-shoe medical device used to support, prevent, align and treat lower extremity, foot deformities and malalignment (Dorlands Medical Dictionary for Health Consumers, 2007). FOs have been used for over two centuries by different health care professionals to treat pain and alignment issues in feet and lower extremities. One of the earliest medical references for use of FOs was from a Dutch physician, Peter Camper, who used FO to treat children with flat foot deformities with a FO design with medial longitudinal arch support (Camper, 1861).

FO are used for both different purposes and populations (e.g. sport, diabetes, cerebral palsy and different types of arthritis) (Brehm et al., 2008; Ferber, 2007; Hinman et al., 2012; Kato et al., 1996). Due to these wide groups, several different types of FO designs exist. The efficiency of FO in general points in different directions depending on the design and user population (Ferber, 2007; Landorf and Keenan, 2000; Raja and Dewan, 2011). For example, a heat-moldable semi-custom FO had no effect on foot kinematics during walking (Ferber and Benson, 2011). Whereas, some types of prefabricated FOs can be effective in altering foot kinematics during walking (Ferber and Hettinga, 2016). Although FOs are often recommended in rheumatologic clinical practice for RA, only a few clinical studies have actually been performed to elucidate the effect of this intervention in relation to pain reduction and changes in biomechanics (Hennessy et al., 2012; Tenten-Diepenmaat et al., 2019). The relatively few studies have reported relief of foot pain in patients with RA using FOs ranging from 18-24 mm on a 100 mm visual analogue scale (VAS) (Bongi et al., 2014; MacSween, 1999; Mejjad et al., 2004). A recent study found that reduction of forefoot plantar pressure leads to improvements in both pain and physical functioning (Tenten-Diepenmaat et al., 2020). However, larger plantar pressure reductions did not result in improved clinical outcomes, suggesting that a threshold may exist, after which there

is limited gain by reducing forefoot plantar pressure further (Tenten-Diepenmaat et al., 2020). Another of the studies found that FO altered activity of the tibialis anterior muscle and the timing of soleus and medial gastrocnemius muscles during gait (Barn et al., 2014). Despite these observed muscle changes, it has not been possible to demonstrate that FO changes lower extremity kinematics during walking in a meta-analysis (Hennessy et al., 2012). This lack of causality is probably because existing studies investigated different gait parameters. However, it is well-known that FO can redistribute foot plantar pressure but also reduce ankle eversion and forefoot abduction in patients with RA (Barn et al., 2014; Bongi et al., 2014; Jackson et al., 2004; Novak et al., 2009; Woodburn et al., 2003). FO can also reduce muscle activity of the TP muscle during gait (Murley et al., 2010). In summary, current knowledge suggests that FO can provide pain relief and reduce elevated forefoot pressure in patients with RA. However, due to a knowledge gap concerning the interaction between altered gait mechanics and pain relief, is it difficult to determine the optimal FO design for patients with RA.

In general, there is consensus that adherence to the use of orthotics and physical activity is a prerequisite for increasing the effectiveness of FO (Lutjeboer et al., 2018). Previous studies investigating adherence to FO have primarily been performed by use of patient-reported outcome measures (PROM), by use of questionnaires, interviews or diaries (Fransen and Edmonds, 1997; Jannink et al., 2005; Knowles and Boulton, 1996; Saag et al., 1996; Sykes et al., 1995; Van Netten et al., 2010a, 2010b). These data sources have a poor accuracy due to recall and response bias (Adams et al., 1999; Sackett, 1979). However, none of the previous FO intervention studies among patients with RA have measured adherence to FO or physical activity during the intervention period.

1.4 MOTION CAPTURE AND MUSCULOSKELETAL MODELING

Motion capture is the process of recording motion of moving objects/people. Motion capture is used across many different fields from animation to health care. Typically, 3D motion is captured by recording small reflective markers placed on anatomical

landmarks of the subject/patient and these recordings can be used to drive biomechanical models (musculoskeletal models), which can be used to estimate, joint angles, internal forces in the musculoskeletal system and can e.g. be used to get a better understanding of how FO alters the internal loading of joints and muscles.

A musculoskeletal model is a mathematical model of the musculoskeletal system of humans or animals containing bones, joints and muscles, Figure 1-1. Presently, it is challenging, or maybe impossible, to measure forces in the human body. However, over the last decades, major progress has been made within development and validation of musculoskeletal models for estimation of reaction forces in the body including muscles, ligaments and joints (Carbone et al., 2015; Marra et al., 2015). Furthermore, musculoskeletal models can be used for the purpose of simulation, which makes is feasible to perform 'what if" (e.g. the muscle properties are changed) investigations (Reinbolt et al., 2011). Different types of musculoskeletal computer-aided engineering software systems exist. The most commonly used software are: AnyBody Modeling System (Damsgaard et al., 2006), and OpenSim (Reinbolt et al., 2011; Seth et al., 2011).

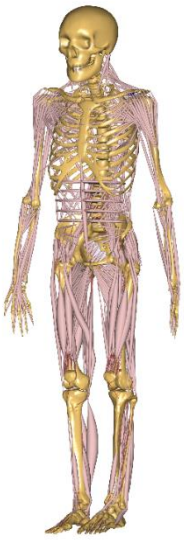

Figure 1-1: Musculoskeletal model (Adapted from the AnyBody modeling system)

Inverse dynamics is a technique to estimate internal forces and moments. Inverse dynamics uses rigid-body dynamics to estimate internal forces and moments based on kinematics, external forces and inertial properties of body segments guided via equations of dynamic equilibrium (Crowninshield et al., 1978; Damsgaard et al., 2006; Rasmussen et al., 2001). Consequently, if the motion and external forces are known, the equations of dynamic equilibrium can be used to compute internal forces in e.g. muscles and joints. However, the human body is statically indeterminate because it has far more muscles than degrees of freedom (Rasmussen et al., 2001). This means that there are not enough equations to uniquely determine the internal forces of the muscles (Rasmussen et al., 2001; Van Bolhuis and Gielen, 1999). In the real world, the central nervous system (CNS) solves this problem. However, it is unknown how the CNS determines the muscle recruitment (de Rugy et al., 2012). To solve the muscle recruitment as a mathematical problem, an optimization principle to determine the distribution of muscle forces must be applied.

1.4.1 THE MUSCLE RECRUITMENT PROBLEM

Several studies indicate that the CNS does not recruit muscles in a random order (Lombard, 1903; Prilutsky and Gregor, 1997; Van Bolhuis and Gielen, 1999). Electromyography measurements from repetitive movements such as cycling have identified identical muscle activity patterns (Prilutsky and Gregor, 2000, 1997). Additionally, muscles acting across the same joint can assist each other in a synergistic manner. However, some muscles appear to work against the direction of the motion; these muscles are antagonistic muscles. Antagonistic muscles can be helpful in performing a movement. An example is Lombard's paradox, which explains why both the hamstrings and quadriceps muscles contract at the same time when rising from a sitting position, despite being antagonists to each other (Lombard, 1903). It has been hypothesized that the CNS tries to minimize loading on the muscles and joints, which would make it possible to estimate unknown internal forces by an optimization problem (Nubar and Contini, 1961; Prilutsky et al., 1997; Rasmussen et al., 2001; Weber et al., 1836). This parallels well to Darwin's natural selection theory that the "survivors" manage their resources in the best possible way (Darwin, 1859). This

principle is implemented in the musculoskeletal model, though using an optimization principle where a cost function is minimized (Rasmussen et al., 2001). Different muscle recruitment criteria exist, but for the current work, muscle recruitment was solved by minimizing a polynomial cost function G. The cost function is defined as (G):

$$\min_{\mathbf{f}} G\left(\mathbf{f}^{(\mathrm{M})}\right) = \sum_{i=1}^{n^{(\mathrm{m})}} n_{\mathrm{i}} \left(\frac{f_{\mathrm{i}}^{(\mathrm{M})}}{N_{\mathrm{i}}}\right)^{\mathrm{p}}$$
$$\text{Subject to} \quad \begin{matrix} \mathbf{Cf} = \mathbf{d} \\ 0 \leq f_i^{(M)} \leq N_{i,} \end{matrix}$$

Where, $\mathbf{f}^{(\mathrm{M})}$ is a vector of all the muscle forces, **C** is a coefficient matrix for all the unknown forces in the problem and **f** denotes joint reaction and muscle forces. **d** contains all the known external loads and inertia forces. $\mathrm{n}^{(\mathrm{m})}$ denotes the number of muscles in the model, $f_{\mathrm{i}}^{(\mathrm{M})}$, denotes the muscle force of the i^{th} muscle, and N_i is the instantaneous muscle strength (can be taken from maximum strength tests or physiological cross-sectional areas) of the i^{th} muscle. Finally, the optimization problem is subjected to constraint, stating that the muscles can only pull and that the maximal muscle force must remain lower than the instantaneous muscle strength $(0 \leq f_i^{(m)} \leq N_{i,})$.

However, the mentioned optimization principles are only valid in a healthy system. At present, there is no recruitment principle including the effect of pain. However, attempts have been made to apply recorded electromyography of superficial muscles and include it as known variables in the optimization (Lloyd and Besier, 2003). Another way is to adjust the muscle properties by for example changing the strength of individual muscles or apply more advanced muscle models (de Zee et al., 2009; Heinen et al., 2019). Marra et al. developed and compared different models to estimate internal knee loading of an individual with knee osteoarthritis and total knee arthroplasty as part of the grand challenge to predict knee forces (Fregly et al., 2012). To account for the reduced strength of the knee flexion/extension, the strength of these

muscles was reduced with 35% of their normal physiological cross-sectional area (Marra et al., 2015; Silva et al., 2003). The results of Mara et al. were comparable to in-vivo measured knee forces ($r^2 = 0.90$) (Marra et al., 2015).

1.5 EXPERIMENTAL MODELS

Patients with RA typically walk at a slower pace, have reduced range of motion of the major joints and increased muscle activity in the lower leg muscles (Baan et al., 2012; Barn et al., 2013; Ringleb et al., 2006; Wang et al., 2020). However, comparing gait patterns of patients with asymptomatic individuals is vulnerable to many confounding factors such as age, gait speed, body size, normal variation in gait pattern and co-morbidities. Therefore, it is not well understood how RA-associated pain affects motion and muscle recruitment patterns and whether the adapted compensations lead to further development of joint deformities. A way of controlling for these confounding factors is by using experimental models. Pohl et al. used an experimental fatigue model to investigate how asymptomatic individuals adapted to fatigue of the TP muscle during gait. It was found that fatigue of the TP muscle was not sufficient to alter rearfoot motion during gait (Pohl et al., 2010). Another way to reduce the complexity is to apply experimental pain models in asymptomatic healthy subjects. Inducing pain by injections of hypertonic saline is a frequently used pain model to induce a short-lasting pain close to the pain reported by patients in clinical practice (Kellgren, 1938; Svensson et al., 1995). Hypotonic saline evokes pain by stimulating the group III and IV afferent nerves. Experimental pain using healthy volunteers provides insight into the nature of pain in specific anatomical structures and allows for controlled investigations of the immediate effect on pain in a crossover design controlling for the confounding factors that might be present in a patient population (Graven-Nielsen, 2006). For example, a previous study has shown that experimental pain in the patella fat pad can replicate the motion pattern of patients with osteoarthritis (Henriksen et al., 2010). Therefore, the patella fat pad model can be used to investigate possible compensation mechanisms in a controlled setting. Interestingly, it has also been found that experimental pain alone can reduce the force

produced by a muscle, implying that pathological changes are not necessarily present in impaired muscle function (Henriksen et al., 2011).

1.6 THE EFFECT OF PAIN ON MOTION

It has been widely studied that pain affects the movement pattern (Arendt-Nielsen et al., 1996; Farina et al., 2005; Graven-Nielsen et al., 1997; Matre et al., 1998; Sohn et al., 2000; Zedka et al., 1999). However, the underlying mechanisms are still poorly understood (Hodges and Tucker, 2011). Different theories have tried to explain how and why we move differently upon perception of pain. These are the *vicious cycle* (Roland, 1986), the *pain adaption model* (Lund et al., 1991) and an unnamed theory by Hodges and Tucker (Hodges and Tucker, 2011).

The vicious cycle theory suggests that the activity in a painful muscle increases and sustained activity causing ischaemia and accumulation of algetic agents both of which contribute to the perceived burden of pain (Hodges and Tucker, 2011; Roland, 1986). The pain adaption model, on the other hand, proposes that muscle activity changes with pain to limit movement and protect the system from further injury (Lund et al., 1991; Peck et al., 2008). Both the vicious cycle and the pain adaption model have been shown to be congruent with studies investigating the effect of experimental pain (Farina et al., 2005; Graven-Nielsen et al., 1997; Hodges and Tucker, 2011; Matre et al., 1998; Sohn et al., 2000; Zedka et al., 1999). However, not all observations can be explained by the vicious cycle or the pain adaption theory, alone or in combination (Hodges and Tucker, 2011). Therefore, a new theory has been proposed taking both clinical and experimental observations into consideration (Hodges and Tucker, 2011). The theory consists of five items: Firstly, the theory proposes that distribution and redistribution of muscle activity occurs within and between muscles during pain (Farina et al., 2004; Hodges et al., 2008; Sohn et al., 2000). In order to perform a movement, the CNS sends signals to the muscles to execute the movement. However, due to the abundance of muscles in the human body, there is an infinite number of combinations of muscle recruitment solutions to perform any given movement

(Bernstein, 1967). This abundance is commonly referred to as the abundance of the musculoskeletal system (Bernstein, 1967; Bizzi and Cheung, 2013; Latash et al., 2002; Van Emmerik and Van Wegen, 2002). In theory, it would be possible that a person uses a unique activation pattern to perform a specific movement task. However, it appears that the CNS does not select a random activation patterns (Hirashima and Oya, 2016). One of the common theories is that muscle recruitment is performed in the most energy conserving way (Fagg et al., 2002; Shadmehr and Krakauer, 2008). However, this assumption is not fully applicable if pain is present since limping, which is an example of a pain restricting mechanism, increases energy consumption (Waters and Mulroy, 1999).

Secondly, a change in the mechanical behavior such as modified movement and stiffness can occur during pain (Hodges and Tucker, 2011). For example, individuals with neck pain walk with less rotation of truncus compared to individuals without neck pain (Falla and Dieterich, 2017; Treleaven et al., 2019). Patients with RA also walk slower and with reduced range of motion of the ankle, knee and hip joints compared to healthy controls (Weiss et al., 2007).

Thirdly, it is believed that the selected compensation strategy is to protect from further pain or injury (Falla and Dieterich, 2017; Hodges and Tucker, 2011; Murray and Peck, 2007). In cases of e.g. unilateral pain, the painful side can be protected by limping or reducing walking velocity or stride length (Rolf et al., 1997; Weiss et al., 2007).

Fourthly, the compensation is not always explained by simple changes but involves changes at multiple levels of motor systems (Martin et al., 2008). Although changes in muscle activity occur during pain, is it not always sufficient to explain the adaptation (Hodges and Tucker, 2011). Changes in other pathways may also play a role. Spinal effects may be mediated by nociceptive input on motor neurons (Kniffki et al., 1979) or plasticity in the spinal cord provoked by nociceptive primary afferent inputs, also known as central sensation (Woolf, 1983).

Lastly, the compensation has a short-term benefit (Christensen et al., 2017; Friel et al., 2006) but can potentially lead to long-term consequences due to reduced variability and altered loading (Friel et al., 2006; Hodges and Moseley, 2003). It has previously been found that individuals with a unilateral chronic ankle sprain have reduced hip abduction strength and less planter flexion range of motion in the involved side (Friel et al., 2006).

1.7 KNOWLEDGE GAPS

The extent to which the altered gait pattern in patients with RA is caused by structural changes (deformities), compensation due to pain or both remains unknown (Barn et al., 2013; Ringleb et al., 2006; Wang et al., 2020). Knowledge about this association could contribute to our understanding on how FO may benefit correction of the foot during gait. Experimental pain models can be used to further explore this area. However, making an RA pain model would be infeasible due to the complexity of the disease. However, TP muscle pain and dysfunction are common among patients with RA and have previously been reported with a prevalence as high as 64 % (Michelson et al., 1995). Due to the high prevalence of TP muscle pain among patients with RA and foot problems, it would be relevant to gain a better understanding of how TP muscle pain affects gait and muscle compensation strategies and whether these may potentially lead to further progression of injury structural changes (Hodges and Tucker, 2011).

Studies have demonstrated benefits of FO regarding relief of pain perception and altered gait mechanics (Barn et al., 2014; Hodge et al., 1999; Jackson et al., 2004; Kavlak et al., 2003; MacSween, 1999; Mejjad et al., 2004; Woodburn et al., 2003). To make recommendations for the optimal use of FO, it is relevant to understand current compensatory mechanisms as well as the gait parameters the FO is aiming at changing. However, there are still many unknown factors; among them which compensatory mechanisms in RA associated foot pain are inexpedient, what occurs at knee and hip level and which parameters are relevant to modify with a FO. It is thus crucial to understand how pain affects both gait pattern and pain perception. Within

knee osteoarthritis, the well-established goal of a FO is to reduce the medial knee forces, often quantified in clinical trials using the knee adduction moment (Arnold et al., 2016). However, within RA it remains uncertain which gait parameters the FO is intended to change. We lack an understanding of how FO and pain relief are related to internal forces and moments during gait in RA (Tenten-Diepenmaat et al., 2019). Studies on FO treatment in patients with RA have primarily focused on the foot region, and not included assessment of how FO influences pain perception, kinematics and kinetics of the knee and hip joints (Barn et al., 2014; Bowen et al., 2011; Davitt et al., 2006; Jackson et al., 2004; Konings-Pijnappels et al., 2019; Otter et al., 2004; Tenten-Diepenmaat et al., 2019; Woodburn et al., 2002). Furthermore, variables which may affect the treatment, such as daily activity and adherence to the FO therapy, have not been monitored in previous studies. It is also unknown if patients adapt their gait pattern after adjusting to the FO.

1.8 AIMS AND GOALS OF THE PHD PROJECT

The overall aim of this dissertation was to investigate biomechanical adaptations to experimental pain in the TP muscle and to investigate the effect of FO on pain and gait in patients diagnosed with RA. To accomplish this, two experimental studies and two clinical studies were conducted.

1. The aim of Study I was to investigate the effect of experimental TP muscle pain on gait in healthy volunteers.
2. The aim of Study II was to investigate potential muscle compensation mechanisms when the TP muscle was recruited less.
3. The aim of Study III was to investigate immediate changes in gait mechanics with a custom-made FO in patients with RA.
4. The aim of Study IV was to investigate potential adaptations in pain intensity, activity, and gait after four weeks treatment with a custom-made FO in patients with RA.

1.8.1 STUDIES:

Study I: Simonsen, M.B., Yurtsever, A., Næsborg-Andersen, K., Leutscher, P.D.C., Hørslev-Petersen, K., Andersen, M.S., Hirata, R.P. *Tibialis posterior muscle pain effects on hip, knee and ankle gait mechanics*. Human Movement Science 66, 98–108. 2019

Study II: Simonsen, M.B., Yurtsever, A., Næsborg-andersen, K., Leutscher, P.D.C., Hørslev-petersen, K., Hirata, R.P., Andersen, M.S. *A parametric study of effect of experimental tibialis posterior muscle pain on joint loading and muscle forces — Implications for patients with rheumatoid arthritis?* Gait & Posture 72, 102–108. 2019

Study III: Simonsen, M.B., Hirata, R.P., Næsborg-andersen, K., Leutscher, P.D.C., Hørslev-Petersen, K., Woodburn, J., Andersen, M.S.,. *Different types of foot orthoses effect on gait mechanics in patients with rheumatoid arthritis*. Journal of biomechanics, under review

Study IV: Simonsen, M.B., Næsborg-andersen, K., Leutscher, P.D.C., Hørslev-Petersen, K., Woodburn J,. Andersen, M.S., Hirata, R.P., *Relief of pain in the ankle and the foot in conjunction with altered joint moments in patients with rheumatoid arthritis – outcome of a four-week trial with use of custom-made foot orthoses*. Arthrithis Care & Reseach, under review

These papers will be referred to as Study I, Study II, Study III and Study IV.

CHAPTER 2. STUDY DESIGN

This chapter describes the study designs of the two experimental and two clinical studies.

2.1 EXPERIMENTAL TIBIALIS POSTERIOR PAIN STUDIES

Studies I and II were conducted as randomized blinded crossover studies, where experimental pain was induced by single injections of hypertonic saline into the TP muscle and isotonic saline was applied as a control intervention after a short pause. The injections were performed in a randomized order (figure 2-1). Twelve healthy volunteers were recruited for this experimental study. Participant characteristics (mean ± SD) were: (mean ± SD) age 28.3 ± 1.8 years, height 180.3 ± 9.8 cm, body mass 83.7 ± 12.0 kg. Motion capture during gait, pain intensity scores and body charts were measured in the studies. An anatomical landmark scaled musculoskeletal model was made for each participant and used to estimate joint angles and moments for the ankle, knee and hip joints, respectively. The model is scaled with reference to the reflective markers used for the motion capture system, height and weight (Lund et al., 2015). (Study I and Study II)

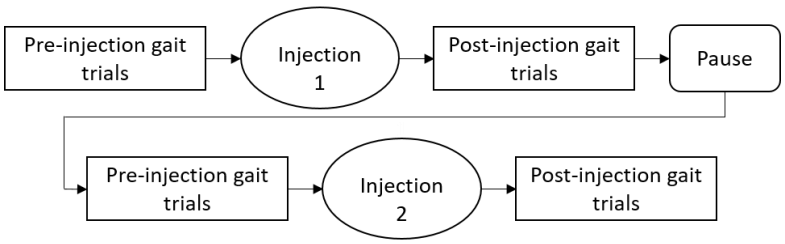

Figure 2-1: Procedure for the gait trials before and after injection of either isotonic or hypotonic saline, respectively. The injections were given in a randomized order.

Describing movements in 3D can be complicated. To simplify the description of movements, a specific theology is used for the different directions of movement, Figure 2-1 shows terms and directions that are used in the present dissertation.

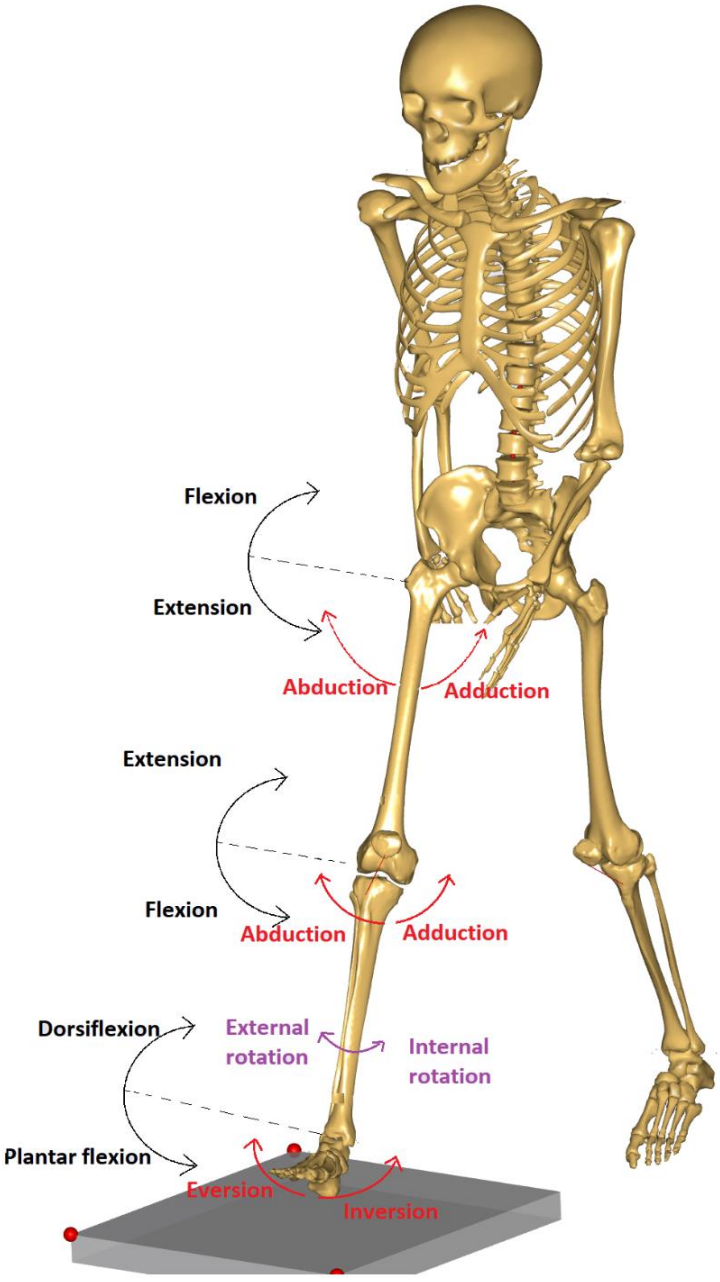

Figure 2-1: Joint angles of the lower extremity for the ankle knee and hip joints. (Adapted from the AnyBody modeling system)

2.1.1 PARAMETRIC STUDY

The parametric Study II expanded on Study I by investigating muscle recruitment compensation mechanisms as a result of inducing dysfunctionality of the TP muscle. A previous study has shown that patients with TP muscle dysfunction have reduced muscle strength of the TP muscle (Michelson et al., 1995). Additionally, experimental muscle pain have also been found to reduce the maximal strength of a muscle (Henriksen et al., 2011). To implement the experimental pain into the musculoskeletal model was muscle strength of the TP muscle penalized by reducing the maximal isometric muscle force of the muscle. The reduction was performed in steps of 10% from the default isometric muscle strength of the TP muscle (from 40% to 100 %).

2.1.2 STATISTICS

In the present dissertation, statistical parametric mapping (SPM) was used to compare spatiotemporal continuous data such as kinematics, kinetics and foot plantar pressure. SPM was originally developed within neuroimaging in the 1990s but has later become more frequently used within biomechanics (Pataky, 2012; Pataky et al., 2008, 2009). In summary, SPM uses random field theory to calculate statistical interferences on n-dimensional data to test where data statistically differ (Friston, 2007; Maharaj et al., 2018). SPM are explained in greater detail in the literature (Friston, 2007; Pataky, 2012; Pataky et al., 2008, 2009).

The aim of the experimental Study I was to investigate how induced pain in the TP muscle of healthy volunteers affected the movement pattern. SPM paired t-tests were used to compare joint angles and moments. A paired t-test was used to compare pain intensity, gait velocity and duration of the stance phase.

The aim of the combined experimental and simulation Study II was to investigate which muscles are best suited to compensate for impairment of the TP muscle using musculoskeletal modeling. Only descriptive data are presented due to uncertainties regarding the extent of impairment of the TP caused by the pain-inducing injection.

2.1.3 ETHICS

The study was approved by The North Denmark Region Committee on Health Research Ethics (N20170066).

2.2 CLINICAL STUDY DESIGN

Study III was applied a cross-over design, whereas Study IV was a quasi-experimental study. During the first four weeks of the experimental study, the participants were instructed to use a flat latex insole (sham) followed by four weeks usage of the custom-made FO (figure 2-3). As patients with RA have diurnal variation in joint pain and stiffness in the morning typically lasting one to two hours, gait examinations were performed from 10:00 AM. The trial took place over a period of eight weeks and consisted of four study sessions:

(1) A baseline session containing foot measurement for manufacturing of the custom-made FO and recording baseline pain intensity and body charts of participants.

(2) A short session where the insole was adjusted to fit the preferred footwear of each participant.

(3) Four weeks after baseline, a gait analysis was performed in conjunction with recording of pain intensity and body pain charts.

(4) After another four weeks, gait analysis and pain measurements were repeated.

The daily number of walking steps was measured by a watch-based activity tracker (Polar M200) during the entire trial. The anatomical landmark scaled musculoskeletal model from Lund et al. was used to make a musculoskeletal model for each participant to estimate ankle, knee and hip joint angles and moments.

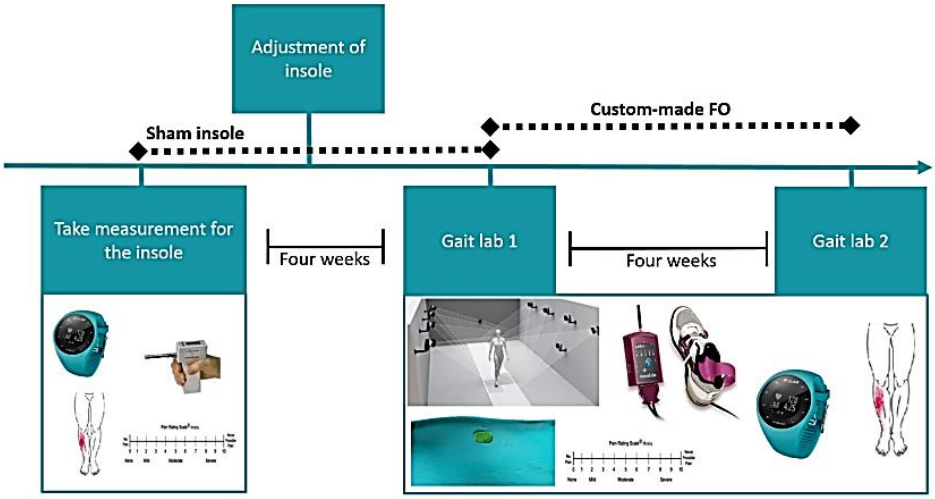

Figure 2-3: Timeline of the different sessions in Study III and Study IV. Measurements of the insoles were obtained in conjunction with the baseline pain recordings and the activity tracker. Approximately 2-3 weeks later, the FO was adjusted to fit the participant's preferred footwear. In the two gait analyses, pain perception and motion capture during gait were recorded.

2.2.1 PATIENTS

In total, 27 patients with RA participated in Study III. Two participants dropped out before the final measurement and they were, thus, excluded from the analysis in study IV. An overview of the participants for study III and Study IV is provided in table 2-1.

Table 2-1: Clinical characteristics and demographics of patients in Study III and Study IV.

	Study III **N=27**	**Study IV** **N=25**
Age, years (mean ± SD)	55.8 ± 12	56.2 ± 10
Height, cm (mean ± SD)	173.6 ± 8.3	172.6 ± 8.4
Body weight, kg (mean ± SD)	84 ± 15	84 ± 16
Baseline VAS foot pain (mean ± SD)	50.2 ± 25.6	47.8 ± 24.6
HAQ[1] (mean ± SD)	0.65 ± 0.59	0.59 ± 0.5

DAS28[2](mean ± SD)	2.55 ± 0.88	2.47 ± 0.7
Male, n, (%)	8 (30) %	8 (32)
Treatment		
bDMARD[3], (%)	22.2 %	20 %
csDMARD[4], (%)	88.9 %	96 %

1 HAQ (The Health Assessment Questionnaire), 2. DAS28 (Disease Activity Score – 28 joints), 3. bDMARD (Biological disease-modifying anti-rheumatic drugs), 4. csDMARD (Conventional synthetic disease-modifying anti-rheumatic drugs) (mean +/- SD if not otherwise indicated. (Adapted from Study III and IV)

To reduce the impact of other musculoskeletal-related pain and other similar problems, strict criteria were set for inclusion and exclusion of participants. Study inclusion criteria are presented in Study III and Study IV.

2.2.2 THE CUSTOM-MADE FO

The principles of the custom-made FO used in Study III are based on the concept of the short foot exercise (SFE). The SFE is an exercise aiming at activating the intrinsic muscles of the foot and actively form the longitudinal and horizontal arch, respectively (Kim and Kim, 2016; Saeki et al., 2015). The footprint is captured in a foam box while the foot is maintained in the short foot position, and patella align with the second toe in a full weight-bearing setting. The insole was manufactured in ethylene-vinyl acetate as a ¾ insole, since the shorter insole makes it easier to fit in the shoe and to conveniently switch the insole between different shoes (Figure 2-2). A small temperature sensor was used to measure adherence (Orthotimer (Rollerwerk, Germany)) in Study IV, Figure 2-4. The sensor is a commercially available sensor (9 x 13 x 4.5 mm) measuring the temperature every 15 minute; the sensor has a lifespan of more than 18 months (Lutjeboer et al., 2018).

Figure 2-4: Custom-made FO with the green Orthotimer sensor

2.2.3 STATISTICS

The aim of Study III was to compare the immediate effect of two different types of prefabricated FOs on plantar pressure, joint angles and moments during gait. To accomplish this aim, the SPM version of a repeated measures ANOVA was used to compare joint angles and moments in addition to plantar pressure. Further, a regular repeated measures ANOVA was used to compare gait velocity and stance phase.

The aim of Study IV was to investigate pain intensity, daily activity and movement adaptations at four weeks follow-up using the custom-made FO. To accomplish this aim, the SPM version of a paired-t test was used to compare joint angles and moments between the custom-made FO and the sham insole. A Wilcoxon signed ranks test was used to compare daily walked steps.

2.2.4 ETHICS

The study was approved by The North Denmark Region Committee on Health Research Ethics (N20180007). The project was presented to the patient council at the Danish Hospital for Rheumatic Diseases in Sønderborg who endorsed the project and pointed out that foot pain in patients with RA is an important research area. The patient council was involved in the development of patient information material and the study protocol. The study was registered at clinicaltrials.gov (NCT03561688).

2.3 DEFINING A RESPONDER: SUPPLEMENTARY ANALYSES

A supplementary analysis was added to compare if any of the variables measured in Study III and Study IV could uncover who would benefit and thus experience pain relief.

Although statistical significance is considered important to determine if the effect of one type of intervention is superior compared to another intervention, it may not necessarily imply that the statistical difference between the two types of intervention can be translated into a context of clinical relevance (Kelly, 1998). Knox et al. (1995) found that the minimum clinically significant difference in patient pain intensity was 13-mm on a VAS (Todd et al., 1996). Another study by Kelly et al. (1991) found that a change in pain intensity of approximately 10-mm represents a small treatment effect and that an approximately 20-mm change represents a large treatment effect (Kelly, 1998). Therefore, it would be interesting to compare if patients reporting a major treatment effect differ from patients reporting a minor effect.

For simplicity, patients in Study IV have been sub-divided into two groups: patients with a major treatment effect (≥20mm reduction in pain intensity) and patients with a minor treatment effect ((<20mm reduction in pain intensity). All patients who had used the FO less than two hours per day were excluded in this post-hoc analysis.

2.3.1 STATISTICS

In the post-hoc analysis, the group of participants in Study IV who experienced a major effect of the custom-made FO intervention on relief of foot pain was compared with the group of participants with a minor effect. Clinical characteristics and demographics were compared using a t-test, and the baseline ankle plantar flexion moment, ankle eversion moment and knee adduction moment were compared between the two groups with the SPM t-test. Finally, a paired t-test was used to investigate a difference in the ankle plantar flexion moment between the sham and custom-made FO in responders and non-responders, respectively.

CHAPTER 3. RESULTS

This chapter presents the key results from Studies I-IV and an additional analysis comparing major and minor pain relief responders.

3.1 EXPERIMENTAL TIBIALIS POSTERIOR MUSCLE PAIN

3.1.1 PAIN PERCEPTION

In Study I, pain intensity was highest during the effect of the hypertonic saline injection (5.8 ± 1.7 NRS) in the TP muscle compared with the isotonic saline injection (1.8 ± 1.4 NRS), ($t(11)=-3.97$, $p < 0.001$). Pain intensity declined rapidly (approximately 5-8 minutes) after the injection. However, pain intensity was stable during the three gait trails. Figure 3-1 presents pain ratings of each participant for the hypertonic and isotonic saline injection, respectively. (Study I)

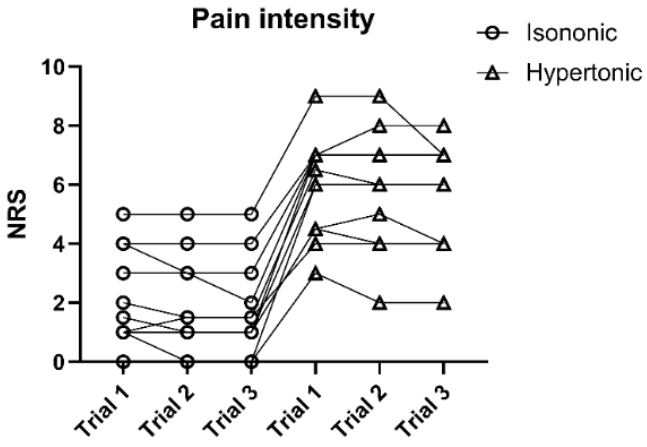

Figure 3-3-1: Median pain intensity values by use of Numerical Rating Score (NRS) for each participant after each gait trial out of six, testing the effect of the isotonic and hypertonic saline injection, respectively. The order of injections was randomized. However, for graphical simplification, data are presented in a fixed order. (Adapted from Study I)

As expected, the area of reported pain in the TP muscle was larger after injection of hypertonic saline compared with injection of the control isotonic ($t(11) = -3.859$, $p = 0.003$), Figures 3-2 A and B. Pain was only felt in the injected leg, primarily close to the injection site and the surrounding muscles (Rha et al., 2010). A few participants also experienced pain close to the ankle joint. (Study I)

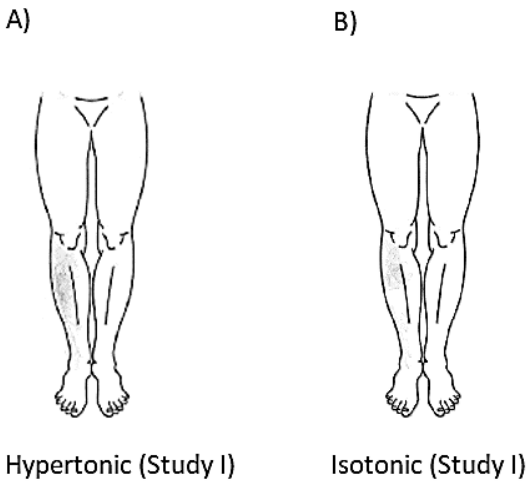

Figure 3-3-2: A) Average body chart recorded pain after injection of hypertonic saline in the tibialis posterior muscle in healthy volunteers. B) Average body chart recorded pain after injection of isotonic saline in the tibialis posterior muscle in healthy volunteers. (Adapted from Study I)

3.1.2 GAIT ADAPTIONS

Interestingly, no difference in ankle joint angles or moments between the isotonic and hypertonic conditions were observed. Hip internal rotation was reduced between 91% and 100% of the stance phase and the hip external moment between 57% and 67% upon injection of hypertonic saline in the TP muscle (Figure 3-3). Finally, the external knee rotation moment was also reduced between 59% and 84% of the stance phase upon injection of hypertonic saline (Figure 3-3). (Study I)

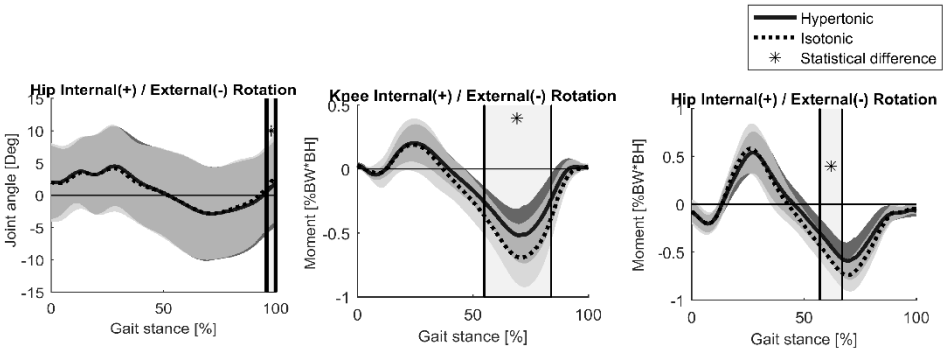

Figure 3-3: Mean joint angles for the hip internal external rotation and knee and hip internal/external rotation for joints of all subjects. The dotted line represents values for the isotonic condition, the solid line is the hypertonic condition. The light gray shaded area marked with a star indicates a significant difference in the angle values between the isotonic versus the hypertonic saline injection. (Adapted from Study I)

3.1.3 MUSCLE COMPENSATIONS

The results from Study II showed that the contribution from the TP muscle declined upon injection of hypertonic saline, whereas other muscles (flexor hallucis longus and flexor digitorum longus) in the deep compartment of the lower leg compensated for the impairment of the TP muscle as it became weaker (Figure 3-4). As a result, the compensation mechanism increased the forces of the ankle joint (Figure 3-5). (Study II).

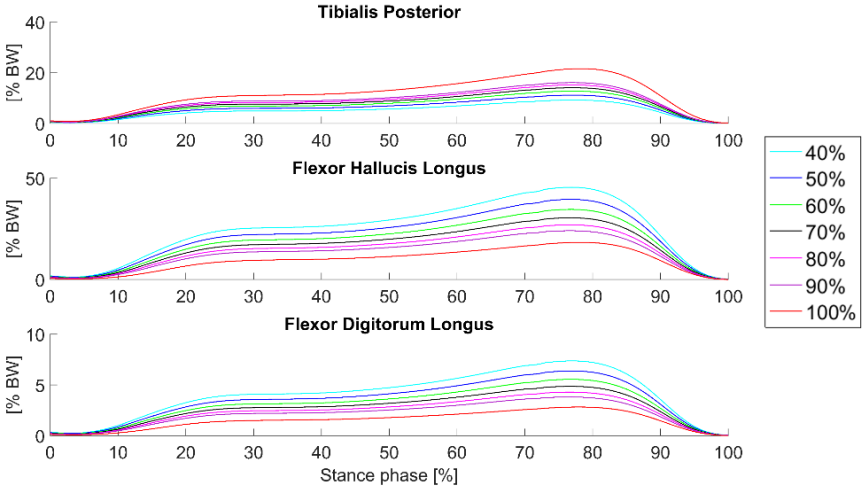

Figure 3-4: Muscle forces of tibialis posterior, flexor halluces longus and flexor digitorum longus, with pain and reduced muscle force of tibialis posterior in intervals of 40-100% of default tibialis posterior muscle strength. Normalized to percentage of body weight (BW) and % of stance phase. (Adapted from Study II).

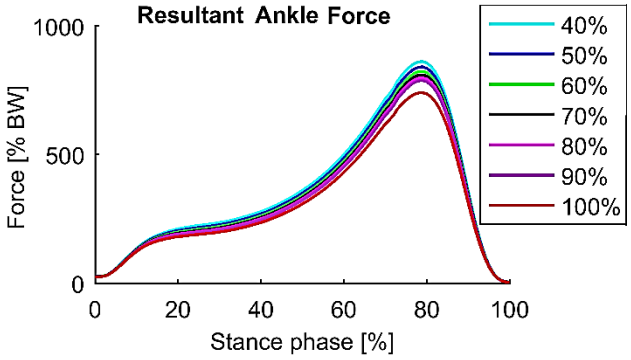

Figure 3-5: The total resultant ankle force during the stance phase with pain and reduced muscle force of the tibialis posterior in intervals of 40-100% of default strength. Normalized to percentage of body weight (BW) and stance phase. (Adapted from Study II)

3.2 EFFECT OF FOOT ORTHOSES

3.2.1 GAIT

After four weeks use of the custom-made FO, the ankle plantar flexion moment was reduced from 67% to 76% of the stance phase compared to the sham (Figure 3-6). The custom-made FO also reduced the ankle eversion moment from 3% to 40% of the stance phase (Figure 3-6). The custom-made FO increased the knee adduction moment from 23% to 57% of the stance phase (Figure 3-6). No changes in the ankle, knee and hip joint moments were observed between baseline and follow-up using the custom-made FO. (Study III and Study IV)

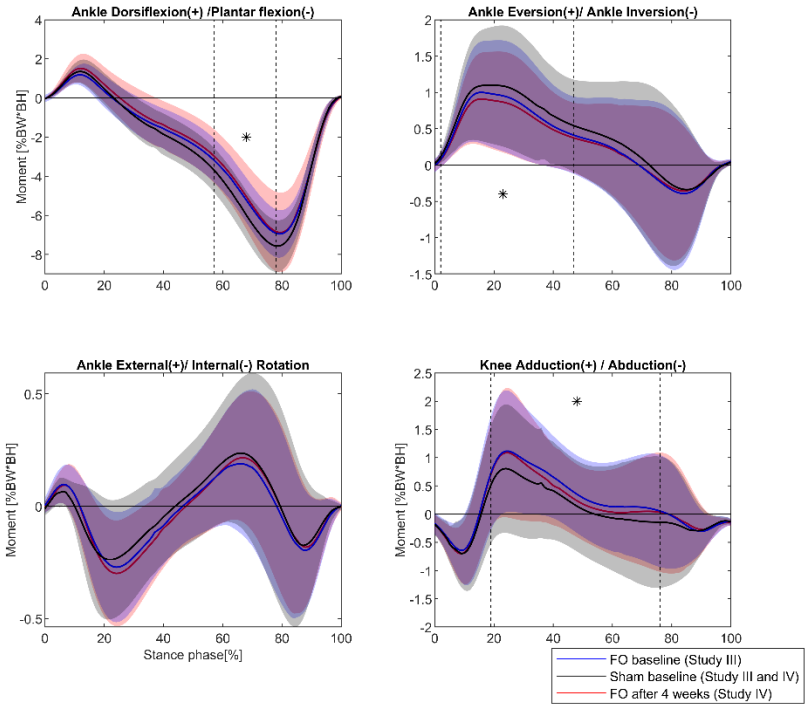

Figure 3-6: Mean moments of the ankle and knee joints. The black line represents the findings during the sham insole intervention; the blue line shows the custom-made FO intervention findings at baseline and the red line custom-made FO intervention at study closure. Statistical difference is the area between the dotted lines marked with a star between the sham and the custom-made FO. Normalized to percentage of body weight (BW) and stance phase (Adapted from Study III and Study IV).

3.2.2 PAIN PERCEPTION

The participant's foot/ankle pain intensity was reduced after the four weeks custom-made FO treatment period compared to baseline and the sham test, respectively, ($Z(24) = -3.365$, $p > 0.001$) Figure 3-7. The foot/ankle pain was reduced by 17.3 mm on average. No change in pain intensity was observed for the knee and hip joints after the four weeks intervention (Study IV).

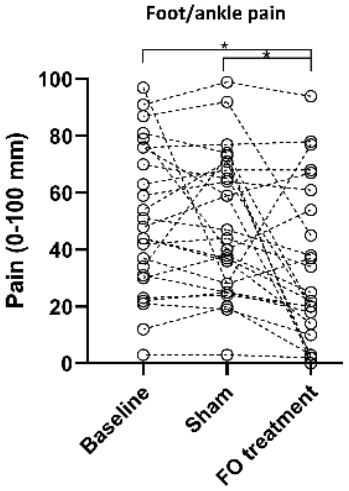

Figure 3-7: Foot/ankle pain intensity ratings at baseline (visual analogue scale), after intervention with the sham and custom-made FO, respectively. (Adapted from Study IV)

The average baseline foot and ankle pain intensity in Study III and Study IV was 50.2 mm ± 25.6. This result is in agreement with previously reported study findings within the range of the 40-61 mm using VAS to assess foot/ankle pain prior to initiation of custom-made FO treatment (Barn et al., 2013; Kavlak et al., 2003; Linberg and Mengshoel, 2018; Stewart et al., 2018).

Interestingly, the area of perceived pain was reduced not only in the feet but also in legs, arms and hands (Figure 3-8 and Table 3-1). (Study IV)

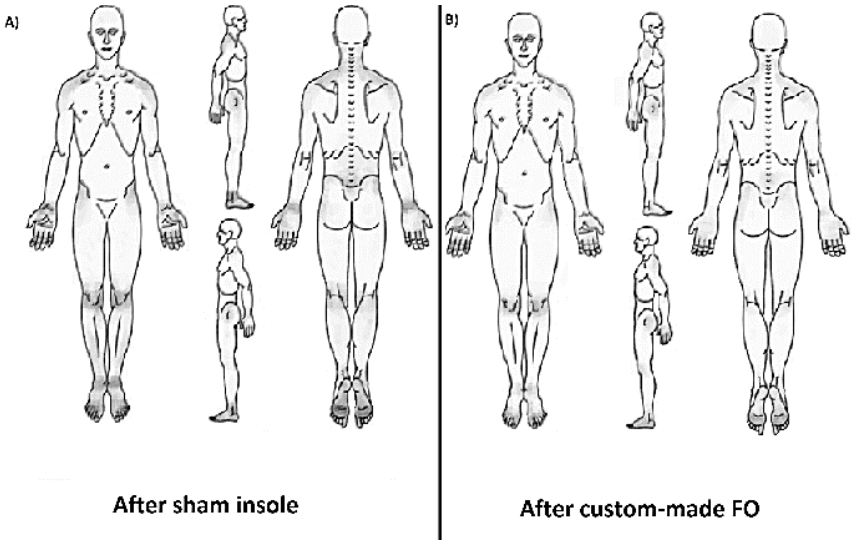

Figure 3-8: A) Average body charts of the measurement after the sham intervention in patients with rheumatoid arthritis. B) Average body charts of the measurement after the custom-made foot orthoses intervention in patients with rheumatoid arthritis. (Adapted from Study IV).

Table 3-1: Median and interquartile range of the measured area of perceived pain for the foot/ankle region, legs, trunk and arms/hands from the body charts at baseline, after the sham and custom-made FO interventions, respectively. (Adapted from Study IV)

	After sham insole	After custom-FO	P value
Feet/ankles	52.69 IQR: 29.6-92.1	26.9 IQR: 11.7-56.6	P = 0.009*
Legs	68.91, IQR: 10.1-153.5	29.3, IQR: 0-51.1	P < 0.01*
Trunk	0, IQR: 0-29.0	0, IQR: 0-11.9	P = 0.5
Arms/hands	43.0, IQR: 10.8-125.5	28.3 IQR: 0-71.7	P = 0.012*

3.2.3 DAILY ACTIVITY

The participants did not change their daily activity in the four-week-period between the sham test and end of the custom-made FO intervention study ($Z(24) = 0.444$ ($p = 0.657$). Figure 3-9 presents the mean walking steps measured in each participant daily. (Study IV)

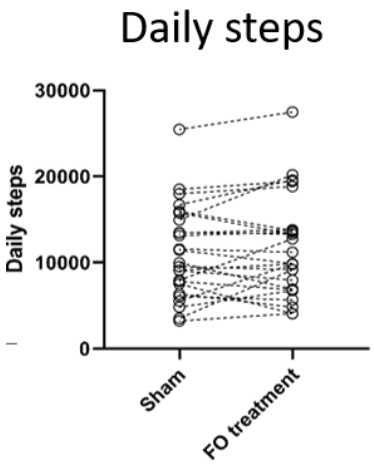

Figure 3-9: Mean daily steps walked for each participant during the sham and custom-made FO interventions periods. (Adapted from Study IV)

3.2.4 SATISFACTION AND ADHERENCE

Generally, patients were satisfied with the custom-made FO. A majority of the patients (85.1%) expressed that they were either satisfied or very satisfied with the custom-made FO (Figure 3-10A). The participants used the FO for 4.55 hours per day on average (IQR: 2.7-7) (Figure 3-10B).

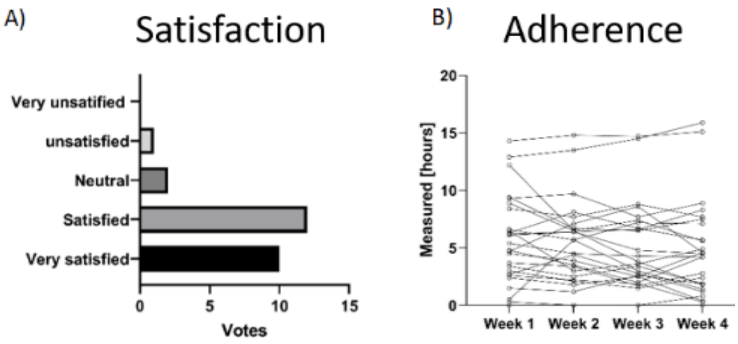

Figure 3-10: A) Patients with rheumatoid arthritis reported thee levels of satisfaction with the custom-made FO after the intervention. B) Adherence of the custom-made FO measured with the Orthotimer for each individual patient. (Adapted from Study IV)

3.2.5 CLINICAL FEATURES AND DEMOGRAPHICS OF MAJOR AND MINOR RESPONDERS

Table 3-2 presents the demographics and clinical features of the major and minor responders, respectively. The reported foot/ankle pain at baseline by the major responders was higher (62.1± 19.6) compared with the minor responders (40.66 ± 26.6) (p= 0.041). This indicates that FO should be prioritized for the patients with major complaints of foot/ankle pain. However, this result could also be because the patients with the highest levels of foot/ankle pain intensity are more likely to experience a reduction in pain that falls within the definition used in the present work (major treatment effect (≥20mm reduction in pain intensity) and patients with a minor treatment effect ((<20mm reduction in pain intensity)). None of the remaining demographics and clinical features provided further information to determine which patients will benefit from the custom-made FO (Table 3-2).

Table 3-2: Comparison of demographics and clinical features of the major and minor responders using t-test.

	Major Responder, N=8		**Minor Responder, N=15**		**t-value**	**p-value**
Male, (%)	12.5		26.6		-	-
Age, years, (mean ± SD)	55.8	± 12.6	54.9	± 8.7	0.17	0.863
Disease age, years, (mean ± SD)	3	± 1.5	4.1	± 1.9	-1.40	0.179
Body weight, kg (mean ± SD)	85	± 17	81.7	± 15.1	0.43	0.669
Height, m (mean ± SD)	1.73	± 0.09	1.72	± 0.08	0.36	0.722
Daily steps, n (mean ± SD)	9923	± 4957	12790	± 5899	-1.43	0.171
Adherence, hours (mean ± SD)	6.6	± 3.5	5.3	± 3.3	0.84	0.413
Baseline foot and ankle pain, VAS[1] (mean ± SD)	62.1	± 19.6	40.66	± 26.6	2.19	0.041*
Foot and ankle pain relief, VAS[1] (mean ± SD)	-40.1	± 13.1	-4.3	± 4.3	-7.47	< 0.01*
HAQ[2] (mean ± SD)	0.77	0.71	0.54	0.38	0.86	0.411
DAS-28[3] (mean ± SD)	2.15	0.34	2.56	0.88	-1.54	0.137
Satisfaction (mean ± SD)	4.6	0.5	3.9	0.9	2.43	0.023*
Baseline walking speed, m/s (mean ± SD)	1.04	± 0.19	1.07	± 0.14	-0.38	0.705

1Visual anlage scale, [2]Health Assessment Questionnaire score, [3]Disease Activity Score (28 joints)

5.3 GAIT PARAMETERS

The major responders did not have altered baseline moments (ankle plantar flexion, eversion and knee abduction) compared with the minor responders when walking with the sham insole (Figure 3-11). Therefore, baseline gait analysis with the sham insole can probably not be used to identify which patients will respond well to the custom FO.

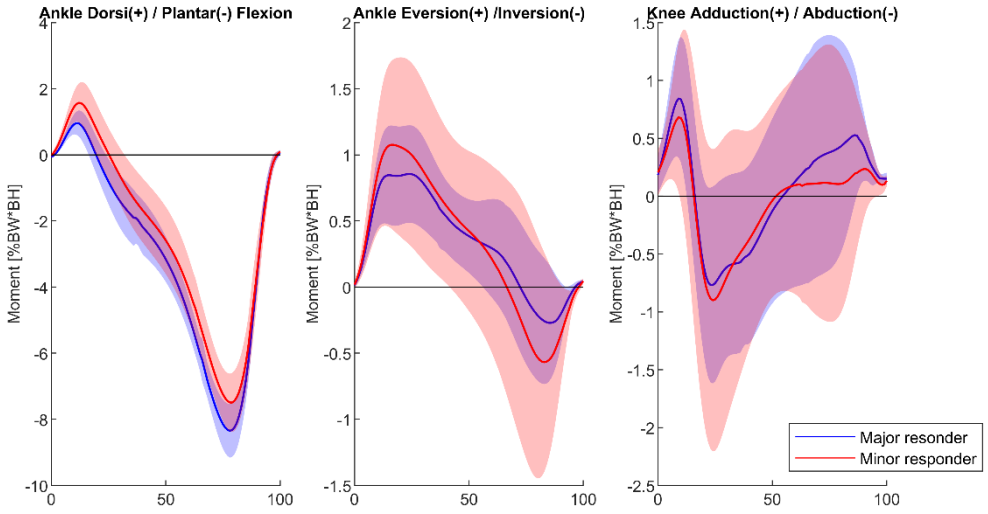

Figure 3-11: Comparison of baseline sham insole use between major responders (blue line) and minor responders (red line). Statistical difference is the area between the dotted lines marked with a star between the sham and the custom-made FO. Normalized to percentage of body weight (BW) and stance phase

The ankle planter flexion moment was reduced for the custom-made FO compared to the sham between 54 – 71 % of the stance phase for the major responders at baseline (3-12A). However, no difference between the custom-made FO and the sham was observed for minor responders at baseline, Figure 5-2B.

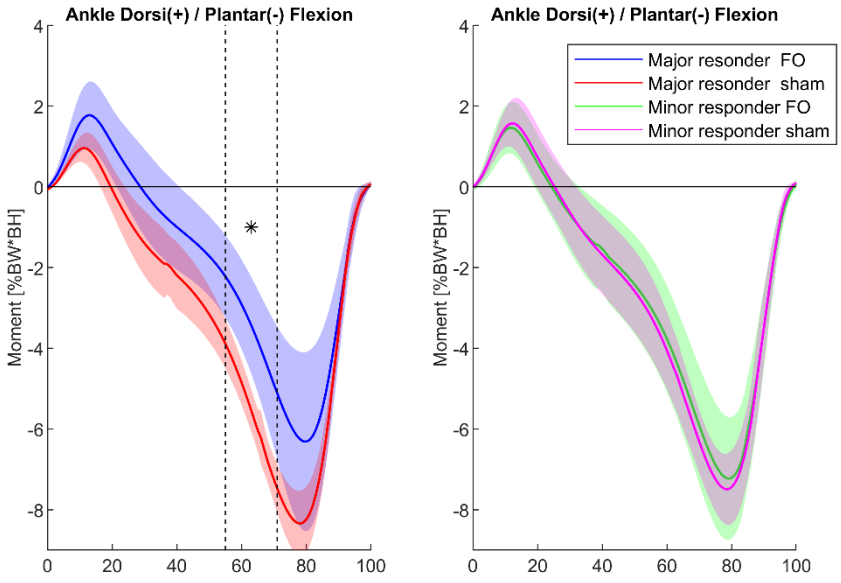

Figure 3-12: Comparison of the ankle plantar flexion moment with the sham (red) custom-made FO (blue) in major responders. Custom-made (green) and sham among minor responders. Statistical difference is the area between the dotted lines marked with a star between the sham and the custom-made FO. Normalized to percentage of body weight (BW) and stance phase

CHAPTER 4. DISCUSSION

The findings of the four studies have been discussed separately, and in detail in each publication (Studies I-IV). The purpose of this chapter is to outline how the findings in the four studies complement each other.

4.1 THE EFFECT OF EXPERIMENTAL PAIN ON GAIT

In Study I, an experimental pain model was introduced to get a better understanding of how the TP muscle pain affects lower extremity locomotion. The pain intensity findings reported in Study I was similar to previous studies using hypertonic saline injection models to induce localized muscle pain. (Bennell et al., 2004; Christensen et al., 2017; Qu et al., 2019; Shiozawa et al., 2015). Study I showed that healthy volunteers compensated in the hip and knee joint moments when being exposed to experimentally induced pain in the TP muscle. Hip internal rotation, hip external moment, and external knee rotation moment were reduced upon injection with hypertonic saline (Study I). These findings are consistent with previous studies showing that the gait of patients with RA or a dysfunctional TP muscle reduced knee and hip moments (Laroche et al., 2007; Maeda et al., 2018; Weiss et al., 2007). However, no difference in ankle joint angles or moments was observed in Study I. This absence of response is in contrast to previous studies examining patients with RA or TP muscle dysfunction where ankle planter flexion, eversion and internal rotations moments are increased (Barn et al., 2013; Ringleb et al., 2006; Wang et al., 2020). (Study I)

The findings from Study I indicate that the initial gait adaptations due to TP muscle pain does not involve the ankle joint at first. The findings in Study I are supported by a previous study examining the effects of TP muscle fatigue on ankle kinematics in healthy adults (Pohl et al., 2010). This could indicate that structural injury to the TP tendon and not isolated pain is the driver for the ankle compensation strategies observed in patients with TP dysfunction (Barn et al., 2013; Ringleb et al., 2006; Wang et al., 2020). Instead of alterations of the ankle joint, Study I found

compensations at the knee and hip joints. Study I indicated that pain alone caused gait changes and therefore a prolonged pain relief could possibly reduce the need for compensation at the knee and hip joints. To determine if any multi joint compensation strategy occurred at the knee and hip joints, an assessment of these joints was included in Study III and Study IV. (Study I)

Study II elaborates on results from Study I, which showed that the contribution from the TP muscle was reduced and the flexor hallucis longus and flexor digitorum longus compensated for the TP muscle dysfunction. This observation suggests that the CNS counteracts as a response to the inhibition of the dysfunctional TP muscle by choosing a muscle recruitment strategy of the neighboring muscles to reduce load and fatigue of the affected TP muscle at the same time maintaining equilibrium of the body (De Zee and Rasmussen, 2009). However, several theoretical assumptions have been made, such as a) only the strength of TP muscle is reduced, b) individual anatomical differences in muscle origin and insertion are not considered. Nevertheless, these muscle compensatory mechanisms are consistent with evaluations of the cross-sectional area of the TP and flexor digitorum longus muscles in patients with unilateral TP muscle dysfunction, where the area of the TP muscle was reduced by 10.7 % (atrophy), whereas the area of flexor hallucis longus muscle was increased by 17.2 % (hypertrophy) (Wacker et al., 2003). From an anatomical-physiological point of view, it also makes sense that the flexor hallucis longus and the flexor digitorum longus muscles compensate for the dysfunctional TP muscle, since the muscles both perform plantar flexion and inversion of the foot (Kaye and Jahss, 1991; Kong and Van Der Vliet, 2008; Panchbhavi et al., 2008). The compensatory muscle recruitment strategy found in Study II increases internal loading of the ankle complex. Therefore, the compensation strategy in Study II is believed to be an adverse outcome. (Study II)

4.2 ADVANTAGEOUS PROPERTIES OF A FOOT ORTHOSES FOR PATIENTS WITH RHEUMATOID ARTHRITIS

Reducing the load of the plantar flexor, evertor and inverter muscles is considered the main purpose of using a FO in patients with TP dysfunction (Murley et al., 2010;

Ringleb et al., 2006). Ringleb et al. found increased electromyography activity in the peroneals, tibialis anterior and gastrocnemius muscles in patients with TP muscle dysfunction compared with healthy volunteers Based on the study findings, it was recommend that the aim of FO therapy was to reduce activity of the muscles performing inversion, eversion, dorsiflexion and plantar flexion of the foot (Ringleb et al., 2006). On the basis of existing knowledge and findings in Study II, it seems beneficial for the patient aiming at declining ankle plantar flexion moments, since reduction of these moments is expected to have a potentially pain relieving effect by unloading the muscles performing inversion, eversion and planter flexion of the foot (Caldwell and Li, 2000; Kaye and Jahss, 1991; Kong and Van Der Vliet, 2008; Panchbhavi et al., 2008). A previous study has found that a custom-made FO can reduce plantar flexion (Barn et al., 2014). The immediate effect of the custom-made FO was assessed in Study III and showed that it reduced the ankle plantar flexion and eversion moments in patients with RA. Whether this would lead to reduction in pain intensity was explored further in Study IV. (Studies II-III)

4.3 THE EFFECT OF FOUR WEEKS USAGE OF AN FOOT ORTHOSES

Study IV found reduced foot and ankle pain intensity after four weeks usage of a custom-made FO. This is in line with similar findings reported in systematic reviews, although the overall evidence in these studies was weak (Hennessy et al., 2012; Santos et al., 2019). It is a limitation of VAS that it only assesses the intensity and not the location of the pain. Therefore, body charts were used in Study IV. To the author's knowledge, body charts have not previously been used to evaluate the effect of FO in patients with RA (Farrow et al., 2005; Gijon-Nogueron et al., 2018; Hennessy et al., 2012; Tenten-Diepenmaat et al., 2019). Applying body charts was considered helpful to understand the anatomical origin of the patient-reported pain and assess the potential pain-relieving effect of the custom-made FO (Study IV).

The reduced area of pain location in the muscles of the lower leg as observed in Study IV might be explained by the reduced foot planter flexor and inverter moments found

in Study III. These findings persisted in Study IV, since reduction of these moments will offload the plantar flexor and inverter muscles of the ankle as reported in Study II (Michelson et al., 1995; Yeap et al., 2001). It is unlikely that the mechanical properties of the custom-made FO have reduced the pain in the hands and arms directly. A more plausible explanation could be that the custom-made FO affects central sensitization (Woolf, 1983). Further investigations are, however, needed to test this assumption. (Studies III-IV)

Interestingly, Study IV indicated that the immediate biomechanical changes observed in Study III were maintained at the end of the custom-made FO intervention period. Therefore, reduction of foot pain intensity and perceived pain areas in the body as observed in Study IV might be due to the cumulative effect of the immediate changes reported in Study III and not necessarily because patients adapted to new gait patterns. However, the patients used only the custom-made FO for a four-week-period. Therefore, adaptations could potentially occur with continued usage after the four weeks. (Study IV)

Even though increased knee adduction moment was observed in Study III and Study IV, no statistical difference was found regarding knee pain intensity. This is an interesting observation because progression of knee osteoarthritis is associated with increased knee adduction moments (Arnold et al., 2016). The elevated knee adduction moment is probably due to the custom-made FO shifting the ground reaction force medially due to the medial wedge (Bennell et al., 2013; Parkes et al., 2013). However, it might be worthwhile to pay attention to any onset or worsening of existing knee pain when patients with RA start using FO. (Studies III-IV)

The patient's daily activity did not change between the sham and custom-made FO intervention period (Study IV). However, the patients included in Study III and Study IV were already physically very active and walked more than 10 000 steps daily on average. In comparison, a previous study found that healthy adults normally walk 4 000 to 16 000 steps per day (Tudor-Locke et al., 2011). Katz et al. found that patients with RA walk on average around 6 000 steps per day (Katz et al., 2018). Therefore,

the patients in Study IV might not be representative of the population of patients with RA. Also, the patients in Study IV probably also had limited potential to increase their activity, since they were already very active. (Study IV)

4.4 MAJOR RESPONDERS VERSUS MINOR RESPONDERS

The baseline foot and ankle pain ratings among the major responders were higher compared with the minor responders. However, no other differences in demographic and clinical features between the two groups were found. Further, no statistical differences were found between the participants' gait patterns at baseline. Therefore, based on the measurements performed at the baseline (Study III and Study IV), it cannot necessarily be anticipated who would respond well to the custom-made FO, except those with the highest foot and ankle pain ratings. Interestingly, the custom-made FO reduced the ankle planter flexion among the major responders, but not among the minor responders. The finding of reduced planter flexion moments with the custom-made FO in the major responders highlights the benefits of unloading the ankle plantar flexors. This indicates that a plantar flexion moment assessment could be used to ensure that the FO had the desired mechanical effect.

The custom-made FO did probably not remedy the minor responders' foot problems, or an error may have occurred during the manufacturing process of their custom-made FO. However, it is interesting that both groups rated their satisfaction with the custom-made FO high (Table 3-2), despite the major differences in reported foot and ankle pain relief.

4.5 STRENGTHS AND LIMITATIONS

To the author's knowledge, the current dissertation provides one of the most extensive investigations to date on the effect of foot orthotics on pain, gait, daily activity and adherence to use of FO among patients with RA. Based on experimental trials (Study I and Study II), hypotheses have been formed based on how FO could provide pain relief among patients with RA. In the clinical part of this dissertation (Study III and Study IV), strict inclusion and exclusion criteria for the patients were made to

minimize the effect of severe deformities or other musculoskeletal diseases on outcomes. However, some limitations still need to be addressed.

Firstly, it is a limitation of a single-injection pain model that it cannot replicate the complex widespread pain experienced by patients with RA. This limitation is obvious when comparing the body charts from Study I with Study IV (Figure 3-2 and Figure 3-8). Despite similar pain intensity, the area of perceived pain was in the experimental pain model localized at the injected leg, whereas the pain distribution in patients with RA extended to other body segments (Study IV). This difference in pain response has also been observed previously when comparing experimental pain models applied on healthy volunteers with pain response in a patient population (Christensen, 2017; Qu, 2019). The experimental pain model used in the present work thus has some natural limitations as the model only replicates pain in the TP muscle and the surrounding structures. Secondly, the intervention study was not designed as a controlled clinical trial; there was no real control group and it is thus vulnerable to bias. However, the intervention study included a sham period, which made it possible to monitor daily activity and pain prior starting the intervention. Thirdly, the effects of changes in muscle activity were not addressed, since electromyography signals were not measured in neither the experimental nor the clinical part of the dissertation. Muscle activity can be estimated from the applied musculoskeletal models. However, due to the uncertainty concerning the influence of RA on muscle recruitment strategies, muscle forces were only estimated in Study II. Finally, validity and reliability of the activity tracker used in Study IV was not satisfactory. In a previous study, we tested the reliability and validity of the Polar M200 compared with a gold standard and found that the activity tracker tended to underestimate the number of steps ($r = 0.67$) (Simonsen et al., 2020).

4.5 CONCLUSIONS

The results of the present dissertation have shown that experimentally induced pain in the TP muscle caused alterations at the knee and hip joint among healthy subjects (Study I), which was also observed among patients with RA. In Study II we found

that reduced force contribution by the TP muscle causes the flexor digitorum longus and flexor hallucis longus muscles to compensate for the dysfunctional TP muscle. These two experimental studies highlight the role of the plantar flexor and inverter muscles of the foot during gait.

Study III showed that the custom-made FO was efficient in altering gait mechanics. Specifically, the custom-made FO reduced the ankle planter flexion and eversion moments. Study IV showed that a four-week treatment intervention with a custom-made FO reduced foot pain intensity, area of perceived pain (foot, legs, arms and hands) and that the immediate biomechanical changes evoked by the custom-made FO were subsequently maintained. Reduced ankle plantar flexion and eversion moments occurred in conjunction with pain intensity relief of the foot and ankle. This dissertation may act as a starting point for future randomized controlled trials on foot orthotic interventions in patients with RA or mechanistic studies striving to improve FO design and therapeutically protocols.

CHAPTER 5. FUTURE DIRECTIONS

The experimental pain model study demonstrated unique findings by separating the effect of pain in the TP muscle during gait. The pain model has some limitations, which should be addressed in future studies with the following research areas to be investigated: a) outcome of changing the injection site to the area of the TP tendon. b) The activation patterns for the TP, flexor hallucis longus and flexor digitorum longus muscles during exposure to experimental pain. c) the capability of FO to counter the adapted compensatory mechanisms caused by pain, d) effects on foot kinematics and kinetics and e) other pain models with longer effects such as nerve growth factor which provides a milder pain intensity but last up to a week compared to hypertonic saline of minutes effect duration (De Martino et al., 2018).

Regarding future directions regarding use of FO to RA patients, larger randomized controlled trials are needed to examine the biomechanics and pain response to FO. Future studies should also investigate whether pain relief is sustained or even further improved, and whether any gait adaptations including feet, ankle, knee and hips occurs after prolonged use of a custom-made FO. Additionally, it is relevant to investigate if the support provided by the custom-made FO slows the progression, and maybe even prevents development, of deformities in the foot and ankle. Prediction of patient response to custom-made FO by use of screening tool like ultrasound for examination of the tendons constitute are another interesting research topics for the future. Study IV demonstrated that the areas of perceived pain in the arms and hands were reduced. Further studies are needed to elucidate how FO may influence general pain perception in patients with RA. This objective could be achieved by investigating temporal summation before and after FO intervention (Staud et al., 2003).

CHAPTER 6. SUMMARY

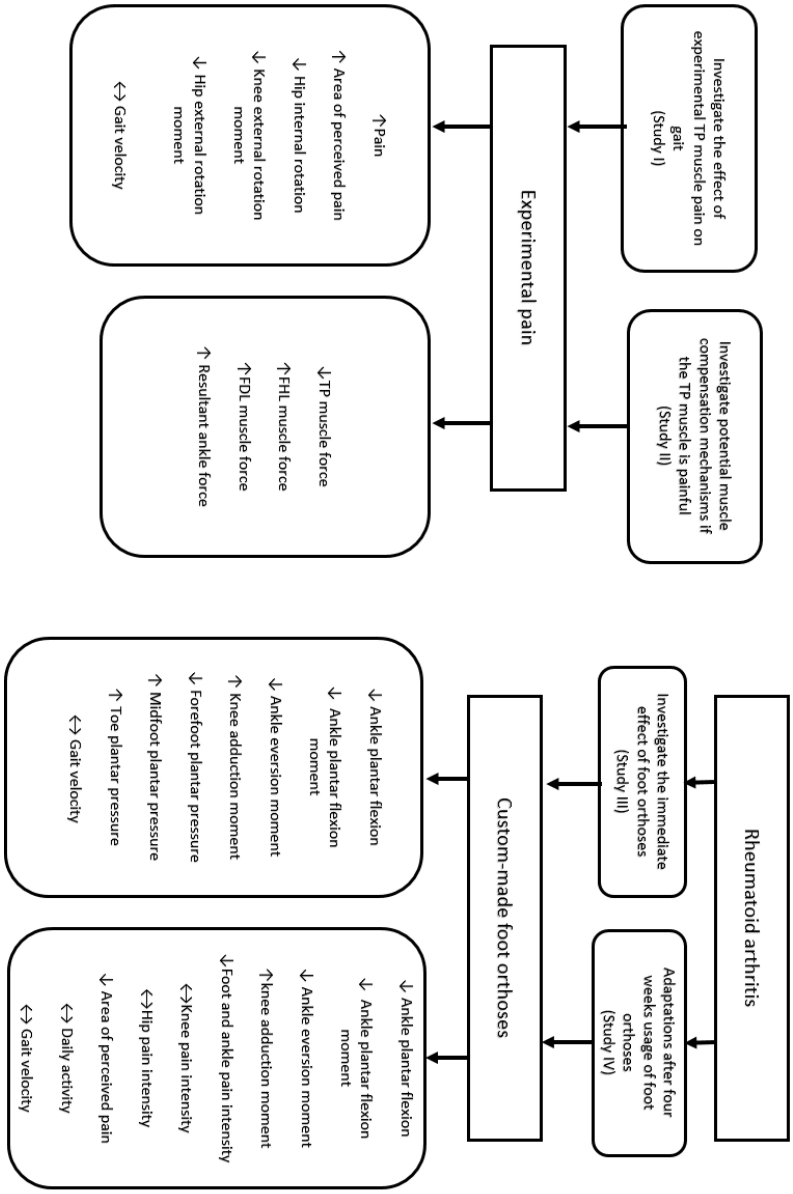

Figure 6-1: Summary of the effect of experimental pain or foot orthoses on pain perception and gait mechanics in healthy volunteers or patients with RA, respectively

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APPENDICES

APPENDIX: STUDY I-IV

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