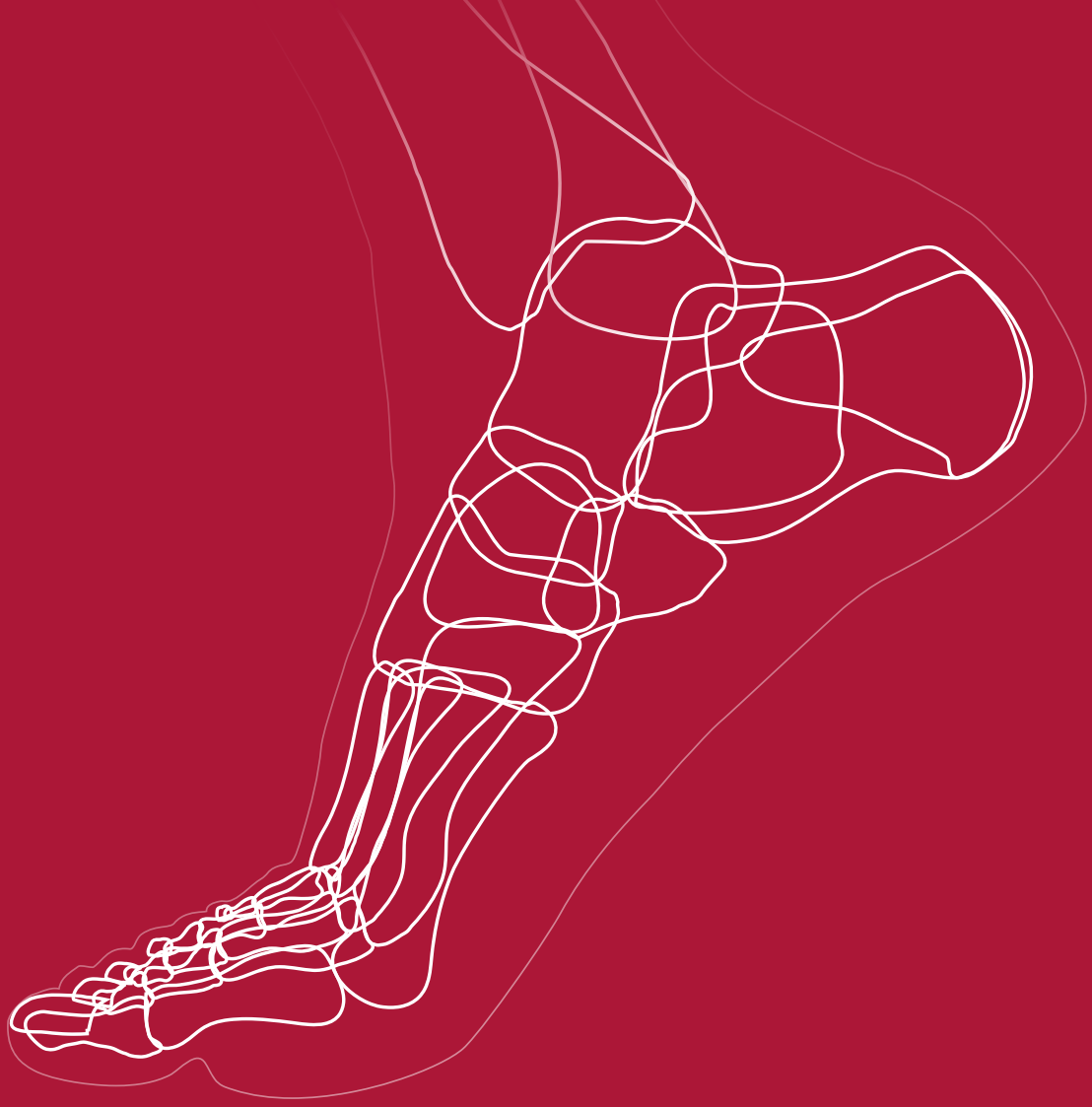
Management of foot problems in patients with rheumatoid arthritis



Marloes Tenten-Diepenmaat

Management of foot problems in patients with rheumatoid arthritis

VRIJE UNIVERSITEIT

Management of foot problems in patients with rheumatoid arthritis

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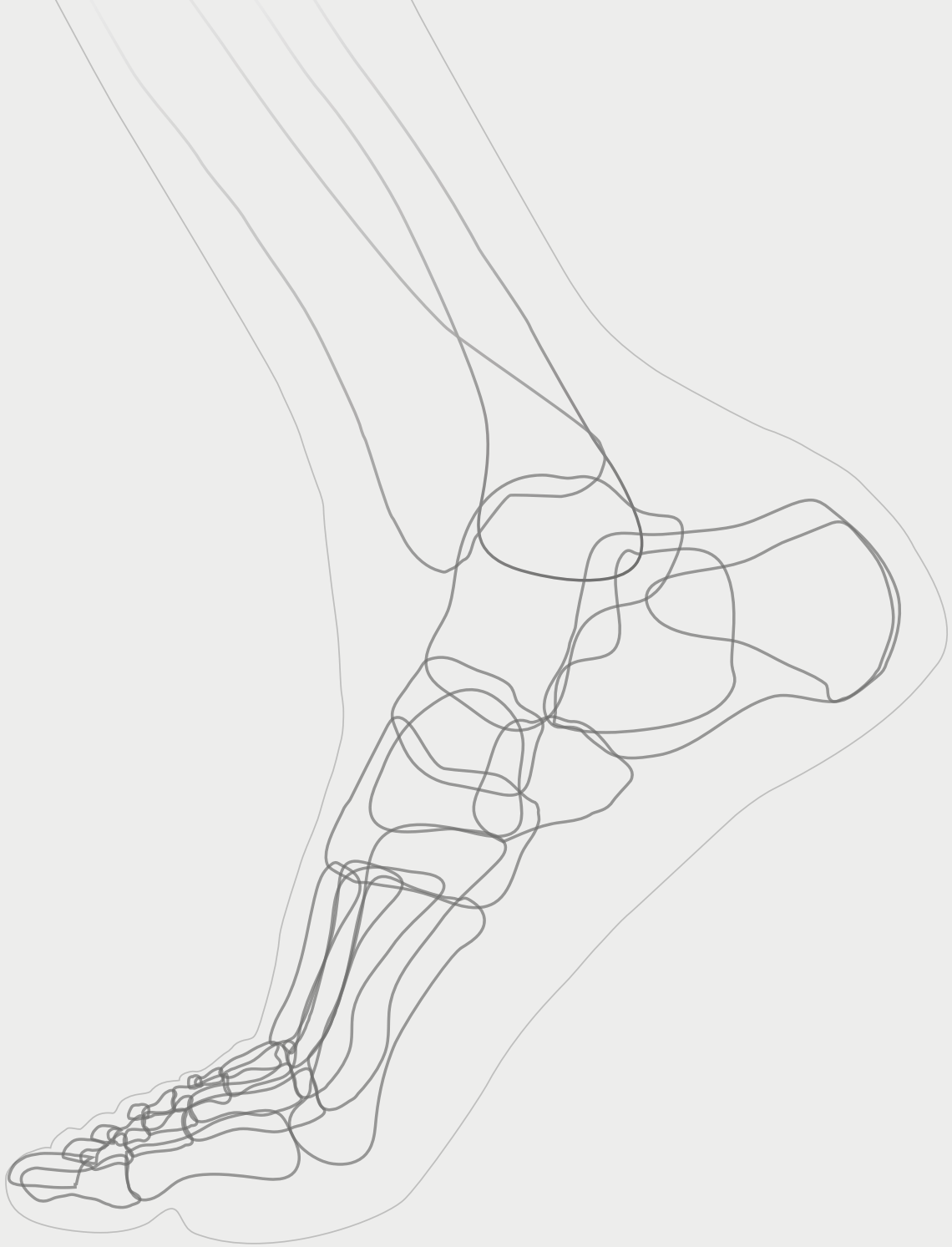


CHAPTER 1

General introduction

Rheumatoid arthritis

Rheumatoid Arthritis (RA) is a chronic, inflammatory, autoimmune disease with widespread synovial joint involvement [1]. The etiology of RA is unknown [1]. Certain genetic and environmental factors (such as smoking) can result in an immune reaction which leads to persistent synovitis and systemic inflammation [2]. The primary manifestations are pain, swelling, and limited motion of joints due to inflammation of the synovial membrane. The synovial joints of the hands and feet are often the first structures affected. Furthermore, fatigue, stiffness and restrictions in activities and participation occur frequently in patients with RA, and may lead to a reduced quality of life [3]. Severity of disease activity varies between patients and is characterized by exacerbations and remission [2]. RA affects approximately 1% of the population both in The Netherlands and worldwide [1]. The disease is more common in women and elderly people [2]. Nowadays, drug treatment is effective in the majority of patients provided that it is started early in the disease course and targeted at remission (treat to target) [3, 4]. However, in some patients remission is not achieved, with persisting disease activity, including inflammation of foot joints and surrounding soft tissues [3].

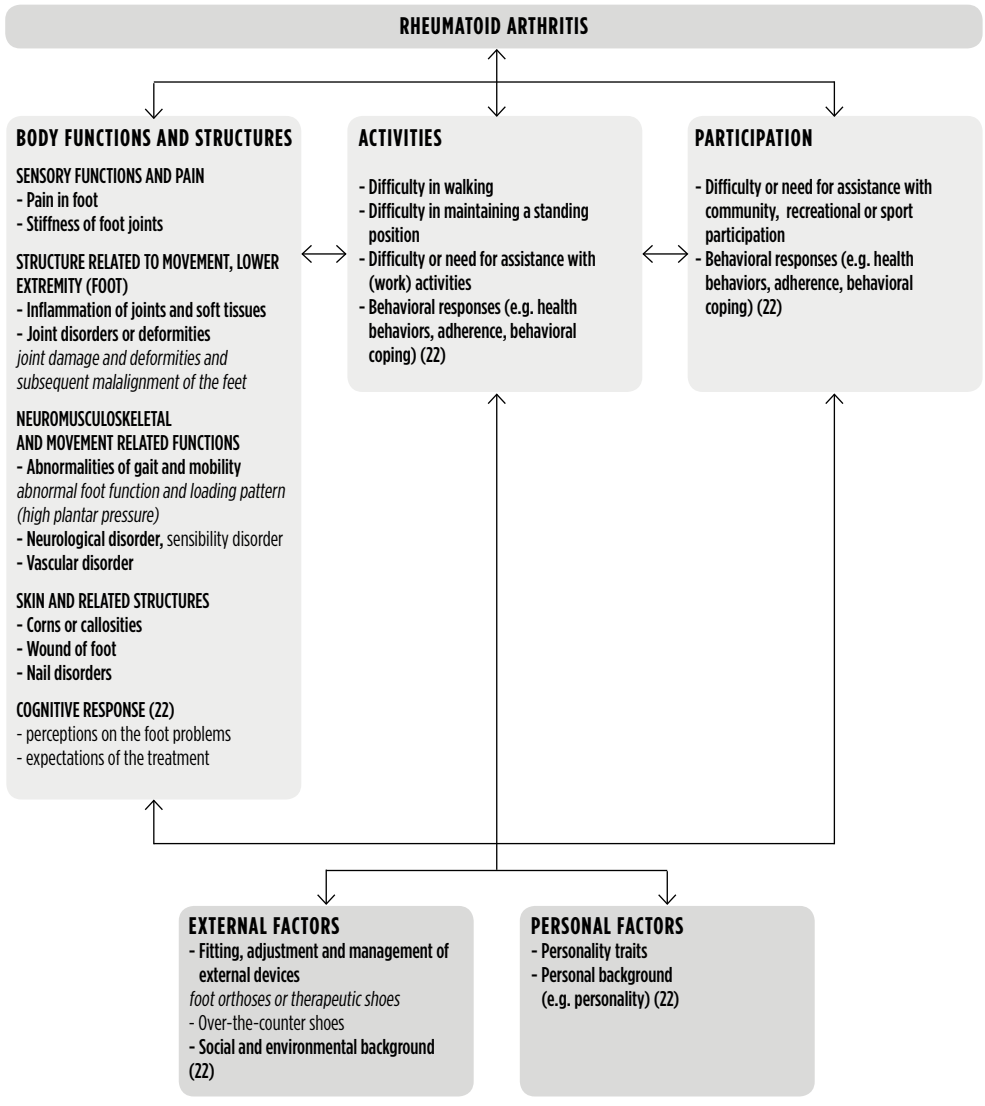
Foot problems in patients with rheumatoid arthritis

Foot problems are highly prevalent in patients with RA [5-9]. Approximately 90% of the patients experience foot or ankle problems during the course of the disease [6]. These foot problems often start with pain, swelling and stiffness caused by synovial joint involvement, especially in the metatarsophalangeal joints of the forefoot [5, 10, 11]. Inflammation of other foot joints occurs usually later in the disease process [12, 13]. Synovitis of foot joints can have a destructive impact on the quality and structure of the joints and surrounding soft tissues [10, 11]. This may lead to structural malalignment of the feet due to damage and deformities of foot joints [5]. Common foot deformities in RA patients are subluxation of the metatarsophalangeal (MTP) joints, splaying of the forefoot, toe-deformities and valgus alignment of the rearfoot [14, 15]. Malalignment of the feet may result in pain and biomechanical alterations in foot function, i.e. the loading pattern of the foot, resulting in high plantar pressure, especially in the forefoot [6, 8, 16, 17]. In addition to inflammation and biomechanical impairments, dermatological and neurovascular impairments, and external and personal factors can also play a role in RA-related foot problems [18, 19]. These foot problems may lead to restrictions in daily activities and participation, and a reduced quality of life [20, 21].

An overview of foot problems in patients with RA is presented in ***Figure 1***. This figure is based on the International Classification of Functioning, Disability and Health (ICF) of the World Health Organization [22] and the adaptations and clarifications on this framework as proposed by Dekker et al. [23]. External factors with a direct influence on the feet are shown in ***Figure 1***. Additional external factors and the personal factors are globally described in ***Figure 1***.

Management of foot problems

It seems important to prevent deterioration of foot function by starting management of foot problems in an early disease stage, in order to reduce pain and activity limitations [24]. In the management of foot problems in patients with RA health care providers from several disciplines could be involved. Insight into the timing and content of mono- and multidisciplinary foot care is needed.



Bold text = ICF-terms or terms used by Dekker et al. (22). Italic text = clarification in the context of this thesis.

Figure 1. An ICF-overview of foot problems in patients with RA

Underuse of foot care

Despite the high prevalence and substantial impact of RA-related foot problems on the patients' quality of life, there is limited attention for management of these foot problems in research and in clinical practice. In patients with RA-related foot problems underuse of foot care seems apparent [25]. The results of a cohort study at Reade, a specialized center for rheumatology and rehabilitation in Amsterdam, showed that only 40% of RA patients received specific foot care [25]. In primary care, RA-related foot problems appear to be treated even less. In clinical practice there is limited attention to the management of RA-related foot problems. For example, the most frequently used instrument to detect disease activity (with a 28 joint count [26]) excludes examination of the feet. Furthermore, among healthcare providers there is often limited expertise in managing RA-related foot problems [27, 28]. Similarly, among patients there is limited knowledge of the possibilities of, and access to, foot care [28, 29].

Multidisciplinary foot care

Management of RA-related foot problems consists of various aspects within the domains of different disciplines. Therefore, healthcare providers from several disciplines can be involved in the management of these foot problems. The primary treatment of foot problems related to disease activity is systemic medication prescribed by the rheumatologist. In foot joints and soft tissues with persistent inflammation an additional local pharmacological treatment (corticosteroid injections) can be applied. To further reduce foot pain and maintain or improve physical functioning, including independent mobility, conservative or surgical treatment can be prescribed [25]. Conservative treatment can include therapeutic shoes, custom-made foot orthoses, exercise therapy, toenail braces, and treatment of toenails and skin. Surgical treatment can be considered when a conservative treatment is not successful or indicated, e.g. due to persistent synovitis in foot joints or severe malalignment of the foot. Apart from rheumatologists and orthopaedic surgeons, healthcare providers from various professions can be involved. In the Netherlands there is a role for rehabilitation physicians, specialized nurses, podiatrists, orthopaedic shoe-technicians, and pedicurists in the management of RA-related foot problems [25]. In complex cases, it may be necessary to involve several disciplines in order to offer a treatment with sufficient content and timing for the individual patient [24, 30, 31]. However, professionals from these different disciplines often lack insight into the specific skills of professionals from another discipline. In order to improve foot care for patients, an overview of the multidisciplinary diagnosis and treatment of foot problems in RA is first necessary. This is needed to provide guidance to healthcare providers and patients in the organisation of timely, appropriate and evidence-based foot care. Therefore, we developed multidisciplinary recommendations for diagnosis and treatment of foot problems in patients with RA (Chapter 2).

Treatment with foot orthoses or therapeutic shoes

Conservative treatment of pain, malalignment or inadequate function of the feet usually consists of custom-made foot orthoses or therapeutic shoes. Foot orthoses are frequently prescribed in an early disease stage and therapeutic shoes in a more advanced stage when foot problems

are worsened [25]. The treatment with foot orthoses and therapeutic shoes is mainly aimed at reducing or adapting to biomechanical impairments, e.g. malalignment and insufficient foot function. Foot orthoses and therapeutic shoes can be prescribed according to a stepped care approach [19]. When adequate-over-the-counter shoes are insufficient in reducing foot symptoms, foot orthoses can be used in patients with an abnormal foot function [19]. Ready-made therapeutic shoes can be prescribed when the patients' feet do not fit in over-the-counter shoes [19]. Custom-made therapeutic shoes can be prescribed when the patients' feet do not fit in ready-made therapeutic shoes [19].

Therapeutic shoes are recommended in guidelines and are frequently used in the treatment of foot problems, especially in patients with established RA [25, 31-34]. Two outdated systematic reviews indicate that therapeutic shoes may be effective in reducing pain during weight-bearing activities in patients with RA [35, 36]. However, there are more recently published studies on this subject. Therefore, we have updated the scientific evidence regarding the effectiveness of therapeutic shoes in the treatment of RA-related foot problems in a systematic review **(Chapter 3)**.

Foot orthoses are an important and frequently used treatment option for RA-related foot problems, especially in early disease stage [25]. According to two systematic reviews on the effectiveness of custom-made foot orthoses, treatment with foot orthoses is effective in reduction of foot pain [37, 38]. In one of these reviews also weak evidence for the improvement of foot function (i.e. reduction of forefoot plantar pressure) was found [37]. A broad variation in foot orthoses is used in the treatment of specific RA-related foot problems. Foot orthoses may have several characteristics concerning materials used (e.g. rigid or soft), type (e.g. custom-made or ready-made; contoured or non-contoured) and modifications (e.g. metatarsal domes or bars, shock-absorbing paddings) [14]. Furthermore, foot orthoses can be constructed in different ways, e.g. by using custom moulding techniques or more sophisticated CAD-CAM (computer-aided design/computer-aided manufacturing) or laser sintering systems. An overview on the outcomes of the treatment with different kinds of foot orthoses in patients with RA and a specific foot problem is lacking. Therefore, we systematically summarized the literature on the comparative effectiveness of foot orthoses in the treatment of various foot problems in patients with RA **(Chapter 4)**.

The role of plantar pressure in treatment with foot orthoses

The general aims of prescribing foot orthoses are reducing foot pain and improving physical functioning by influencing biomechanical factors, such as plantar pressure, to an optimum. Since high plantar pressures are related to foot pain in RA [17], one of the assumed working mechanisms of foot orthoses is redistribution of plantar pressure by creating a larger weight-bearing area [39-41].

The feedback of plantar pressure measurements in optimizing foot orthoses

Overall, the reported treatment effect of foot orthoses on foot pain in RA is small to medium (effect size 0.40 – 0.45) [37, 38, 42]. Therefore, we developed a protocol for optimizing the plantar pressure reduction achieved with foot orthoses treatment, by using the feedback of in-shoe plantar pressure measurements ***(Figure 2)***. The Pedar-X-system (Novel GmbH, Munich, Germany) was used to measure plantar pressure while walking with shoes (including foot orthoses). This system includes 2mm thick flexible insoles which were placed in the shoes, on top of the foot orthoses, to measure plantar pressures at the sock versus foot orthoses interface. Each insole includes 99 pressure sensors which measure the vertical plantar pressure at a sample frequency of 50Hz. Plantar pressure was expressed as Peak Pressure (PP; the highest pressure measured by a single sensor in the forefoot-region) and Pressure Time Integral (PTI; the integral of pressure over time measured in the single sensor showing the PP within the forefoot-region) [17]. With the protocol, we aimed to achieve a maximum reduction of plantar pressure in painful foot regions because of the established relationship between high plantar pressure and foot pain [17, 39]. In a proof of concept study **(Chapter 5)** the outcome of foot orthoses, developed according to the protocol, on immediate plantar pressure reduction were assessed. The feasibility of the plantar pressure criteria and the process of adapting foot orthoses were evaluated.

The majority of the included patients in the proof of concept study suffered from forefoot pain. We aimed at improved forefoot plantar pressure reduction and subsequent reduction of pain and improvement of physical functioning by using the feedback of in-shoe plantar pressure measurements in evaluation and adaptation of foot orthoses. In foot orthoses treatment an acclimation period of wearing foot orthoses is needed before the final result (on pain) will be reached [14]. Therefore, we assessed the outcomes of wearing foot orthoses that were developed according to the protocol regarding foot pain, physical function and forefoot plantar pressure after three months **(Chapter 6)**.

Potential working mechanisms

Since high plantar pressures are related to foot pain in RA, it is hypothesized that a reduction of forefoot plantar pressure leads to reduction of pain and subsequent improvement of physical functioning [17]. However, this assumed relationship has never been investigated. Moreover, also low forefoot plantar pressures has been observed in patients with forefoot symptoms [10]. This implies that only in patients with combined pain and high plantar pressure in a specific foot region (biomechanical impairment), the working mechanism of foot orthoses may be related to plantar pressure reduction. Therefore, a subgroup analysis was performed to investigate whether pressure reduction is associated with outcomes on pain and physical functioning **(Chapter 6)**.

The presence of low plantar pressure in a painful forefoot region could possibly be explained by a pain avoidance strategy triggered by inflammation in the forefoot [18, 43]. To avoid regions with swelling or pain due to inflammation (i.e. high disease activity), offloading of these regions may occur [18]. Better understanding of the association of pathology in the forefoot with either high or low plantar pressure in patients with RA could help to better formulate and specify goals for treatment with foot orthoses and therapeutic footwear. Therefore we investigated and quantified the relationship of forefoot disease activity (inflammation) and forefoot deformity (biomechanical impairment) with plantar pressure in a relatively large cohort of patients with RA

and forefoot problems (**Chapter 7**). In this study plantar pressure measurements were obtained using an EMED-nt (Novel Electronics, Novel gmbh, Munich, Germany) system (4 sensors per cm^2, sample frequency of 50Hz), displaying plantar pressures of the foot when walking barefoot over a pressure measurement platform. The platform was mounted in the middle of a 3.6 meter walkway. A two-step protocol was used for pressure measurements [44]. Plantar pressure in the forefoot was expressed as peak pressure (PP) and as pressure time integral (PTI). PP is defined as the highest pressure measured by a single sensor in a region [17] and is expressed as Newton per squared cm (N/cm^2). PTI is defined as the integral of pressure over time measured in the single sensor showing the PP within that region [17] and is expressed as Newton per squared cm multiplied by time in seconds ($(N/cm^2)*s$). Inflammation in the forefoot was assessed by palpation of swelling or pain in the MTP-joints according to a part of the disease activity score with a 44 joint count (DAS-44) [45]. Furthermore, forefoot deformity was assessed by inspection according to Platto's structural index [46].

Aim and outline of this thesis

The aim of this thesis is twofold. The first aim is to provide an overview of multidisciplinary foot care for patients with rheumatoid arthritis (RA). In **Chapter 2**, the development of multidisciplinary recommendations, based on scientific literature and expert opinion, for diagnosis and treatment of foot problems in patients with RA is described. Treatment options for pain, malalignment or inadequate function of the feet in RA are addressed in two systematic reviews (**Chapter 3 and 4**). In **Chapter 3**, the effectiveness of therapeutic shoes is summarized whereas in **Chapter 4** the effectiveness of different kinds of foot orthoses is compared.

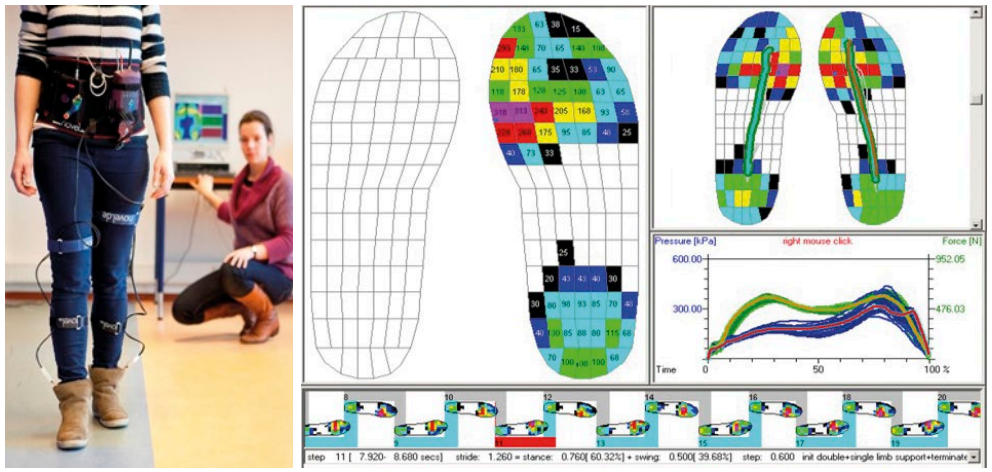


Figure 2. a. Pedar-X system for measuring in-shoe plantar pressure during walking with and without foot orthoses developed according to the protocol, **b.** Feedback generated by the system, identifying regions of high plantar pressure.

The second aim is to investigate the role of plantar pressure measurements in the management with foot orthoses. In **Chapter 5** a protocol for optimizing foot orthoses by using the feedback of in-shoe plantar pressure measurements is evaluated. In a proof of concept study in 43 patients with RA-related foot problems the protocols' feasibility and the immediate outcomes on plantar pressure of foot orthoses developed according to the protocol are investigated. The outcomes of these foot orthoses after three months follow-up on forefoot pain, physical function and forefoot plantar pressure are assessed in **Chapter 6**. In this chapter the relationship between change in forefoot plantar pressure and change in pain and physical functioning is also investigated. Furthermore, a cross-sectional study was performed to better understand the influence of foot pathology on plantar pressure. In **Chapter 7** the relationship of forefoot disease activity (inflammation) and forefoot deformity (biomechanical impairment) with plantar pressure is investigated using data of 172 patients with RA from the Amsterdam Foot (AMS-foot) cohort.

Finally, in **Chapter 8**, the results of this thesis are summarized and discussed.

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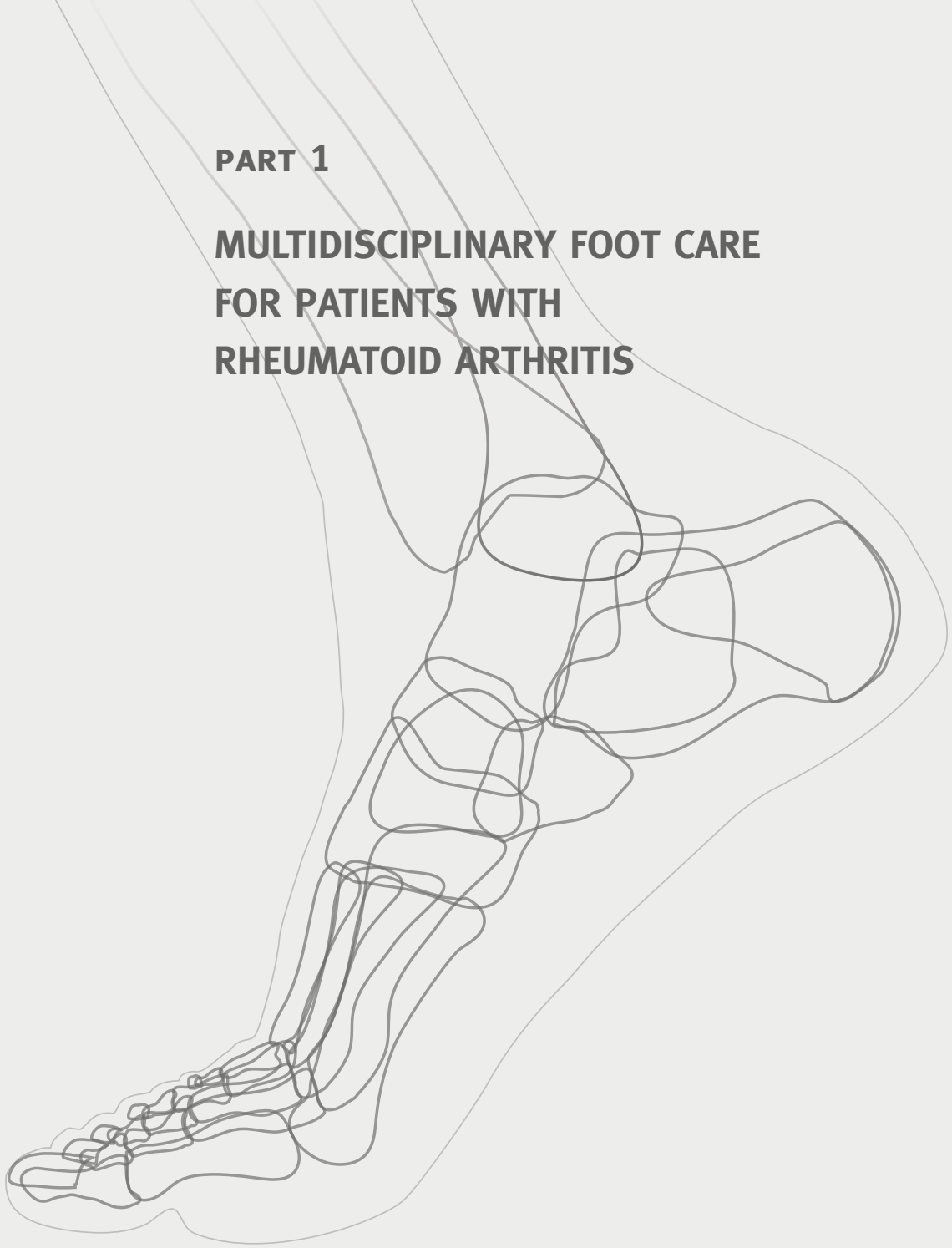
PART 1

MULTIDISCIPLINARY FOOT CARE FOR PATIENTS WITH RHEUMATOID ARTHRITIS



CHAPTER 2

Multidisciplinary recommendations for diagnosis and treatment of foot problems in people with rheumatoid arthritis

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Marike van der Leeden
Thea P.M. Vliet Vlieland
Joost Dekker
on behalf of the RA Foot Expert Group

Journal of Foot and Ankle Research. 2018;11:37

Abstract

Background

Foot problems in people with rheumatoid arthritis (RA) are highly prevalent and have a substantial impact on quality of life. Healthcare professionals from various professions can be involved in the management of these foot problems. There is currently no consensus on optimal management. Therefore, the aim of the present study was to develop multidisciplinary recommendations for the management of foot problems in people with RA in the Netherlands.

Methods

The recommendations were based on research evidence and consensus among experts, following published strategies for the development of practice recommendations. The expert group was composed of 2 patients and 22 experienced professionals (rheumatologists, rehabilitation physicians, orthopaedic surgeons, specialized nurses, podiatrists, orthopaedic shoe technicians, pedicurists, and researchers) in the Netherlands. For each developed recommendation i) the level of evidence was determined, and ii) the level of agreement (among the expert group) was set by an anonymous voting procedure using a numeric rating scale. The mean and range of the level of agreement for each recommendation was calculated. A recommendation was approved when ≥70% of the expert group voted an NRS-agreement ≥7.

Results

In total, 41 recommendations were developed. Two recommendations concerned a framework for diagnosis and treatment. Thirty-nine recommendations on foot care were developed: seven on diagnosis (including check-ups of feet and shoes and diagnostic imaging), 27 on treatment (including corticosteroid injections, foot surgery, therapeutic shoes, foot orthoses, exercise therapy, toe-orthoses and toenail-braces, treatment of toenails and skin), four on communication, and one on organisation of RA-related foot care. All recommendations were approved by the expert group. The percentage score of NRS-agreement ≥7 ranged from 80 to 100%.

Conclusions

These are the first published multidisciplinary recommendations specific to the management of foot problems in people with RA. Multidisciplinary recommendations can provide guidance in timely referrals and access to adequate foot care. More research is needed to strengthen the evidence on diagnosis and treatment of RA-related foot problems. These national recommendations may be a first step towards developing international multidisciplinary recommendations for the management of foot problems in RA.

Background

Approximately 90% of patients with rheumatoid arthritis (RA) experience foot problems, such as pain, swelling, and stiffness, during the course of the disease [1-4]. In a more advanced stage of RA, joint damage and foot deformities may occur [5]. In addition, dermatological abnormalities and reduced sensitivity are more frequent in people with RA compared with the healthy population [6]. Foot involvement in RA may result in an abnormal foot function, limitations in daily activities such as standing and walking, and a reduced quality of life [7, 8].

It seems important to start management of foot problems in an early disease stage to reduce pain and activity limitations, and to prevent deterioration of foot function [9]. The primary treatment of foot problems related to disease activity is systemic medication. In addition, local pharmacological treatment (corticosteroid injections), surgical treatment, or conservative treatment (such as foot orthoses, therapeutic shoes, removal of callosities) can be applied [10]. Apart from rheumatologists and orthopaedic surgeons, healthcare professionals from various professions can be involved. In the Netherlands there is a role for rehabilitation physicians, specialized nurses, podiatrists, orthopaedic shoe-technicians, and pedicurists in the management of RA-related foot problems [10]. A multidisciplinary approach is necessary in order to offer treatment with adequate content and timing for the individual patient [9, 11, 12].

Despite the high prevalence of foot problems in RA, underuse of foot care seems apparent. In a specialized center for rheumatology and rehabilitation in the Netherlands only 40% of the people with RA received specific foot care (10), while in primary care foot problems appear to be treated even less. Among healthcare professionals there is often limited expertise in detecting and managing RA-related foot problems, as shown in a survey among podiatrists in New South Wales [13]. Similarly, among patients there is limited knowledge of the possibilities of, and access to, foot care [13, 14]. A survey among patients in the Netherlands showed that 94% of the patients reported insufficient knowledge about the content and accessibility of health care services [14].

Multidisciplinary recommendations provide guidance on timely referrals and access to adequate foot care. Previously published guidelines were recently critically appraised by Hennessy et al. [15]. In their work, 24 guidelines recommending management of RA-related foot problems were identified. Of these guidelines, only five (general) guidelines were of high quality and recommended for use without modifications. Moreover, only a small section of the guidelines (ranging from one sentence to one page) were foot-specific [15]. Only two published guidelines were foot and ankle specific, one of low [12] and one of high [11] quality [15]. Additionally, these guidelines are monodisciplinary (podiatry) [11, 12]. The aim of the present study was to develop multidisciplinary recommendations and frameworks for the diagnosis and treatment of foot problems in people with RA.

Methods

Recommendations for management of RA-related foot problems were based on research evidence and consensus among experts (healthcare providers, patients, and researchers). The methodology for the development of the recommendations was based on published strategies for the development of practice recommendations [16, 17]. The expert group was composed of patients (experienced with foot problems and related treatments) and experienced professionals (from leading expertise centres or nominated by professional bodies) of several professions involved in RA foot care in the Netherlands. The expert group included two patients, two rheumatologists, two rehabilitation physicians, three orthopaedic surgeons, four specialized nurses, two podiatrists, three orthopaedic shoe technicians, two pedicurists, and four researchers (the core members; MTD, MvdL, TPMVV and JD). Three expert group meetings took place between February 2015 and July 2016.

There were four phases in the development of the recommendations. A detailed description of the steps taken in the different phases, is given in ***Table 1***. In the first phase, definitive research questions and semi-definitive frameworks for diagnosis and treatment were developed based on: i) a preliminary literature search, ii) semi-structured interviews with four persons with RA, iii) a field consultation among 39 RA foot care professionals (medical doctors/allied healthcare professionals), iv) discussion within the core members, and v) discussion with the experts during the first expert group meeting.

In the second phase, draft recommendations were formulated (by the core members) based on relevant literature, to answer the research questions. Literature was searched in PubMed by MTD. ***Appendix 1*** gives an overview of the search-details. The available (systematic) reviews on the subject of interest were used to develop the draft recommendations. When no (systematic) review was available, core publications (according to the expert group) or available guidelines were used.

In the third phase definitive recommendations and frameworks with a level of evidence were developed. The draft recommendations and semi-definitive frameworks were discussed with the experts during a second expert meeting and by email rounds. The draft recommendations and semi-definitive frameworks were refined into definitive recommendations and frameworks. For each final recommendation/framework, the level of evidence was determined. The methodological quality was determined according to the "Evidence-Based Guideline Development" of the Quality Institute for Public Healthcare in The Netherlands, as shown in ***Table 2*** [18]. Five levels of evidence were distinguished (ranging from 1 to 4b), as shown in ***Table 3***. When a recommendation was based on a review or guideline, the level of evidence reported in the review/guideline was used. If the level of evidence was not reported, the original sources were retrieved (individual studies/ expert opinion).

In the fourth phase, the level of agreement for each recommendation/framework was set by an anonymous voting procedure during the third expert meeting. A numeric rating scale for agreement (NRS-agreement) from 0 (total disagreement) to 10 (total agreement) was used. The mean and range of the level of agreement for each recommendation was calculated. A recommendation was approved when ≥70% of the expert group voted an NRS-agreement ≥7 [19].

Table 1. Development of the recommendations

Phase 1. ***Development of research-questions and semi-definitive frameworks for diagnosis and treatment***	
a	Preliminary literature search in books, protocols and review articles
b	Semi-structured interviews with 4 RA patients experienced with foot problems and related treatments
c	Field consultation among 39 RA foot care professionals (medical doctors/allied healthcare professionals) by assessing a semi-structured interview (n=6) or by using a questionnaire during an expert meeting (n=33). The overall question to be answered: *"Which questions would you like to see answered by the recommendations? Regarding to your field of expertise (diagnostics and treatment) and in the context of a multidisciplinary approach"*
d	Draft research questions and draft frameworks (for diagnosis and treatment) were developed, by the core members of the expert group (MTD, MvdL, TPMVV and JD), based on the results of point a-c.
e	Discussion with the experts on the draft research questions and frameworks, during the first expert group meeting.
f	Refining draft research questions and frameworks into definitive research questions and semi-definitive frameworks with the expert group, during the first expert group meeting.
Phase 2. ***Development of draft recommendations***	
g	A search strategy was developed for each research question (see ***Appendix 1***). Literature was searched in PubMed by MTD. The available (systematic) reviews on the subject of interest were used. When no (systematic) review were available, core publications (according to the expert group) were used.
h	Draft recommendations were formulated (by the core members) based on the literature found at point g.
Phase 3. ***Development of definitive recommendations and frameworks with a level of evidence***	
i	Discussion with the experts on the draft recommendations and semi-definitive frameworks, during the second expert group meeting and 2 email-rounds.
j	Refining draft recommendations and semi-definitive frameworks into definitive recommendations and frameworks, during the second expert group meeting and 2 email-rounds.
k	Determining the level of evidence for each definitive recommendation/framework according to "Evidence-Based Guideline Development" of the Quality Institute for Public Healthcare in The Netherlands. Five levels of evidence were distinguished (ranging from 1 to 4b). When a recommendation was based on a review or guideline, the level of evidence reported in the review/guideline was used. If the level of evidence was not reported, the original sources were retrieved (individual studies/ expert opinion).
Phase 4. ***Determining the level of agreement for the definitive recommendations and frameworks***	
l	During the third expert group meeting an anonymous voting procedure was followed. For each recommendation/framework a numeric rating scale for agreement (NRS-agreement) from 0 (total disagreement) to 10 (total agreement) was assessed.
m	The mean and range of the level of agreement for each recommendation was calculated. A recommendation was approved when ≥70% of the expert group voted an NRS-agreement ≥7.

Table 2. EBRO classification of methodological quality of individual studies [18]

A1	Systematic review of at least two independent studies of A2-level
A2	Randomized double-blind controlled clinical trial of good quality and of sufficient size
B	Controlled trial but not with all the characteristics as mentioned under A2
C	Non-controlled studies
D	Expert opinion

Table 3. Level of evidence

	Evidence is based on
1	Research of level A1 or at least 2 independently conducted studies of level A2
2	1 study of level A2 or at least 2 independently conducted studies of level B
3	1 study of level B or C
4a	Expert opinion described in the literature
4b	Opinion of the expert group

Results

Fifteen research questions were developed during phase 1. Two (out of 15) research questions concerned the quality of the developed frameworks for diagnosis and treatment. These frameworks and answers to the related research questions were based on expert opinion. The answers of 13 (out of 15) research questions were based on both literature and expert opinion. ***Appendix 1*** shows an overview of the developed research questions and the answering methods. The developed frameworks were reflected in two recommendations. Furthermore, 39 care-related recommendations were developed: seven on diagnosis, 27 on treatment, four on communication and one on organisation of foot care. All recommendations were approved. ***Tables 4, 5, 6, 7, 8 ,9*** give an overview of the developed recommendations with references to the literature used, the level of evidence, and the level of agreement. The percentage score of NRS-agreement ≥7 ranged from 80 to 100%.

Frameworks for diagnosis and treatment

A framework for diagnosis and a framework for treatment were developed by using the terminology of the International Classification of Functioning, Disability and Health (ICF) of the World Health Organization [20]. ***Table 4*** provides an overview of the developed recommendations on the frameworks for diagnosis and treatment.

The framework for diagnosis, as shown in ***Figure 1***, provides an overview of the different objectives in diagnosis of foot problems in RA and the corresponding instruments. Different objectives in diagnosis can be distinguished: i) detection of RA-related foot conditions; ii) medical diagnosis of RA; iii) (work-) diagnosis of foot function, dermatological factors, neuro-vascular factors, limitations in daily activities and restrictions in participation, external factors, and personal factors; and iv) monitoring of the progression of foot conditions/problems. For the Dutch situation, the role of the healthcare professions involved was described per objectives in diagnosis, as shown in ***Appendix 2***.

The framework for treatment, as shown in ***Figure 2***, provides an overview of the treatment options for RA-related foot problems. The primary objectives in treatment are i) treatment of RA, ii) treatment of abnormal foot function, and iii) treatment of dermatological problems. In addition, treatment of neuro-vascular abnormalities should be considered. For the Dutch situation, the role of the involved healthcare professions was described per objectives in treatment, as shown in ***Appendix 3***.

Table 4. Recommendations on the framework for diagnosis and the framework for treatment of RA-related foot problems

	LoE	Ref	LoA
The "Framework for diagnosis of RA-related foot problems" (Figure 1) provides an overview of the different objectives in detection, diagnosis, and monitoring of foot problems in people with RA, as well as the corresponding instruments.	4b	n/a	9.2 (7-10)
The "Framework for treatment of RA-related foot problems" (Figure 2) provides an overview of the potential treatment per diagnostic outcome.	4b	n/a	9.1 (6-10)

LoE = Level of Evidence for the recommendations: (1) research of level A1 or at least 2 independently conducted studies of level A2, (2) 1 study of level A2 or at least 2 independently conducted studies of level B, (3) 1 study of level B or C, (4a) expert opinion described in the literature, (4b) opinion of the expert group. Ref. = references. LoA = Level of Agreement for the recommendations: Numeric Rating Scale from 0 (total disagreement) to 10 (total agreement) reported as mean (range). n/a = not applicable.

DOMAIN	DIAGNOSTICAL QUESTION	DIAGNOSTICAL INSTRUMENT
	foot problems or suspicion of RA? diagnosed RA and (history with) foot problems?	patient history
	↓ 1 x yes ↓ 2 x no: no further diagnostics	
rheumatoid artritis (RA)	**damage of foot joints**	X-ray (non-weigth bearing)
	inflammation of foot joints / soft tissue	palpation swelling and pain ultrasonography[0]
alignment and function of the feet	**malalignment**	inspection
	abnormalities in function	assessment of function muscle strength/tone joint mobility inspection gait characteristics plantar pressure measurements[0]
dermatological factors	**abnormalities in skin and nails** high risk for foot wounds?	patient history question on medication inspection
neuro-vascular factors	**sensiblity disorder**	sensitivity tests
	vascular disorder	inspection skin and color presence of varicosities or edema palpation skin temperature pulsations of tibialis posterior artery and dorsalis pedis artery assessment with doppler[0] assessment of Ankle Arm Index[0]
activity and participation	**foot-related impairments in daily activities** e.g., walking	patient history
	foot-related restrictions in participation e.g., social participation and work	patient history
external factors	**fit of over-the-counter shoes**	patient history inspection fit and function of shoes
	fit of assistive device foot orthoses ready-made or custom-made therapeutic shoes silicone toe orthosis	patient history inspection fit and function of assistive device
personal factors	**perceptions on the foot symptoms**	patient history
	expectations of the treatment	patient history

[0] additional diagnostical assessment

Figure 1. Framework for diagnosis of RA-related foot disease

Diagnosis

Check-ups of feet and shoes

Regular check-ups (for example annually) of the feet of people with RA are of great importance in detecting disease activity in an early stage. Especially because the most frequently used instrument to detect disease activity (with a 28 joint count [21]) excludes examination of the feet. Regular check-ups are also important in people with RA in remission, since pain and swelling of MTP joints are present in a substantial part of this patient group [22-24]. Long-term synovitis of foot joints can lead to joint damage and deformity [22]. Furthermore, check-ups of over-the-counter shoes worn by the patient are indicated. Malalignment of the feet is very common in people with RA and can cause pain during weight-bearing activities and difficulties with shoe-fitting. Inadequate shoe fit can lead to high local pressure and subsequent pain. The required fit and function of the shoes varies per person with RA. ***Table 5*** provides an overview of the developed recommendations on check-ups of feet and shoes.

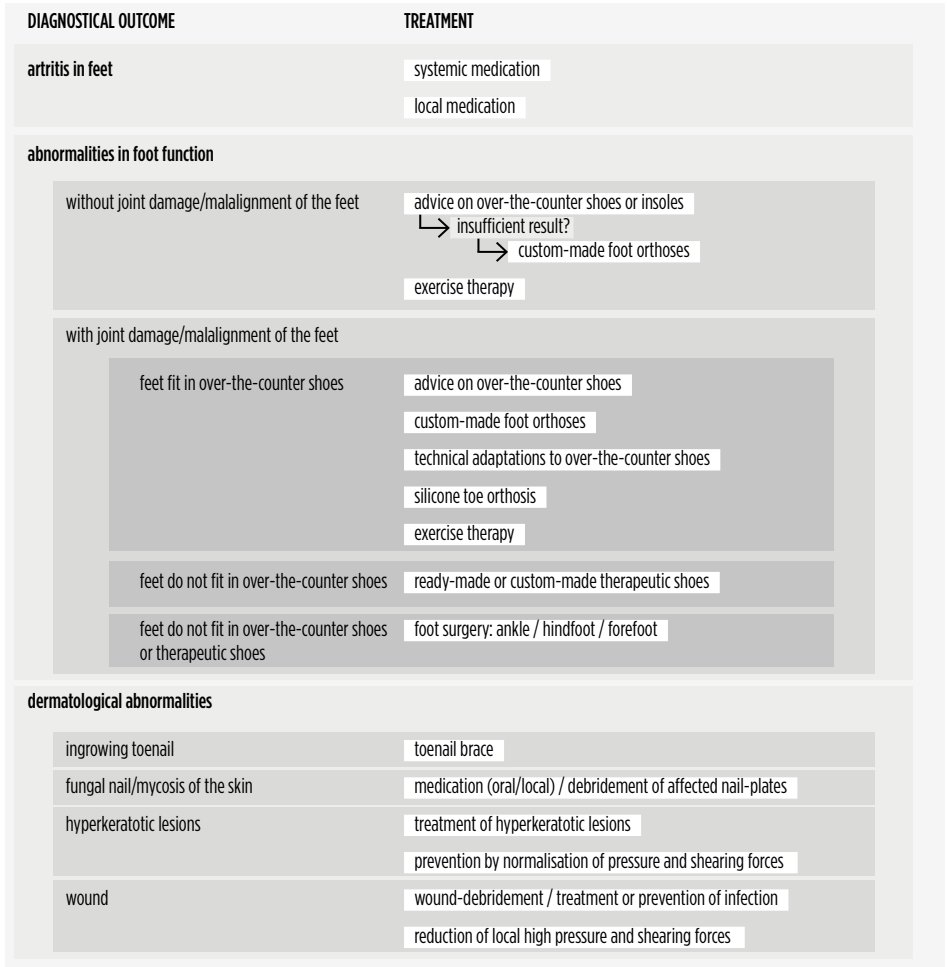

Figure 2. Framework for treatment of RA-related foot problems

Diagnostic imaging

Diagnostic imaging can be performed in addition to assessment of patient history and physical examination. Assessment of X-rays is an essential part of diagnosis of foot involvement (erosions and deformities of forefoot joints) by the rheumatologist. Ultrasonography can optionally be applied to detect and monitor foot involvement (synovitis in foot joints and inflammation of soft tissues). ***Table 6*** provides an overview of the developed recommendations on diagnostic imaging.

Table 5. Recommendations on check-ups of feet and shoes

	LoE	Ref	LoA
Rheumatologists and nurses specialised in rheumatology should perform regular feet check-ups. These check-ups should include, at least, patient history of foot disease, foot inspection, and palpation of foot joints for the detection of swelling and pain.	4b	n/a	9.2 (8-10)
Over-the-counter shoes should have, at least, sufficient room in the toe box and a stiff sole allowing a heel-to-toe gait.*	*3	*(46)	9.3 (7-10)
The following additional shoe features may be important, depending on the foot conditions and wishes of the patient: i) light weight; ii) spacious, adjustable, and easy to close in-step/heel girth; iii) strong, raised, and padded heel part; iv) inflection point at the MTP joints; v) adequate length and width, measured in standing position; vi) no seams on the inside; vii) removable insoles so that custom-made foot orthoses can be placed in it.**	**4a	** (32, 33)	

LoE = Level of Evidence for the recommendations: (1) research of level A1 or at least 2 independently conducted studies of level A2, (2) 1 study of level A2 or at least 2 independently conducted studies of level B, (3) 1 study of level B or C, (4a) expert opinion described in the literature, (4b) opinion of the expert group. Ref. = references. LoA = Level of Agreement for the recommendations: Numeric Rating Scale from 0 (total disagreement) to 10 (total agreement) reported as mean (range). n/a = not applicable. * refers to the first part of the recommendation with corresponding level of agreement and references. ** refers to the second part of the recommendation with corresponding level of agreement and references.

Table 6. Recommendations on diagnostic imaging

	LoE	Ref	LoA
For the detection of joint damage in the feet, a non-weight-bearing X-ray in anterior-posterior (AP) direction is the preferred method.	4b	n/a	8.6 (0-10)
For the detection of joint deformity and malalignment of the foot, a weight-bearing X-ray in anterior-posterior (AP) and lateral directions is the preferred method.	4b	n/a	9.6 (7-10)
Ultrasonography can be applied in the diagnosis of inflammation of joints* and soft tissue.**	2	*(47, 48) **(49, 50)	9.4 (7-10)
When clinical examination is inconclusive in the diagnosis of inflammation of joints and soft tissue, ultrasonography should be considered.*	*4a	*(51)	9.2 (8-10)
When ultrasonography is inconclusive, additional diagnostic imaging (MRI or CT scan) can be considered.**	**4b	** n/a	

LoE = Level of Evidence for the recommendations: (1) research of level A1 or at least 2 independently conducted studies of level A2, (2) 1 study of level A2 or at least 2 independently conducted studies of level B, (3) 1 study of level B or C, (4a) expert opinion described in the literature, (4b) opinion of the expert group. Ref. = references. LoA = Level of Agreement for the recommendations: Numeric Rating Scale from 0 (total disagreement) to 10 (total agreement) reported as mean (range). n/a = not applicable. * refers to the first part of the recommendation with corresponding level of agreement and references. ** refers to the second part of the recommendation with corresponding level of agreement and references.

Treatment

Medical treatment

Medical treatment primarily consists of the prescription of systemic medication by the rheumatologist. In addition, local medication can be applied in foot joints and soft tissues by corticosteroid injections. Furthermore, foot surgery can be performed to reduce pain and improve/maintain independent mobility, especially when a conservative treatment (neither medication nor surgery) is not successful or indicated. ***Table 7*** provides an overview of the developed recommendations on medical treatment.

Table 7. Recommendations on medical treatment

	LoE	Ref	LoA
Corticosteroid injections can be applied in joints and soft tissue of the foot in the treatment of local arthritis and synovitis.*	*2	*(52) (53)	8.7 (7-10)
Corticosteroid injections may also be applied in the treatment of tendinitis and pain.**	**4a/b	**(32, 54, 55)	
A corticosteroid injection conducted by ultrasonography (if available) is preferred, because this may result in a more accurate determination of the location of the injection.	4b	n/a	9.4 (7-10)
Early in the treatment process, consultation by an orthopaedic surgeon should be considered. Surgical intervention should be considered when the following foot conditions do not respond to conservative therapy: i) persistent pain and stiffness, ii) >6 months of synovitis in foot and ankle joints, iii) tenosynovitis or tendon ruptures, iv) malalignment of the foot (e.g., hammer toes) causing mobility limitations and pain or problems finding adequate shoes, v) returning callosity/ clavus, vi) wounds/(pre)ulcers, and vii) osteomyelitis/septic arthritis.	4a/b	(29, 32, 56)	9.1 (6-10)
Resection arthroplasty of the MTP joints can be applied to improve joint mobility and to reduce pain, forefoot plantar pressure, and problems finding well-fitting shoes.*	*3	*(57)	8.9 (6-10)
In severe malalignments of the toes or damage to the MTP joints, resection arthroplasty is preferred. Without severe malalignments/damage, a MTP joint-preserving surgical technique can be considered.**	**4a	**(56)	
An arthrodesis of the MTPI joint can be performed to reduce pain and improve the weight-bearing capacity of the forefoot.	3	(57)	9.1 (7-10)
When surgical treatment of the hindfoot is necessary, arthrodesis of the subtalar joint is preferred. For flat feet, an additional arthrodesis of the calcaneocuboid joint and talonavicular joint should be considered (triple arthrodesis).	4a	(39)	8.9 (6-10)
In the treatment of severe pain and damage of the tibiotalar joint, an arthrodesis of the tibiotalar joint or an ankle prosthesis can be applied.*	*1	*(58)	9.0 (7-10)
An arthrodesis is preferred, provided that the Chopart-joint-line is intact and the status of other joints does not form a contraindication. An ankle prosthesis can be considered when preservation of mobility in the tibiotalar joint is important (according to the patient) and the preoperative status of the patient does not form a contra-indication.**	**4b	** n/a	

LoE = Level of Evidence for the recommendations: (1) research of level A1 or at least 2 independently conducted studies of level A2, (2) 1 study of level A2 or at least 2 independently conducted studies of level B, (3) 1 study of level B or C, (4a) expert opinion described in the literature, (4b) opinion of the expert group. Ref. = references. LoA = Level of Agreement for the recommendations: Numeric Rating Scale from 0 (total disagreement) to 10 (total agreement) reported as mean (range). n/a = not applicable. * refers to the first part of the recommendation with corresponding level of agreement and references. ** refers to the second part of the recommendation with corresponding level of agreement and references.

Conservative treatment

Conservative treatment can be prescribed in addition to medical treatment. Conservative treatment can include therapeutic shoes, custom-made foot orthoses, exercise therapy, custom-made silicone toe orthoses, toenail braces, and treatment of toenails and skin. ***Table 8*** provides an overview of the developed recommendations on conservative treatment.

Therapeutic shoes can be prescribed in patients with abnormal foot function, damage/ deformity of foot joints, or malalignment of the feet. Therapeutic shoes can be ready-made or custom-made. Ready-made shoes are i) over-the-counter shoes with technical adaptation, or ii) serially-produced shoes with extra depth, support, incorporated inlays, and optional technical adaptations [25, 26]. Custom-made shoes are developed for the individual patient based on specific measures and specifications, whereby a variety of technical adaptations can be incorporated [25, 26].

Custom-made foot orthoses can be prescribed to facilitate physical functioning by reducing pain and improving foot function [27-31]. In order to reduce pain and to improve foot function, the specific objectives of the foot orthoses can include i) normalising vertical plantar foot pressure, ii) reducing shear-forces acting on the feet, iii) correcting malalignment in feet with adequate joint mobility, and iv) supporting feet when correction is not indicated [28, 29, 32, 33].

Exercise therapy, in general, can be applied in people with RA to improve social participation and functioning in daily life [34]. Exercise therapy specific to the foot and ankle can be prescribed for the treatment of pain, muscle weakness, imbalance, and limited joint mobility [33].

Custom-made silicone toe orthoses can be applied to i) correct a non-rigid abnormal toe-position and ii) to reduce local high pressure at the toes [35].

Toenail braces (made of surgical steel wire, titanium wire, or plastics, and attached to the nail with gel, acrylic, or composite) can be applied to improve the shape of the toenail by lifting the medial or lateral side [36].

Treatment of toenails and skin can include treatment of i) nail fungus, ii) hyperkeratotic lesions, and iii) (pre-)ulcers or infections. Treatment of nail fungus consists of i) debridement of all hypertrophic and dystrophic nail-plates, ii) medication (oral or local), iii) patient-advice regarding the cause and treatment of the toenail fungus [32, 36]. In people with RA, prominent metatarsal heads are subject to high pressure and excessive shear forces during gait. These stresses stimulate the skin (stratum corneum) to produce hyperkeratotic lesions [32]. This can cause pain, corns, and wounds/ulcers [32, 36]. Scalpel or mechanical trimming techniques can be used to treat excessive hyperkeratotic lesions [36].

Communication and organisation of RA-related foot care

Adequate communication between the patient and healthcare professional about the cause of foot problems, available treatment options, and anticipated outcomes are of great importance during the course of treatment. Understanding and involvement of the patient in determining the treatment strategy are important for adherence to the treatment and coping with the disease. Furthermore, specific advice on shoes and preventive and curative RA-related foot care is important for adequate self-management.

Healthcare professionals from various professions can be involved in the diagnosis and treatment of RA-related foot disease. The involvement of various professions depends on the severity of the foot problems, the work-field and expertise of the attending healthcare professionals, the organisation of foot care in the geographical area, and the preferences of the patient. Good communication and shared decision-making between the involved professionals is of great importance for adequate, multidisciplinary foot care in people with RA. ***Table 9*** provides an overview of the developed recommendations on communication and organisation of RA-related foot care.

Table 8. Recommendations on conservative treatment

	LoE	Ref	LoA
Technical adaptations to over-the-counter shoes can reduce pain and improve physical functioning.*	*3	*(59)	9.3 (8-10)
These adaptations can be prescribed in patients with abnormal foot function, foot joint damage/deformity, or malalignment of the feet, provided that the feet fit in over-the-counter shoes.**	**4b	**n/a	
Ready-made therapeutic shoes with extra depth, support, incorporated inlays, and optional technical adaptation can reduce forefoot plantar pressure and foot pain and improve gait characteristics, physical functioning, and health-related quality of life.*	*3	*(46, 60-64)	9.3 (7-10)
These ready-made shoes can be prescribed in patients with i) abnormal foot function, foot joint damage/deformity, or malalignment of the feet, and ii) feet that do not fit in over-the-counter shoes, but for whom custom-made shoes are not indicated.**	**4b	**n/a	
Custom-made therapeutic shoes can reduce pain and improve physical functioning.*	*3	*(25)	9.5 (8-10)
These custom-made shoes can be prescribed in patients with i) abnormal foot function, foot joint damage/deformity, or malalignment of the feet, and ii) feet that do not fit in over-the-counter shoes or ready-made therapeutic shoes.**	**4b	**n/a	
Custom-made therapeutic shoes should be worn all day, after a habituation period.	3	(25)	8.5 (0-10)
Foot orthoses are recommended in patients with abnormal foot function, when adequate over-the-counter shoes are insufficient in reducing foot symptoms.	4a/b	(27-31)	9.0 (2-10)
Foot orthoses in adequate shoes can reduce forefoot plantar pressure and pain.	1	(27, 30)	9.4 (7-10)
The function of foot orthoses should be assessed in relation to the patient's footwear, due to the interaction between the two.	3	(60)	9.3 (8-10)
Rigid foot orthoses are recommended in feet with correctable malalignment, to control the position of the feet during weight-bearing.	4a	(28, 29, 32, 33)	8.9 (7-10)
Total contact foot orthoses are recommended in feet with uncorrectable malalignment or fragile skin. The material used for the production of total contact foot orthoses depends on the required characteristics of the foot orthoses.	4a/b	(28, 32)	9.0 (6-10)
General exercise therapy is recommended according to the Dutch KNGF Guideline for Physical Therapy in Patients with Rheumatoid Arthritis.	1	(34)	9.1 (7-10)
When an (pre-)ulcer or infection is detected, the treating physician should be consulted.	4a/b	(32)	9.2 (6-10)

Discussion

These are the first published multidisciplinary recommendations specific to the management of foot problems in RA. The recommendations are based on the best available evidence and the opinions of experts with varying specialities and of patients. Forty-one recommendations (eight on diagnosis, 32 on treatment (of which four on communication) and one on organisation of foot care) were developed and approved by the expert group.

In a recently published critical appraisal on clinical practice guidelines for the foot and ankle in RA, domains for foot and ankle management were identified [15]. The domains included in the previously published guidelines were multidisciplinary team care, access to foot healthcare, foot health assessment/review, orthoses/insoles/splints, therapeutic footwear, and other foot care treatments (patient education; corticosteroid injections; and treatment of hyperkeratotic lesions, wounds, and fungal infections) [15]. The present study covers these domains with up-to-

Table 8. (continued)

Exercise therapy specific to the foot and ankle can include i) strengthening exercises for the intrinsic foot muscles and m. tibialis posterior; ii) active stretch exercises for the plantar fascia, achilles-tendon, and peroneal muscles; and iii) active exercises to improve joint mobility.	4a	(33)	8.8 (7-10)
A silicone toe orthosis can be used in the treatment of malalignment of toes and secondary pain or high pressure.	3	(65)	9.2 (7-10)
In the prescription of a silicone toe orthosis, the following factors should be considered: i) a sensibility disorder or peripheral artery disease; ii) a skin defect on the foot of interest; and iii) sufficient room in the shoe for wearing the toe orthosis.	4a/b	(36)	9.3 (8-10)
A toenail brace can be used in the treatment of an ingrowing or ingrown toenail.^	2	(66, 67)	8.8 (5-10)
In the prescription of a toenail brace, the following factors should be considered: i) a sensibility disorder or peripheral artery disease; ii) a skin defect, inflammation, or onycholysis on the toe of interest; and iii) the use of biologicals.	4a/b	(36)	9.3 (7-10)
When a fungal nail or mycosis of the skin is detected, treatment should be started to prevent ulcers and secondary bacterial infections.	4a/b	(32)	9.0 (7-10)
Pressure and shearing forces should be normalised in feet with hyperkeratotic lesions. For normalisation of pressure and shearing forces, i) an individual shoe- and sock advice can be given; or ii) foot orthoses, silicone toe orthosis, technical adaptations to over-the-counter shoes, ready- or custom-made therapeutic shoes, or a provisional therapy (e.g., felt padding or taping) can be prescribed.	4a/b	(32, 36)	9.0 (6-10)
Excessive hyperkeratotic lesions should be treated. During the treatment the following factors should be considered: i) a sensibility disorder or peripheral artery disease, and ii) fragile skin, plantar bursa, and prominent metatarsal heads on the foot of interest.	4a/b	(32, 36)	9.1 (7-10)
When an (pre-)ulcer or infection is detected, the treating physician should be consulted.	4a/b	(32)	9.2 (6-10)
In wound-care, a provisional therapy (e.g., felt padding) can be applied to reduce pressure. When material with an adhesive layer is used, fragile skin should be taken into consideration.	4a	(32)	8.8 (7-10)

LoE = Level of Evidence for the recommendations: (1) research of level A1 or at least 2 independently conducted studies of level A2, (2) 1 study of level A2 or at least 2 independently conducted studies of level B, (3) 1 study of level B or C, (4a) expert opinion described in the literature, (4b) opinion of the expert group. Ref. = references. LoA = Level of Agreement for the recommendations: Numeric Rating Scale from 0 (total disagreement) to 10 (total agreement) reported as mean (range). n/a = not applicable. * based on literature not specific for RA. * refers to the first part of the recommendation with corresponding level of agreement and references. ** refers to the second part of the recommendation with corresponding level of agreement and references.

date recommendations, based on literature and expert opinion. In addition, recommendations were developed on communication, foot surgery, exercise therapy, and the application of toenail-braces and provisional therapy (e.g. felt padding or taping) with clearly described contra-indications. The present recommendations address the total range of diagnostics and treatment options as applied in The Netherlands. Treatment of excessive callosities is recommended, although it is in contrast to the limited available evidence. One RCT showed no benefit of callus debridement over a sham procedure in terms of pain reduction, while sharp debridement may introduce potential risks [37]. Another RCT showed no-long term effect of sharp scalpel debridement of painful forefoot plantar callosities [38]. Despite this evidence, the expert group had the opinion that hyperkeratotic lesions can be treated if the pre-defined contra-indications are taken into account. Moreover, for the Dutch situation, the role of the healthcare professions involved was described per objective in diagnosis and treatment. It should be noted that the present recommendations are aimed at managing RA-related foot problems in the Netherlands. Since the content, (expertise of) involved disciplines, and organisation of RA-related foot care may vary per country, this may hamper the generalizability of the frameworks and recommendations to other countries.

Table 9. Recommendations on communication and organisation of RA-related foot care

	LoE	Ref	LoA
Regular consultation and shared decision-making between the patient and healthcare professional should be included in RA-related foot care and should be customised to the individual patient.	4b	n/a	8.8 (5-10)
Individual shoe-advice to people with RA with foot problems is essential and should include information on fit, cosmetics, function, durability and correct use of the shoes.	4a/b	(32, 33, 35)	9.4 (8-10)
Foot care in patients with RA should include patient education.*	*1	*(68)	9.6 (7-10)
Patient education may consist of preventive and curative care.**	**4b	**n/a	
Patient education on preventive care for RA-related foot problems should contain information about i) the cause and course of RA and RA-related foot disease; ii) recognition of infection and increased disease activity (systemic and local); iii) foot care and hygiene; iv) recognition and use of adequate footwear (for indoors and outdoors); v) timely consultation by a healthcare professional in the case of foot infection, symptoms of increased disease activity, pain, problems finding adequate footwear, and skin and nail conditions; and vi) the healthcare professional who may be consulted for a specific indication.	4a	(11, 32, 33, 35)	9.3 (8-10)
Patient education on curative care for RA-related foot problems should contain information about i) the treatment strategy (short and long term); ii) the importance of treatment adherence and compliance; iii) the expected treatment results according to pain, physical functioning, activities, and participation; iv) the possible adverse events; and v) costs and reimbursement of the treatment.	4a	(33, 35, 39, 51, 69)	9.2 (7-10)
A multidisciplinary approach in management of RA-related foot problems is recommended. The diagnosis and treatment of RA-related foot disease consists of different aspects, which require the expertise of several disciplines.	4a/b	(11, 32)	9.6 (8-10)

LoE = Level of Evidence for the recommendations: (1) research of level A1 or at least 2 independently conducted studies of level A2, (2) 1 study of level A2 or at least 2 independently conducted studies of level B, (3) 1 study of level B or C, (4a) expert opinion described in the literature, (4b) opinion of the expert group. Ref. = references. LoA = Level of Agreement for the recommendations: Numeric Rating Scale from 0 (total disagreement) to 10 (total agreement) reported as mean (range). n/a = not applicable. * refers to the first part of the recommendation with corresponding level of agreement and references. ** refers to the second part of the recommendation with corresponding level of agreement and references.

The level of evidence of the developed recommendations varies from 1 (highest) to 4 (lowest). Overall, most of the developed recommendations were based on expert opinion, as there is a lack of research evidence. Only a few number of the topics addressed in the recommendations were subject of investigation in previously published high-quality research. Evidence, based on randomised controlled trials' ("RCT") between-group differences, was found for the application of corticosteroid injections (in finger joints, based on a single RCT), foot orthoses (for treatment of pain and high forefoot pressure, based on multiple RCTs), ready-made therapeutic shoes (for treatment of high plantar pressure, based on a single RCT), patient education (not foot specific), and exercise therapy (not foot specific). A lower level of evidence (based on uncontrolled studies) was found for the application of ultrasonography, foot surgery, therapeutic shoes, silicone toe-orthoses, and toenail braces. Our findings clearly indicate that there are gaps in scientific literature on the management of foot problems in people with RA. More research is needed to strengthen the evidence on diagnosis and treatment of RA-related foot problems. Multiple areas with a lack of evidence were identified. The following topics for future research on diagnosis are indicated: i) diagnostic research on the psychometric properties, timing and frequency of ultrasonography for the detection of erosions and inflammation in the feet, and ii) the value of (yearly) check-up of the feet for the prevention or delay in progression of RA-related foot problems. For treatment the following topics for future research are identified: i) a definitive, high-quality RCT to investigate the effectiveness of corticosteroid injections in the foot, ii) RCTs on the effectiveness of different types of (fore-)foot surgery, therapeutic shoes, treatment of nails and hyperkeratotic lesions, and the comparative effectiveness of foot orthoses, and iii) development and evaluation of a foot-specific patient education program.

A multidisciplinary approach in the diagnosis and treatment of RA-related foot problems is recommended, as supported by several previously published guidelines [11, 12, 39-41]. Based on the opinion of the expert group, a multidisciplinary approach should consist of i) regular check-ups of the feet (for example annually) by a rheumatologist or a specialized nurse and, if indicated, ii) referral to another discipline (rehabilitation physician, orthopaedic surgeon, podiatrist, orthopaedic shoe-technician, pedicurist, or physical therapist). Referral should be considered when foot problems exist after reaching clinical remission [22-24, 42], when patients with increased disease states have mechanical foot impairments [5, 8], or when patients do not respond to or are ineligible for biological therapy and therefore continue to have active foot involvement [9]. Furthermore, adequate communication between the healthcare professionals involved and the patient (including shared decision-making and patient education) should be part of the treatment [43]. For example, in the prescription of therapeutic footwear communication and shared decision are of importance, especially to promote compliance of wearing them [44]. Adequate communication could be supported by a combined consultation with the professionals involved. In addition, (web-based) educational material may be helpful in patient education and could be developed within a network of specialised healthcare professionals or by patient organisations [45]. The healthcare professionals involved in, the access to, and the timing and content of management of foot problems may vary per country/geographical region. Therefore, developing and maintaining a network of specialised healthcare professionals, as

well as developing a foot care pathway for diagnosis and treatment within this network are important steps in supporting multidisciplinary management [11, 12].

These are the first published multidisciplinary recommendations specific to the diagnosis and treatment of foot problems in people with RA. Expert opinions of several involved healthcare professions and patients (experienced in living with RA-related foot problems) were included in the recommendations. These national recommendations may be a first step towards developing international multidisciplinary recommendations for the management of foot problems in RA. The developed recommendations aim to contribute to i) uniformity in diagnosis, treatment, and guidance of people with RA-related foot problems; and ii) improved communication between, on the one hand, patient and treating healthcare professionals, and, on the other hand, between the healthcare professionals themselves. In future recommendations, the inclusion of more healthcare professions, such as general practitioners and physical therapists, who also have a role in RA foot management, could be considered. The development of the recommendations gave insight into the limited research evidence available on management of foot problems in RA. The gaps in literature could be topics for future research. Overall, more attention to RA-related foot problems in research is justified, as these are highly prevalent and have a substantial impact on patient quality of life.

Conclusions

These are the first published multidisciplinary recommendations specific to the management of foot problems in people with RA. Multidisciplinary recommendations can provide guidance in timely referrals and access to adequate foot care. More research is needed to strengthen the evidence on diagnosis and treatment of RA-related foot problems. These national recommendations may be a first step towards developing international multidisciplinary recommendations for the management of foot problems in RA.

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Appendices

Appendix 1. Overview of the developed research questions and the used answering methods.

	Research-question	Method
1.	Does the "Framework for diagnosis of RA-related foot disease" (Figure 1) provide an adequate overview of the different functions of diagnosis, detection, and monitoring of foot disease in patients with RA and the corresponding instruments?	- expert opinion
2.	Is an X-ray in a weight-bearing position or an X-ray in a non-weight-bearing position the preferred method for the detection of joint damage and joint deformity/malalignment in the feet?	- literature search (PubMed accessed April 13th 2015) ("radiograph*"[tiab] OR "x-ray"[tiab]) AND ("foot"[MeSH Terms] OR "feet"[tiab]) AND ("systematic review"[tiab] OR "review"[Publication Type]) - expert opinion
3.	Is ultrasound detection of foot arthritis the preferred method, above palpation?	- literature search (PubMed accessed April 29th 2015) ("ultrasonography"[tiab] OR "Ultrasound"[tiab] OR "ultrasonography"[MeSH Terms] OR "ultrasonics"[MeSH Terms] OR "ultrasonics"[-tiab] OR "Sono graph*"[tiab]) and (inflam*[tiab] OR arthri*[tiab]) and ("foot"[MeSH Terms] or "feet"[tiab]) and ("system atic review"[tiab] OR "review"[Publication Type]) - expert opinion
4.	Which aspects should be included in individual shoe-advice on over-the-counter shoes for RA patients with foot disease?	- literature search (PubMed accessed May 4th 2015) (footwear [tiab] OR shoe*[tiab]) AND rheum* AND ("systematic review"[tiab] OR "review"[Publication Type]) - expert opinion
5.	Communication between patient and treating healthcare professional: which aspects on preventive and curative care should be included in patient advice?	- literature search (PubMed accessed April 13th 2015) (advise [tiab] OR communication [tiab] OR education) AND rheum* AND ("foot"[MeSH Terms] OR "feet"[tiab]) AND ("systematic review"-[tiab] OR "review"[Publication Type]) - expert opinion
6.	Does the "Framework for treatment of RA-related foot disease" (Figure 2) provide an adequate overview of the potential treatment per diagnostic outcome?	- expert opinion
7.	What is the evidence on the effectiveness of a corticosteroid injection in the treatment of pain and impairment during walking?	- literature search (PubMed accessed May 5th 2015) ("corticosteroid" [tiab] OR "steroid" [tiab] OR "glucocorticoids"[tiab]) AND (" injection"[tiab] OR "intra-articular" [tiab] OR "intra-articular"[tiab] OR "local" [tiab]) AND ("foot"[MeSH Terms] OR "feet"[tiab]) AND ("systematic review"[tiab] OR "review"[Publication Type]) - expert opinion
8.	Is the application of a corticosteroid injection conducted by ultrasonography the preferred method, above the application of a corticosteroid injection without ultrasonography?	- literature search (PubMed accessed May 5th 2015) ("corticosteroid" [tiab] OR "steroid" [tiab] OR "glucocorticoids"[tiab]) AND (" injection"[tiab] OR "intra-articular" [tiab] OR "intra-articular"[tiab] OR "local" [tiab]) AND ("foot"[MeSH Terms] OR "feet"[tiab]) AND ("systematic review"[tiab] OR "review"[Publication Type] - expert opinion
9.	What is the evidence on the effectiveness of foot surgery in the treatment of pain, impairment, and high local pressures?	- literature search (PubMed accessed May 5th 2015) ("surgery"[tiab] OR "operat*"[tiab]) AND ("foot"[MeSH Terms] OR "feet"[tiab] OR "ankle"[tiab] OR "ankles"[tiab] OR "metatars*"[tiab] OR "mtp*"[tiab] OR "forefoot"[tiab] OR "tars*"[tiab] OR phalang*[tiab] OR "toe"[tiab] OR "toes"[tiab] OR "hallux"[tiab] OR "midfoot"-[tiab] OR calcane*[tiab] OR "heel"[tiab] OR "hindfoot"[tiab] OR "talus"[tiab] OR subtal*[tiab] OR talonavicul*[tiab] OR "tibia*"[tiab] OR "navicula*"[tiab] OR fibul*[tiab])AND (rheum*[tiab] OR arthri*[tiab]) AND ("systematic review"[tiab] OR "review"[Publication Type]) - expert opinion
10.	What is the evidence on the effectiveness of therapeutic shoes on foot function, foot pain, physical functioning, health-related quality of life, adherence, adverse events, and patient satisfaction in RA patients?	- literature search (PubMed accessed March 12th 2015) (("Arthritis, Rheumatoid"[Mesh] OR rheumatoid arthritis [tiab])) AND ("Shoes"[Mesh] OR shoe* [tiab] OR footwear* [tiab]) - expert opinion
11.	What is the evidence on the effectiveness of foot orthoses in the treatment of pain and impairment during walking?	- literature search (PubMed accessed May 6th 2015) ("Foot Orthoses" [MeSH Terms] OR "Orthotic Devices"[MeSH Terms] OR "Foot Orthoses" [tiab] OR "inlay*" [tiab] OR "Orthose*" [tiab]OR "Insole*"[tiab]) AND ("foot"[MeSH Terms] OR "feet"[tiab] OR "ankle"[tiab] OR "ankles"[tiab] OR "metatars*"[tiab] OR "mtp*"[tiab] OR "forefoot"[tiab] OR "tars*"[tiab] OR phalang*[tiab] OR "toe"[tiab] OR "toes"[tiab] OR "hallux"[tiab] OR "midfoot"[tiab] OR calcane*[tiab] OR "heel"[tiab] OR "hindfoot"[tiab] OR "talus"[tiab] OR subtal*[tiab] OR talonavicul*[tiab] OR "tibia*"[tiab] OR "navicula*"[tiab] OR fibul*[tiab])AND (rheum*[tiab] OR arthri*[tiab]) AND ("systematic review"[tiab] OR "review"[Publication Type]) - expert opinion
12.	What is the evidence on the effectiveness of exercise therapy in the treatment of pain and impairment during walking?	- literature search (PubMed accessed May 6th 2015) ("exercise*" [tiab] OR "stretch*"[tiab] OR " therap*" [tiab]) AND ("foot"[MeSH Terms] OR "feet"[tiab] OR "ankle"[tiab] OR "ankles"[tiab] OR "metatars*"[tiab] OR "mtp*"[tiab] OR "forefoot"[tiab] OR "tars*"[tiab] OR phalang*[tiab] OR "toe"[tiab] OR "toes"[tiab] OR "hallux"-[tiab] OR "midfoot"[tiab] OR calcane*[tiab] OR "heel"[tiab] OR "hindfoot"[tiab] OR "talus"[tiab] OR subtal*[tiab] OR talonavicul*[tiab] OR "tibia*"[tiab] OR "navicula*"[tiab] OR fibul*[tiab])AND (rheum*[tiab] OR arthri*[tiab]) AND ("systematic review"[tiab] OR "review"-[Publication Type]) - expert opinion
13.	What is the evidence on the effectiveness of silicone toe orthoses and toenail braces in the treatment of pain and impairment during walking?	- literature search (PubMed accessed May 7th 2015) ("toe"[tiab] OR "toes"[tiab]) AND ("splint*" [tiab] OR "orthosis*"[tiab]) AND ("silicone*"[tiab]) (onychocryptosis[tiab] OR unguis incarnatus[tiab] OR ingrowing toenail*[tiab]) AND (orthonyxia [tiab] OR brace[tiab] OR treatment[tiab]) AND ("systematic review"[tiab] OR "review"[Publication Type]) - expert opinion
14.	What is the evidence on the effectiveness of the treatment of toenail fungus, calluses, gorges, and corns, wounds/ulcers, and of the application of pressure-reducing provisional therapies on pain and impairment during walking?	- literature search (PubMed accessed May 7th 2015) (callus[tiab] OR callosities OR hyperkeratosis[tiab] OR mycoses[tiab] OR onychomycoses[tiab]) AND (debridement [tiab] OR treatment-[tiab]) AND ("foot"[MeSH Terms] OR "feet"[tiab] OR "toe"[tiab] OR "toes"[tiab] OR "plantar"[tiab]) AND (rheum*[tiab] OR arthri*[tiab]) AND ("systematic review"[tiab] OR "review"[Publication Type]) - expert opinion
15.	How can RA-related foot care be organised?	- literature: guidelines as detected in the systematic of Hennessy et al. (15) - expert opinion

Appendix 2. Framework for diagnosis with an overview of the role of the involved healthcare professions in the Netherlands. part 1

DOMAIN	DIAGNOSTICAL QUESTION	FUNCTION PER PROFESSION* DIAGNOSE ˆ	SIGNAL AND MONITOR	DIAGNOSTICAL INSTRUMENT
	foot problems or suspicion of RA? **diagnosed RA and (history with) foot problems?** ↓ 1 x yes ↓ 2 x no: no further diagnostics			patient history
rheumatoid artritis (RA)	**damage of foot joints**	med. specialist	med.specialist	X-ray (non-weigth bearing)
	inflammation of foot joints / soft tissues	med. specialist	all	palpation swelling and pain ultrasonography °
alignment and function of the feet	**malalignment**	med. specialist podiatrist med. pedicurist orth. shoe technologist orth. shoe technician	all	inspection
	abnormalities in function	med. specialist podiatrist orth. shoe technologist orth. shoe technician	all	assessment of function muscle strength/tone joint mobility inspection gait characteristics plantar pressure measurements °
dermatological factors	**abnormalities in skin and nails** high risk for wounds/ulcers?	all	all	patient history question on medication inspection

med. specialist = medisch specialist (rheumatologist (with nursing rheuma consultant as extended arm)/specialized rheuma nurse/physician assistant rheumatoloy, rehabilitation physician, orthopaedic surgeon). med. pedicurist = medical pedicurist. orth. shoe technologist = orthopaedic shoe technologist. orth. shoe technician = orthopaedic shoe technician. All = medical-, and non-medical specialists (podiatrists, orth. shoe technologists, orth. shoe technicians, med. pedicurists). *The involvement of various healtcare professions depends on the organisation of footcare in the geographical area and the preferences of the patient. ˆ Diagnosis of (possible) RA-related foot problems can consist of medical diagnosis in the RA domain and (work-) diagnosis in the other domains. ° Additional diagnostical assessment.

Appendix 2. Framework for diagnosis with an overview of the role of the involved healthcare professions in the Netherlands. part 2

		DIAGNOSE	SIGNAL AND MONITOR	
neuro-vascular factors	**sensibility disorder**	med. specialist podiatrist med. pedicurist	all	sensitivity tests
	vascular disorder	med. specialist podiatrist	all	inspection skin and color presence of varicosities or edema palpation skin temperature pulsation of tibialis posterior artery and dorsalis pedis artery assessment with doppler ° assessment of Ankle Arm Index °
activity and participation	**foot-related impairments in daily activities** e.g., walking	all	all	patient history
	foot-related restrictions in participation e.g., social participation and work	all	all	patient history
external factors	**fit of over-the-counter shoes**	med. specialist podiatrist med. pedicurist orth. shoe technologist orth. shoe technician	all	patient history inspection fit and function of shoes
	fit of assistive device		all	patient history inspection
	foot orthoses	med. specialist, orth. shoe technologist, orth. shoe technician, podiatrist		fit and function of assistive device
	ready-made or custom-made therapeutic shoes	med. specialist, orth. shoe technologist, orth. shoe technician, podiatrist		
	silicone toe orthosis	med. specialist, orth. shoe technologist, podiatrist, med. pedicurist		
personal factors	**perceptions on the foot symptoms**	all	all	patient history
	expectations of the treatment	all	all	patient history

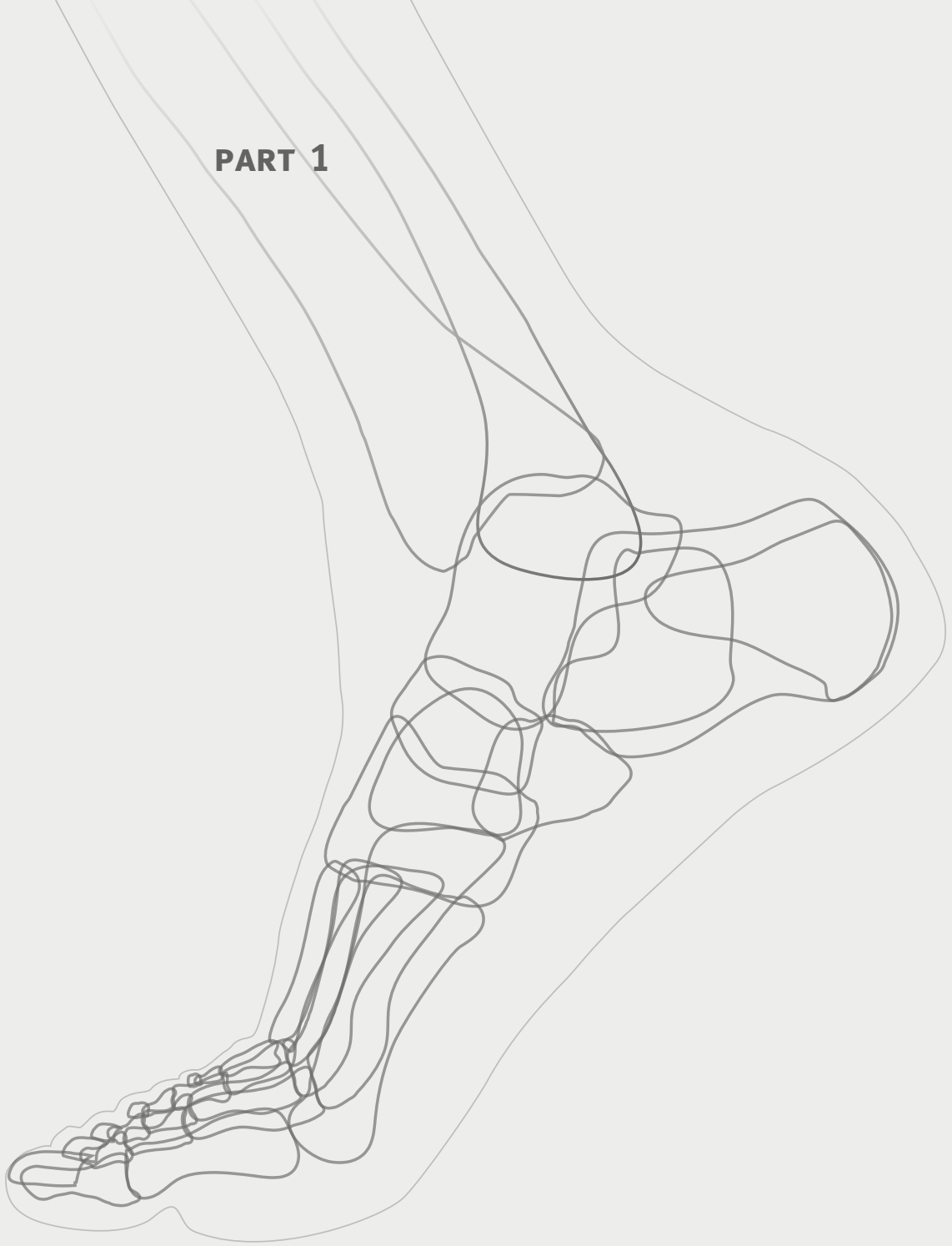
med. specialist = medisch specialist (rheumatologist (with nursing rheuma consultant as extended arm)/specialized rheuma nurse/physician assistant rheumatoloy, rehabilitation physician, orthopaedic surgeon). med. pedicurist = medical pedicurist. orth. shoe technologist = orthopaedic shoe technologist. orth. shoe technician = orthopaedic shoe technician. All = medical-, and non-medical specialists (podiatrists, orth. shoe technologists, orth. shoe technicians, med. pedicurists). *The involvement of various healtcare professions depends on the organisation of footcare in the geographical area and the preferences of the patient. ˆ Diagnosis of (possible) RA-related foot problems can consist of medical diagnosis in the RA domain and (work-) diagnosis in the other domains. ° Additional diagnostical assessment.

Appendix 3. Framework for treatment with an overview of the role of the involved healthcare professions in the Netherlands.

DIAGNOSTICAL OUTCOME	TREATMENT *MEDICAL TREATMENT*	*NON-MEDICAL TREATMENT*	PROFESSION*
artritis in feet	systemic medication local medication		rheumatologist (nurs. R-consulent) / spec. R-nurse / PA-R reumatologist / spec. R-nurse / PA-R / orth. surgeon / rehab. phys.
abnormalities in foot function			
without joint damage / malalignment of the feet		advice on over-the-counter shoes or insoles ↳ insufficient result? ↳ custom-made foot orthoses exercise therapy	med. spec. / podiatr. / orth. technologist / orth. technician / med. pedi podiatr. / orth. technician podiatr.
with joint damage / malalignment of the feet			
feet fit in over-the-counter shoes		patient-advice according over-the-counter shoes custom-made foot orthoses technical adaptations to over-the-counter shoes silicone toe orthosis exercise therapy	med. spec. / podiatr. / orth. technician / orth. technologist podiatr. / orth. technician orth. technician / orth. technologist podiatr. / med. pedi podiatr.
feet do not fit in over-the-counter shoes	ready-made or custom-made therapeutic shoes		med. spec./ orth. technologist / orth. technician
feet do not fit in over-the-counter shoes or therapeutic shoes	foot surgery: ankle / hindfoot / forefoot		orth. surgeon
dermatological abnormalities			
ingrowing toenail	toenail brace		podiatr. / med. pedi
fungal nail / mycosis of the skin	medication (oral/local) / debridement of affected nail-plates		med. spec. / podiatr. / med. pedi
hyperkeratotic lesions	treatment of hyperkeratotic lesions prevention by normalisation of pressure and shearing forces		podiatr. / med. pedi med. spec. / podiatr. / med. pedi / orth. technologist / orth. technician
wound	wound-debridement / treatment or prevention of infection reduction of local high pressures and shearing forces		med. spec. / podiatr. med. spec. / podiatr. / orth. technologist / orth. technician / med. pedi ^

*The involvement of various healthcare proffesions depends on the organisation of footcare in the geographical area and the preferences of the patient. Nurs. R-consulent = nursing rheuma-consulent. Spec. R-nurse = specialized rheuma-nurse. PA-R = physician assistant rheumatology. Orth. surgeon = orthopeadic surgeon. Rehab. phys. = rehabilitation physician. Med. spec. = medical specialist (rheumatologist (with nursing rheuma-consulent as extended arm) / specialized rheuma-nurses / physician assistant rheumatology, rehabilitation specialist, orthopeadic surgeon). Podiatr. = podiatrist. Orth. technician = orthopeadic shoe technician. Orth. thechnologist = orthopeadic shoe technologist. Med. pedi = medical pedicurist. ^Treatment by the medical pedicure under supervision of the medical specialist / podiatrist.

PART 1



CHAPTER 3

The effectiveness of therapeutic shoes in patients with rheumatoid arthritis: a systematic review and meta-analysis

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Abstract

The study summarizes the evidence on the effectiveness of therapeutic shoes on foot function, foot pain, physical functioning, health-related quality of life, adherence, adverse events and patient satisfaction in patients with rheumatoid arthritis (RA). Studies investigating the effect of (ready- or custom-made) therapeutic shoes were included. For between-group designs, studies comparing therapeutic shoes versus non-therapeutic shoes were included. A literature search was conducted in The Cochrane Central Registry for Controlled Trials (CENTRAL), PubMed, EMBASE and PEDro up to January 19, 2017. Quantitative data analysis was conducted; when this was not possible qualitative data analysis was performed. Eleven studies were identified. For custom-made shoes, no studies reporting between-group differences were available. Qualitative data-syntheses of the within-group differences resulted in weak evidence for the reduction of foot pain and improvement of physical functioning. For ready-made shoes, one study reported between-group differences, resulting in inconclusive evidence for improvement of foot function. Quantitative data-analyses of within-group differences resulted in a medium to large effect for the reduction of foot pain (SMD 0.60, 95% CI 0.28–0.92; $P \leq 0.001$; 184 participants) and a small to medium effect for the improvement of physical functioning (SMD 0.30, 95% CI 0.04–0.56; $P = 0.02$; 150 participants). Qualitative data-synthesis of within-group differences resulted in weak evidence for improvement of foot function. Within-group results indicate that therapeutic shoes are likely to be effective in patients with RA. Definitive high-quality RCTs are necessary to investigate the between-group effectiveness of therapeutic shoes in patients with RA.

Background

Foot problems are highly frequent in patients with rheumatoid arthritis (RA) [1-4]. Synovitis of foot joints can lead to joint damage and deformity and subsequently to pain, disability and inability of wearing over-the-counter shoes [5, 6]. The primary approach in the management of RA is systemic pharmacological treatment. An additional locally administered (surgical or conservative) treatment could be required, for example therapeutic shoes [7, 8]. Therapeutic shoes include custom-made and ready-made shoes. Custom-made shoes are developed for the individual patient based on specific measures and specifications, whereby a variety of technical adaptations can be incorporated [9, 10]. Ready-made shoes are serial-produced shoes with extra depth, support, incorporated inlays or technical adaptations [9, 10].

Therapeutic shoes are recommended in guidelines for the treatment of foot problems in patients with RA [11-13]. Especially in patients with established RA and foot deformities or erosions in foot joints, therapeutic shoes are commonly prescribed and frequently used [14, 15]. Two systematic reviews reported evidence that extra-depth therapeutic shoes (with or without foot orthoses) are effective in reducing pain during weight-bearing activities in patients with RA [7, 8]. One systematic review showed positive effects of custom-made foot orthoses on foot pain and plantar pressure distribution in RA [16]. The findings of the reviews on therapeutic shoes (published in 2001 and 2005) were based on a limited number of studies, older than 10 years, while more recent studies are published [7, 8]. Furthermore, the included studies did not cover the whole range of therapeutic shoes available, and no quantitative data-syntheses were conducted [7, 8]. Therefore, the aim of the present review was to systematically summarize the literature (up to January 2017) on the evidence on (i) the effectiveness of therapeutic shoes on the primary outcomes foot function (gait characteristics or plantar foot pressure), foot pain, physical functioning and health-related quality of life (HRQoL), and on (ii) the secondary outcomes compliance (adherence), adverse events and patient satisfaction in patients with RA who received therapeutic shoes.

Methods

Protocol and registration

A detailed protocol for the present study has been previously published in PROSPERO (Prospero Record Registration No.: CRD42016047225). The manuscript was written in accordance with the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) statement [17].

Eligibility criteria

Types of studies

Randomized controlled trials (RCT), randomized controlled cross-over trials, (quasi-experimental) clinical trials, prospective- and retrospective uncontrolled studies were included. Only full-text original research reports, published in English, German, French, or Dutch were included. No restrictions concerning the year of publication were used.

Types of participants

The study population comprised adult patients diagnosed with RA, or a defined subgroup of RA patients existed in the study population for whom data were presented separately.

Type of intervention and comparisons

Patients received therapeutic custom-made or ready-made shoes for the treatment of RA related foot problems. For between-group designs, studies comparing therapeutic shoes *versus* non-therapeutic shoes (the patient's own shoes or standardized conventional shoes) were included.

Type of outcomes

Studies were eligible if foot function (pressure or gait parameters), foot pain, physical functioning (performance-based or self-reported), health related quality of life (HRQoL), participant satisfaction, adverse events or adherence were assessed. If the study provided data from more than one measurement instrument, data were analyzed that were highest in hierarchy based on the psychometric properties of the instruments used [18]. The following hierarchies (highest to lowest within the categories i-iv) were used: (i) foot function: *plantar pressure measurement, gait analyses, (ii)* foot pain: *Foot Function Index subscale pain (FFI pain), Visual Analogue Scale for foot pain during walking (VAS foot pain), other instrument, (iii)* physical functioning: *Foot Function Index subscale disability (FFI disability), timed walking test, other instrument,* and (iv) HRQoL: *Foot Health Status Questionnaire subscale general health (FHSQ general health), Visual Analogue Scale for general well-being (VAS general well-being), other instrument.*

Information sources, search and study selection

The following electronic databases were searched from inception to January 19, 2017: the Cochrane Central Registry for Controlled Trials (CENTRAL), PubMed, EMBASE and PEDro. A two-way search strategy was employed using "rheumatoid arthritis" with "shoes" and related synonyms. The following database search strategy for PubMed was used: (("Arthritis, Rheumatoid"[Mesh] OR rheumatoid arthritis [tiab])) AND ("Shoes"[Mesh] OR shoe* [tiab] OR footwear* [tiab]). Each database was searched independently by two researchers (MTD and MvdL). In addition, references lists of all selected publications were checked to retrieve relevant publications which have not been found with the computerized search.

Titles or abstracts were first screened independently by two reviewers (MTD and MvdL). For each selected study, the full article was retrieved. Next, the two reviewers independently performed final selection of studies to be included in the review based on the eligibility criteria. Disagreements on inclusion were resolved by discussion between the two reviewers.

Data collection process, data items and summary measures

Data were extracted by one reviewer (MTD) using a standardized template, and verified by a second reviewer (MvdL). Information was extracted from each included study on: authors, year of publication, study design, participant description (number of participants, setting, diagnosis, age and clinical characteristics), description of intervention, longest point of follow-up, outcome measures and -if applicable- mean and standard deviations for baseline, follow-up and change scores in the outcomes, or percentages of change in the outcomes. Means were estimated from graphs, when no numerical data were supplied [19]. Disagreements or discrepancies on data extraction were resolved by discussion.

Methodological quality of individual studies

The methodological quality of RCTs for between group comparisons was assessed with the Physiotherapy Evidence Database (PEDro) scale [20]. The PEDro scale has been shown to be a valid, reliable and frequently used tool [21-23]. It consists of 11 items to measure the quality of each included trial. Eight items (item 2-9) are used to assess internal validity and two items to assess interpretability of results (item 10-11). Item 1, assessing external validity, is excluded in calculating the total score [24]. Therefore, the score may range from 0 to 10 points. When blinding of subjects or therapists was not feasible the maximum possible score is 8, e.g. when the patient's own shoes were used as control intervention. The score obtained for each study was divided by the maximum possible score and multiplied by 100 to provide a "study quality percentage". Study quality percentages were then classified as high (60-100%), fair (40-50%), or low (≤30%) according to Teasell et al. [25].

The methodological quality for within-group comparisons in RCTs, randomized controlled cross-over trials, (quasi-experimental) clinical trials, prospective- and retrospective uncontrolled studies was assessed by using the Downs and Black checklist [26]. This checklist is recommended by the COCHRANE for quality assessment of non-controlled trials [27]. The checklist consists of 27 items which assess the strength of reporting, external validity, internal validity and statistical power. As recommended in the literature, the power subscale (question 27) was not used in this study due to item ambiguity [28]. Moreover, the five questions (5, 14, 23, 24 and 25) specific for between-group comparison were excluded. Therefore, a 21-item scale was used with a score ranging from 0 to 21 points. The score obtained for each study was divided by the maximum possible score and multiplied by 100 to provide a "study quality percentage". Study quality percentages were then classified as low (< 50.0%), fair (≥ 50.0 and < 66.6%) and high (≥ 66.7%)[29].

Quality assessments were independently evaluated by two reviewers (MTD and MvdL). Disagreements were resolved by discussion and, if necessary, by consultation of the third reviewer (JD).

Data synthesis

Data synthesis was conducted for the effect of therapeutic shoes on foot function, foot

pain, physical functioning, HRQoL, participant satisfaction, adverse events or adherence. A distinction was made between (i) ready-made and custom-made therapeutic shoes, and (ii) within-group and between-group comparisons.

Quantitative data analysis (meta-analysis) was conducted for outcome measures that had pre- and post-test scores available. Sensitivity meta-analyses (fair- and high- quality studies versus low-, fair- and high- quality studies) were conducted in case of a sufficient number of studies. Pooling of effect sizes across studies was performed using the standardized mean difference (SMD) and 95% confidence intervals (CI) in a random effects model [30]. SMDs were interpreted as 0.2 (small), 0.5 (medium) and 0.8 (large) [31]. The results are presented in forest plots for each comparison. Meta-analyses were conducted in Review Manager (RevMan 5.3) computer software. Heterogeneity was tested using the eye ball test (forest plot) and by calculating I^2. The level of heterogeneity was categorized as low (<25%), moderate (>25% and <75%) and high (>75%) [32]. Results of meta-analyses with a high level of heterogeneity across studies were interpreted with caution.

When quantitative data analysis was not possible a qualitative data analysis (best-evidence synthesis) was conducted for outcome measures that had pre- and post-test scores available. The data were summarized by assigning five levels of evidence (strong, moderate, weak, inconclusive and inconsistent) according to criteria adapted from Ariëns et al. (***Table 1***) [33].

Results

Study selection

The literature search resulted in a total number of 505 hits. After duplicate removal, 288 hits were screened on title or abstract. This resulted in 16 full-text articles that were studied for eligibility, of which 11 articles were included in the systematic review ***(Figure 1)***. A post hoc search for ongoing clinical trials was conducted in the trial registers of the U.S. National Library of Medicine and the World Health Organization, as suggested by peer reviewers. No relevant ongoing trials were identified.

Characteristics of included studies

The included studies consisted of three randomized controlled trials [34-36], two randomized controlled cross-over trials [37,38], four prospective uncontrolled studies [9,39-41], and two retrospective uncontrolled studies [42, 43]. Two studies comprised a between-group design comparing ready-made therapeutic shoes with non-therapeutic shoes [35, 38] of which one study reported between-group differences [38]. A detailed description of the included studies is presented in ***Table 2***.

Table 1. Strength of evidence criteria [33]

Strong	At least 2 high-quality studies with consistent findings
Moderate	1 high-quality study and at least 2 low-quality studies with consistent findings
Weak	At least 2 low-quality studies with consistent findings
Inconclusive	Insufficient or conflicting studies
Inconsistent	Agreement of findings in <75% of studies

Methodological quality of included individual studies

Initial overall agreement on methodological quality scores for between-group comparisons was 100% and for within-group comparisons 94%. No consultation of the third reviewer was necessary to resolve disagreement. Two studies with a between-group design (ready-made therapeutic shoes *versus* non-therapeutic shoes) were included, of which one was considered to be of high quality [38], and one of fair quality [35]. Ten studies reported within-group differences after wearing custom-made therapeutic shoes [9, 42, 43] or ready-made therapeutic shoes [34-37, 39-42]. Two studies were considered to be of high quality [9, 37], and three of low quality [41-43]. Methodological quality for between-group differences is presented in ***Table 3*** and for within-group differences is presented in ***Table 4***.

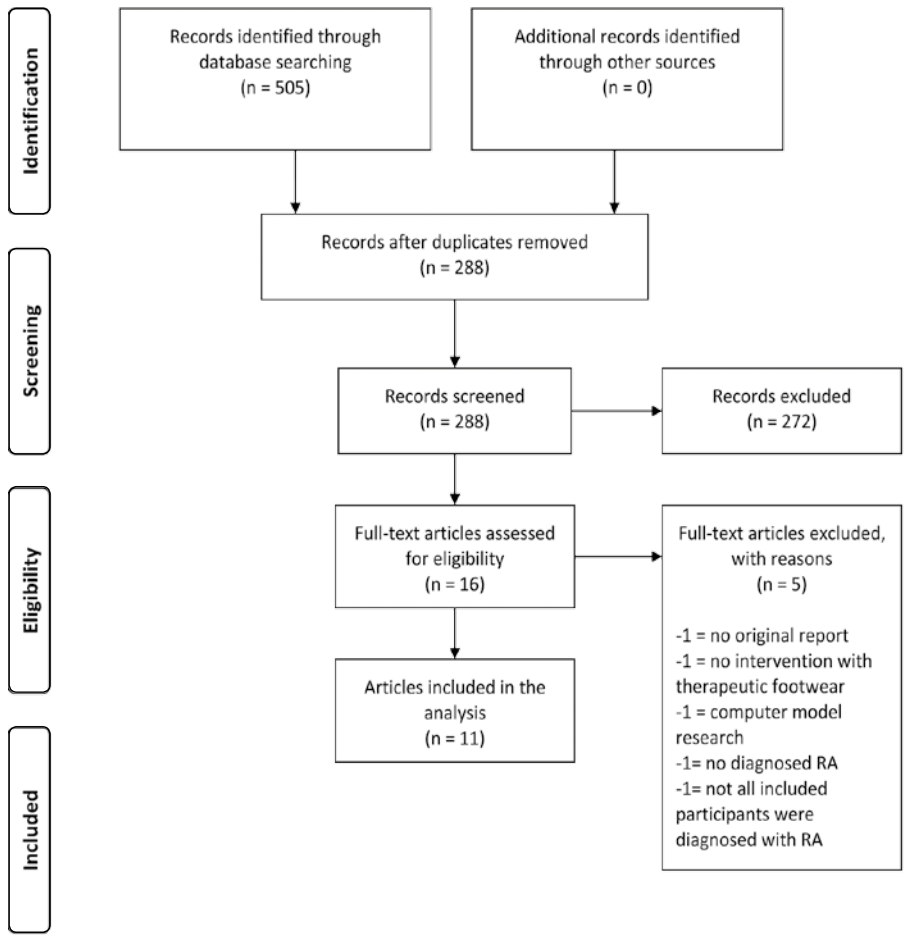


Figure 1. PRISMA flow diagram

Table 2. Characteristics of included studies

Author (year)	Study design	Participant description	Intervention	Time	Outcome
Dahmen et al. 2014 (9)	prospective uncontrolled study	- N=114 - outpatient clinic - definite diagnosis of RA - median age 60 (IQR 48-67) - prescription of custom-made therapeutic footwear for the first time	*Custom-made therapeutic shoes:* - hand-made therapeutic shoes for the individual patient	26 weeks	WOMAC *(primary outcome)* VAS pain Likert scale for joint pain HAQ wearing quotient (actual/maximum wearing duration) *(primary outcome)* actual wearing duration (hours per day)
Park et al. 1981 (43)	retrospective uncontrolled study	- N=71 - RA - Mean age 58.3 (range 38-75) - foot problems (metatarsalgia, bunions, etc.)	*Custom-made therapeutic shoes:* - individually made surgical shoes	-	relief of symptoms^ adherence^ reasons for dissatisfaction with footwear^ footwear acceptability^
Pullar et al. 1983 (42)	retrospective uncontrolled study	- N=39 - RA - age range 29-78 - prescription for special footwear	*Custom-made therapeutic shoes:* - individually made surgical shoes Ready-made therapeutic shoes: - shoes made to more general specifications (comfort shoes)	-	adherence^ adverse events^ satisfaction^
Chalmers et al. 2000 (37)	randomized controlled cross-over trial	- N=28 - occupational therapy department of hospital - definitive diagnosis of RA - age women: mean 60 (SD 10) - age men: mean 63 (SD 2) - subluxed MTP joints - bilaterally MTP joint pain	*Ready-made therapeutic shoes:* - extra-depth supportive shoes with semi-rigid orthoses - extra-depth supportive shoes with soft orthoses - extra-depth supportive shoes with original insoles	12 weeks for each intervention, separated by 2 week washouts	50 foot walking time, s* VAS pain *(primary outcome)* RB* TADL VAS treatment effectiveness treatment preference questionnaire
Cho et al. 2008 (34)	randomized controlled trial	- N=42 (22 intervention-group, 20 control-group) - university hospital - definitive diagnosis of RA - stable disease activity - mean age 48.7 (SD 11.7) - foot pathology	*Ready-made therapeutic shoes:* - forefoot-rockered extra depth shoes with a wide toebox with custom made insoles consisting of a medial longitudinal arch support, medial heel post and metatarsal pad. - forefoot-rockered extra depth shoes with a wide toebox with ready-made soft simple insoles	6 months	VAS pain *(primary outcome)* FFI *(primary outcome)*
Fransen et al. 1997 (35)	randomized controlled trial	- N=30 (15 intervention-group, 15 control-group) - public hospital - RA - stabilized arthritis medication - mean age intervention-group: 59.1 (SD 14.2) - mean age control-group: 60.1 (SD 8.9) - foot pain	*Ready-made therapeutic shoes:* - extra depth shoes with long inside counter, pillow back foam-padded collar, soft leather upper with removable cushion inlay *Non-therapeutic shoes:* - the patient's own shoes	2 months	8-meter electric footswitch walkway (velocity, cadence, stride)* pain free walking time in minutes^ VAS pain during walking VAS pain during ascending/descending stairs VAS general fatigue VAS general well-being HAQ

2. Continued

r (year)	Study design	Participant description	Intervention	Time	Outcome
ssy et al. 38)	randomized, single blind, cross-over trial	- N=20 - community sample of patients recruited - definite diagnosis of RA - stable RA - mean age 59.9 (SD 11.0) - forefoot pain	*Ready-made therapeutic shoes:* - off-the shelf orthopaedic footwear: Canfield Leisure and Leisure for women and men (P.W. Minor and Son, Batavia, New York, USA) *Non-therapeutic shoes:* - standardized conventional (control) shoes: Dunlop Volley (Pacific Dunlop Ltd., Melbourne, Australia) worn without the sockliner - running footwear: Brooks Glycerin 3 (Texas Peak Pty Ltd., Melbourne, Australia), commercially available 'premium' cushioned	-	in-shoe plantar foot pressure (peak pressure, pressure-time integral) *(primary outcome)* VAS perception of footwear comfort nomination of the most acceptable footwear^
ms et al. 36)	randomized controlled trial	- N=80 (40 traditional design-group, 40 new design-group) - four local rheumatology clinics - definite diagnosis of RA - foot deformity and pain - difficulty in obtaining retail footwear	*Ready-made therapeutic shoes:* - traditional design ready-made therapeutic shoes (current footwear developed by clinicians to meet the clinician's perceptions of patient's needs, with flat insole) - new design ready-made therapeutic shoes (incorporation of several features that were identified by the patient as being their preferred features of footwear, with firm contoured insole)	12 weeks	FFI *(primary outcome)* FHSQ (primary outcome)
t et al. 1976	prospective uncontrolled study	- N=25 - hospital - stable RA - forefoot deformities and callosities - high functional level	*Ready-made therapeutic shoes:* - experimental and individually adapted sandal with adequate width and length, a forgiving innersole with a short heel, and sole lever arms.	6 months	Harris mat footprint test (plantar pressure assessment) Brand slipper sock test (plantar pressure assessment) Likert scale for foot pain
rzadeh et al. 2013	prospective uncontrolled study	- N=18 - definite diagnosis of RA, with non-active disease - mean age 47.16 (SD 8.1) - foot and ankle pain	*Ready-made therapeutic shoes:* - high-top shoes extended above the lateral malleoli, wide toe box and velcro closures adapted with a custom made heel-to-toe rocker sole	30 days	FFI
r et al. 1990	prospective uncontrolled study	- N=25 - outpatient clinic - definite diagnosis of RA - mean age 57 (range 35-74) - forefoot pain and deformity - difficulty in obtaining retail footwear	*Ready-made therapeutic shoes:* - light weight heath-mouldable shoes with extra depth and extra forefoot width	≥3 months	NRS walking ability NRS comfort

visual analogue scale. RB = Robinson Bashall Functional Assessment. TADL = Toronto Activities of Daily Living Measure. FFI = foot function index. WOMAC = Western ontario and McMasters universities osteoarthritis Index. HAQ = Health Assessment Questionnaire. numeric rating scale. FHSQ = Foot Health Status Questionnaire. ^= interview-based. *= performance-based. Age mean (SD).

Table 3. Methodological quality for between-group designs of RCTs as evaluated using the PEDro checklist

Reference	External validity (0-1)	Internal validity (0-10)										Total score	Quality
	1	2	3	4	5	6	7	8	9	10	11		
Fransen et al. 1997 (35)*	1	1	0	1	na	na	0	7	8	9	10	4/8 (50%)	Fair
Hennessy et al. 2007 (38)*	1	1	1	1	1	0	0	7	8	9	10	8/10 (80%)	High

* = ready-made therapeutic shoes. High quality = study quality percentage 60-100%. Fair quality = study quality percentage 40-50%. *Low quality = study quality percentage <40%. na = not applicable.*

Table 4. Methodological quality of within-group differences as evaluated using the Downs & Black checklist

Reference	Reporting (0-11)											External validity (0-3)			Internal validity: bias (0-7)							Internal validity: Confounding (0-6)			Total score	Quality
	1	2	3	4	6	7	8	9	10	11	12	13	15	16	17	18	19	20	21	22	26		
Dahmen et al. (9)*	1	1	1	1	1	1	1	1	1	0	1	0	0	1	1	1	1	1	1	1	1	18/21 (86%)	High
Park et al. (43)*	1	0	0	1	1	0	1	0	0	0	0	0	0	1	0	0	0	0	0	0	0	5/21 (24%)	Low
Pullar et al. (42)**	1	0	1	1	1	1	1	0	0	0	0	0	0	1	0	0	0	0	1	1	0	9/21 (43%)	Low
Chalmers et al. (37)	1	1	1	1	1	1	1	1	1	0	0	0	1	1	1	1	1	1	1	1	1	18/21 (86%)	High
Bagherzadeh Cham et al. (39)*	1	1	1	1	1	1	0	1	1	0	0	0	0	1	1	1	0	1	0	1	1	13/21 (62%)	Fair
Cho et al. (34)*	1	1	1	1	1	1	0	0	1	0	0	0	0	0	1	1	0	1	1	1	0	12/21 (57%)	Fair
Fransen et al. (35)*	1	1	1	1	1	1	0	0	1	0	0	0	0	0	1	0	0	1	1	1	1	12/21 (57%)	Fair
Moncur et al. (40)*	1	1	0	1	1	0	1	1	1	0	0	0	0	1	0	1	1	1	1	0	1	13/21 (62%)	Fair
Williams et al. (36)*	1	1	1	1	1	1	1	0	1	0	0	1	1	1	1	1	0	1	0	0	0	13/21 (62%)	Fair
Barrett et al. (41)*	1	1	0	1	1	0	0	1	0	0	0	0	0	1	0	0	0	0	1	0	1	8/21 (38%)	Low

* = custom-made therapeutic shoes. * = ready-made therapeutic shoes. High quality = study quality percentage ≥66.7%. Fair quality = study quality percentage ≥50.066.6%. Low quality = study quality percentage <50.0%. na = not applicable.

Custom-made therapeutic shoes: between-group effects

For custom-made shoes no data-synthesis was performed due to a lack of studies investigating the between-group effects.

Custom-made therapeutic shoes: within-group effects

For custom-made therapeutic shoes qualitative syntheses of within-group results and an overview of evidence is presented in ***Appendix 1***.

Foot pain

Qualitative data-synthesis resulted in weak evidence for the effect of custom-made therapeutic shoes on foot pain in a within-group comparison. Reduction of foot pain was found in one high quality study [9] and one low quality study [43]. In the high quality study a significant foot pain reduction of 10% was found, after wearing custom-made therapeutic shoes [9].

Physical functioning

Qualitative data-synthesis resulted in weak evidence for the effect of custom-made therapeutic shoes on physical functioning in a within-group comparison. Improvement in physical functioning was found in one high quality study [9] and one low quality study [43]. In the high quality study a significant 9% improvement in self-reported physical functioning was found, after wearing custom-made therapeutic shoes [9].

Secondary outcomes

Adherence was investigated in three studies: one of high [9] and two of low quality [42, 43]. A mean wearing quotient of 54% (SD 25.0) and a mean wearing time of 7.7 (SD 3.8) hours a day was reported in one study of high quality [9]. Adverse events and patient satisfaction were reported in two studies of low quality [42, 43]. A detailed description is presented in ***Appendix 1***.

Ready-made therapeutic shoes: between-group effects

For ready-made therapeutic shoes qualitative synthesis of between-group results and an overview of evidence is presented in ***Appendix 2***. Only one included RCT reported between-group differences for the comparison of (ready-made) therapeutic shoes *versus* non-therapeutic shoes (standardized conventional shoes).

Foot function

Qualitative data-syntheses resulted in inconclusive evidence for the effect of ready-made therapeutic shoes on foot function in a between-group comparison. One high quality randomized, single blind, cross-over trial was included in this analysis [38]. In this study a comparison was made between ready-made therapeutic shoes and standardised conventional (control) shoes. A significant reduction of in-shoe plantar peak pressure (kPa) and in-shoe pressure-time integral (kPa s) in regions of interest was found favoring patients wearing ready-made therapeutic shoes compared to those wearing control shoes [38].

Secondary outcomes

Qualitative data-syntheses resulted in inconclusive evidence for the effect of ready-made therapeutic shoes on patient satisfaction in a between-group comparison. Patient satisfaction was investigated in one high quality [38] randomized controlled cross-over trial. A significant higher patient satisfaction was found in patients who received ready-made therapeutic shoes compared to patients who received standardised conventional (control) shoes.

Ready-made therapeutic shoes: within-group effects

For ready-made therapeutic shoes an overview of within-group results is presented in ***Appendix 3***.

Figure 2. Forest plot of data pooling for the within-group differences of (a) foot pain, (b) physical functioning, and (c) health related quality of life, after wearing ready-made therapeutic shoes.

Figure 2a. forest plot for within group differences of foot pain after wearing ready-made therapeutic shoes

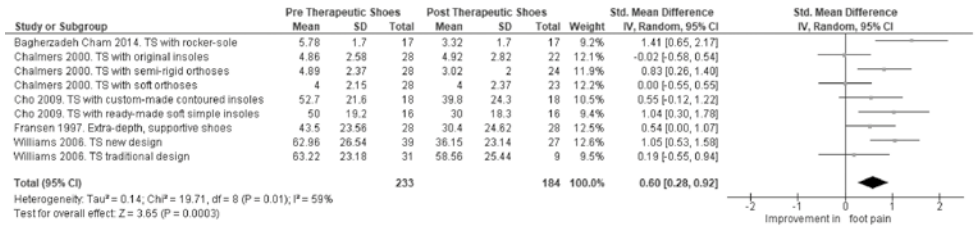


Figure 2b. forest plot for within group differences of physical functioning (self-reported and performance-based) after wearing ready-made therapeutic shoes

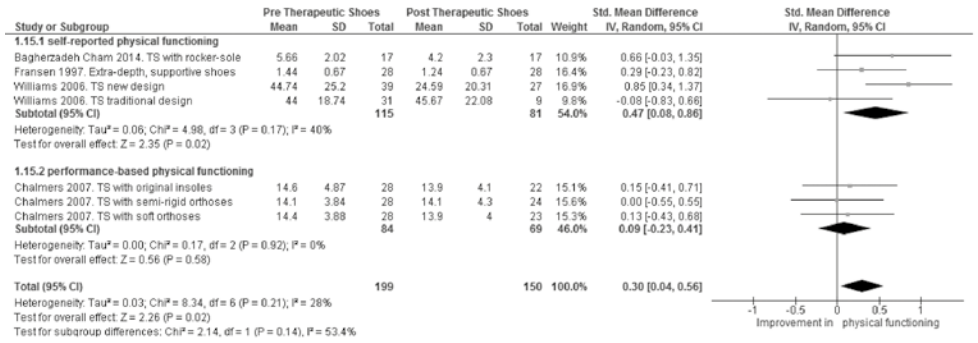
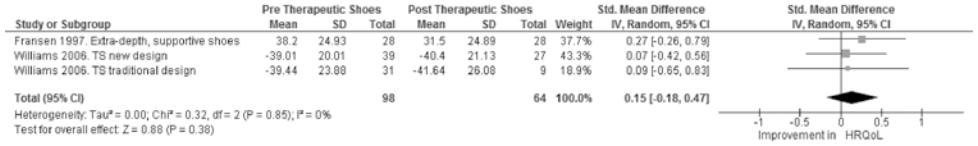


Figure 2c. forest plot for within group differences of health related quality of life after wearing ready-made therapeutic shoes



Foot function

Qualitative data-synthesis resulted in weak evidence for the effect of ready-made therapeutic shoes on foot function in a within-group comparison. Improvement of gait characteristics (gait velocity, cadence and stride length) were found in one fair quality study [35]. Reduction of plantar pressure in high pressure areas was found in one low quality study [43].

Foot pain

The effect of ready-made therapeutic shoes on foot pain was investigated in a within-group comparison in six studies: three RCT's [34-36], one randomized controlled cross-over trial [37], and two prospective uncontrolled studies [39, 41]. The within-group differences reported in five out of six studies were included in a meta-analysis to pool the final pain scores [34-37, 39]. Pooled scores showed a medium to large, statistically significant, effect for the reduction of foot pain after wearing ready-made therapeutic shoes (SMD 0.60, 95% CI 0.28 to 0.92; P≤0.001; 184 participants; ***Figure 2a***). Statistical heterogeneity was moderate (Heterogeneity: Chi^2=19.71, df=8 (P=0.01); I^2=59%).

Physical functioning

The effect of ready-made therapeutic shoes on physical functioning was investigated in a within-group comparison in five studies: two RCT's [35, 36], one randomized controlled cross-over trial [37] and two prospective uncontrolled study's [39, 40]. The within-group differences reported in four out of five studies were included in a meta-analysis to pool the final physical functioning scores [35-37, 39]. Pooled scores showed a small to medium, statistically significant, effect for the improvement of physical functioning after wearing ready-made therapeutic shoes (SMD 0.30, 95% CI 0.04 to 0.56; P=0.02; 150 participants; ***Figure 2b***). Statistical heterogeneity was moderate (Heterogeneity: Chi^2=8.34, df=6 (P=0.21); I^2=28%). Additional sensitivity analysis showed a medium, statistically significant, effect for the improvement on self-reported physical functioning after wearing ready-made therapeutic shoes (SMD 0.47, 95% CI 0.08 to 0.86; P=0.02; 81 participants; ***Figure 2b***), but no effect on performance-based physical functioning was found (SMD 0.09, 95% CI -0.23 to 0.41; P=0.92; 69 participants; ***Figure 2b***).

Health related quality of life

The effect of ready-made therapeutic shoes on HRQoL was investigated in a within-group comparison in two RCT's [35, 36]. The within-group differences reported in the RCT's were included in a meta-analysis to pool the final HRQoL scores [35, 36]. Pooled scores showed a non-significant effect for the improvement of HRQoL after wearing ready-made therapeutic shoes (SMD 0.15, 95% CI -0.18 to 0.47; P=0.38; 64 participants; ***Figure 2c***). Despite the clinical heterogeneity of HRQoL measures, statistical heterogeneity was absent (Heterogeneity: Chi^2=0.32, df=2 (P=0.85); I^2=0%).

Secondary outcomes

Adherence was investigated in three studies (one of high quality [37], one of fair quality [40] and one of low quality [42]). In the high quality study a mean wearing time of 6.2 (SD 2.3) and 5.9

(SD 2.4) hours a day was reported for two types of ready-made therapeutic shoes [37]. The fair quality study reported that the ready-made therapeutic shoes were worn all day in 80% of the patients [40].

Adverse events were investigated in three studies (two of fair quality [36, 40] and one of low quality [42]). In these fair quality studies the most common adverse events were "heels slipped out of the shoes" in 5% of the patients [36] and "the shoes are hot to wear" in 5% [36] and 12% [40] of the patients.

Patient satisfaction was investigated in two studies (one of fair quality [40] and one of low quality [42]). In the fair quality study a significant improvement of 4.4 points on a Numeric Rating Scale for comfort was found after wearing ready-made therapeutic shoes [40].

Discussion

The objective of the present study was to investigate whether therapeutic shoes reduce pain and improve foot function, physical function and HRQoL in patients with RA. Furthermore, the secondary outcomes adherence, adverse events and patient satisfaction after wearing therapeutic shoes in patients with RA were investigated. For custom-made therapeutic shoes, no studies were available investigating the effect in a between-group design (therapeutic shoes *versus* non-therapeutic shoes). In within-group designs, weak evidence was found for the reduction of foot pain and improvement of self-reported physical functioning. For ready-made therapeutic shoes, improvement in foot function (reduction of plantar pressure) was inconclusive, based on one controlled, between-group design [38]. In within-group designs, (i) weak evidence was found for the improvement of foot function, (ii) a medium to large effect was found for the reduction of foot pain and (iii) a small to medium effect was found for improvement of physical function.

Compared to the previously published systematic reviews on therapeutic shoes [7, 8], five additional studies were included in the present systematic review (two RCT's [34, 36], one randomized controlled cross-over trial [38], and two prospective non-controlled studies [9, 39]). The results of the present review confirmed the finding by Egan et al. [7] and Farrow et al. [8] that therapeutic shoes are likely to be beneficial in reducing foot pain in patients with RA (based on within-group effects). Additionally, our review showed evidence for the improvement of physical functioning after wearing custom-made and ready-made therapeutic shoes. Finally, in the present study the within-group differences of foot function, foot pain, physical functioning and HRQoL after wearing ready-made therapeutic shoes were quantified.

Overall, few high quality studies with relatively small sample sizes were included in the present review. Due to a limited number of studies, there was inconclusive evidence from between-group comparisons that therapeutic shoes are more effective than non-therapeutic shoes. Only one included study (n=20) compared (ready-made) therapeutic shoes with the control intervention (non-therapeutic shoes; standardized conventional shoes) [38]. Furthermore, within this study running shoes were compared with the control intervention [38]. The results of this study showed a significant better perceived comfort and significant

plantar pressure reduction for the therapeutic- and running shoe-conditions compared to the control-condition. However, more plantar pressure reduction was found during wearing the running shoes than during wearing the therapeutic shoes. Another study (n=30) investigated the effect of (ready-made) therapeutic shoes compared to non-therapeutic shoes (the patient's own shoes) [35]. However, no between-group results were reported in this study [35]. The results of this study showed an improvement (with small to large effect sizes) in the therapeutic shoes-group in weight-bearing pain scores, physical function, gait velocity and gait stride length [35]. In contrast, no significant changes in pain, physical functioning or gait scores in the non-therapeutic shoes-group were found [35]. For quantification of between-group differences of therapeutic shoes on foot function, foot pain, physical functioning and HRQoL additional research is necessary. In future research it is recommended to conduct definitive, high-quality RCTs with adequate sample sizes to investigate the effect of (i) custom-made therapeutic shoes *versus* control shoes or the patient's own shoes, (ii) ready-made therapeutic shoes *versus* control shoes or the patient's own shoes, and (iii) custom-made therapeutic shoes *versus* ready-made therapeutic shoes. Recruitment of patients with an indication for therapeutic shoes should be considered, whereby patients on a waiting list for therapeutic shoes could serve as a control group. Furthermore, conducting a randomized controlled cross-over trial with washout-periods between interventions can be considered [37]. Whether such an RCT should be conducted in a national or international context should also be taken into consideration. Across countries there are significant differences in prescribing, designing and producing therapeutic shoes, as well as financial compensation from health care insurances.

Adherence was reported in six out of thirteen included studies, showing variable wearing-duration across studies. Adherence is an important factor for the effectiveness of therapeutic shoes [44]. Assessment of adherence can be based on observational measurements or on self-report, for example by using patient diaries or the Monitor-Orthopedic-Shoes questionnaire [9, 45]. Preferably an objective measurement instrument is used, for example a temperature-based adherence-to-treatment monitor which can be incorporated in the therapeutic shoes [46]. Low adherence of therapeutic shoes is a well-known problem [47]. Strategies to improve adherence target the usability (effectiveness, efficiency and satisfaction) and acceptance of therapeutic shoes by the patient [45, 48]. Usability and acceptance can be influenced by involving the patient in the designing and monitoring process of the therapeutic shoes to meet both clinical needs of the patient and personal needs related to body image [36]. Good communication between prescribing clinicians and the individual patients is of great importance [48]. Using specific communication techniques for improved acceptance and adherence of therapeutic shoes can be considered [49].

The systematic review highlights some areas for further research. Foot function was understudied, only three studies report on this outcome domain [35, 38, 41], and in the oldest study non-digital measurements were used [41]. Nowadays, digital walkway systems and plantar pressure measurements (especially in-shoe plantar pressure measurements) would be more applicable [46, 50]. Another area for further research is the responsiveness of measurement instruments. For most of the measurement instruments in the included studies, the ability to detect change over time in the construct to be measured is unknown [18]. Furthermore,

different shoe characteristics of therapeutic shoes were investigated in the included studies (e.g. different types of incorporated foot orthoses and technical adaptations and the use of different materials). In the present review we made a distinction between custom-made and ready-made therapeutic shoes. However, also within these types of therapeutic shoes the shoe characteristics varied. It is therefore not possible to draw conclusions from our review regarding the effect of specific shoe characteristics on foot-related outcomes. This implies that defining indications for specific shoe characteristics could be topics for future research. Also, further investigation on summarizing the effect of studies comparing different orthoses can be recommended [34, 36, 37]. This was not within the focus of the present study.

The present study has some limitations. A possible limitation is that we included only published full-text articles. It may be that not all studies carried out have actually been published. Therefore publication bias cannot be ruled out. Another limitation could be the method used for assessing the methodological quality of within-group comparisons. Due to the absence of a checklist specific for within-group designs, a checklist (Downs and Black) developed for assessing randomized and non-randomized trails was used. The items specific for between-group designs were omitted.

Conclusions

Within-group results indicate that therapeutic shoes are likely to be effective in patients with RA. Definitive, high-quality RCTs with adequate sample sizes are necessary to investigate the between-group effectiveness of therapeutic shoes in patients with RA.

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Appendices

Appendix 1. Qualitative synthesis of within-group results and overview of evidence for custom-made therapeutic shoes

Author, year (ref.)	Intervention	Outcome	Results pre-TS median (IQR)	post-TS median (IQR)	p-value	Level of evidence
Foot pain						**Weak** *Consistent findings (reduction of foot pain) in one high quality study (9) and one low quality study (43)*
Dahmen et al, 2014 (9)	hand-made therapeutic shoes for the individual patient	VAS pain during walking (0-100)	68 (49-85)	48 (22-67)	<0.001	
		VAS pain at rest (0-100)	26 (10-51)	24 (8-49)	0.18	
		VAS pain during standing (0-100)	46 (27-72)	36 (18-57)	<0.001	
		WOMAC pain (0-100)	40 (30-60)	30 (15-45)	<0.001	
Park et al, 1981 (43)	individually made surgical shoes	63% relieve, 6% no relieve and 31% reduction of symptoms (metatarsalgia)				
Physical functioning						**Weak** *Consistent findings (improvement in physical functioning) in one high quality study (9) and one low quality study (43)*
Dahmen et al, 2014 (9)	hand-made therapeutic shoes for the individual patient	WOMAC physical functioning (0-100)	38 (24-59)	29 (16-46)	<0.001	
		WOMAC stiffness (0-100)	50 (25-63)	38 (25-50)	<0.001	
		HAQ total (0-3)	1.13 (0.75-1.63)	1.00 (0.63-1.47)	0.003	
		HAQ walking (0-3)	1.00 (0.00-2.00)	1.00 (0.00-1.00)	<0.001	
Park et al, 1981 (43)	individually made surgical shoes	63% relieve, 6% unrelieve and 31 reduction of symptoms (walking ability)				
Adherence						**Not applicable**
Dahmen et al, 2014 (9)	hand-made therapeutic shoes for the individual patient	Wearing quotient, % (SD)	54 (25)			
		Mean wearing time, h (SD)	7.7 (3.8)			
		VAS wear-and-tear (SD) (0-100)	40 (19)			
		69% worn (almost) continuously, 14% worn only on special occasions, 17% worn rarely or never				
Pullar et al, 1983 (42)	individually made surgical shoes	33% worn all day, 37% worn ≥0.5 day, 30% worn <0.5 day				
Park et al, 1981 (43)	individually made surgical shoes	52% worn all day, 35% worn part of the day, 10% worn occasionally, 3% never worn				
Adverse events						**Not applicable**
Pullar et al, 1983 (42)	individually made surgical shoes	15% with reasons “poor fit”, “hard leather”, “high ankles”				
Park et al, 1981 (43)	individually made surgical shoes	36% “difficult to break in”, 23% “weight”, 35% “fit and comfort”				
Patient satisfaction						**Not applicable**
Pullar et al, 1983 (42)	individually made surgical shoes	78% satisfied, 7% unsatisfied, 15% neither				
Park et al, 1981 (43)	individually made surgical shoes	51% satisfied, 49% unsatisfied				

TS = therapeutic shoes. IQR = interquartile-range. VAS = visual analogue scale. WOMAC = Western ontario and McMasters universities osteoarthritis Index. HAQ = Health Assessment Questionnaire. SD = standard deviation.

Appendix 2. Qualitative synthesis of between-group results and overview of evidence for ready-made shoes

Author, year (ref.)	Intervention	Outcome	Results TS mean (SD)	non-TS mean (SD)	p-value	Level of evidence
Foot function						**Inconclusive**
Hennessy et al, 2007 (38)	ready-made therapeutic shoes: *- off-the shelf orthopaedic footwear* versus non-therapeutic shoes: *- standardized conventional (control) shoes*	In-shoe plantar peak pressure (kPa) total foot	332.6 (79.9)	409.5 (98.6)	<0.05	*Insufficient included studies investigated the effect of ready-made shoes on foot function in a between-group comparison*
		In-shoe plantar peak pressure (kPa) rearfoot	209.4 (53.1)	260.3 (70.3)	<0.05	
		In-shoe plantar peak pressure (kPa) midfoot	96.3 (37.9)	111.3 (50.6)	≥0.05	
		In-shoe plantar peak pressure (kPa) forefoot	326.0 (85.4)	404.5 (100.1)	<0.05	
		In-shoe plantar pressure-time integral (kPa s) total foot	116.8 (18.5)	143.5 (30.6)	<0.05	
		In-shoe plantar pressure-time integral (kPa s) rearfoot	62.2 (18.0)	66.2 (17.7)	≥0.05	
		In-shoe plantar pressure-time integral (kPa s) midfoot	35.5 (13.9)	36.4 (20.3)	≥0.05	
		In-shoe plantar pressure-time integral (kPa s) forefoot	83.0 (14.7)	107.3 (26.3)	<0.05	
Patient satisfaction			**TS mean (SD)**	**non-TS mean (SD)**	**p-value**	**Inconclusive**
Hennessy et al, 2007 (38)	ready-made therapeutic shoes: *off-the shelf orthopaedic footwear* versus non-therapeutic shoes: *- standardized conventional (control) shoes*	VAS perception of footwear comfort (0-150)	91.2 (40.3)	56.0 (44.4)	0.012	*Insufficient included studies investigated the effect of ready-made shoes on patient satisfaction in a between-group comparison*

TS = therapeutic shoes. non-TS = non-therapeutic shoes (conventional standardized shoes / the patient's own shoes. SD = standard deviation. VAS = visual analogue scale.

Appendix 3. Qualitative / quantitative synthesis of within-group results and overview of evidence for ready-made therapeutic shoes

Author, year (ref.)	Intervention	Outcome	Results			Level of evidence
			pre-TS mean (SD)	post-TS mean (SD)	p-value	
Foot function						**Weak** *Consistent findings (improvement of foot function) in one fair quality study (35) and one low quality study (41)*
Fransen et al, 1997 (35)	extra depth shoes with long inside counter, pillow back foam-padded collar, soft leather upper with removable cushion inlay	normal gait velocity (cm.s^{-1})*	96.5 (22.6)	101.8 (21.8)	0.0004	
		normal cadence (steps.min^{-1})*	104.1 (8.9)	105.1 (8.3)	0.35	
		normal stride length (cm)*	109.3 (22.6)	116.1 (22.6)	0.0001	
		fast gait velocity (cm.s^{-1})*	114.7 (26.3)	122.0 (26.2)	0.0012	
		fast cadence (steps.min^{-1})*	116.5 (11.4)	118.6 (10.1)	0.045	
		fast stride length (cm)*	118.2 (24.5)	124.6 (25.1)	0.0009	
Barrett et al, 1976 (41)	experimental and individually adapted sandal with adequate width and length, a forgiving innersole with a short heel, and sole lever arms.	plantar foot pressure with Harris mat footprint test	plantar pressure reduction in 80% of the high-pressure areas			
		plantar foot pressure with Brand slipper sock test	plantar pressure reduction in 91% of the high-pressure areas			
Foot pain						**Medium to large effect** *SMD 0.60 95% CI 0.28 to 0.92 P≤0.001*
Cho et al, 2009 (34)	forefoot-rockered extra depth shoes with a wide toebox with custom made insoles consisting of a medial longitudinal arch support, medial heel post and metatarsal pad	VAS foot pain (0-10)	52.7 (21.6)	39.8 (24.3)	<0.05	
Cho et al, 2009 (34)	forefoot-rockered extra depth shoes with a wide toebox with ready-made soft simple insoles	VAS foot pain (0-10)	50.0 (19.2)	30.0 (18.3)	<0.05	
Fransen et al, 1997 (35)	extra depth shoes with long inside counter, pillow back foam-padded collar, soft leather upper with removable cushion inlay	VAS foot pain during walking (0-100)	43.5 (23.56)	30.4 (24.62)	0.0002	
		VAS foot pain during stair descending/ascending	48.4 (22.46)	32.4 (24.13)	0.0001	
		VAS foot pain non-weight bearing	29.7 (27.86)	20.6 (23.97)	0.007	
		pain-free walking time (minutes)*	10.0 (14.65)	22.1 (20.49)	0.0007	
Williams et al, 2006 (36)	traditional design ready-made therapeutic shoes (current footwear developed by clinicians to meet the clinician's perceptions of patient's needs, with flat insole)	FFI pain (0-100) FHSQ foot pain (0-100)	63.22 (23.18) 44.04 (26.27)	58.56 (25.44) 39.45 (23.63)	0.13 0.37	
Williams et al, 2006 (36)	new design ready-made therapeutic shoes (incorporation of several features that were identified by the patient as being their preferred features of footwear, with firm contoured insole)	FFI pain (0-100) FHSQ foot pain (0-100)	62.96 (26.54) 39.13 (28.44)	36.15 (23.14) 65.04 (16.36)	0.00 0.00	
Chalmers et al, 2000 (37)	extra-depth supportive shoes with semi-rigid orthoses	VAS foot pain (0-10)	4.89 (2.37)	3.02 (2.00)	0.013	

Appendix 3. Qualitative / quantitative synthesis of within-group results and overview of evidence for ready-made therapeutic shoes

Author, year (ref.)	Intervention	Outcome	Results			Level of evidence
			pre-TS mean (SD)	post-TS mean (SD)	p-value	
Chalmers et al, 2000 (37)	extra-depth supportive shoes with soft orthoses	VAS foot pain (0-10)	4.00 (2.15)	4.00 (2.37)	≥0.05	
Chalmers et al, 2000 (37)	extra-depth supportive shoes with original insoles	VAS foot pain (0-10)	4.86 (2.58)	4.92 (2.82)	≥0.05	
Bagherzadeh Cham, 2014 (39)	high-top shoes extended above the lateral malleoli, wide toe box and velcro closures adapted with a custom made heel-to-toe rocker sole	FFI pain (0-10)	5.78 (1.7)	3.32 (1.7)	0.001	
Barrett et al, 1976 (41)	experimental and individually adapted sandal with adequate width and length, a forgiving innersole with a short heel, and sole lever arms.	Likert scale for foot pain (1= no pain, 5=pain with each step)	60% improved from category 5 to 2 40% improved from category 3 to 1			
Physical functioning						**Small to medium effect** *SMD 0.30 95% CI 0.04 to 0.56 P=0.02*
Fransen et al, 1997 (35)	extra depth shoes with long inside counter, pillow back foam-padded collar, soft leather upper with removable cushion inlay	VAS general fatigue (0-100)	41.2 (29.06)	35.7 (25.41)	0.20	
		HAQ disability index (0-3)	1.44 (0.67)	1.24 (0.67)	0.0001	
Williams et al, 2006 (36)	traditional design ready-made therapeutic shoes (current footwear developed by clinicians to meet the clinician's perceptions of patient's needs, with flat insole)	FFI disability (0-100)	44.00 (18.74)	45.67 (22.08)	0.51	
		FFI limitation (0-100)	6.67 (2.83)	8.56 (5.86)	0.15	
		FHSQ physical activity (0-100)	27.44 (27.41)	26.84 (30.70)	0.83	
Williams et al, 2006 (36)	new design ready-made therapeutic shoes (incorporation of several features that were identified by the patient as being their preferred features of footwear, with firm contoured insole)	FFI disability (0-100)	44.74 (25.20)	24.59 (20.31)	0.00	
		FFI limitation (0-100)	7.52 (4.23)	2.56 (2.19)	0.00	
		FHSQ physical activity (0-100)	30.99 (22.58)	36.98 (27.02)	0.02	
Chalmers et al, 2000 (37)	extra-depth supportive shoes with semi-rigid orthoses	RB walking, s*	88.2 (17.5)	86.9 (21.4)	≥0.05	
		RB stairs, s*	92.8 (8.2)	92.4 (11.3)	≥0.05	
		RB stand, s*	576.3 (77.1)	561.1 (100.5)	≥0.05	
		TADL walking	7.1 (0.90)	7.0 (1.08)	≥0.05	
		TADL stairs	5.0 (0.20)	5.0 (0.20)	≥0.05	
		50 foot walking time, s*	14.1 (3.84)	14.1 (4.3)	≥0.05	
Chalmers et al, 2000 (37)	extra-depth supportive shoes with soft orthoses	RB walking, s*	83.5 (21.0)	88.9 (19.6)	≥0.05	
		RB stairs, s*	92.0 (10.7)	91.6 (11.0)	≥0.05	
		RB stand, s*	538.7 (146.7)	570.4 (86.5)	≥0.05	
		TADL walking	7.0 (0.98)	7.0 (1.11)	≥0.05	
		TADL stairs	5.0 (0.00)	5.0 (0.21)	≥0.05	

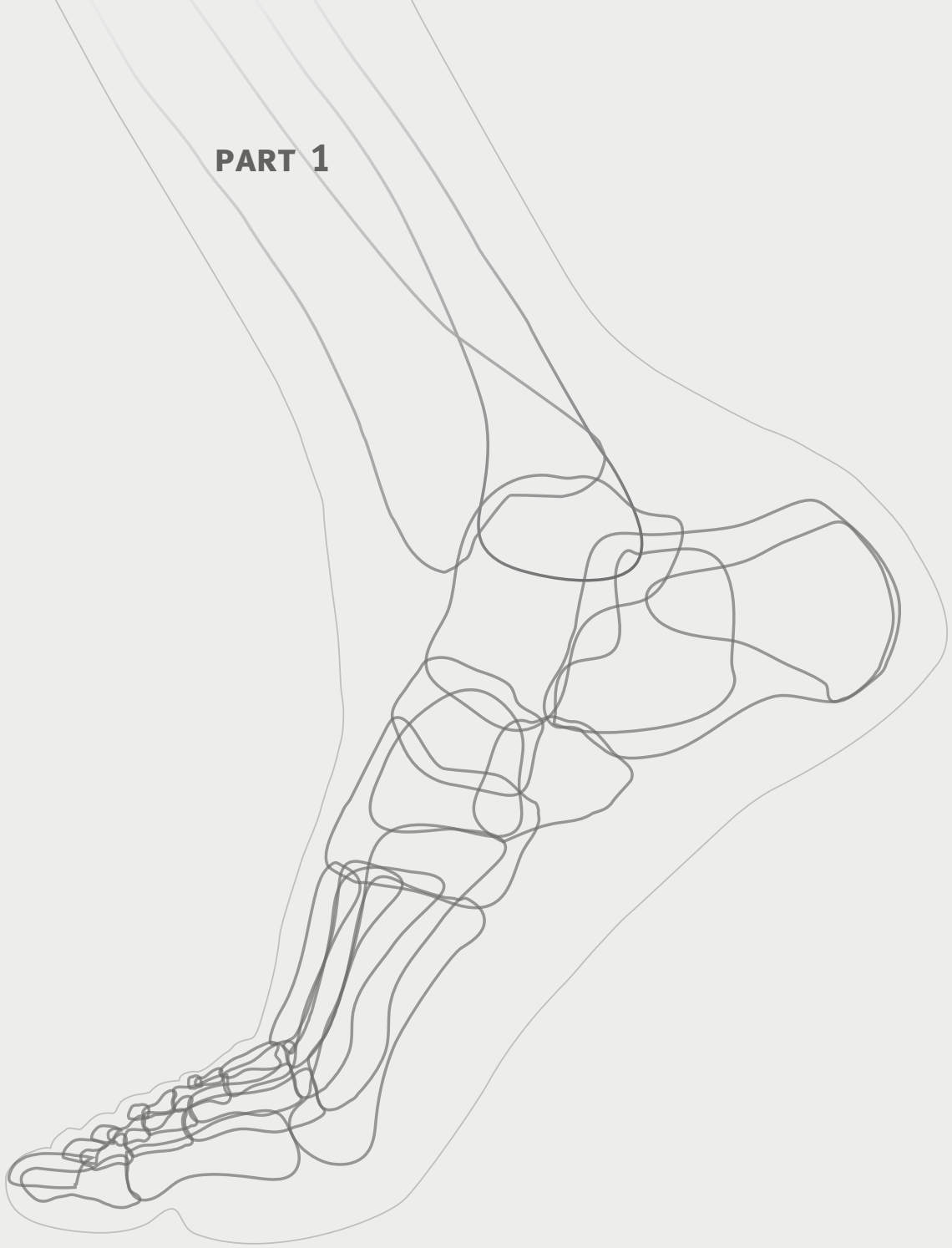
Appendix 3. Qualitative / quantitative synthesis of within-group results and overview of evidence for ready-made therapeutic shoes

Author, year (ref.)	Intervention	Outcome	Results			Level of evidence
			pre-TS mean (SD)	post-TS mean (SD)	p-value	
Chalmers et al, 2000 (37)	extra-depth supportive shoes with original insoles	RB walking, s*	86.1 (21.0)	86.4 (19.9)	≥0.05	
		RB stairs, s*	90.9 (15.6)	90.9 (11.9)	≥0.05	
		RB stand, s*	556.6 (113.3)	556.8 (131.1)	≥0.05	
		TADL walking	6.9 (1.15)	6.9 (1.15)	≥0.05	
		TADL stairs	5.0 (0.20)	5.0 (0.21)	≥0.05	
		50 foot walking time, s*	14.6 (4.87)	13.9 (4.1)	≥0.05	
Bagherzadeh Cham, 2014 (39)	high-top shoes extended above the lateral malleoli, wide toe box and velcro closures adapted with a custom made heel-to-toe rocker sole	FFI disability (0-10) FFI activity limitation (0-10)	5.66 (2.02) 2.82 (2.4)	4.2 (2.3) 1.3 (1.5)	0.044 0.04	
Moncur et al, 1990 (40)	light weight heath-mouldable shoes with extra depth and extra forefoot width	NRS walking ability (0-10)	4.5	8.5	0.01	
Health related quality of life						**Non-significant effect**
Fransen et al, 1997 (35)	extra depth shoes with long inside counter, pillow back foam-padded collar, soft leather upper with removable cushion inlay	VAS general well-being (0-100)	38.2 (24.93)	31.5 (24.89)	0.017	
Williams et al, 2006 (36)	traditional design ready-made therapeutic shoes (current footwear developed by clinicians to meet the clinician's perceptions of patient's needs, with flat insole)	FHSQ general health (0-100)	39.44 (23.88)	41.64 (26.08)	0.70	
		FHSQ general foot health (0-100)	20.14 (18.44)	19.44 (21.17)	0.85	
		FHSQ social capacity (0-100)	55.56 (27.53)	56.53 (29.06)	0.83	
		FHSQ vigour	44.11 (18.86)	44.11 (19.24)	0.99	
Williams et al, 2006 (36)	new design ready-made therapeutic shoes (incorporation of several features that were identified by the patient as being their preferred features of footwear, with firm contoured insole)	FHSQ general health (0-100)	39.01 (20.01)	40.40 (21.13)	0.66	
		FHSQ general foot health (0-100)	16.12 (15.72)	39.29 (22.58)	0.00	
		FHSQ social capacity (0-100)	54.99 (27.31)	60.33 (28.33)	0.17	
		FHSQ vigour	37.15 (16.4)	40.82 (19.71)	0.24	
Adherence						**Not applicable**
Chalmers et al, 2000 (37)	extra-depth supportive shoes with semi-rigid orthoses	Mean wearing time, h (SD)	6.15 (2.32)			
Chalmers et al, 2000 (37)	extra-depth supportive shoes with soft orthoses	Mean wearing time, h (SD)	5.89 (2.36)			
Chalmers et al, 2000 (37)	extra-depth supportive shoes with original insoles	Mean wearing time, h (SD)	5.79 (2.53)			

Appendix 3. Qualitative / quantitative synthesis of within-group results and overview of evidence for ready-made therapeutic shoes

Author, year (ref.)	Intervention	Outcome	Results			Level of evidence
			pre-TS mean (SD)	post-TS mean (SD)	p-value	
Moncur et al, 1990 (40)	light weight heath-mouldable shoes with extra depth and extra forefoot width	80% worn always, 20% worn sometimes				
Pullar et al, 1983 (42)	shoes made to more general specifications (comfort shoes)	33% worn all day, 17% worn ≥0.5 day, 50% worn <0.5 day				
Adverse events						**Not applicable**
Williams et al, 2006 (36)	traditional design ready-made therapeutic shoes (current footwear developed by clinicians to meet the clinician's perceptions of patient's needs, with flat insole)	10% with reasons "hotter than previous footwear", "unfit", "slippage at heel"				
Williams et al, 2006 (36)	new design ready-made therapeutic shoes (incorporation of several features that were identified by the patient as being their preferred features of footwear, with firm contoured insole)	8% "slippage at the heel"				
Moncur et al, 1990 (40)	light weight heath-mouldable shoes with extra depth and extra forefoot width	12% "shoes are hot to wear"				
Pullar et al, 1983 (42)	shoes made to more general specifications (comfort shoes)	8% with reason "poor fit"				
Patient satisfaction						**Not applicable**
Moncur et al, 1990 (40)	light weight heath-mouldable shoes with extra depth and extra forefoot width	NRS comfort (0-10)	5.0	9.4	<0.0001	
Pullar et al, 1983 (42)	shoes made to more general specifications (comfort shoes)	75% satisfied, 25% unsatisfied				

TS = therapeutic shoes. non-TS = non-therapeutic shoes (conventional standardized shoes / the patient's own shoes). SD = standard deviation. FO = foot orthoses. VAS = visual analogue scale. FFI = foot function index. FHSQ = Foot Health Status Questionnaire. HAQ = Health Assessment Questionnaire. RB = Robinson Bashall Functional Assessment. TADL = Toronto Activities of Daily Living Measure. NRS = numeric rating scale. *= performance-based.



PART 1

CHAPTER 4

Systematic review on the comparative effectiveness of foot orthoses in patients with rheumatoid arthritis

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Abstract

Background

Foot orthoses (FOs) are prescribed as an important conservative treatment option in patients with foot problems related to rheumatoid arthritis. However, a broad variation in FOs is used, both in clinical practice and in research. To date, there is no overview on the outcomes of the treatment with different kinds of FOs in patients with rheumatoid arthritis and a specific foot problem. The objectives of the present study were to summarize the comparative effectiveness of FOs in the treatment of various foot problems in patients with rheumatoid arthritis, on the primary outcomes foot function and foot pain, and the secondary outcomes physical functioning, health related quality of life, compliance, adverse events, the costs of FOs and patient satisfaction.

Methods

Studies comparing different kinds of FOs, with a presumed therapeutic effect, in the treatment of foot problems related to rheumatoid arthritis were included. A literature search was conducted in The Cochrane Central Registry for Controlled Trials (CENTRAL), PubMed, EMBASE and PEDro up to May 18th, 2018. Data was meta-analyzed, when this was not possible qualitative data analysis was performed.

Results

Ten studies were identified, with a total number of 235 patients. These studies made a comparison between different materials used (soft versus semi-rigid), types of FOs (custom-made versus ready-made; total-contact versus non-total contact), or modifications applied (metatarsal bars versus domes). Also, different techniques to construct custom-made FOs were compared (standard custom-molding techniques versus more sophisticated techniques). A medium effect for (immediate) reduction of forefoot plantar pressure was found in favor of treatment with soft FOs compared to semi-rigid FOs (SMD 0.60, 95% CI 0.07-1.14; P=0.03; 28 participants). Other comparisons between FOs resulted in non-significant effects or inconclusive evidence for one kind of FOs over the other.

Conclusions

Foot orthoses made of soft materials may lead to more (immediate) forefoot plantar pressure reduction compared to foot orthoses constructed of semi-rigid materials. Definitive high quality RCTs, with adequate sample sizes and long-term follow-up, are needed to investigate the comparative (cost-) effectiveness of different kinds of foot orthoses for the treatment of foot problems related to rheumatoid arthritis.

Background

Foot problems are frequently identified in patients with rheumatoid arthritis (RA) [1-5]. Synovitis of foot joints, especially in the forefoot, may lead to damage and deformity of these joints [1]. Subsequently, foot pain and disability may occur resulting in a reduced quality of life [1, 6, 7]. Treatment of RA consists of systemic medication and, if necessary, additional conservative or surgical treatment.

Foot orthoses (FOs) are an important conservative treatment option for RA-related foot problems [8]. FOs can be prescribed for optimizing foot mechanics and function, or for providing cushioning and off-loading of foot structures [9-11]. In general, the aim of prescribing FOs is to reduce foot pain and to improve physical function and quality of life [9, 12-15]. FOs are placed between the plantar surface of the foot and the sole of the patient's shoe, have a presumed therapeutic effect and are either ready- or custom-made. FOs are provided according to the individual requirements of the patient.

The effectiveness of custom-made FOs in the treatment of RA-related foot problems has been summarized in three published systematic reviews [9, 14, 16]. Two reviews reported evidence for the reduction of foot pain [9, 14], one review also found weak evidence for the reduction of forefoot plantar pressure [9]. Within these systematic reviews, the effectiveness of custom-made FOs was compared to placebo/simple FOs or no FOs.

A broad variation in FOs is used in the treatment of specific RA-related foot problems, both in clinical practice and research. FOs may have several characteristics concerning materials used (e.g. rigid or soft), type (e.g. custom-made or ready-made; contoured or non-contoured) and modifications (e.g. metatarsal domes or bars, shock-absorbing paddings) [12]. Furthermore, custom-made FOs can be constructed in different ways, e.g. by using custom molding techniques or more sophisticated CAD-CAM (computer-aided design/computer-aided manufacturing) or laser sintering systems. The characteristics of FOs prescribed may depend on the target of treatment (i.e. pressure redistribution or support, stabilization or correction of foot structures) in a specific foot region (forefoot, midfoot, rearfoot or a combination). Moreover, disease stage, the expertise of health professionals, patients' preferences, costs, access to foot care, and national and international referral patterns can play a role in the prescription of FOs [17].

To date, there is no overview on the outcomes of the treatment with different kinds of FOs in patients with RA and a specific foot problem. In addition, there is a lack of knowledge on the costs that are related to treatment with different types of FOs. Therefore, the aim of the present review was to systematically summarize the literature on the comparative effectiveness of FOs in the treatment of various foot problems in patients with RA, on the primary outcomes foot function and foot pain, and the secondary outcomes physical functioning, health related quality of life (HRQoL), compliance, adverse events, the costs of FOs and patient satisfaction.

Methods

Protocol and registration

A detailed protocol for the present study has been previously published in PROSPERO (Prospero Record Registration No.: CRD42018082039). The manuscript was written in accordance with the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) statement [18].

Eligibility criteria

Types of studies

(non) Randomized controlled trials (RCT), (non) randomized controlled cross-over trials and quasi-experimental clinical trials comparing different kinds of FOs were included. Only full-text original research reports, published in English, German, French, or Dutch were included. No restrictions concerning the year of publication were used.

Types of participants

The study population comprised patients ≥18 years of age and diagnosed with RA, or a defined subgroup of RA patients for whom data were presented separately.

Type of intervention and comparisons

Studies were eligible if patients received FOs with a presumed therapeutic effect for the treatment of RA related foot problems. Studies compared different FOs characteristics (i.e. materials used, type of FOs, or modifications applied) or different construction methods for manufacturing FOs. The only difference between the interventions was related to the FOs, while shoe condition and the target of the treatment remained stable.

Type of outcomes

Studies were eligible if at least one of the following outcomes was assessed: foot function (i.e. plantar pressure or gait parameters), foot pain, physical functioning (performance-based or self-reported), HRQoL, compliance, adverse events, the costs of FOs, or participant satisfaction.

Information sources, search and study selection

The following electronic databases were searched from inception to May 18th 2018: the Cochrane Central Registry for Controlled Trials (CENTRAL), PubMed, EMBASE and PEDro. Detailed search strategies are presented in ***Appendix 1***. Each database was searched independently by two researchers (MTD and MvdL). In addition, references lists of all selected publications were checked to retrieve relevant publications which have not been found with the computerized search.

Titles or abstracts of all studies were first screened independently by two reviewers (MTD and MvdL). For each selected study, the full article was retrieved. Next, the two reviewers independently performed final selection of studies to be included in the review based on the eligibility criteria. Disagreements on inclusion were resolved by discussion between the two reviewers.

Data collection process, data items and summary measures

Data were extracted by one reviewer (MTD) using a standardized template, and verified by a second reviewer (MvdL). From each included study, information was extracted on: authors, year of publication, study design, participant description (number of participants, setting, diagnosis, age and other clinical characteristics), description of intervention (including FOs characteristics and target of treatment for a specific foot region), longest point of follow-up, outcome measures and -if applicable- mean and standard deviations for baseline, follow-up and change scores in the outcomes, or percentages of change in the outcomes. Means were estimated from graphs, when no numerical data were supplied [19]. Disagreements or discrepancies on data extraction were resolved by discussion. If the study provided data from more than one measurement instrument, then the outcome measure most prevalent across studies was used in the analysis. For the studies in which the most prevalent outcome measure was not reported, data of the instrument highest in hierarchy was used. Based on the psychometric properties of the instruments [20] the following hierarchies (highest to lowest within the categories i-v) were applied: (i) foot function (plantar pressure): *pressure time integral, peak pressure, other instrument,* (ii) foot function (gait): *cadence, stride length, other instrument*, (iii) foot pain: *Foot Function Index subscale pain (FFI pain), Visual Analogue Scale for foot pain during walking (VAS foot pain), other instrument,* (iv) physical functioning: *Foot Function Index subscale disability (FFI disability), timed walking test, other instrument,* and (v) HRQoL: *Foot Health Status Questionnaire subscale general health (FHSQ general health), Visual Analogue Scale for general well-being (VAS general well-being), other instrument.*

Methodological quality of individual studies

The methodological quality of included studies was assessed with the Physiotherapy Evidence Database (PEDro) scale [21]. The PEDro scale has been shown to be a valid, reliable and frequently used tool for assessing methodological quality of randomized controlled trials and clinical controlled trials [22-24]. It consists of 11 items to measure the quality of each included trial. Eight items (item 2-9) are used to assess internal validity and two items to assess interpretability of results (item 10-11). Item 1, assessing external validity, is excluded in calculating the total score [25]. Therefore, the score may range from 0 to 10 points. When a repeated measures or cross-over design was used, item 4 (similarity of baseline prognostic indicators between groups) was not applicable and the maximum possible score was 9. The score obtained for each study was divided by the maximum possible score and multiplied by 100 to provide a "study quality percentage". Study quality percentages were then classified as high (≥55-100%), fair (≥35-<55%), or low (<35%) according to Teasell et al. [26].

Quality assessments were independently evaluated by two reviewers (MTD and MvdL). Disagreements were resolved by discussion and, if necessary, by consultation of the third reviewer (JD).

Data synthesis

Data synthesis was conducted for the effect of FOs on (i) the primary outcomes foot function and foot pain and (ii) the secondary outcomes physical functioning, HRQoL, compliance, adverse events, the costs of FOs and participant satisfaction. For studies with no follow-up time, the immediate effect was used in analysis. The immediate effect reflects the differences within the same measurement session between the different FO conditions. Quantitative data analysis (meta-analysis) was conducted for between-group comparison of FOs characteristics or FOs construction methods. Outcomes measured during (in case of single-session measurement (studies with no follow-up)) or after wearing FOs (longitudinal studies with differing follow-up time) were used and aggregated in meta-analyses. Subgroup meta-analyses were performed in case of a sufficient number of studies for further specification, i.e. targeted foot region; follow-up time shoe condition; study quality.

Pooling of effect sizes across studies was performed using the standardized mean difference (SMD) and 95% confidence intervals (CI) in a random effects model [27]. SMDs were interpreted as 0.2 (small), 0.5 (medium) and 0.8 (large) [28]. The results are presented in forest plots for each comparison. Funnel plots were constructed for meta-analyses with ≥2 studies, to assess possible publication bias. Meta-analyses were conducted in computer software R [29]. Heterogeneity was tested using the eye ball test (forest plot).

When quantitative data analysis was not possible, a qualitative data analysis (best-evidence synthesis) was conducted. The data were summarized by assigning five levels of evidence (strong, moderate, weak, inconclusive and inconsistent) according to criteria adapted from Ariëns et al. ***(Table 1)*** [30].

Results

Study selection

The literature search resulted in a total number of 670 hits. After duplicate removal, 429 hits were screened on title or abstract. This resulted in 19 full-text articles that were studied for eligibility, of which 10 articles were included in the systematic review ***(Figure 1)***.

Characteristics of included studies

The included studies consisted of four RCTs [31-34] of which two with a repeated measures design [31, 32], three controlled clinical trials with a repeated measures design [11, 35, 36], one controlled cross-over trial [37], and two quasi-experimental clinical trials with a repeated measures design [38, 39]. FOs targeting forefoot problems were investigated in six studies [11, 31, 35, 36, 39]. FOs targeting hindfoot problems were investigated in one study [37]. Three studies investigated the effect of FOs without a specified region of interest [33, 34, 38]. Four studies specified the shoes in which FOs were worn; extra-depth shoes with a wide toe-box [31, 35, 39] and forefoot-rockered extra-depth shoes with a wide toe-box were used [33]. A detailed description of the included studies is presented in ***Table 2***.

Table 1. Strength of evidence criteria [30]

Strong	At least 2 high-quality studies with consistent findings
Moderate	1 high-quality study and at least 2 low-quality studies with consistent findings
Weak	At least 2 low-quality studies with consistent findings
Inconclusive	Insufficient or conflicting studies
Inconsistent	Agreement of findings in <75% of studies

Methodological quality of included individual studies

Initial overall agreement on methodological quality scores was 96%. No consultation of the third reviewer was necessary to resolve disagreement. Methodological quality of included individual studies is presented in ***Table 3***. Three studies were considered to be of high [31, 32, 34], six of fair [11, 33, 35, 36, 38, 39] and one of low quality [37].

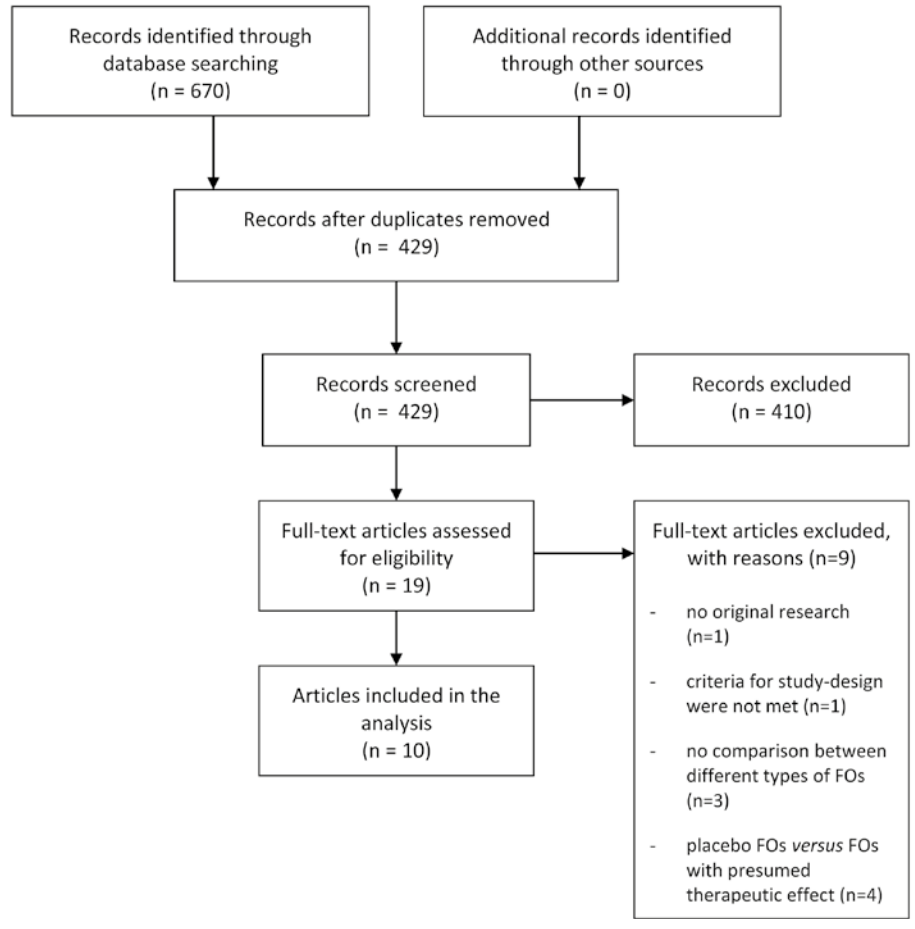


Figure 1. PRISMA flow diagram

Table 2. Characteristics of included studies and overview of FOs characteristics

Author (year)	Study design	Participant description	Intervention	Time	Outcome
Region of interest - forefoot					
Chalmers et al. 2000 (31)	randomized controlled clinical trial with a repeated measures design	*number* - n=28 *setting* - occupational therapy department of hospital *diagnoses* - definitive diagnosis of RA *age (years)* - women: 60 (10) - men: 63 (2) *mean (SD)* *clinical characteristics* - subluxed MTP joints - bilaterally MTP joint pain	**Custom-made, semi-rigid (total-contact) FOs** - based on casts taken in a non-weight bearing position - constructed of semi-rigid material - addition of forefoot cushioning, and forefoot and hindfoot nickleplast posts target of treatment - support, stabilisation or correction of foot structures - cushioning (forefoot) **Custom-made, soft (impression) FOs** - based on an impression in preheated plastazote during weight-bearing - constructed of soft materials - addition of metatarsal lifts *target of treatment* - support, stabilisation or correction of foot structures - cushioning (full length) **Control intervention** - shoe-only	12 weeks for each intervention, separated by 2 week washouts	*foot pain* - VAS pain (primary outcome) *physical functioning* - 50 foot walking time, s* - RB* - TADL *patient satisfaction* - VAS treatment - effectiveness - Nomination of the FOs of preference
Chang et al. 2011 (35)	controlled clinical trial with a repeated measures design (single session)	*number* - n=19 *setting* - podiatric outpatient clinic of a hospital *diagnoses* - definitive diagnosis of RA *age (years)* - 58.6 (10.1) *mean (range)* *clinical characteristics* - forefoot pain - toe-deformities and/or hallux valgus	**Custom-made, semi-rigid (total-contact) FOs** - based on a foot impression (made in a foot impression box) while holding the subtalar joint at a neutral position - constructed of semi-rigid materials (cork) - addition of metatarsal support (cork) and cushioning material (full-length) *target of treatment* - support, stabilisation or correction of foot structures - cushioning, full length - forefoot plantar pressure reduction **Custom-made, soft (impression) FOs** - based on impression in plastazote during weight-bearing (ADL 2-3 weeks) - constructed of soft materials - addition of metatarsal pad and arch support of EVA *target of treatment* - support, stabilisation or correction of foot structures - cushioning, full length - forefoot plantar pressure reduction **Control intervention** - 7-mm flat EVA (40 Shore A hardness) FOs	1 month	*foot function* - In-shoe plantar foot pressure (peak pressure, pressure-time integral, mean force contact area) (primary outcome) *foot pain* - VAS pain *patient satisfaction* - Nomination of the FOs of preference
Gibson et al. 2014 (11)	controlled clinical trial with a repeated measures design (single session)	*number* - n=16 *setting* - early arthritis clinic of a hospital *diagnoses* - definitive diagnosis of RA, >2years previously *age (years)* - 50.7 (8.4) *mean (range)* *clinical characteristics* - acquired and passively correctable pes plano valgus - with or without forefoot pain at MTP joints - orthotic naive	**Custom-made, semi-rigid (total-contact) FOs** - based on a plaster cast model of the foot using the subtalar joint neutral technique. - constructed of semi-rigid material (polypropylene) - optional adaptations (external rearfoot wedge control, arch height, forefoot cushioning) based on an algorithm of design rules. *target of treatment* - support, stabilisation or correction of foot structures - cushioning (forefoot) - forefoot plantar pressure reduction **Custom-made, rigid (total-contact) FOs; CAD design using selective laser sintering** - the CAD design is based on a digitized plaster cast model of the foot using the subtalar joint neutral technique and an algorithm of design rules - manufactured using selective laser sintering using nylon-12 powder *target of treatment* - support, stabilisation or correction of foot structures - forefoot plantar pressure reduction **Custom-made, semi-rigid (total-contact) FOs; CAD design using fused-deposition method** - the CAD design is based on a digitized plaster cast model of the foot using the subtalar joint neutral technique and an algorithm of design rules - manufactured using fused-deposition method using polylactide *target of treatment* - support, stabilisation or correction of foot structures - forefoot plantar pressure reduction **Control intervention** - shoe-only	7 days per intervention (without washout- periods)	*foot function* - Gait characteristics (rearfoot eversion, ankle internal moment, forefoot dorsiflexion, navicular height) *(primary outcome)* - In-shoe plantar foot pressure (forefoot peak pressure, midfoot contact area pressure-time integral, mean force contact area) *(primary outcome)* *patient satisfaction* - Likert scale (orthotic device comfort, orthotic device fit, self-reported efficacy, symptoms, activity levels) *adverse events* - minor and major

Table 2. Continued

Author (year)	Study design	Participant description	Intervention	Time	Outcome
Region of interest - forefoot					
Hodge et al. 1999 (36)	controlled clinical trial with a repeated measures design (single session)	*number* - n=11 *setting* - University faculty of Health Science *diagnoses* - history of RA *age (years)* - 65 (49-82) *mean (range)* *clinical characteristics* - forefoot pain on shod weightbearing	**Custom-made, semi-rigid (total-contact) FOs** - based on the semi-weight bearing technique described by McPoil et al. (1989) using a latex rubber foot moulding board during moulding the EVA-material directly to the foot. - constructed of soft density, semi-rigid EVA - half-length FOs *target of treatment* - support, stabilisation or correction of foot structures - forefoot plantar pressure reduction **Custom-made, semi-rigid (total-contact) FOs with additional metatarsal bars** - based on the semi-weight bearing technique described by McPoil et al. (1989) using a latex rubber foot moulding board during moulding the EVA-material directly to the foot. - constructed of soft density, semi-rigid EVA - addition of metatarsal bar (latex rubber, boomerang shape) - half-length FOs *target of treatment* - support, stabilisation or correction of foot structures - forefoot plantar pressure reduction **Custom-made, semi-rigid (total-contact) FOs with additional metatarsal domes** - based on the semi-weight bearing technique described by McPoil et al. (1989) using a latex rubber foot moulding board during - moulding the EVA-material directly to the foot. - constructed of soft density, semi-rigid EVA - addition of metatarsal dome (latex rubber, teardrop shape) - half-length FOs *target of treatment* - support, stabilisation or correction of foot structures - forefoot plantar pressure reduction **Ready-made, soft FOs** - contoured soft density EVA FOs - half-length FOs *target of treatment* - support, stabilisation or correction of foot structures - forefoot plantar pressure reduction **Control intervention** - shoe-only	-	*foot function* - In-shoe plantar foot pressure (peak pressure, pressure-time integral, average pressure, time in mask) *(primary outcome)* - Gait characteristics (cadence) *foot pain* - VAS pain during standing - VAS pain during walking *patient satisfaction* - Nomination of the FOs of preference
Jackson et al. 2004 (32)	randomized controlled trial with a repeated measures design (single session)	*number* - n=10 *setting* - podiatry centre *Diagnoses* - definitive diagnosis of RA *age (years)* - 61 (32-79) *mean (range)* *clinical characteristics* - forefoot pain on shod weightbearing	**Ready-made, soft FOs with additional metatarsal bars** - manufactured of expanded urethane foam with a hardness of 25 Shore A - addition of metatarsal square bar (latex foam, 29 Shore A) - full-length, contoured FOs *target of treatment* - support, stabilisation or correction of foot structures - forefoot plantar pressure reduction **Ready-made, soft FOs with additional metatarsal domes** - manufactured of expanded urethane foam with a hardness of 25 Shore A - addition of metatarsal dome (latex foam, 29 Shore A) - full-length, contoured FOs *target of treatment* - support, stabilisation or correction of foot structures - forefoot plantar pressure reduction **Control intervention** - shoe-only	-	*foot function* - In-shoe plantar forefoot pressure (peak pressure, pressure-time integral, stance time, contact area) *(primary outcome)* - Gait characteristics (cadence) *patient satisfaction* - Nomination of the FOs of preference
Tenten-Diepenmaat et al. 2016 (39)	quasi-experimental clinical trial with a repeated measures design (single session)	*number* - n=45 *setting* - outpatient centre for rehabilitation and rheumatology *Diagnoses* - definitive diagnosis of RA *age (years)* - 53 (13.5) *mean (range)* *clinical characteristics* - RA related foot pain - indication for treatment with FOs	**Custom-made, semi-rigid (total-contact) FOs** - constructed of prefabricated orthotic devices, custom-moulded to the patient's foot while using the functional suspension subtalar joint neutral position technique. - optional addition of varus-, valgus corrections, metatarsal bars, metatarsal domes, and/or cushioning material *target of treatment* - support, stabilisation or correction of foot structures - forefoot plantar pressure reduction **Custom-made, semi-rigid (total-contact) FOs, with adaptations using the feedback of in-shoe plantar pressure measurements** - custom-made, semi-rigid, total-contact FOs were adapted based on the feedback of in-shoe plantar pressure measurements - optional change or addition of - varus-, valgus corrections, metatarsal bars, metatarsal domes, and/or cushioning material *target of treatment* - support, stabilisation or correction of foot structures - forefoot plantar pressure reduction	-	*foot function* - In-shoe plantar forefoot pressure (peak pressure, pressure-time integral) *(primary outcome)*

Table 2. Continued

Author (year)	Study design	Participant description	Intervention	Time	Outcome
Region of interest - hindfoot					
Gatt et al. 2016 (37)	controlled cross-over trial	*number* - n=10 *setting* - rheumatology outpatient clinic at a general hospital *diagnoses* - definitive diagnosis of RA *age (years)* - 52.2 (9.1) *mean (SD)* *clinical characteristics* - subtalar and/or ankle joint pain ≥6 months - need of orthoses for biomechanical mal-alignment of the feet as per clinical practice	**Custom-made, semi-rigid (total-contact) FOs** - based on a cast (the positive casts were modified as outlined by Philips et al.) - constructed of semi-rigid material (subortolene) *target of treatment* - support, stabilisation or correction of foot structures **Custom-made, soft (total-contact) FOs** - based on a cast (the positive casts were modified as outlined by Philips et al.) - constructed of low density EVA *target of treatment* - support, stabilisation or correction of foot structures	3 months per intervention, with a 2 week washout period in between	*foot pain* - FFI pain - RAI *physical functioning* - FFI disability - FFI limitation
Region of interest - non-specified					
Cho et al. 2008 (33)	randomized controlled trial	*number:* - n=42 (22 intervention-group, 20 control-group) *Setting:* - university hospital *Diagnoses:* - definitive diagnosis of RA *age (years):* - 48.7 (11.7) *mean (SD)* *clinical characteristics:* - stable disease activity - foot pathology (forefoot or hindfoot)	**Custom-made, semi-rigid FOs** - consisting of a medial longitudinal arch support, medial heel post and metatarsal pad. *target of treatment* - support, stabilisation or correction of foot structures **Ready-made, soft FOs** - simple FOs - 6mm plastazote *target of treatment* - cushioning, full length	6 months	*foot pain* - VAS pain (primary outcome)
Pallari et al. 2010 (38)	quasi-experimental clinical trial with a repeated measures design (single session)	*number* - n=7 *setting* - rheumatology outpatient clinic of a hospital *Diagnoses* - definitive diagnosis of RA *age (years)* - 53.4 (29-68) *mean (range)* *clinical characteristics* - current history of foot impairments	**Custom-made, semi-rigid (total-contact) FOs** - based on casts - mainly constructed of semi-rigid material - optional addition of cushioning material *target of treatment* - support, stabilisation or correction of foot structures **Custom-made, semi-rigid (total-contact) FOs; CAD design using selective laser sintering** - the CAD design is based on a weight or nonweight-bearing scan of the foot (in a subtalar joint neutral alignment) and on design rules - manufactured using selective laser sintering using nylon-12 powder *target of treatment* - support, stabilisation or correction of foot structures	-	*foot function* - Gait characteristics (velocity, cadence, cycle-time, stride length) *(primary outcome)* *patient satisfaction* - VAS orthotic comfort - VAS orthotic fit
Rome et al. 2017 (34)	randomized controlled trial	*number* - n=47 *setting* - rheumatology outpatient department *Diagnoses* - definitive diagnosis of RA *age (years)* - 65 (49-82) *mean (range)* *clinical characteristics* - history of foot pain	**Custom-made, semi-rigid (total-contact) FOs** - based on a cast taken of a neutral suspension plaster - constructed of semi-rigid material (50 Shore A) - optional addition of external medial posting correction - addition of cushioning material (full-length) *target of treatment* - support, stabilisation or correction of foot structures - cushioning **Custom-made, soft FOs** - constructed of a 6-mm breathable foam on a rubber-silicone-ethylene compound. - full-length FOs *target of treatment* - support, stabilisation or correction of foot structures - cushioning	16 weeks	*foot pain* - FFI foot pain *physical functioning* - FFI disability - FFI functional imitation *Costs of FOs* - EQ5D utility index (QUALYs) - mean cost of resource use

VAS = visual analogue scale. RB = Robinson Bashall Functional Assessment. TADL = Toronto Activities of Daily Living Measure. FFI = foot function index. NRS = numeric rating scale. EVA = Etylene Vinyl Acetate. RAI = Ritchie Articular Index. QUALYs = quality-adjusted life years.
* performance based.

Comparisons in treatment with FOs

Different FOs characteristics and different construction methods for manufacturing FOs were identified in the included studies, allowing comparisons of effectiveness. Meta-analyses are presented in ***Figures 2 and 3***. Subgroup meta-analyses are shown in ***Appendix 2***. When meta-analysis was not possible, qualitative data-analysis was performed as shown in ***Appendix 3***. Although subgroup meta-analyses on study quality and shoe-condition were planned a priori, these analyses were not possible due to an insufficient number of studies.

Characteristics of FOs

Different FOs characteristics were identified concerning (i) materials used for manufacturing the shell (base-frame) of FOs, (ii) type of FOs, and (iii) modifications applied to the FO-shell. Concerning materials used for manufacturing the shell of FOs a distinction could be made between soft (cushioning effect) [31-35, 37] and semi-rigid [11, 31, 33-39] materials. Semi-rigid FOs are manufactured of materials with a stiffness aimed to provide control of the position of the feet during weight-bearing. A comparison was made for the effect of 'semi-rigid FOs *versus* soft FOs' [31, 33-37]. Within this comparison four subgroups were identified. Two subgroups concerned FO-type, in which the comparisons 'custom-made (semi-rigid) FOs *versus* ready-made (soft) FOs' [33, 36] and 'total-contact (semi-rigid) FOs *versus* non-total contact (soft) FOs' [31, 34-36] were investigated. Furthermore, one subgroup was identified with the forefoot as region of interest for treatment [31, 35, 36], and in one subgroup the effect of treatment was measured after >1 month of wearing FOs (in contrast to immediate effect) [31, 33-35, 37]. For type of FOs a distinction could be made between custom-made FOs [31, 33-40] and ready-made (i.e. off-the-shelf or over-the counter) FOs [32, 33, 36], and between total-contact [11, 31, 34-39] and non-total-contact FOs [31-36]. For modifications applied to the FO-shell a distinction could be made between metatarsal bars [32, 36] and metatarsal domes [32, 36]. A comparison was made for the effect of 'FOs with metatarsal bars *versus* FOs with metatarsal domes' [32, 36].

Table 3. Methodological quality of included studies using the PEDro checklist

Reference	External validity (0-1)	Internal validity (0-10)										Total score	Quality
	1	2	3	4	5	6	7	8	9	10	11		
Chalmers et al. 2000 (31)	1	1	0	n/a	0	0	1	0	1	1	1	5/9 (56%)	High
Chang et al. 2011 (35)	0	0	0	n/a	0	0	0	1	1	1	1	4/9 (44%)	Fair
Cho et al. 2009 (33)	1	1	0	1	0	0	0	0	1	1	1	5/10 (50%)	Fair
Gatt et al. 2016 (37)	1	0	0	n/a	0	0	0	1	1	0	1	3/9 (33%)	Low
Gibson et al. 2014 (11)	1	0	0	n/a	0	0	0	1	1	1	1	4/9 (44%)	Fair
Hodge et al. 1999 (36)	0	0	0	n/a	0	0	0	1	1	1	1	4/9 (44%)	Fair
Jackson et al. 2004 (32)	1	1	0	n/a	0	0	0	1	1	1	1	5/9 (56%)	High
Pallari et al. 2010 (38)	1	0	0	n/a	0	0	0	1	1	1	1	4/9 (44%)	Fair
Rome et al. 2017 (34)	1	1	1	0	1	0	0	0	1	1	1	6/10 (60%)	High
Tenten-Diepenmaat et al. 2016 (39)	1	0	0	n/a	0	0	0	1	1	1	1	4/9 (44%)	Fair

High quality = study quality percentage ≥55-100%. Fair quality = study quality percentage ≥35-<55%. Low quality = study quality percentage <35%. n/a = not applicable.

Comparative effectiveness of semi-rigid FOs versus soft FOs

Six included studies (two of high (75 participants) [31, 34], three of fair (72 participants) [33, 35, 36] and one of low quality (10 participants) [37]) investigated the effect of treatment with FOs constructed of a semi-rigid shell *versus* soft FOs constructed of a soft shell. Pooled scores showed a medium, statistically significant, immediate effect for reduction of forefoot plantar pressure-time integral (PTI) in favor of treatment with soft FOs (SMD 0.60, 95% CI 0.07-1.14; P=0.03; 28 participants; ***Figure 2a)***. A similar effect was found for forefoot plantar peak pressure (PP), although not statistically significant (SMD 0.50, 95% CI -0.08 – 1.08; P=0.09; 28 participants; ***Figure 2b)***. For foot pain, pooled scores (SMD 0.03, 95% CI -0.47 – 0.52; P=0.91; 157 participants; ***Figure 2c)*** and subgroup meta-analyses ***(Appendix 2)*** showed no effect in favor of treatment with one type of FOs over the other, as well as for pooled scores for physical functioning (SMD -0.10, 95% CI -0.48 – 0.28; P=0.59; 54 participants; ***Figure 2d)***. Funnel plots were constructed for the analyses on foot pain and physical functioning ***(Appendix 4)***. Limited evidence for publication bias was found, since for the smaller studies treatment effects are spread evenly on both sides of the average (as shown in ***Appendix 4***). Qualitative data-syntheses resulted in inconclusive evidence for one type of FOs over the other on the secondary outcomes compliance, costs of FOs and patient satisfaction.

Comparative effectiveness of FOs with metatarsal bars versus FOs with metatarsal domes

Two included studies (one of high quality (10 participants) [32] and one of fair quality (11 participants) [36]) investigated the effect of different types of metatarsal support (FOs with metatarsal bar *versus* FOs with metatarsal dome) in the treatment of forefoot problems. Pooled scores showed a small, immediate, not statistically significant, effect in favor of FOs with metatarsal bars for reduction of forefoot plantar pressure (PTI (SMD -0.17, 95% CI -0.78 – 0.43; P=0.58; 22 participants; ***Figure 3a)*** and PP (SMD -0.32, 95% CI -0.93 – 0.29; P=0.30; 22 participants; ***Figure 3b***)). Qualitative data-syntheses resulted in inconclusive evidence for one type of FOs over the other on the primary outcome foot pain and the secondary outcome patient satisfaction.

Construction method for FOs

Within the included studies various methods were used for manufacturing custom-made FOs; selective laser sintering [11, 38] and standard methods for custom-molding of material, i.e. directly to the foot [36, 39], or by using an impression- or plaster cast model [11, 31, 34, 35, 37, 38]. A comparison could be made for the effect of 'selective laser sintered FOs *versus* standard custom-made FOs' [11, 38].

Comparative effectiveness of selective laser sintered FOs versus standard custom-made FOs

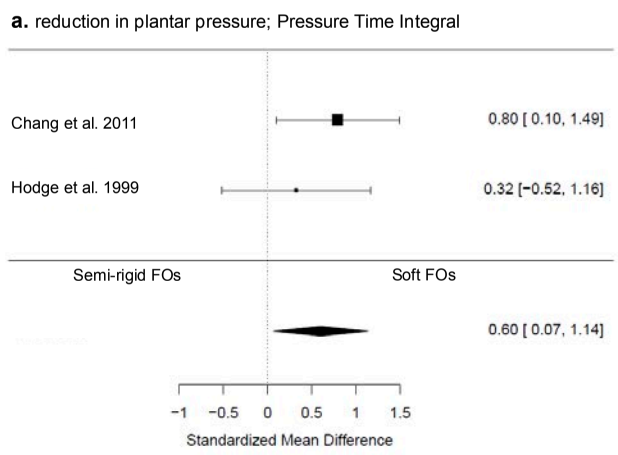
In two studies (of fair quality (23 participants) [11, 38]) the feasibility and outcomes on foot function of custom-made FOs manufactured by using sophisticated construction methods were compared to standard methods. Gibson et al. [11] reported more immediate forefoot plantar pressure reduction in favor of treatment with selective laser sintered FOs, although not statistically significant. Pallari et al. [38] reported a slightly (non-tested) faster cadence in favor of treatment with standard custom-made FOs. Qualitative data-syntheses resulted in inconclusive evidence for foot function measured with either plantar pressure or gait parameters between the different construction methods. Furthermore, inconclusive evidence was found for one type of FOs over the other on the secondary outcome patient satisfaction.

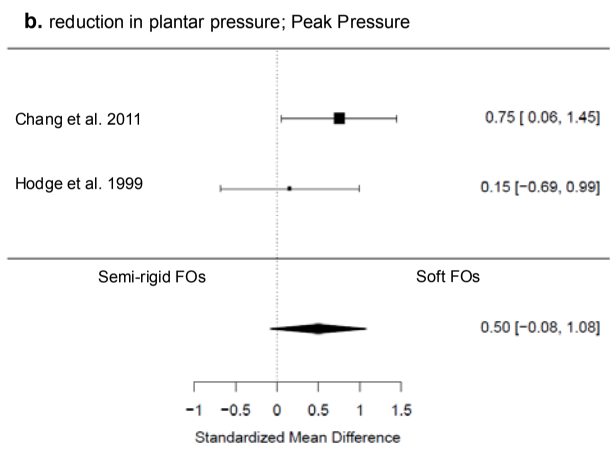
Discussion

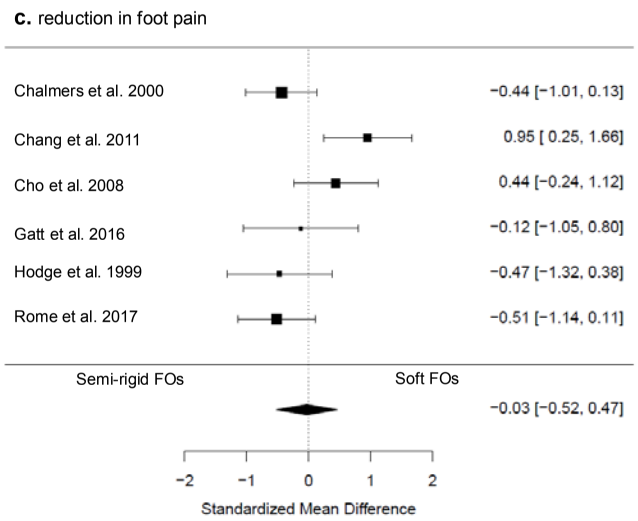
To our knowledge, this is the first published systematic review investigating the comparative effectiveness of FOs in patients with RA. The included studies showed a distinction in FOs characteristics (concerning materials, type and modifications) and construction methods for custom-made FOs (sophisticated *versus* standard techniques). The target of treatment with FOs was mostly reduction of forefoot plantar pressure or forefoot pain. A medium effect for the (immediate) reduction of forefoot plantar pressure was found in favor of treatment with soft FOs compared to semi-rigid FOs. Other comparisons concerning characteristics of FOs or construction methods resulted in non-significant effects or inconclusive evidence for one type of FOs over the other for both primary and secondary outcomes.

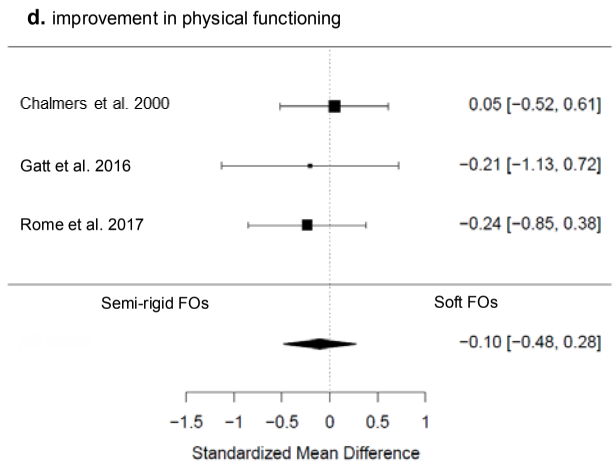
It is known that custom-made FOs are more effective in reducing forefoot plantar pressure and pain than placebo FOs [9, 14]. However, the comparative effectiveness has not yet been summarized. The findings of the present study show that soft FOs may lead to more (immediate) forefoot plantar pressure reduction than semi-rigid FOs (based on a sample size of 28 participants). Pooled scores on foot pain showed no beneficial effect of treatment with soft FOs over semi-rigid FOs. This could possibly be explained by the already small effects on foot pain of treatment with custom-made FOs in general [9, 14], making the potential for demonstrating a beneficial effect between different types of custom-made FOs difficult, especially in case of small sample sizes. Cultural differences may also have contributed to this result. The forest plot of the pooled pain scores ***(Figure 2b)*** shows inconsistent findings across the included studies, for one type of FOs over the other. Four (out of six) studies were performed in the Western parts of the world and showed all a beneficial effect of semi-rigid FOs over soft FOs [31, 34, 36, 37]. The other two studies were performed in Asian countries and showed contrary findings [33, 35]. It is not known whether differences in body structure or shoe wearing habits could explain this difference. Finally, an explanation could be that reduction of plantar pressure may not be the primary mediator between FOs treatment and foot pain. For example, the study of Hodge et al. (fair quality, 11 participants) showed more forefoot plantar pressure reduction after using soft FOs, but more pain reduction was reached by using semi-

Figure 2. Forest plots of data pooling for the effect of semi-rigid FOs versus soft FOs on (**a**) foot function expressed as Pressure Time Integral, (**b**) foot function expressed as Peak Pressure, (**c**) foot pain, and (**d**) physical functioning.









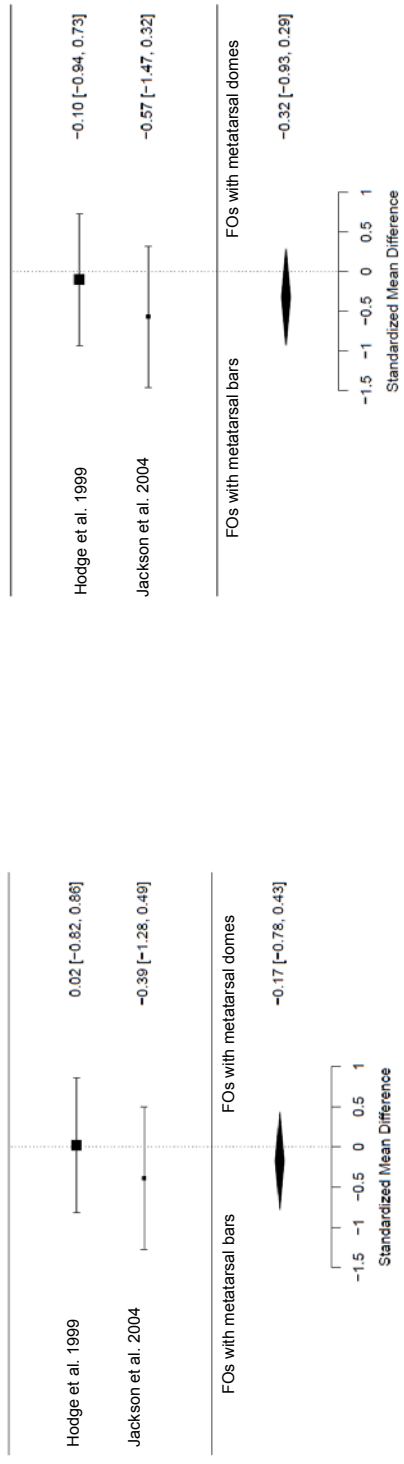


Figure 3. Forest plots of data pooling for the effect of FOs with metatarsal bars versus FOs with metatarsal domes on (a) foot function expressed as Pressure Time Interval, (b) foot function expressed as Peak Pressure.

rigid FOs [36]. To further clarify the mechanism behind the effect of FO's, future research should assess the kinematic and kinetic response to treatment with FOs [41]. In RA patients with early and painful deformity of the rearfoot, correction of deformity and optimization of function of the ankle joint complex were detected by measuring three-dimensional kinematics by using an electromagnetic tracking system after the long-term use of custom-made FOs [42]. Further insight in the kinematic and kinetic response to the use of FOs, as well as the association with clinical outcomes in patients with RA and (fore-) foot problems is required. A clinical trial on this topic is planned by researchers in Denmark (ClinicalTrials.gov (accessed October 22th 2018); Trial Identifier NCT03561688).

More research on the comparative effectiveness of FOs is necessary before firm conclusions can be drawn. Overall, few high-quality studies with small sample sizes were included in the present review. Due to a limited number of studies investigating the outcomes of interest most of the performed qualitative data-analyses resulted in inconclusive evidence. For example, cost effectiveness between different types of FOs was investigated in only one included study (of high quality, 47 participants) [34]. Rome et al. found that custom-made, semi-rigid (total-contact) FOs were far more expensive to manufacture with no significant cost per Quality Adjusted Life Years (QALY) gain, in comparison to custom-made, soft FOs [34]. Due to the included study designs, between-group results of different types of FOs were presented in only a part of the included studies. Some studies reported results of different kinds of FOs (with a presumed therapeutic effect) but were not designed to compare the effect of those [31-33, 35-37]. These studies met our inclusion criteria, but provided limited information with regard to the comparative effectiveness of the different FOs. Furthermore, most of the included studies investigated the immediate effect on foot pain or the immediate mode of action on plantar pressure/gait alteration (in a laboratory setting instead of real-life). Future research with a follow-up of >6 months [10] is necessary. An acclimation period of wearing FOs, especially semi-rigid FOs, is needed before the final result on pain will be reached [10, 31]. Long-term follow-up is also needed to identify the potential role of treatment with semi-rigid FOs (aimed at controlling the position of the feet during weight-bearing) in delaying progression of foot symptoms in patients with early RA [43-45].

The present study provides a first step in gaining insight in the effectiveness of different FOs characteristics. Future research could focus on the development of practice recommendations for prescribing/designing FOs with optimal characteristics for (delaying progression of) specific RA-related foot problems. Therefore, definitive high quality RCTs, with adequate sample sizes and long-term follow-up, are needed to investigate the comparative (and cost-) effectiveness of different types of FOs for the treatment of RA-related foot problems. In anticipation of more up-to-date insights, prescribing custom-made (total-contact) FOs constructed of a semi-rigid shell with soft/cushioning material underneath the forefoot might be the most optimal approach in the treatment of RA-related foot problems, as suggested by recently published expert-based recommendations by our group [45]. The use of soft material underneath the forefoot is supported by the results of the present review. Furthermore, a stepped-care approach was suggested [45]. Based on specific diagnostical outcomes (conservative) stepped care for RA-related foot problems can consist of; i) advice on-over-the-counter shoes, ii) ready-made FOs, iii) custom-made FOs, and iv) therapeutic shoes. Further research on this stepped-care approach is necessary. Gallaher et

al. announced upcoming trial-evidence on custom-made FOs versus ready-made FOs in patients with RA, by publishing their study-protocol [46]. Moreover, further development of sophisticated construction methods may be important for uniformity and (cost-) efficiency in designing custom-made FOs. Gibson et al. [11] and Pallari et al. [38] showed that selective laser sintering is a feasible method for manufacturing FOs with a significant clinical potential.

This study has some limitations. First, publication bias cannot be ruled out. The majority of the included studies were small-sample studies. Inspection of funnel plots, however, showed limited evidence of publication bias. Further, the search strategy did not include unpublished literature, such as theses and conference proceedings. It may be that not all studies carried out have actually been published. Second, there is large heterogeneity in study designs and outcome measures of the included studies. Furthermore, variation may exist between FOs within the different categories (concerning FOs characteristics and construction methods). Third, due to the small evidence base we chose to aggregate the outcome on foot pain of studies with no or differing follow-up time within meta-analyses. In a subgroup analysis, we studied the impact of ≥1 month follow-up, showing no effect (SMD 0.05, p>0.05) on foot pain ***(Appendix 2)***. Fourth, studies using placebo FOs were excluded in the present review. However, the characteristics of placebo FOs varied across these studies [47-50] indicating that the definition of placebo FOs is not yet established.

Conclusions

Foot orthoses made of soft materials may lead to more (immediate) forefoot plantar pressure reduction compared to foot orthoses constructed of semi-rigid materials. Definitive high quality RCTs, with adequate sample sizes and long-term follow-up, are needed to investigate the comparative (cost-) effectiveness of different kinds of foot orthoses for the treatment of foot problems related to rheumatoid arthritis.

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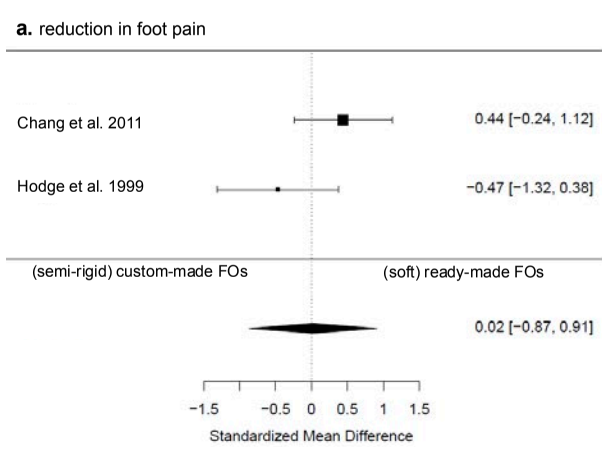
Appendices

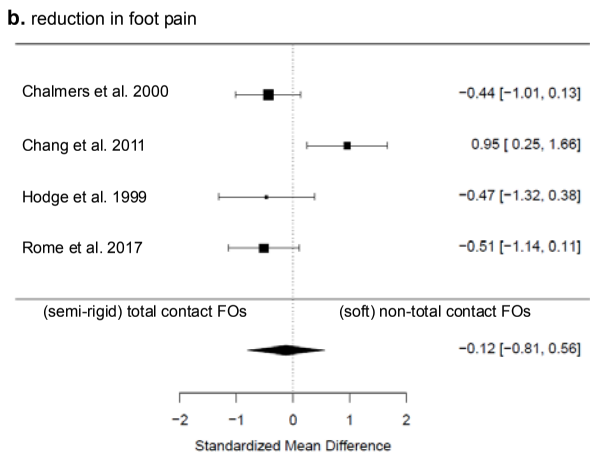
Appendix 1. Search strategy

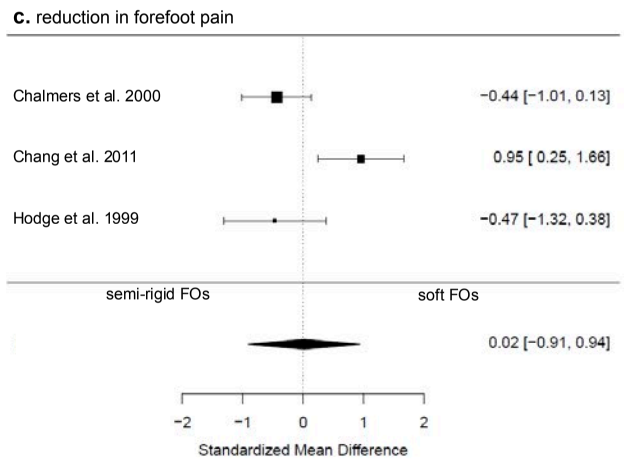
A two-way search strategy was employed using “rheumatoid arthritis”, “foot orthoses” with “foot” and related synonyms of these terms.

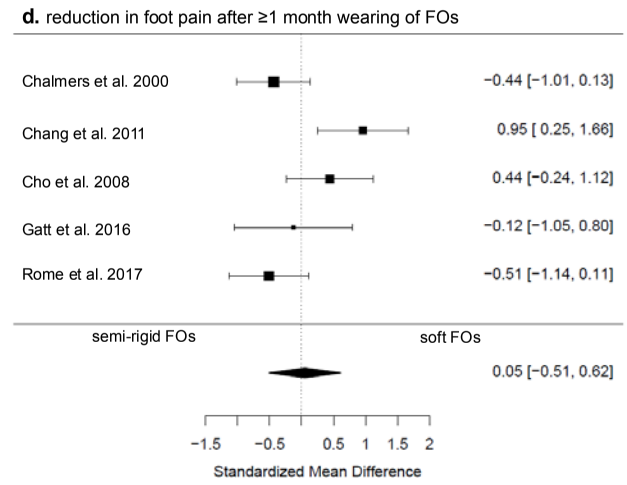
The following database search strategy for PubMed was used:
(“Arthritis, Rheumatoid”[Mesh] ***OR*** rheumatoid arthritis[tiabl]) ***AND*** (“foot orthoses”[Mesh] ***OR*** “orthotic devices”[Mesh] ***OR*** “inlays”[Mesh] ***OR*** orthos*[tiab] ***OR*** orthotic*[tiab] ***OR*** inlay*[tiab] ***OR*** insert*[tiab] ***OR*** insole*[tiab]) ***OR*** foot arch support [tiab]) ***AND*** (“foot”[Mesh] ***OR*** “Foot Bones”[Mesh] ***OR*** “Ankle”[Mesh] ***OR*** foot[tiab] ***OR*** feet[tiab] ***OR*** ankle[tiab] ***OR*** rearfoot[tiab] ***OR*** hindfoot[tiab] ***OR*** midfoot[tiab] ***OR*** “Forefoot, Human”[Mesh] ***OR*** forefoot[tiab] ***OR*** tarsal[tiab] ***OR*** “Talus”[Mesh] ***OR*** talus[tiab] ***OR*** “Calcaneus”[Mesh] ***OR*** calcan*[tiab] ***OR*** subtalar[tiab] ***OR*** sinus tars*[tiab] ***OR*** talonavicular*[tiab] ***OR*** “Metatarsus”[Mesh] ***OR*** metatarsal*[tiab] ***OR*** metatarsophalang*[tiab] ***OR*** “Heel”[Mesh] ***OR*** heel[tiab] ***OR*** “Fibula”[Mesh] ***OR*** fibula[tiab] ***OR*** “Tibia”[Mesh] ***OR*** tibia[tiab] ***OR*** “Toes”[Mesh] ***OR*** toe*[tiab] ***OR*** phalang*[tiab] ***OR*** “Hallux”[Mesh] ***OR*** hallux[tiab])

Appendix 2. Forest plots of data pooling for the effect of semi-rigid FOs versus soft FOs on pain in the subgroups: (a) custom-made FOs versus ready-made FOs, (b) total-contact FOs versus non-total contact FOs, (c) forefoot region of interest, and (d) treatment effect after ≥1 month.







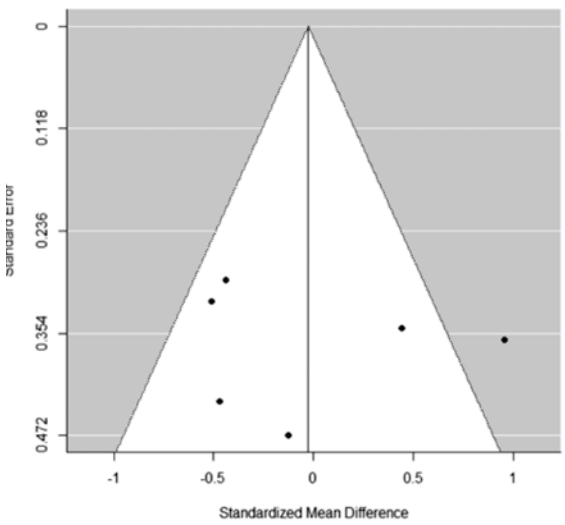


Appendix 3. Qualitative data-synthese

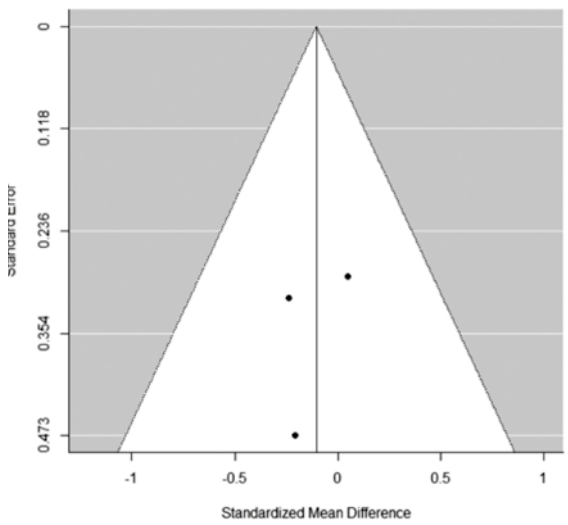
Outcome	Level of evidence	Results	References
semi-rigid FOs (a) versus soft FOs (b)			
compliance	inconclusive	*0.26 hour more wearing time a day in favor of treatment with intervention a; P = n/a*	Chalmers et al. 2000 (31)
costs of FOs	inconclusive	*-0.03 (95% CI -0.08 – 0.03) QALYs in favor of treatment with intervention a; P = 0.46*	Rome et al. 2016 (34)
patient satisfaction	inconclusive	*a and b were both nominated as preferred FOs by 11 (out of 24) participants; P = n/a*	Chalmers et al. 2000 (31)
		82% more participants nominated intervention b as preferred FOs; P = n/a	Chang et al. 2011 (35)
		20% more participants nominated intervention a as preferred FOs; P = n/a	Hodge et al. 1995 (36)
custom-made (semi-rigid) FOs (a) versus ready-made (soft) FOs (b)			
foot function, construct plantar pressure	inconclusive	*0.99 (16%) lower forefoot plantar pressure (PTI) in favor of treatment with intervention b; P = n/a*	Hodge et al. 1995 (36)
patient satisfaction	inconclusive	*20% more participants nominated intervention a as preferred FOs; P = n/a*	Hodge et al. 1995 (36)
total-contact (semi-rigid) FOs (a) versus non-total-contact (soft) FOs (b)			
costs of FOs	inconclusive	*-0.03 (95% CI -0.08 – 0.03) QALYs in favor of treatment with intervention a; P = 0.46*	Rome et al. 2016 (34)
patient satisfaction	inconclusive	*a and b were both nominated as preferred FOs by 11 (out of 24) participants; P = n/a*	Chalmers et al. 2000 (31)
		82% more participants nominated intervention b as preferred FOs; P = n/a	Chang et al. 2011 (35)
		20% more participants nominated intervention a as preferred FOs; P = n/a	Hodge et al. 1995 (36)
selective laser sintered FOs (a) versus standard custom-made FOs (b)			
foot function, plantar pressure	inconclusive	*9.3 (13.6) lower medial forefoot plantar pressure (PP) in favor of treatment with intervention a; P = 1.00*	Gibson et al. (11)
foot function, gait	inconclusive	*2 more steps per minute (cadence) in favor of treatment with intervention b; P = n/a*	Pallari et al. 2010 (38)
patient satisfaction	inconclusive	*2.4 higher VAS fit of FOs in favor of treatment with intervention b; P ≥0.05*	Pallari et al. 2010 (38)
FOs with metatarsal bars (a) versus FOs with metatarsal domes (b)			
foot pain	inconclusive	*7 mm on VAS-score less pain in favor of treatment with intervention b*	Hodge et al. 1995 (36)
patient satisfaction	inconclusive	*intervention a was nominated by 30% of participants and intervention b by 50% as preferred FOs*	Hodge et al. 1995 (36)
		intervention a was nominated by 30% of participants and intervention b by 70% as preferred FOs	Jackson et al. 2004 (32)

FOs = foot orthoses. VAS = visual analogue scale. QUALYs = quality-adjusted life years. PTI = pressure time integral. PP = peak pressure.

Appendix 4. Funnel plots for the comparison 'semi-rigid FOs versus soft FOs' on the outcomes (a) foot pain and (b) physical functioning.



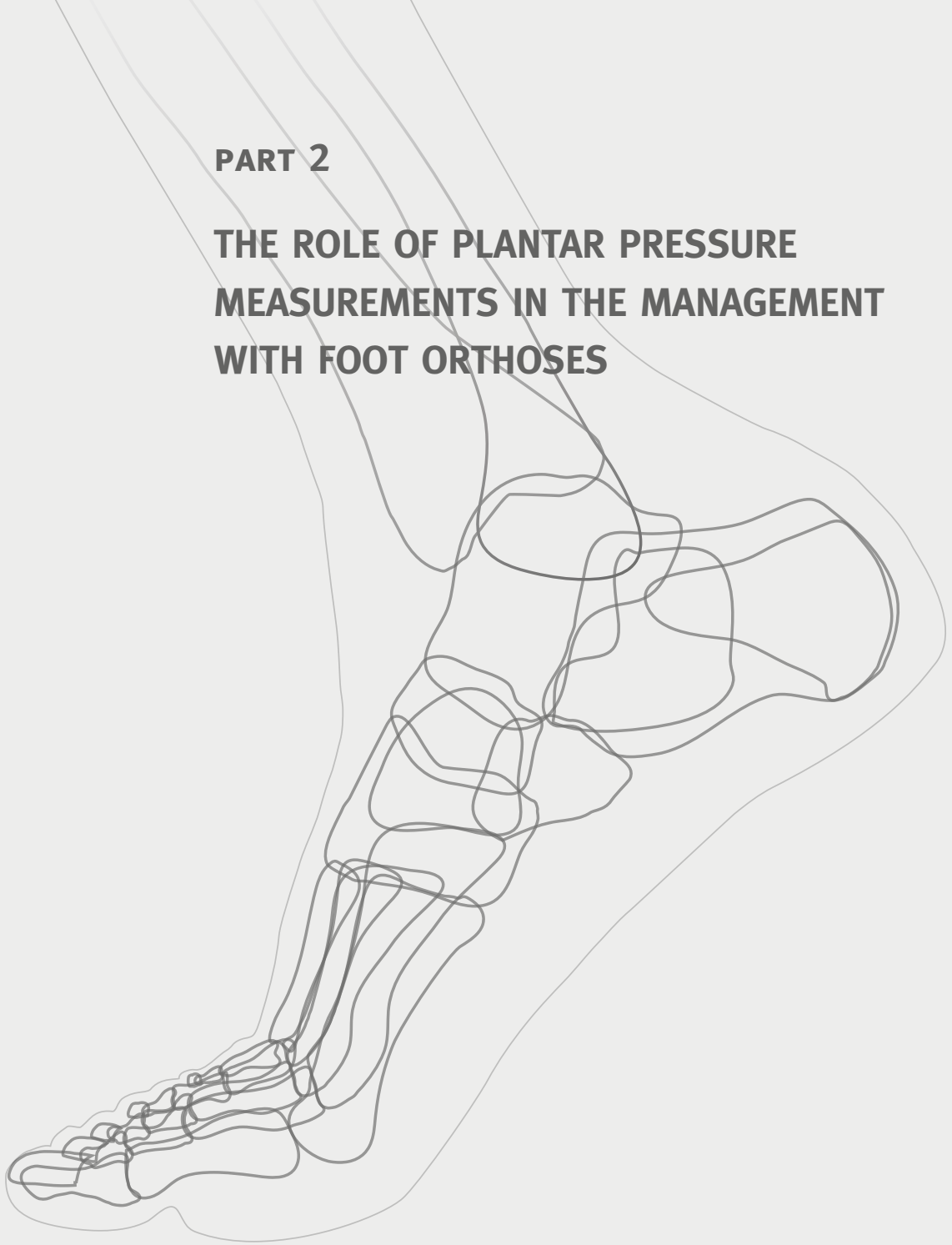
a. foot pain



b. physical functioning

PART 2

THE ROLE OF PLANTAR PRESSURE MEASUREMENTS IN THE MANAGEMENT WITH FOOT ORTHOSES



CHAPTER 5

In-shoe plantar pressure measurements for the evaluation and adaptation of foot orthoses in patients with rheumatoid arthritis: *A proof of concept study*

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Gait & Posture. 2016;45:45-50

Abstract

Objectives

Improving foot orthoses (FOs) in patients with rheumatoid arthritis (RA) by using in-shoe plantar pressure measurements seems promising. The objectives of this study were to evaluate 1) the outcome on plantar pressure distribution of FOs that were adapted using in-shoe plantar pressure measurements according to a protocol and 2) the protocol feasibility.

Methods

Forty-five RA patients with foot problems were included in this observational proof-of concept study. FOs were custom-made by a podiatrist according to usual care. Regions of Interest (ROIs) for plantar pressure reduction were selected. According to a protocol, usual care FOs were evaluated using in-shoe plantar pressure measurements and, if necessary, adapted. Plantar pressure-time integrals at the ROIs were compared between the following conditions: 1) no-FO *versus* usual care FO and 2) usual care FO *versus* adapted FO. Semi-structured interviews were held with patients and podiatrists to evaluate the feasibility of the protocol.

Results

Adapted FOs were developed in 70% of the patients. In these patients, usual care FOs showed a mean 9% reduction in pressure-time integral at forefoot ROIs compared to no-FOs ($p=0.01$). FO adaptation led to an additional mean 3% reduction in pressure-time integral ($p=0.05$). The protocol was considered feasible by patients. Podiatrists considered the protocol more useful to achieve individual rather than general treatment goals. A final protocol was proposed.

Conclusions

Using in-shoe plantar pressure measurements for adapting foot orthoses for patients with RA leads to a small additional plantar pressure reduction in the forefoot. Further research on the clinical relevance of this outcome is required.

Introduction

Inflammation, structural damage and deformities of foot joints are highly frequent in patients with rheumatoid arthritis (RA) [1-4]. These impairments may result in pain, alterations in the loading pattern of the foot during weight bearing [2, 4-6] and subsequently to limitations in daily activities and a reduced quality of life [7, 8].

RA related foot problems can be managed by providing custom made foot orthoses (FOs). Redistribution of plantar foot pressure, by creating a larger weight bearing area, is supposed to be one of the working mechanisms of FOs [9-11]. A recent systematic review showed FOs to be effective in reducing pain and high plantar forefoot pressures. However, only a moderate effect on pain reduction was found (pooled effect size 0.45) [12]. Improving the effects of FOs by using the immediate feedback from plantar pressure measurements seems promising [13, 14]. To date, evaluation and subsequent adaptation of FOs is usually based on patient feedback.

A study of Bus et al. showed that adapting therapeutic footwear (including custom-made inserts) with the use of sequential in-shoe plantar pressure measurements resulted in footwear with better plantar pressure distribution properties in patients with diabetic neuropathy [14, 15]. Because of the differences in foot pathologies between patients with diabetic neuropathy and patients with RA, we developed a specific FO adaptation protocol for patients with RA. With the protocol, we aimed to achieve a maximal reduction of plantar pressure in painful foot regions because of the established relationship between high plantar pressure and foot pain [6, 9].

The objectives of the present study were to evaluate 1) the outcome on plantar pressure distribution of FOs that are adapted according to the developed protocol in patients with RA and 2) the feasibility of this protocol.

Methods

Protocol

For the present study, an existing protocol for adapting therapeutic footwear in patients with diabetic neuropathy [14] was modified, using relevant scientific literature in RA. Our research group, consisting of experts in the fields of podiatry, rehabilitation, rheumatology and biomechanics reached consensus on a draft protocol. Subsequently, this draft protocol was field-tested in seven patients. Adjustments were made based on the feedback of the patients and experts, leading to the protocol that was used in this study.

Process for designing usual care FO

According to usual care at our institute, the patient's medical history was assessed and physical examination was performed. Subsequently, custom made FOs were designed and manufactured by the podiatrist. These FOs were constructed using prefabricated, semi-rigid

orthotic devices with a deep heel cup and contoured medial arch. The orthotic devices were heat-moulded to the patient's foot while using the functional suspension subtalar joint neutral position technique [16, 17]. Based on the findings of the podiatrist, functional corrections [9-11, 16] (i.e. varus-, valgus corrections, metatarsal bars and metatarsal domes) and shock absorbing padding could be added [10, 16]. The FOs were covered with leather, EVA or cushioning material such as PPT.

Process for evaluation and adaptation of usual care FO

Regions of Interest (ROIs) were selected as regions of pain (as indicated by the patient) with relatively high plantar pressure (as measured in-shoe during walking). High plantar pressures in foot regions (hindfoot, medial midfoot, lateral midfoot, forefoot, hallux, toe 2-5) were determined by the podiatrist by viewing a plantar pressure distribution diagram of the feet of the patient. A tentative treatment goal for plantar pressure reduction by wearing FOs was a-priori defined. Based on previous studies [9, 10] and our experiences during testing the draft protocol we aimed to achieve ≥20% plantar pressure reduction in each ROI. Plantar pressure was expressed as peak pressure-time integral (PTI: the integral of peak pressure over time measured in any sensor within the defined ROI). In order to evaluate the PTI change in ROIs, PTI with FOs was compared to PTI with shoes only (no FOs). If the treatment goal of ≥20% PTI reduction in selected ROIs was not achieved, FOs were adapted in order to further reduce PTI. Adaptations could consist of (change in) functional corrections and/or additional shock absorbing padding. Subsequent in-shoe plantar pressure measurements during walking, with adapted FOs, were taken. Again the PTI change in ROIs was evaluated, which could lead to new adaptations. A maximum of three rounds of in-shoe pressure measurements and FO adaptations was set, with a maximal time duration of 45 minutes.

Proof of concept study

Design

Patients of an outpatient center for rehabilitation and rheumatology (Reade, Amsterdam) in the Netherlands served as the study population for this observational proof-of-concept study. In-shoe plantar pressure measurements during walking were taken: 1) prior to the first appointment with the podiatrist (baseline), and 2) during the process of evaluation and adaption of FOs. In addition, descriptive measurements and measurements of pain and disability were taken prior to the appointment with the podiatrist. Follow up measurements were taken after 3 months (end of treatment). For the present study, data assessed at baseline were used.

To assess feasibility, semi-structured interviews with podiatrists and participants were held and characteristics of all individual FO processes were registered.

The medical ethics committee of the Slotervaart Hospital/Reade in Amsterdam approved this study and written informed consent was obtained from each patient.

Patients

Consecutive patients, who were referred by a rheumatologist for podiatric treatment in a specialized center for rheumatology and rehabilitation, were approached to participate in the present study. Inclusion criteria were: 1) RA diagnosed by a rheumatologist according to the revised criteria of the American Rheumatism Association [18], 2) referral for podiatric treatment because of RA related foot problems, 3) indication for FOs according to the podiatrist, 4) ≥18 years of age. Exclusion criteria were: 1) comorbid disease with potentially confounding foot involvement, 2) not able to walk independently without using aids, and 3) inability to fill out questionnaires because of language or cognitive difficulties.

Podiatrists

FOs were manufactured and adapted using the protocol by three podiatrists, accustomed to treating RA-related foot problems with 1.5, 5 and 11 years of experience.

Measurements

Descriptive measures

Sex, age, body mass index, disease duration and site(s) of foot symptoms as indicated by the patient were recorded. Disease activity was measured using the disease activity score including a 44 joint count (DAS-44) [19]. Joint damage of the feet on radiographs was scored by using the Sharp/van der Heijde method, including a score for foot joint erosion and a score for foot joint space narrowing [20]. The Platto-score was used to quantify forefoot deformity and rearfoot deformity [21]. The Foot Function Index (FFI) was used to measure foot pain and disability [22].

Radiographs of the feet were scored by a trained physician. All other measurements were performed by two independent clinical research assistants, trained in taking the measures in a standardized way.

Plantar pressure measurements

The Pedar-X system (Novel GmbH, Munich, Germany) was used to measure in-shoe plantar pressure while walking. Patients wore standard socks and shoes during all measurements in order to eliminate the effect of patients' own shoes and socks, allowing comparison between FO conditions. After accommodation to the system, a test trial was performed to determine comfortable walking speed. The actual measurement consisted of one trial of walking at a self-selected speed along a 25-meter walkway. During all measurements walking speed was monitored and when ≥15% deviant from the test trial, patients were asked to adjust their speed and the trial was repeated [23].

Using Pedar-X Step analysis software (Novel gmbh) 30 midgait steps were selected per measurement. Acceleration, deceleration and turning steps were excluded. Novel-projects software (Novel gmbh) was used to draw automatically a standardized mask that divided the foot into 6 regions, corresponding with the possible ROIs. PTI for each ROI was used to evaluate FO, since PTI is supposed to be an indicator for tissue stress and consequent foot pain [6, 24]. Additionally, peak pressure (PP) was recorded for each ROI.

Feasibility of the protocol

The feasibility of (1) the plantar pressure criteria used and (2) the process of adapting FOs was evaluated. Semi-structured interviews with all 3 podiatrists included the following topics: 'applicability and interpretability of measurements', 'clinical relevance of pressure criteria' and 'usefulness of adaptation process'. Semi-structured interviews with 10 participants (chosen as 1 out of 2 in the first sixteen, and the last two included patients) were held to gain feedback on patient's experience with the protocol, e.g. duration, fatigue, information obtained, and items to be improved. At the end of all interviews a faithful depiction of the experiences was achieved by verifying whether the remarks were interpreted in a correct way by giving a summary.

Characteristics of all individual FO processes were registered, including treatment goal, type of FO corrections, number of adaptation rounds, time duration, and reason for ending the process.

Analysis

In order to evaluate the outcome of the protocol on plantar pressure distribution, data of the in-shoe plantar pressure measurements were transferred to SPSS (SPSS, version 18, Chicago, IL). Pressure-time integrals and peak pressures at the ROIs of patients' feet were compared between the following FO conditions: 1) no FO *versus* usual care FO, and 2) usual care FO *versus* adapted FO. In addition, the plantar pressure distribution of the final FO that the patients took home (either usual care or adapted) was compared to no FO. Differences between FO conditions were calculated using paired t-tests and were considered significant at P≤0.05.

To evaluate the feasibility of the protocol and the a-priori defined plantar pressure treatment goal, the notes taken during the interviews with patients and podiatrists were summarized and registration forms were analyzed.

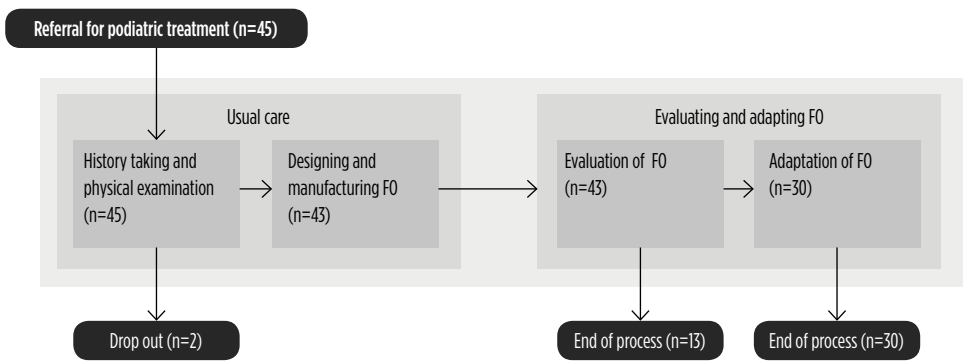

Figure 1. Flow of patients through the different phases of the process

Results

Descriptives

Forty-five patients were included in the present study. Two included patients dropped out due to non-response (n=1) and lack of space in standard shoes with FO (n=1). Data of 43 patients were analyzed: 33 women and 10 men, with a mean age of 53 years. Patient characteristics are shown in ***Table 1***. ***Figure 1*** shows the flow of patients through the various phases of the FO prescription and adaptation process.

Plantar pressure distribution

In total, 86 ROIs were selected in the feet of 43 patients. Nine selected ROIs were located in the rearfoot and five in the hallux. The majority of ROIs was located in the forefoot (84%). Therefore only forefoot ROIs were used in the analyses.

Usual care FOs were adapted in 30 of the 43 patients. In 25 of these 30 patients, forefoot ROIs were selected. In these patients, usual care FOs resulted in a 9% PTI reduction compared to no FOs in the 49 selected forefoot ROIs (mean reduction 8.87 kPa.s, 95% CI 2.36 to 15.38, p=0.01). FO adaptation led to an additional 3% PTI reduction (mean reduction 2.98 kPa.s, 95% CI 0.01 to 5.94, p=0.05) (see ***Table 2***). In 13 of the 43 patients, adaptation of usual care

Table I. Patient characteristics

Characteristics	Value
Age, years	53 (13.5)
Female, n (%)	33 (76.7)
Body-mass index, kg/m2	26.5 (6.4)
Disease duration*, years	5.5 (1.0;10.0)
DAS-44*	1.4 (0.9;2.3)
Sharp / van der Heijde score feet*	
foot joint erosion (range 0-120)	0.0 (0.0;1.0)
joint space narrowing (range 0-48)	0.0 (0.0;0.3)
Platto-score	
forefoot deformity* (range 0-12)	1.0 (0.0;3.0)
rearfoot deformity* (range 0-7)	1.0 (0.0;1.5)
Location of foot pain, n (%)	
rearfoot	3 (7.0)
forefoot	32 (74.4)
hallux	3 (7.0)
combination	5 (11.6)
Uni-/ bilateral foot pain, n (%)	
unilateral	7 (16.3)
bilateral	36 (83.7)
Foot Function Index	
pain (range 0-100)	43.2 (23.2)
disability (range 0-100)	33.4 (23.3)

Values are presented as mean ± SD unless otherwise indicated.
** Values are presented as median (IQR). DAS-44 = disease activity score.*

FOs was not performed for the following reasons: the treatment goal was reached (n=2), relatively low PTI in ROIs (n=8) and fatigue in patients (n=3).

Final FOs, either usual care or adapted, were prescribed in all 43 patients. In 37 of the 43 patients forefoot ROIs were selected. In these patients, final FOs resulted in a 10% PTI reduction compared to no FOs in the 72 selected forefoot ROIs (mean reduction 9.54 kPa.s, 95% CI 4.22 to 14.87, p=0.001) (see ***Table 3***). The a-priori defined treatment goal was reached in 29, out of 72, selected forefoot ROIs. No statistically significant peak pressure reduction in forefoot ROIs was found.

Feasibility of the protocol

The feasibility of the process of adapting FO appeared to be acceptable for a future study. All 10 interviewed patients were positive about the application of the protocol, i.e. the treatment was well tolerated and to satisfaction. All podiatrists gave positive feedback on the topics 'applicability and interpretability of measurements', and 'usefulness of adaptation process', and indicated that the use of in-shoe plantar pressure measurements offered guidance in the process of evaluation and adaptation of FOs.

Analysis of the individual FO processes showed that the duration of the process was feasible for the majority of patients (93%), except for three patients in whom the adaptation protocol was ended due to fatigue. Adaptation of usual care FOs was performed in 30 patients (70%): in 21 patients one adaptation round, and in nine patients two rounds were performed. A maximum of two adaptation rounds was feasible in 45 minutes. The defined plantar pressure

Table 2. PTI (kPa s) and PP (kPa) in forefoot ROIs with different FO conditions (n=25)

ROI	Number of ROIs	No FO (0)	Usual care FO (1)	Adapted FO (2)	Δ 0-1			Δ 1-2		
		Mean (SD)	*Mean (SD)*	*Mean (SD)*	*Mean (SD)*	*95% CI*	*p-value*	*Mean (SD)*	*95% CI*	*p-value*
Forefoot	49									
PTI		97.21 (25.41)	88.34 (27.32)	85.36 (24.65)	-8.87 (22.66)	2.36 to 15.38	0.01	-2.98 (10.33)	0.01 to 5.94	0.05
PP		336.72 (82.12)	326.08 (99.61)	323.65 (101.32)	-10.64 (76.39)	-11.30 to 32.58	0.33	-2.42 (48.08)	-11.39 to 16.24	0.73

ROI=region of interest. FO=foot orthoses. PTI=pressure time integral. PP=peak pressure.

Table 3. PTI (kPa s) and PP (kPa) in forefoot ROIs without FO and with final FO (n=37)

ROI	Number of ROIs	No FO (0)	Final FO (F)	Δ 0-F		
		Mean (SD)	*Mean (SD)*	*Mean (SD)*	*95% CI*	*p-value*
Forefoot	72					
PTI		92.29 (24.71)	82.75 (23.63)	-9.54 (22.66)	4.22 to 14.87	0.001
PP		325.05 (83.43)	317.60 (96.65)	-7.45 (78.57)	-11.01 to 25.91	0.42

ROI=region of interest. FO=foot orthoses. PTI=pressure time integral. PP=peak pressure.

criteria were not acceptable for use in a future study. PTI reduction ≥ 20% in all determined ROIs was not feasible in the majority of patients: in only eight out of 43 patients this goal was achieved. According to the podiatrists, ≥20% plantar pressure reduction was not reasonable to achieve in each ROI.

Final protocol

The protocol was revised based on the evaluation of its feasibility. According to the final protocol, in-shoe plantar pressure measurements are performed prior to designing and manufacturing FOs. ROIs are selected based on site(s) of foot symptoms as indicated by the patient as well as on information from the pressure distribution diagram and the physical examination performed by the podiatrist. Based on the clinical reasoning process of the podiatrist, individual treatment goals are set in order to change the pressure distribution at ROIs. FOs are designed and custom-made by the podiatrist. Subsequently, FOs are evaluated with in-shoe plantar pressure measurements. When individual treatment goals are achieved the process ends. Otherwise, the FOs are adapted. ***Figure 2*** shows a flow chart of the final protocol.

Discussion

In the present study in-shoe plantar pressure measurements were used to evaluate FOs in patients with RA. Based on the feedback of these measurements adapted FOs were developed in 30 out of 45 patients (70%). In these patients, usual care FOs resulted in a mean 9% PTI reduction in forefoot ROIs compared to no FO. Adaptation of usual care FOs led to an additional mean 3% PTI reduction.

The study of Bus et al. [14, 25] in patients with diabetic neuropathy is to our knowledge the only study investigating a comparable protocol. In that study, adaptation of therapeutic footwear resulted in an additional mean PTI reduction of 24% in all ROIs [14]. The greater pressure reduction found by Bus et al. could be related to the intervention. Therapeutic footwear has a greater potential for plantar pressure reduction than FOs. The observed difference could also be related to the study population. Foot pathology and treatment strategy are different in RA patients with painful (sensate) feet compared to patients with diabetic neuropathy and insensate feet. The time needed to adapt to the FO in patients with sensate feet might be longer than in patients with insensate feet, which may have led to a suboptimal short-term effect on pressure distribution (i.e. smaller plantar pressure changes). To limit that effect a considerable amount of time was reserved for patients to walk with their FO before plantar pressure measurements were performed.

Improvement of the protocol related to the treatment goal was deemed necessary. One general treatment goal (≥ 20% PTI reduction in each ROI) in all participating patients was unrealistic. Instead, a mean PTI reduction of 10% was realized after FO intervention in our study. During the development of the protocol we presumed to include patients with mainly forefoot deformities

and subsequent high plantar forefoot pressures related to forefoot pain. However, patients with relatively short disease duration and few deformities were included, resulting in lower forefoot plantar pressures than found in studies that included patients in a more advanced disease stage [9, 10]. This might be the result of advances in early referral and tight disease control in RA

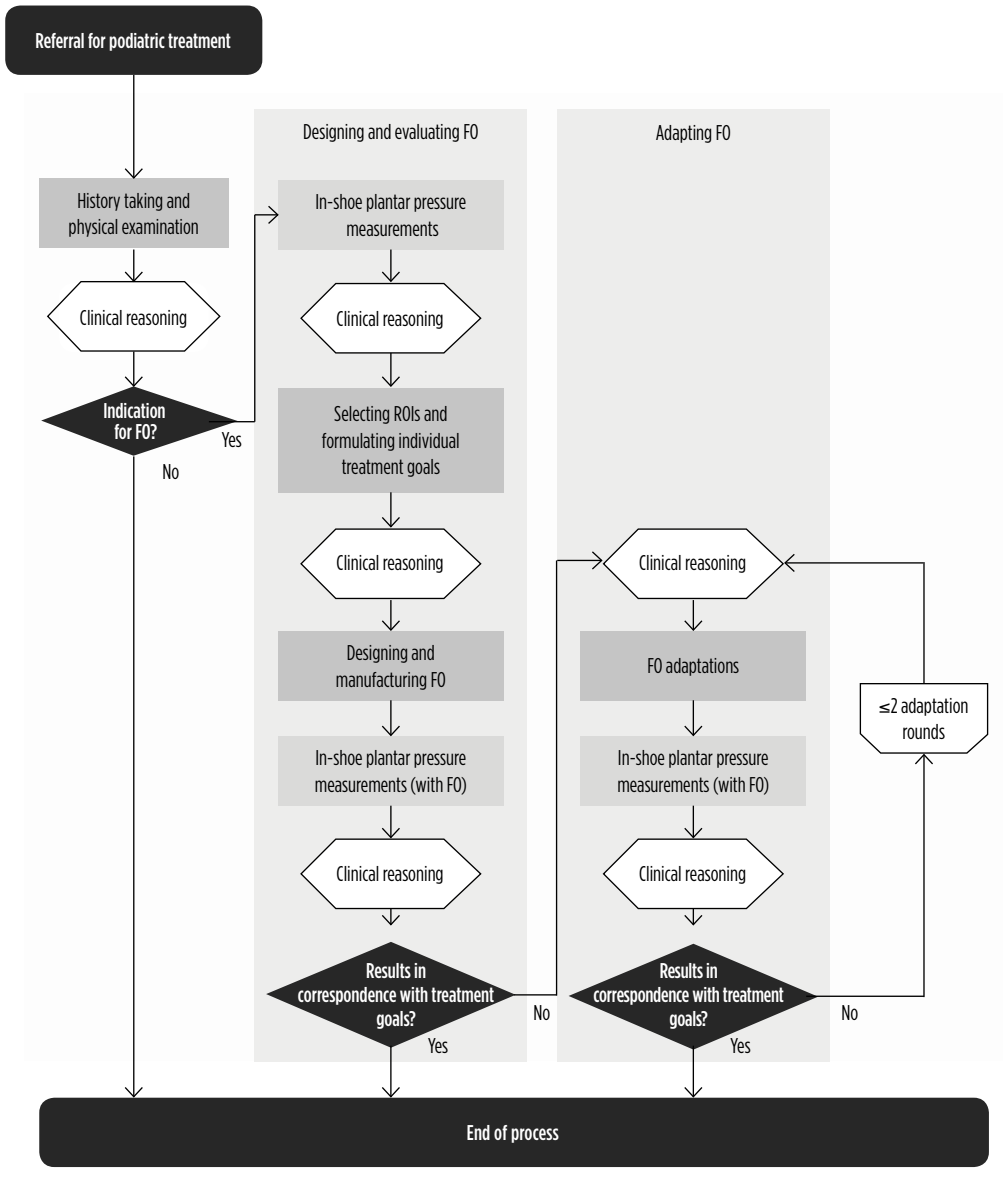

Figure 2. Flow chart final protocol

in recent years. Moreover, a forefoot offloading strategy was detected in some patients [26, 27]. In these patients, using FOs could normalize forefoot loading, resulting in increased forefoot PTI after FO intervention while in other patients decreased forefoot PTI after FO intervention was achieved. These different strategies are reflected by the large standard deviation around the mean PTI change found in our study (see ***Table 3***). In the final protocol individual treatment goals were proposed, instead of a general treatment goal.

The process for adapting FO was considered acceptable for a future study. Although fatigue was reported in only 7% of the patients it is an important aspect to monitor and adapt the process to, in clinical practice but also in future research.

Whether this protocol for adapting FOs with the feedback of plantar pressure measurements is (cost) effective in RA needs further investigation. The 3% additional PTI reduction found in the present study is based on a short term evaluation of biomechanical mode-of-action. Long term clinical impact of this PTI reduction will be reported in a separate manuscript, using data on pain and physical functioning assessed within the present study. Ultimately, a definitive RCT including health economic benefit is warranted. To set up a RCT stratification is recommended in order to control for confounding of pain and function driven by mechanical and/or inflammatory disease.

A limitation of the present study could be the selected study population. The majority of the study population was treated for early RA, with minimal foot joint damage and mild foot deformities, refraining us from conclusions regarding patients with a more advanced disease stage. Furthermore, patients were treated in an outpatient center for rehabilitation and rheumatology which may hamper the generalizability of the results to other care settings.

The results of the present study may have several implications for both clinical practice and podiatry education. First, in-shoe plantar pressure measurements can be used as an additional diagnostic tool in RA patients with foot problems; it provides insight in the relation between foot pain and plantar pressure during walking with shoes. Second, the immediate feedback of in-shoe plantar pressure measurements may offer guidance to the process of evaluation and adaptation of FOs.

In conclusion, using in-shoe plantar pressure measurements for adapting FOs, leads to a small additional plantar pressure reduction in the forefoot in patients with RA and foot problems. Further research on the clinical relevance of this outcome is required.

Acknowledgements

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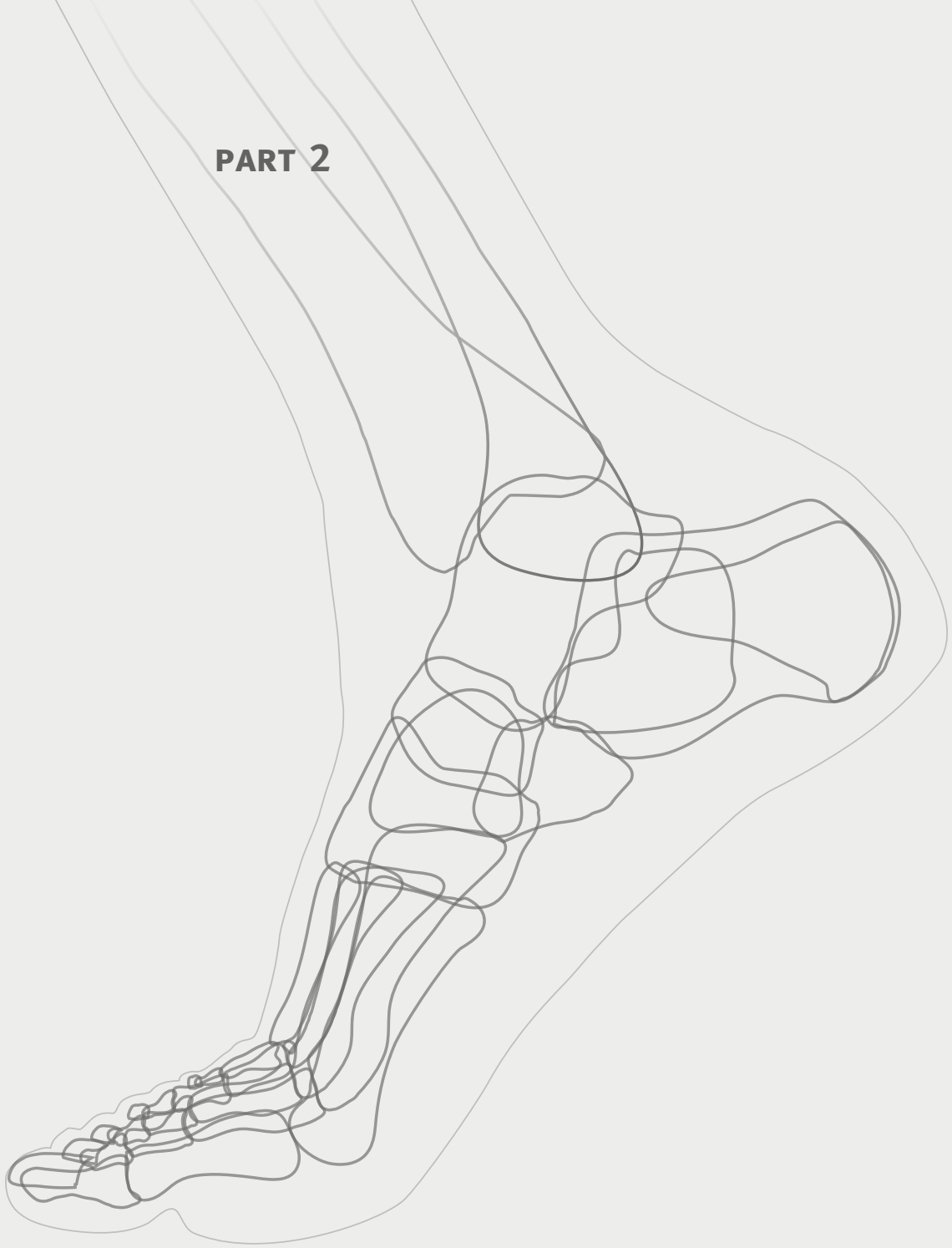

PART 2

CHAPTER 6

Outcomes and potential mechanism of a protocol to optimize foot orthoses in patients with rheumatoid arthritis

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Under review for publication

Abstract

Background

In order to optimize foot orthoses (FOs) for patients with rheumatoid arthritis (RA), a protocol has been developed that makes use of feedback from in-shoe plantar pressure measurements. The objectives of the present study were: 1) to evaluate the 3-months outcome of FOs developed according to the protocol on pain, physical functioning and forefoot plantar pressure in patients with RA-related foot problems, and 2) to determine the relationship between change in forefoot plantar pressure and change in pain and physical functioning.

Methods

Forty-five patients with RA-related foot problems were included and received FOs developed according to the protocol. Outcome measures were assessed at baseline and after three months of wearing FOs in 38 patients. Change scores and effect sizes were calculated for pain, physical functioning and plantar pressure. In a subgroup of patients with combined forefoot pain and high plantar pressure, the relation between change in plantar pressure and change in pain and physical functioning was analyzed.

Results

In the total group of 38 patients, statistically significant changes in pain (ES 0.69), physical functioning (ES 0.82) and forefoot plantar pressure (ES 0.35) were found. In the subgroup (n=23) no statistically significant relations were found between change in plantar pressure and change in pain or physical functioning.

Conclusion

Foot orthoses developed according to a protocol for improving the plantar pressure redistribution properties lead to medium to large improvements in pain and physical functioning. The hypothesis that more pressure reduction would lead to better clinical outcomes could not be proven.

Introduction

Foot problems are highly prevalent in patients with rheumatoid arthritis [1-5]. Inflammation and synovitis of foot joints may lead to changes in foot structure and foot function [1, 6]. Abnormal foot function can result in high plantar foot pressures and subsequent foot pain and disability [7, 8]. This process mainly affects the forefoot [1, 7]. Previous research showed that RA patients with foot problems experience limitations in daily activities and a reduced quality of life [9, 10].

Treatment of RA-related foot problems often consists of custom made foot orthoses (FOs) and a shoe advice by a podiatrist, especially in the early stage of the disease [11]. One of the assumed working mechanisms of FOs is redistribution of plantar pressure by creating a larger weight bearing area [12-14]. Overall, the reported treatment effect of FOs on foot pain in RA is small (effect size 0.4) [15], to medium (effect size 0.45) [16]. In order to optimize the treatment effect of FOs, a protocol for evaluation and adaptation of FOs has been developed that makes use of feedback from in-shoe plantar pressure measurements [17]. The protocol included: (1) setting individual treatment goals on plantar pressure redistribution, (2) manufacturing custom-made FOs according to the patient's needs, based on the clinical reasoning process of the podiatrist, and (3) evaluating and, if necessary, adapting FOs according to the feedback of in-shoe plantar pressure measurements (in one to three rounds). The adapted FOs showed, in a repeated single session design, small additional forefoot plantar pressure reduction over usual care FOs [17]. The immediate feedback of in-shoe plantar pressure measurements provided guidance in the clinical reasoning process of the podiatrist. The outcomes of FOs developed according to the FOs optimization protocol after three months follow-up on pain, physical functioning and forefoot plantar pressure are not yet known.

Since high plantar pressures are related to foot pain in RA it is hypothesized that a reduction of forefoot plantar pressure leads to reduction of pain and subsequent disability [7]. Nevertheless, there is a lack of evidence supporting this hypothesis. Previously published systematic reviews indicate that custom made FOs are effective in reducing forefoot plantar pressures [16] and pain in RA [15, 16]. However, the relationship between change in forefoot plantar pressure and change in pain has never been investigated. Furthermore, in our previous study investigating the FOs optimization protocol we found that a subgroup of patients with forefoot pain also had high forefoot plantar pressure at baseline [17]. This implicates that only in the patients with combined forefoot pain and high forefoot plantar pressure, the working mechanism of FOs may be related to plantar pressure reduction. Therefore, subgroup analysis is necessary to investigate whether pressure reduction is associated with outcomes on pain and physical functioning.

The objective of the present study was twofold: 1) to evaluate the outcomes of FOs developed according to the FOs optimization protocol on pain, physical functioning and forefoot plantar pressure in patients with RA-related foot problems, and 2) to determine the relationship between change in forefoot plantar pressure and change in pain and physical functioning.

Materials and methods

Design

Patients of an outpatient center for rehabilitation and rheumatology in the Netherlands served as the study population for this quasi-experimental clinical trial. In a previously published proof of concept study the outcomes of FOs (developed by using a FOs optimization protocol) on immediate plantar pressure redistribution and the feasibility of the protocol were reported [17]. In this FOs optimization protocol, the feedback of in-shoe plantar pressure measurements was used for the evaluation and adaptation of FOs. For the purpose of the present study, in-shoe plantar pressure measurements were assessed (in the patient's own shoes) without FOs at baseline (To) and with FOs at three months after delivery (follow-up (T1)). Pain and physical functioning were measured before FOs delivery (To) and after three months of wearing FOs (T1). The outcomes on pain, physical functioning and forefoot plantar pressure were analyzed in all included patients (total group). Out of this total group, a subgroup was selected of patients with combined forefoot pain and high plantar pressure (Peak Pressure≥200 kPa in the central forefoot region (metatarsophalangeal joints 2-3) [18]) at baseline. We hypothesized that in these patients the working mechanism of FOs on pain and physical functioning outcomes is related to plantar pressure reduction. Therefore, the relationship between change in forefoot plantar pressure and change in pain and physical functioning was investigated in the subgroup. In addition, clinical characteristics were assessed. This study was approved by a medical ethics committee and written informed consent was obtained from each patient.

Patients

Consecutive patients, who were referred by a rheumatologist for podiatric treatment in a specialized center for rheumatology and rehabilitation, were approached to participate in the present study. Inclusion criteria were: 1) ≥18 years of age, 2) RA diagnosed by a rheumatologist according to the revised criteria of the American Rheumatism Association [19], 3) referral for podiatric treatment because of RA-related foot problems, and 4) indication for FOs according to the podiatrist. Exclusion criteria were: 1) another medical condition that underlies the foot problems, 2) not able to walk independently without using aids, and 3) inability to fill out questionnaires because of language or cognitive difficulties.

Podiatric treatment according to the FOs optimization protocol

The podiatric treatment consisted of custom-made FOs according to the patient's needs, based on the feedback of in-shoe plantar pressure measurements and the clinical reasoning process of the podiatrist [17]. If necessary, an individual advice (oral and written) concerning over-the-counter shoes was provided to the patient. The podiatric treatment was performed by three qualified podiatrists, accustomed to treating RA-related foot problems with 1.5, 5 and 11 years of experience.

The process for designing, evaluating and adapting FOs according to the FOs optimization protocol is shown in ***Figure 1***. This process started with a podiatric intake, including anamnesis, physical examination and in-shoe plantar pressure measurements. Based on clinical reasoning, individual treatment goals were set concerning redistribution of plantar pressure in painful foot regions. Initially, it was considered whether plantar pressure reduction was desirable for the painful region. If this was not the case, for example due to pain avoidance as a result of inflammation, correction or support of foot structures to improve the loading pattern of the foot was considered. Then, a target value for plantar pressure in the painful region was established. Custom-made FOs were designed and manufactured by the podiatrist. These FOs were constructed using prefabricated, semi-rigid supplements with a deep heel cup and contoured medial arch. The supplements were heat-molded to the patients' foot while using the functional suspension subtalar joint neutral position technique [20, 21]. Based on the findings of the podiatric intake, functional corrections [12-14, 20] (i.e. varus-, valgus corrections, metatarsal bars and metatarsal domes) and shock absorbing padding could be added [13, 20]. The FOs were covered with leather, ethylene vinyl acetate (EVA) or cushioning material. Finally, the achieved plantar pressure redistribution was evaluated by using the feedback of in-shoe plantar pressure measurements. If necessary, the FOs were adapted according to this feedback and the clinical reasoning process of the podiatrist (in one to three rounds).

Measurements

Demographic and clinical characteristics

Sex, age (years), body mass index (kg/m²), disease duration (years) and site(s) of foot symptoms as indicated by the patient were recorded. Disease activity was measured using the disease activity score including a 44 joint count (DAS-44; range 0-10) [22]. Joint damage on radiographs in the most affected foot was scored by using the Sharp/ van der Heijde method, including a score for foot joint erosion (range 0-120) and a score for foot joint space narrowing (range 0-48) [23]. The Platto-score was used to quantify forefoot deformity (range 0-12) and rearfoot deformity (range 0-7) in the most affected foot [24]. Radiographs of the feet were scored by a trained physician. All other measurements were performed by two independent clinical research assistants trained in standardized measurements.

Foot pain and physical functioning

Foot pain was assessed by using the Foot Function Index (FFI) subscale pain as primary outcome [25], and with an additional Numeric Rating Scale (NRS) for foot pain during walking and during standing. Physical functioning was measured by using FFI subscale disability as primary outcome [25] and an additional 10-meter-timed walking test. For this performance-based test, patients were instructed to walk 10 meters on a self-selected, comfortable walking pace while wearing their own shoes (without FOs at baseline (To) and with FOs at follow-up (T1)).

Forefoot plantar pressure

Forefoot plantar pressure was expressed as Peak Pressure (PP; the highest pressure measured by a single sensor in the forefoot-region) and Pressure Time Integral (PTI; the integral of peak pressure over time measured in the single sensor showing the PP within the forefoot-region, it reflects the amount of pressure applied to the forefoot-region during the total stance phase) [7]. In-shoe plantar pressure measurements without FOs were assessed at baseline (To) and with

FOs at three months after delivery (follow-up (T1)). The Pedar-X system (Novel GmbH, Munich, Germany) was used to measure in-shoe plantar pressure in the patient's own shoes at the shoe-sock interface, while walking. After accommodation to the Pedar-X system, a test trial was performed to determine comfortable walking speed. The actual measurement consisted of one

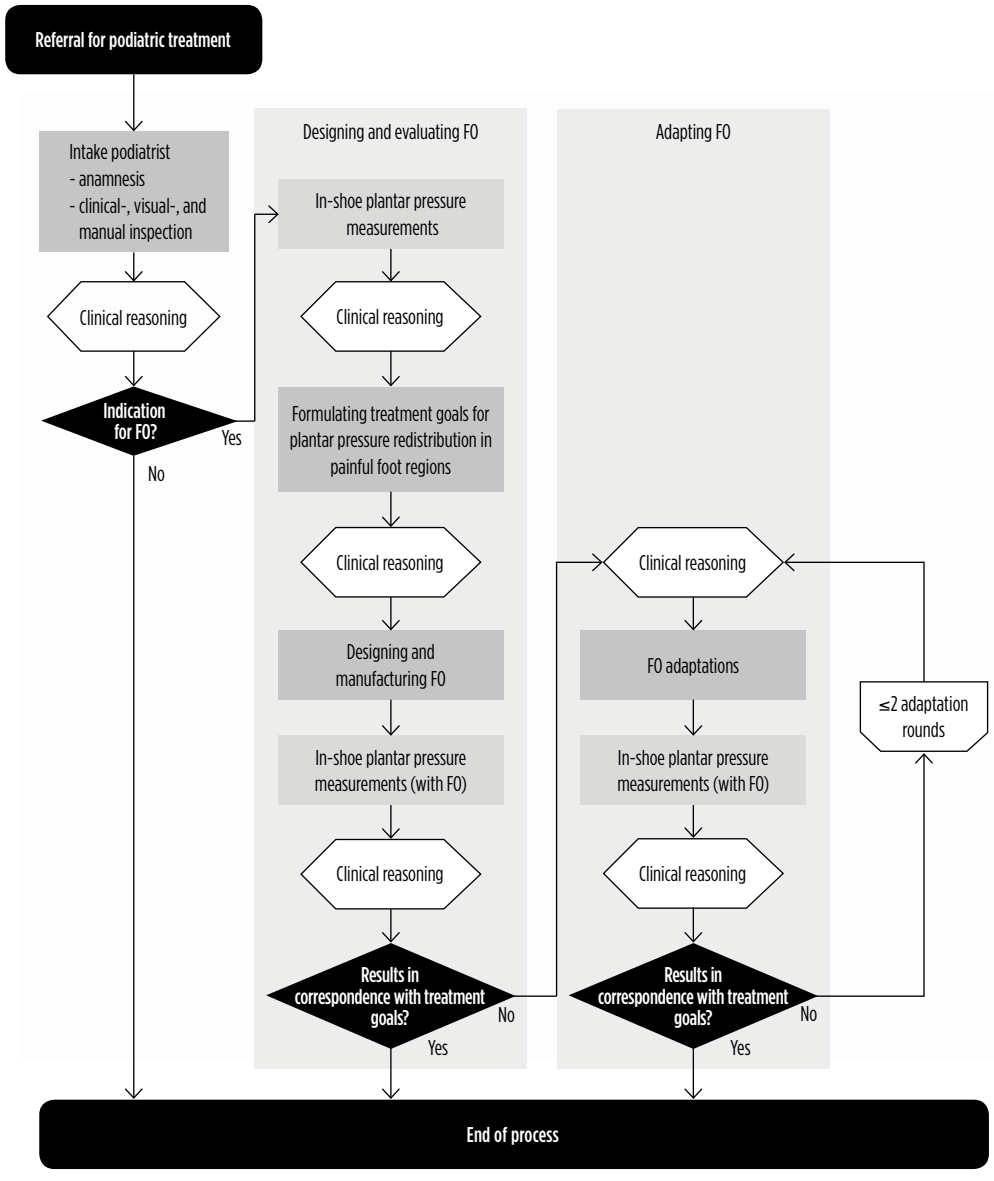

Figure 1. FOs optimization protocol

trial of walking at a self-selected speed along a 25-meter walkway. During all measurements walking speed was monitored and when ≥15% deviant from the test trial, patients were asked to adjust their speed and the trial was repeated [26]. Using Pedar-X Step analysis software (Novel gmbh, Munich, Germany) 30 midgait steps were selected per measurement. Acceleration, deceleration and turning steps were excluded.

Statistical analysis

Clinical characteristics were described with descriptive statistics. Change scores and effect sizes were calculated for pain, physical functioning and observed forefoot plantar pressure in both the total group and the subgroup. The change (T1-T0) in outcome measures was tested for statistical significance by using paired t-tests. Effect sizes were calculated by using Cohen's D and were interpreted as 0.2 (small), 0.5 (medium) and 0.8 (large) [27]. For observed forefoot plantar pressure (PP and PTI) the patients' most painful foot was included in the analysis. Additionally, estimated differences in forefoot plantar pressure (PP and PTI) were assessed in all measured feet by using multi-level analyses, in which a two-level structure was used (i.e. foot (left/right) clustered within patients) [28]. For the subgroup, generalized estimated equation (GEE) analyses were used to investigate the relationship between change (T1-T0) in forefoot plantar pressure (PTI and PP (independent variables)) and change (T1-T0) in pain or physical functioning as the dependent variables [28]. In both multi-level analysis and GEE analysis, an adjustment was made for plantar pressure at baseline [28]. PASW Statistics 18 software (v.18, SPSS Inc. Chicago, IL, USA) was used to perform the analyses. A significance level of $p<0.05$ was used in all analyses.

Results

Patient characteristics

Patient flow is depicted in ***Figure 2***. Forty-five patients were included in the study. Two of the included patients dropped out due to inability to complete the FOs optimization protocol, and in 5 patients T1 measurements were missing, leaving a total group 38 patients for analyses. Out of this group, a subgroup was selected of 23 patients with combined forefoot pain and high plantar pressure (PP≥200 kPa in the central forefoot region (metatarsophalangeal joints 2-3)) at baseline. In the subgroup the relation between change in forefoot plantar pressure and change in pain and physical functioning was investigated. ***Table 1*** shows the patient characteristics for both groups.

Outcomes on pain, physical functioning and forefoot plantar pressure

Total group

Table 2 shows the outcomes and effect sizes on pain, physical functioning and forefoot plantar pressure after three months of FO delivery for the total group of 38 patients. Statistically significant improvement on pain and physical functioning were found with, respectively, a medium and large effect size. In-shoe plantar pressure measurements showed a statistically

significant PTI reduction (11%) with a small effect size and a non-significant PP reduction (4%) in the patient's most painful foot (38 feet out of the 38 patients). Similar results were found with the analyses of estimated forefoot plantar pressures in all 72 measured feet (out of the 38 patients).

Subgroup

The subgroup consisted of 23 patients with both forefoot pain and high plantar pressure (PP≥200 kPa in the central forefoot region (metatarsophalangeal joints 2-3)) at baseline. ***Table 3*** shows the outcomes and effect sizes on pain, physical functioning and forefoot plantar pressures after three months of FO delivery for the subgroup. Statistically significant improvements on pain and physical functioning were found, with a medium effect size. For observed forefoot PP and PTI a statistically significant reduction, respectively 14% and 16%, in the patients' most painful foot (23 feet out of the 23 patients) with a medium effect size

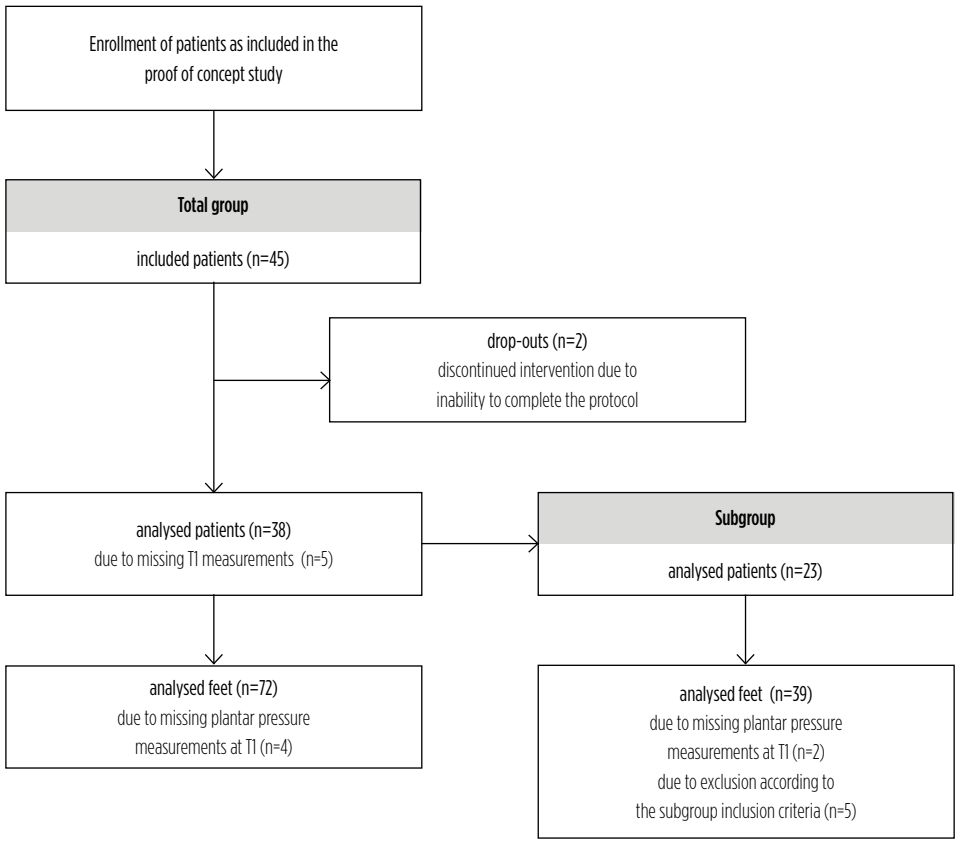

Figure 2. Flow-diagram of patients through the study

was found. Results were similar for forefoot PP and PTI reduction in all 39 measured feet (out of the 23 patients).

Relation between change in forefoot plantar pressure and change in pain and physical functioning

Table 4 shows the relation between change in forefoot plantar pressure and change in pain and physical functioning in the subgroup. The effect estimate (*B* in ***Table 4***) reflects the amount of units in which the dependent variable (pain or physical functioning) changes when

Table 1. Patient characteristics

	Total group (n= 38)	Subgroup (n= 23)
Age, *years*	52.5 (13.9)	53.9 (12.1)
Female, *n (%)*	28 (73.7)	18 (78.3)
Body-mass index, *kg/m2*	26.7 (8.8)	26.3 (4.9)
Disease duration*, *years*	5.5 (1.0;8.5)	6.0 (2.0;10.0)
DAS-44*	1.7 (0.9;2.3)	1.4 (1.0;2.0)
remission (<1.6), *n (%)*	22 (57.9)	14 (60.9)
low disease activity (1.6 -2.3), *n (%)*	9 (23.7)	6 (26.1)
moderate disease activity (2.4-3.6), *n (%)*	5 (13.2)	2 (8.7)
high disease activity (≥ 3.7), *n (%)*	2 (5.3)	1 (4.3)
Location of foot pain, *n (%)*		
rearfoot	2 (5.3)	-
forefoot	29 (76.3)	23 (95.8)
hallux	2 (5.3)	-
combination	5 (13.2)	1 (4.2)
Uni-/ bilateral foot pain, *n (%)*		
unilateral	5 (13.2)	2 (8.7)
bilateral	33 (86.8)	21 (91.3)
Sharp / van der Heijde score feet*		
total score *(range 0-168)*	1.0 (0.0;13.8)	1.0 (0.0;28.0)
foot joint erosion *(range 0-120)*	0.0 (0.0;1.0)	0.0 (0.0;11.0)
joint space narrowing *(range 0-48)*	0.0 (1.0;0.3)	0.00 (0.0;4.0)
Platto-score*		
total score *(range 0-19)*	2.0 (1.0;4.0)	1.8 (1.0;4.4)
forefoot deformity *(range 0-12)*	1.0 (0.0;3.0)	0.8 (0.0;3.0)
rearfoot deformity *(range 0-7)*	1.0 (1.0;1.5)	1.0 (1.0;1.5)
FOs wearing time a day, *n (%)*		
<1 hour	1 (2.9)	0 (0)
1-4 hours	8 (22.9)	4 (16.7)
4-8 hours	13 (37.1)	10 (41.7)
8-12 hours	8 (22.9)	2 (8.3)
>12 hours	5 (14.3)	3 (12.5)

*Values are presented as mean ± SD unless otherwise indicated. * Values are presented as median (IQR). DAS-44 = disease activity score including 44 joints.*

Table 2. Baseline- (T0), follow up- (T1) and change- (Δ T0-T1) scores, and effect sizes for pain, physical functioning and forefoot plantar pressure in the total group (n=38)

Analysed patients	N	T0	T1	Δ T0-T1	ES	P-value
pain						
FFI pain (range 0-100), *primary outcome*	38	42.53 (23.92)	28.66 (23.50)	-13.87 (20.00)	0.69	<0.001
NRS foot pain during walking (range 0-10)	38	5.03 (2.49)	3.37 (2.76)	-1.66 (2.15)	0.77	<0.001
NRS foot pain during standing (range 0-10)	37	3.95 (2.84)	2.97 (2.70)	-0.97 (2.28)	0.43	0.014
physical functioning						
FFI disability (range 0-100), *primary outcome*	38	32.47 (23.38)	22.40 (24.66)	-10.07 (12.25)	0.82	<0.001
10-m walking time, seconds	37	8.78 (1.97)	8.30 (1.33)	-0.49 (1.48)	0.33	0.054
observed forefoot plantar pressure						
PP central forefoot (kPa)	38	246.98 (78.22)	236.62 (89.28)	-10.37 (76.62)	0.14	0.40
PTI central forefoot (kPa s)	38	68.84 (28.21)	61.61 (20.27)	-7.23 (20.64)	0.35	0.033
Analysed feet	**N**			**Δ T0-T1**		**P-value**
estimated forefoot plantar pressure						
PP central forefoot (kPa)	72			-14.20 (10.27)*		0.18
PTI central forefoot (kPa s)	72			-7.07 (2.23)*		0.003

*Values are presented as mean ± SD unless otherwise indicated. * Values are presented as estimated mean difference and standard error. PP = Peak Pressure. PTI = Pressure Time Integral. FFI=foot function index. NRS=numeric rating scale. ES=effect size.*

Table 3. Baseline- (T0), follow up- (T1) and change- (Δ T0-T1) scores, and effect sizes for pain, physical functioning and forefoot plantar pressure in the subgroup of patients with combined forefoot pain and high plantar pressure at baseline (n=23)

Analysed patients	N	T0	T1	Δ T0-T1	ES	P-value
pain						
FFI pain (range 0-100), *primary outcome*	21	34.18 (15.91)	25.23 (19.29)	-8.95 (14.44)	0.62	0.010
NRS foot pain during walking (range 0-10)	21	4.10 (2.53)	2.81 (2.16)	-1.29 (1.95)	0.66	0.007
NRS foot pain during standing (range 0-10)	20	3.15 (2.52)	2.55 (1.99)	-0.60 (1.70)	0.35	0.131
physical functioning						
FFI disability (range 0-100), *primary outcome*	21	25.35 (13.88)	17.13 (13.99)	-8.22 (10.38)	0.79	0.002
10-m walking time, seconds	22	8.27 (1.08)	8.00 (1.02)	-0.27 (0.77)	0.35	0.110
observed forefoot plantar pressure						
PP central forefoot (kPa)	23	288.23 (62.90)	246.85 (66.14)	-41.37 (65.07)	0.64	0.006
PTI central forefoot (kPa s)	23	76.03 (15.01)	63.77 (15.14)	-12.26 (17.83)	0.69	0.003
Analysed feet	**N**			**Δ T0-T1**		**P-value**
estimated forefoot plantar pressure						
PP central forefoot (kPa)	39			-28.43 (10.53)*		0.012
PTI central forefoot (kPa s)	39			-12.52 (2.69)*		<0.001

*Values are presented as mean ± SD unless otherwise indicated. * Values are presented as estimated mean difference and standard error. PP = Peak Pressure. PTI = Pressure Time Integral. FFI=foot function index. NRS=numeric rating scale. ES=effect size.*

the independent variable (PP or PTI) changes one unit. No statistically significant associations between change in forefoot plantar pressure and change in pain and physical functioning were found.

Discussion

The results of our study showed that wearing FOs, developed according to a FOs optimization protocol by using the feedback of in-shoe plantar pressure measurements, leads to significant improvements on pain and physical functioning, as well as a significant reduction of forefoot plantar pressure. However, there were no statistically significant relations between change in plantar pressure and changes in pain or physical functioning.

In the present study reduction of pain and improvement of physical functioning, with respectively medium and large effect sizes were found. The outcome on pain is comparable to within-group differences reported in RCTs investigating the effect of FOs, showing pain reduction with medium [20, 29] and large [30, 31] effect sizes. In these studies follow-up ranged from 3 [31] to 30 [20] months, and sample sizes from 24 [31] to 81 [20] patients. Since we studied the results of an optimization protocol we expected to find greater effects on pain reduction. Future research with a head-to-head comparison is needed to demonstrate whether the optimization protocol has an added value over FOs developed without the use of plantar pressure feedback. The results on pain and physical functioning of our subgroup (23 patients with forefoot pain and high plantar pressure) were comparable to results found for the total group (38 patients). Furthermore, results were clinically relevant as the minimal important differences (MID) for FFI pain (12.3 points improvement [32]) and for FFI disability (6.7 points improvement [32]) were reached in the present study. Therefore, wearing FOs developed according to the FOs optimization protocol may lead to clinically relevant improvements in pain and physical functioning.

In the present study a forefoot plantar pressure (PTI) reduction of 11% with a small effect size was found, based on measurements assessed before FOs delivery and after three months of wearing FOs. Several studies reported forefoot plantar pressure reduction in RA patients while wearing conventional custom-made FOs compared to a control-condition [12-14, 17, 33, 34]. However,

Table 4. Relation between change in forefoot plantar pressure and change in foot pain and physical functioning (n=23)

	Δ Foot pain				**Δ Physical functioning**					
	FFI pain		NRS walking		NRS standing		FFI disability		10-m walking time*	
	B (SE)	*p-value*	*B (SE)*	*p-value*	*Δ (SE)*	*p-value*	*B (SE)*	*p-value*	*B (SE)*	*p-value*
Δ *Plantar pressure*										
PP / 10 kPa	-2.2 (0.8)	0.79	-0.1 (0.1)	0.58	0.0 (0.1)	0.63	0.3 (0.5)	0.59	0.0 (0.0)	0.70
PTI / 10 kPa s	-3.2 (2.2)	0.15	0.4 (0.3)	0.14	0.2 (0.2)	0.43	-0.5 (1.7)	0.78	0.0 (0.1)	0.85

*FFI = foot function index. NRS walking = numeric rating scale foot pain during walking. NRS standing = numeric rating scale foot pain during standing. PP = peak pressure (kPa). PTI = Pressure Time Integral (kPa s). * performance-based test.*

in these studies repeated measures were assessed in a single session and no follow-up results of plantar pressure were reported. Furthermore, forefoot plantar pressure reduction with varying percentages were reported in the literature: PP reduction ranges from 7% to 34% [12-14, 17, 33, 34], and PTI reduction from 12% to 36% [12, 13, 17, 34]. This variation can possibly be explained by different methods for designing FOs or by different baseline characteristics of the studied populations. In a population with higher forefoot plantar pressure at baseline there is a greater potential for reduction, as illustrated by the greater pressure reduction achieved in our subgroup (14% PP reduction and 16% PTI reduction) compared to our total group (4% PP reduction and 11% PTI reduction).

The hypothesis that more plantar pressure reduction leads to more pain reduction and subsequent improvement in physical functioning is not supported by the findings of the present study. Nevertheless, the hypothesis is biologically plausible and forms one of the basic principles for prescribing FOs in patients with RA-related foot problems [12, 17, 20]. A possible explanation for the inability to detect a relationship could be the small sample size of the subgroup. Furthermore, it could be possible that there is a threshold for plantar pressure reduction. Perhaps, plantar pressure reduction up to the threshold-value would lead to relevant improvement on pain and physical functioning outcomes, and additional pressure reduction (over the threshold-value) would not trigger further improvements. This would implicate that focussing on plantar pressure reduction in FO-treatment is only to a certain level useful. Moreover, reduction of plantar pressure seems to be important in patients with a combination of pain and high pressure in a certain foot region (biomechanical impairment). In these patients FOs designed for off-loading in this foot region seems justified. In cases with relatively low plantar pressure values in the painful foot region (for example due pain avoidance in case of inflammation) another FOs-treatment strategy seems necessary. Likely, the working-mechanism of FOs in patients with RA-related foot problems is based on more components than solely plantar pressure reduction. Probably, the amount in which FOs correct or support foot structures in order to control the position of the feet during weight-bearing and to reduce shearing forces, play an important role in the working mechanism of FO [35]. Furthermore, a placebo effect is a mechanism that should be considered [29]. To better understand how FOs work in the treatment of RA-related foot problems, larger studies exploring the potential mechanisms underlying the observed effects on pain and physical functioning are warranted.

Although the results of the present study showed no evidence of the supposed relation between plantar pressure and clinical outcomes, an optimal plantar pressure distribution may contribute to delaying forefoot joint damage and deformities, and prevention of abnormal callosities and wounds on the plantar surface of the foot [7, 35]. Besides the characteristics of the prescribed FOs, compliance and the interaction between FOs and shoes worn by the patient may play an important role in the clinical results of the treatment [35]. Analyses of compliance in the present study showed that only 37% of the included patients wore the FOs more than 8 hours a day. Therefore, strategies to improve compliance (targeting usability and acceptance) should be considered [36]. Furthermore, good communication between prescribing clinicians and the individual patients is of great importance [35].

The present study has some strengths and limitations. A strength is the follow-up measurements of in-shoe plantar pressure after three months of wearing FOs. Another strength is the mixed model multilevel analyses which enabled us to use different areas of both feet of the same patient, apart from dependency within a person. Therefore, data from both feet of one patient could be used. The following limitations were identified. First, in comparison with the literature the follow-up of three months was relatively short for the outcomes pain and physical functioning [15, 16]. Second, due to the relatively small sample size, the statistical power to establish associations of change in pressure with change in outcomes was limited. Third, an individual shoe-advice was given based on the clinical reasoning process of the podiatrist. This advice consisted at least of sufficient room in the toe box and a stiff sole allowing a heel-to-toe gait. Data on the numbers, specific content and degree of follow-up of the individual shoe-advices is lacking. Therefore, analysis of the potential role of the shoe-advise on the outcomes was not possible.

In conclusion, foot orthoses developed according to a protocol for improving the plantar pressure redistribution properties lead to medium to large improvements in pain and physical functioning. The hypothesis that more pressure reduction would lead to better clinical outcomes could not be proven.

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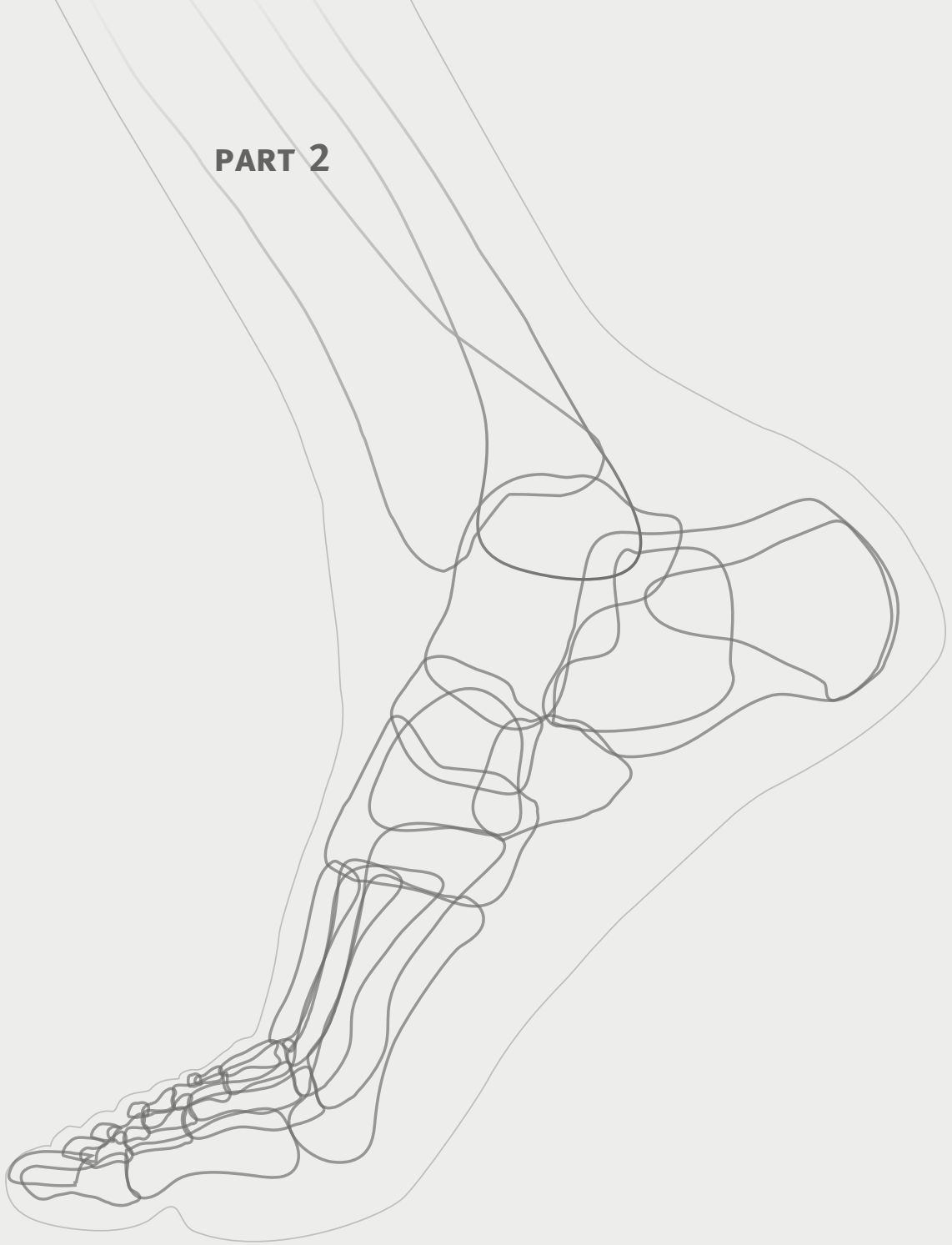
PART 2



CHAPTER 7

Forefoot pathology in relation to plantar pressure distribution in patients with rheumatoid arthritis: *A cross-sectional study in the Amsterdam Foot cohort*

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Abstract

Background

In patients with rheumatoid arthritis (RA), both high and low forefoot plantar pressures have been reported. Better understanding of pathology in the forefoot associated with altered pressure distribution in patients with RA could help to better formulate and specify goals for treatment with foot orthoses or therapeutic footwear.

Objectives

To investigate the association of plantar pressure with disease activity and deformity in the forefoot in patients with rheumatoid arthritis and forefoot symptoms.

Methods

A cross sectional study, using data of 172 patients with rheumatoid arthritis and forefoot symptoms, was conducted. Peak pressure (PP) and pressure time integral (PTI) in the forefoot were measured with a pressure platform. Forefoot deformity was assessed using the Platto score. Forefoot disease activity was defined as swelling and/or pain assessed by palpation of the metatarsophalangeal joints. The forefoot was divided in a medial, central and lateral region, in which the following conditions could be present: 1) no pathology, 2) disease activity, 3) deformity or 4) disease activity and deformity. A multilevel analysis was performed using condition per forefoot region as independent variable and PP or PTI in the corresponding region as dependent variable.

Results

Statistically significant higher plantar pressures were found in forefoot regions with deformities (RR 1.2, CI 1.1-1.3, P<0.0001), compared to forefoot regions without forefoot pathology. No significant differences in plantar pressures were found when solely forefoot disease activity was present in forefoot regions.

Significance

Forefoot deformities are related to higher plantar pressures measured in the corresponding forefoot regions. The absence of an association between local disease activity and plantar pressure might be explained by the low prevalence of metatarsophalangeal joint pain or swelling. Future research with sensitive imaging measures to detect disease activity is recommended to reveal the effect of forefoot disease activity on plantar pressure.

Introduction

Forefoot symptoms are common in patients with rheumatoid arthritis (RA). Of all patients with RA, 56-91% develop forefoot symptoms at any time during their disease [1-3]. These symptoms include pain, swelling and stiffness, which can be caused by inflammation in joints and surrounding tissue and/or forefoot joint damage [2, 4]. Also, forefoot deformities, such as subluxation of metatarsophalangeal (MTP) joints, hallux valgus and lesser toe deformities may develop [2, 4]. As a result, patients often experience limitations in daily functioning and a reduced health related quality of life [5].

Among other treatments, foot orthoses (whether or not in combination with therapeutic footwear) are used to relieve forefoot symptoms and thereby to improve daily functioning [6]. Reduction of plantar foot pressure in symptomatic areas is supposed to be one of the working mechanisms of foot orthoses [4, 7, 8]. Elevated plantar pressure might occur since the ability to adapt has decreased in deformed areas [9]. Several studies showed a significant correlation between forefoot deformities and high plantar pressure in patients with RA [7, 9-13]. However, the populations in these studies were relatively small, varying from 28 to 62 participants.

Beside elevated plantar pressure, also low plantar pressure in the forefoot has been observed in patients with RA [8]. Low forefoot pressure could be the result of a pain avoidance strategy [8, 14, 15]. To avoid regions with swelling and/or pain due to inflammation (i.e. high disease activity), offloading of these regions may occur [14]. However, the relationship between local disease activity and decreased plantar pressure is inconclusive. Only one study in RA studied this relation and showed that the presence of forefoot joint hypertrophy, measured with ultrasound, was associated with lower plantar peak pressure in the lateral forefoot region [2]. Assessment of disease activity with ultrasound is usually not used within standard care, in contrast to clinical assessment by palpation. Whether disease activity as assessed by palpation of forefoot joints is related to plantar pressure is unknown.

Better understanding of the association of pathology in the forefoot with either high or low plantar pressure in patients with RA could help to better formulate and specify goals for treatment with foot orthoses and therapeutic footwear. Previous studies investigating the relationship between forefoot pathology and plantar pressure were relatively small, mainly focused on the relation between deformities and plantar pressure, and calculated these relationships by correlational techniques. Only one study was able to provide an estimation of the effect of deformity on plantar pressure [16]. Moreover, the investigation of plantar pressure in relation to forefoot pathology by relatively easy to obtain clinical measures, of both forefoot deformities and forefoot disease activity, within one study has not been done before. This allows for comparison of plantar pressures between different forefoot conditions. The aim of the present study was to investigate and quantify the relationship of forefoot disease activity and forefoot deformity with plantar pressure in a relatively large cohort of patients with RA and forefoot symptoms.

Methods

Design & subjects

A cross-sectional study with data of the Amsterdam Foot (AMS-foot) cohort was conducted. The AMS-foot is a cohort of consecutive patients (≥18 years of age) who are referred to a rehabilitation physician or podiatrist of the multidisciplinary foot-care clinic of our outpatient rehabilitation center (Reade, Centre for Rehabilitation and Rheumatology, Amsterdam, The Netherlands). Patients who were not able to fill in questionnaires because of language difficulties were excluded from the cohort. Data were collected prior to the first visit to the rehabilitation physician or podiatrist by a trained research assistant at Reade.

For the present study patients from the AMS-foot cohort were selected who 1) were diagnosed with RA according to the revised criteria of the American Rheumatism Association [17], 2) had impairments in structure (e.g. deformities) and/or in function (e.g. pain or stiffness) of the forefoot, 3) had pressure measurement data available and 4) provided informed consent. Data collected between December 2011 and April 2017 were used. The study protocol was approved by the medical ethics committee of the Slotervaart Hospital/Reade in Amsterdam.

Measurements

Descriptive variables

The following variables were used descriptively: age, gender, body mass index (BMI), disease duration, disease activity score including a 44 joint count (DAS-44), Platto's structural index score, Foot Function Index (FFI) and Leeds Foot Impact Scale (LFIS). Length, measured with a tape measure attached to a wall, and weight, measured with a balance scale, were used to calculate BMI (in kg/m²). Disease duration was based on the rheumatologists' reported year of diagnosis. DAS-44 and Platto score were assessed by a trained research assistant during clinical examination [18, 19]. The FFI and LFIS are self-reported questionnaires assessing the impact of foot related pain and disability on activities of daily living [20, 21].

Figure 1. Division of the Emed pressure measurement into regions by a common division mask (Novel mask) (1 = medial, 2 = central, 3 = lateral, as used in the current study).

Dependent variables: forefoot peak pressure and pressure time integral

Plantar pressure in the forefoot was expressed as peak pressure (PP) and as pressure time integral (PTI). PP is defined as the highest pressure measured by a single sensor in a region [10] and is expressed as Newton per squared cm (N/cm²). PTI is defined as the integral of pressure over time measured in the single sensor showing the PP within that region [10] and is expressed as Newton per squared cm multiplied by time in seconds ((N/cm²)*s).

Plantar pressure measurements were obtained using an EMED-nt (Novel Electronics, Novel gmbh, Munich, Germany) system (4 sensors per cm², sample frequency of 50Hz), displaying plantar pressures of the foot when walking barefoot over a pressure measurement platform. The platform was mounted in the middle of a 3.6 meter walkway. A two-step protocol was used for pressure measurements since this was found to be the least time-consuming and least strenuous for the patient, but still a reproducible protocol [17]. In the two-step protocol the patient stands two steps away from the platform and makes contact with the platform on the second step. After familiarization with the protocol the measurement started. A measurement was considered correct when the whole foot was planted on the platform and it looked (researcher) and felt (patient) like a normal step. Incorrect measurements were immediately deleted. This protocol was repeated until both feet were correctly measured three times. The EMED software (Novel Ortho, Novel-Win) was used to analyze pressure data. See ***Figure 1*** for the division mask used. To process pressure measurement data, the mean of the three correct steps was calculated [17]. This mean was used in further analyses. Data from both feet for three forefoot regions (i.e. medial, central and lateral) were used in the analyses.

Independent variables: forefoot disease activity and forefoot deformity

Forefoot disease activity was defined as swelling and/or pain in the MTP joints, determined by palpation as part of the DAS-44 [18]. Forefoot disease activity was scored present or absent for every MTP joint.

Forefoot deformities were determined with Platto's structural index [19]. The presence of hammertoes, claw toes, subluxation of the MTP joints, hallux valgus and exostosis of MTP-5 were scored as absent or present for all digits and MTP joints.

The forefoot was divided in a medial, central and lateral region, in which the following conditions could be present: 1) no pathology, 2) disease activity, 3) deformity or 4) disease activity and deformity. See ***Table 1*** for the assignment of specific clinical findings (pain/swelling and/or forefoot deformities) to the medial, central and lateral forefoot region. The presence of one of the variables mentioned in a single cell of ***Table 1*** was considered presence of that condition in that specific region. For example, when subluxation of MTP-5 was present in the left foot, deformity in the lateral region of that foot was scored as present.

Statistical analysis

Descriptive variables were calculated and presented as mean (standard deviation [SD]) or median (interquartile range [IQR]). Percentages were calculated for stages of disease activity using cut of criteria as described by the European League Against Rheumatism (EULAR) [18].

Table 1. Division of disease activity and deformity measures into forefoot regions

Forefoot region	Disease activity	Deformity
Medial	Swelling MTP-1 and/or pain MTP-1	Hallux valgus and/or hammer- and/or claw digit 1 and/or subluxation MTP-1
Central	Swelling MTP-2 and/or 3, and/or pain MTP-2 and/or 3	Hammer- and/or claw digit 2 and/or 3 and/or subluxation MTP-2 and/or 3
Lateral	Swelling MTP-4 and/or 5, and/or pain MTP-4 and/or 5	Hammer- and/or claw digit 4 and/or 5 and/or subluxation MTP-4 and/or 5 and/or exostosis MTP-5

MTP = metatarsophalangeal

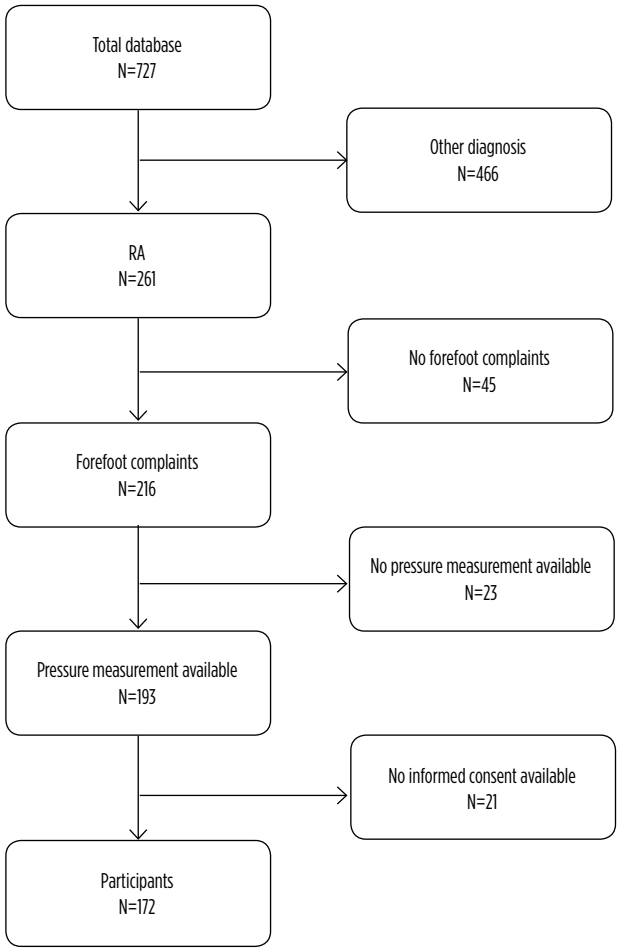

Figure 2. Flow of the patient selection

All variables were checked for normal distribution. The dependent variables PP and PTI were skewed to the right and therefore log transformed by use of a common logarithm (Log^{10}) before the analyses. All analyses were carried out on the transformed data. Regression coefficients and confidence intervals (CI) were retransformed, providing a ratio of the outcome variable between different conditions.

A multilevel analysis was performed using condition per forefoot region as the independent variable and PP or PTI in the corresponding region as the dependent variable. The independent variable was categorical, consisting of the following categories: 0) no pathology, 1) disease activity, 2) deformity, 3) disease activity and deformity. Multilevel analysis takes into account that information from multiple forefoot regions and both feet of a single participant is not independent. A three level structure was used, i.e. the three forefoot regions were clustered within the foot and the two feet were clustered within the patient. Analyses were done crude and adjusted for age, gender and BMI. Cases with missing values were excluded list wise. A significance level of $p<0.05$ was used in all analysis. PASW Statistics 18 software (v.18, SPSS Inc. Chicago, IL, USA) was used to perform the analyses.

Results

Descriptives

A total of 172 patients were included in the present study. ***Figure 2*** visualizes the patient flow. Patient characteristics are summarized in ***Table 2***. The mean age of the patients was 57.9 (± 12.9) years and most were female. A total of 97 patients were referred to podiatry (with foot orthoses as the main intervention) and 75 to the rehabilitation physician and shoe technician (with therapeutic shoes as the main intervention).

Table 3 summarizes the plantar pressure values per forefoot condition in the medial, central and lateral forefoot region. PP and PTI were highest in all regions when deformities, or a combination of deformities and disease activity, are present. Of the three forefoot regions, the lateral forefoot region showed the lowest PP and PTI in all conditions.

Association between forefoot condition and plantar pressure

Table 4 shows the results of the multilevel analyses comparing PP and PTI between the forefoot conditions. It was found that the presence of forefoot deformity in a forefoot region presented a 1.2 times higher PP and PTI ($p < 0.0001$) compared to the absence of forefoot pathology. Thus, PP and PTI were 20% higher when forefoot deformities were present, corresponding with a 15.5 N/cm^2 higher PP and a 5.2 $(N/cm^2)*s$ higher PTI. The combination of forefoot disease activity and deformity also showed a 1.2 times higher PP and PTI ($p = 0.020$ and $p = 0.014$ respectively), corresponding to a 16.1 N/cm^2 higher PP and 8.3 $(N/cm^2)*s$ higher PTI. Forefoot disease activity alone, i.e. the presence of pain and/or swelling of MTP joints in a forefoot region, was not significantly associated with PP and PTI. Similar results were found when local disease activity was defined as either MTP-joint pain or MTP-joint swelling.

Discussion

The results of this study showed that plantar pressure in the central, medial or lateral forefoot region was significantly higher in the presence of deformity in the corresponding forefoot region. No significant association between disease activity in a forefoot region and plantar pressure was found.

The observed association between the presence of forefoot deformities and higher plantar pressure is consistent with previous studies with smaller sample sizes [7, 9-13]. It suggests that persons with forefoot deformities are not able to avoid elevated pressure [9]. Plantar pressures were about 20% higher when deformities were present. Elevated pressure often results in hyperkeratosis and subsequent pain and discomfort in the forefoot [14, 22].

Our finding that there was no relation between the presence of disease activity in the MTP joints and plantar pressure is in contrast with the findings of Bowen et al. who found a statistically significant relationship between synovial hypertrophy in the MTP joints, as detected with ultrasound (US), and lower forefoot plantar pressure in a population of 114

Table 2. Patient characteristics (n = 172)

		% missing
Age (years) [b]	57.9 (12.9)	0%
Gender (male/female) [a]	29/143	0%
BMI (kg/m2) [b]	27.4 (5.1)	0%
Disease duration (years) [c]	7 (3;13)	0%
DAS-44 [c]	2.0 (1.3;2.7)	2.3%
- Remission (<1.6)	34.9%	
- Low disease activity (1.6 till 2.4)	27.3%	
- Moderate disease activity (2.4 till 3.7)	30.2%	
- High disease activity (≥ 3.7)	5.2%	
Platto score [c]		
- Total (range 0-38)	7.0 (4.0;12.0)	9.9%
- Forefoot (range 0-24)	5.0 (2.0;10.0)	6.4%
- Rear foot (range 0-14)	2.0 (1.0;3.0)	3.5%
FFI [c]		
- Total (range 0-100)	32.0 (16.6;49.6)	2.3%
- Pain (range 0-100)	35.7 (19.8;53.4)	7.0%
- Disability (range 0-100)	27.8 (13.9;47.2)	2.9%
LFIS [c]		
- Pain (range 0-14)	6.0 (4.0;8.6)	1.7%
- Disability (range 0-22)	7 .0 (3.0;11.0)	2.9%
PP in the forefoot (N/cm2) [c]	49.3(32.7;76.0)	0%
PTI in the forefoot ((N/cm2)*s) [c]	18.4(12.7;28.5)	0%
MTP count pain [c] (range 0-10)	3 (0;7)	5.2%
MTP count swelling [c] (range 0-10)	0 (0;2)	5.2%

Data are [a] numbers, b mean (SD) or c median (IQR). BMI = body mass index, DAS = Disease Activity Score, FFI = Foot Function Index, LFIS = Leeds Foot Impact Scale, PP = peak pressure, PTI = pressure time integral, MTP = metatarsophalangeal

patients with RA (r = -0.412, p=0.046) [2]. Although the population of the present study was larger, the prevalence of disease activity in the forefoot was low in our sample. This may have led to low statistical power to detect associations. The low prevalence of forefoot disease activity could be typical for our study population since, overall, disease activity and functional limitations were low to moderate. It could also be explained by the way disease activity was assessed. In our study, palpation of MTP joints was used to detect pain and swelling. Using US to assess disease activity has been shown to be more sensitive than clinical examination and similar or even better than magnetic resonance imaging (MRI) [23, 24]. Therefore, the use of US to detect the presence of disease activity could have led to a higher percentage of regions with forefoot disease activity, possibly leading to different results. Further research using sensitive imaging measures to detect local disease activity should reveal whether or not a relation between disease activity and plantar pressure exists.

It is known that walking speed has an effect on plantar pressure and patients with greater disease activity or deformity are likely to walk slower [25]. Therefore, in addition to age, gender and BMI, walking speed was added as a covariate in a separate analysis. This did not result in

Table 3. Median (IQR) values for PP and PTI per forefoot condition

	No pathology		Disease activity		Deformity		Disease activity and deformity	
Region	*PP (N/cm²)*	*PTI ((N/cm²)*s)*	*PP (N/cm²)*	*PTI ((N/cm²)*s)*	*PP (N/cm2)*	*PTI ((N/cm²)*s)*	*PP (N/cm²)*	*PTI ((N/cm²)*s)*
Medial	54.8 *(38.2;72.1)*	18.5 *(14.5;26.4)*	41.3 *(27.5;54.1)*	13.1 *(11.5;19.0)*	60.8 *(41.3;90.7)*	22.9 *(16.4;35.6)*	65.8 *(60.5;75.2)*	28.3 *(21.9;31.2)*
Central	48.0 *(36.0;63.8)*	17.1 *(12.5;21.3)*	44.7 *(36.5;61.0)*	17.8 *(14.1;20.6)*	73.7 *(50.2;110.6)*	29.7 *(17.6;43.4)*	68.0 *(42.7;92.6)*	25.5 *(16.3;34.8)*
Lateral	27.5 *(21.4;36.0)*	11.2 *(9.1;14.0)*	32.9 *(28.8;39.7)*	13.9 *(11.2;21.3)*	41.5 *(27.0;72.3)*	15.7 *(11.1;26.2)*	31.0 *(25.0;50.0)*	12.7 *(10.6;21.9)*

PP = peak pressure, PTI = pressure time integral

Table 4. Results for multilevel analyses of forefoot condition with PP/PTI

	PP		PTI	
	Crude ratio	*Adjusted* ratio*	*Crude ratio*	*Adjusted* ratio*
No pathology	*Reference category*			
Disease activity	1.04 *CI* 0.86 – 1.25 *p* 0.714	1.03 *CI* 0.86 – 1.24 *p* 0.749	1.03 *CI* 0.85 – 1.25 *p* 0.744	1.02 *CI* 0.85 – 1.23 *p* 0.850
Deformities	1.21 *CI* 1.13 – 1.31 *p* <0.0001	1.19 *CI* 1.10 – 1.29 *p* <0.0001	1.24 *CI* 1.15 – 1.34 *p* <0.0001	1.20 *CI* 1.11 – 1.29 *p* <0.0001
Disease activity and deformities	1.25 *CI* 1.05 – 1.48 *p* 0.011	1.23 *CI* 1.03 – 1.45 *p* 0.020	1.27 *CI* 1.07 – 1.51 *p* 0.007	1.24 *CI* 1.04 – 1.46 *p* 0.014

*CI = 95% confidence interval, p = p-value, PP = peak pressure, PTI = pressure time integral. * = adjusted for age, gender and BMI*

significant change of effect estimates (results not shown), indicating that walking speed did not have an impact on the associations found.

Foot pathology (here: deformities or inflammation) as well as the results of plantar pressure measurement should be considered when determining the most appropriate treatment strategy in case of forefoot symptoms. In patients with forefoot deformities and mechanical overloading, plantar pressure measurement can be used to identify the exact location of elevated pressure in order to target these areas [9, 26, 27]. Using plantar pressure measurement gives a better indication of areas with elevated pressure than clinical examination [22]. Treatment with custom-made foot orthoses or therapeutic footwear has been shown to decrease elevated plantar pressure and to reduce forefoot pain [26, 28]. In patients with inflammatory driven forefoot symptoms, reduction of disease activity should have treatment priority. Systemic medication or local steroid injections are recommended treatment options [29]. Additionally, foot orthoses could normalize forefoot loading in case of an offloading strategy, resulting in increased forefoot pressure after foot orthosis intervention [27]. A multidisciplinary approach in the management of RA-related foot problems is required to align the different diagnostic and treatment options [30].

A strength of our study is the large sample size relative to other studies on the same topic. Another strength is the multilevel analysis, which enabled us to use different areas of both feet of the same participant, apart from dependency within a person. Therefore, more detailed data could be used. To our knowledge this has only been done in one other study related to the RA foot [16].

A possible limitation of the present study is the use of a common division mask (Novel mask) to divide the forefoot in three regions. It could be that the regions did not completely correlate with the anatomical location of the MTP joints. Furthermore, we only investigated the forefoot, as this is the most commonly affected area of the foot in RA. Pathology in relation to plantar pressure in other regions of the foot were beyond the scope of this study. Finally, we did not investigate a possible load shift between different foot regions. An in-depth investigation of load shifting between foot regions (both forefoot and other foot regions) in the presence of forefoot pathology could be a topic for future research.

Conclusions

The effect of forefoot disease activity and forefoot deformities on plantar pressure was investigated. Deformities in the medial, central and lateral forefoot regions are related to higher plantar pressures measured in these regions. The absence of an association between local disease activity and plantar pressure might be explained by the low prevalence of MTP pain or swelling as detected by palpation. Future research with medical imaging measures to detect disease activity is recommended to reveal the effect of forefoot disease activity on plantar pressure.

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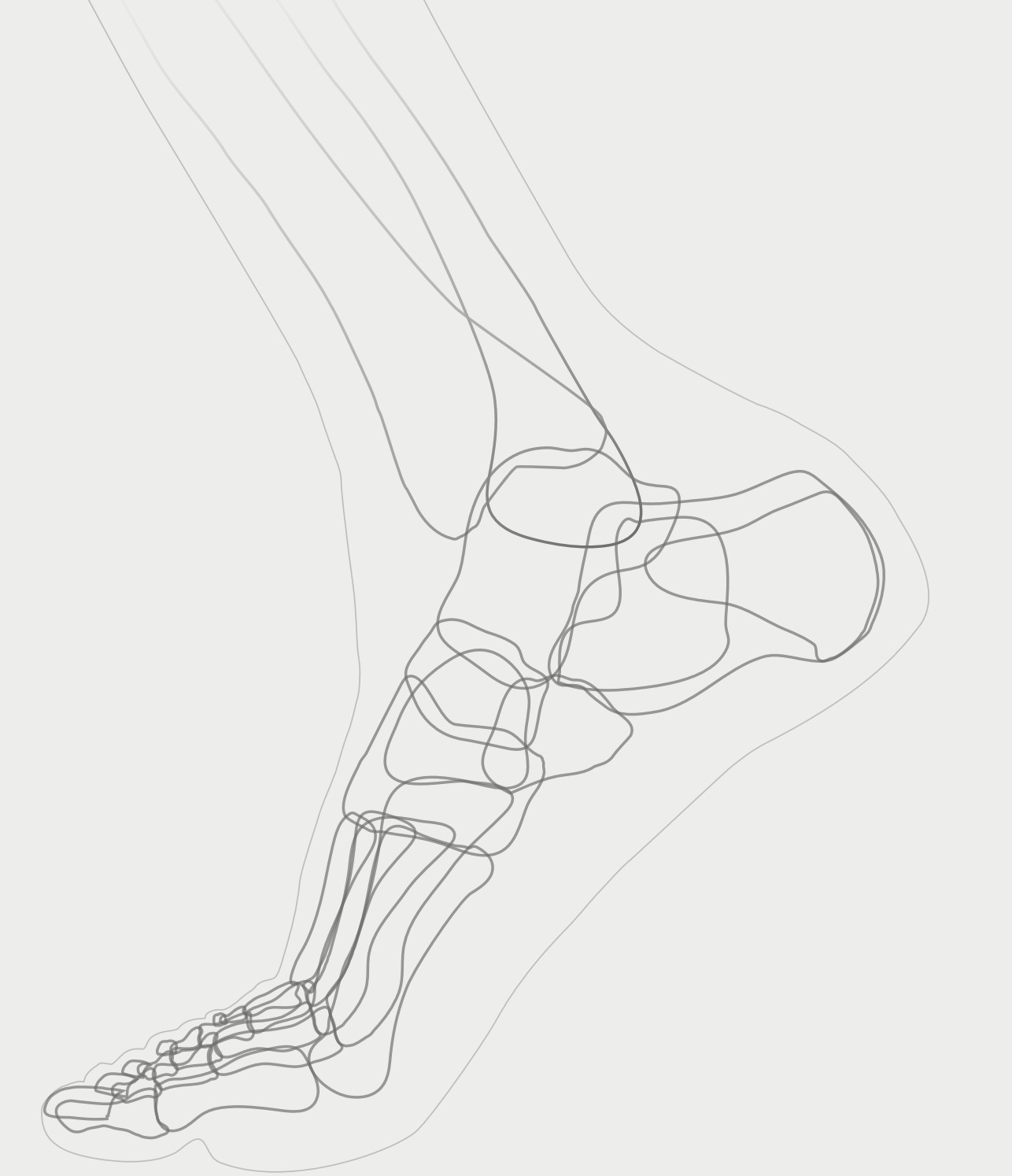

CHAPTER 8

General Discussion

Foot problems are highly prevalent in patients with RA, but receive limited attention in clinical practice and research. The first part of this thesis (**Chapters 2-4**) covers multidisciplinary foot care for patients with rheumatoid arthritis (RA). Multidisciplinary recommendations for diagnosis and treatment of foot problems in patients with RA were developed based on scientific literature and expert opinion (**Chapter 2**). Systematic reviews were performed to summarize the evidence on therapeutic shoes (**Chapter 3**) and different types of foot orthoses (**Chapter 4**). In the second part of the thesis (**Chapters 5-7**) the role of plantar pressure measurements in the management with foot orthoses was investigated. In this chapter (**Chapter 8**), the main results of the studies in this thesis are summarised and discussed. Furthermore, suggestions for future research are given.

Multidisciplinary foot care

In **Chapter 2** multidisciplinary recommendations for diagnosis and treatment of foot problems in patients with RA were developed. The recommendations were based on the best available evidence and the opinions of experts with varying specialities and of patients. Forty-one recommendations were developed and approved by the expert group. Two recommendations concerned a framework for diagnosis and treatment with involvement of multiple disciplines. Thirty-nine recommendations addressed foot care: seven on diagnosis (including check-ups of feet and shoes and diagnostic imaging), 27 on treatment (including corticosteroid injections, foot surgery, therapeutic shoes, foot orthoses, exercise therapy, toe-orthoses and toenail-braces, treatment of toenails and skin), four on communication, and one on organisation of RA-related foot care.

In **Chapter 3** the evidence on the effectiveness of therapeutic shoes was summarized. For custom-made therapeutic shoes weak evidence for the reduction of foot pain and improvement of physical functioning was found. For ready-made therapeutic shoes a medium to large effect was found for the reduction of foot pain and a small to medium effect for the improvement of physical functioning. All results were based on within-group differences.

In **Chapter 4** the comparative effectiveness of foot orthoses in the treatment of various foot problems in RA were summarized. In the literature comparisons between foot orthoses were made concerning different materials used (soft versus semi-rigid), types of foot orthoses (custom-made versus ready-made; total contact versus non-total contact), or modifications applied (metatarsal bars versus domes). Also, different techniques to construct custom-made foot orthoses were compared (standard custom-moulding techniques versus more sophisticated techniques). A medium effect for (immediate) reduction of forefoot plantar pressure was found in favour of treatment with soft foot orthoses compared to semi-rigid foot orthoses. Other comparisons between foot orthoses resulted in non-significant effects or inconclusive evidence for one kind of foot orthoses over the other.

The findings of **Chapters 2-4** clearly indicate that there are gaps in scientific literature on the management of foot problems of patients with RA. Most of the developed recommendations were based on expert opinion, as there is a lack of research evidence. The results of both systematic reviews were based on a small number of studies (**Chapter 3** eleven and **Chapter 4** ten studies, respectively) and with relatively small sample sizes. Moreover, only a few randomized controlled trials with repeated measures design could be included in both reviews. More research is needed to strengthen the evidence on management of RA-related foot problems.

The recommendations in **Chapter 2** were developed in collaboration with a multidisciplinary RA Foot Expert Group. In this expert group multiple healthcare providers (rheumatologists, rehabilitation physicians, orthopaedic surgeons, specialized nurses, podiatrists, orthopaedic shoe technicians, pedicurists and researchers) involved in the management of RA-related foot problems were represented. In addition to these professionals, patients with a history of foot problems were also part of the expert group. The expert group reached consensus on the role and specific skills of the different disciplines involved in management of inflammation (e.g. (teno)synovitis, or bursitis), biomechanical, dermatological and neurovascular impairments, and external and personal factors related to RA-foot disease. This has been translated into a framework for diagnosis and treatment. Furthermore, communication and organisation of foot care were adressed, both from the point of view of the patient and the health professional. The collaboration with this multidisciplinary expert group made the development of the recommendations a unique project. Especially since these are the first multidisciplinary recommendations on RA-related foot care worldwide [1].

The framework for diagnosis of RA-related foot problems in **Chapter 2** was based on the International Classification of Functioning, Disability and Health (ICF) of the World Health Organization [2]. The ICF-concept is in development, particularly with regard to the personal factors [3]. It seems more plausible to include only items related to the personal background under the personal factors [3]. In the introduction to this thesis (**Chapter 1**), we used a more up-to-date approach of the ICF-classification compared to the diagnostic framework in **Chapter 2**.

Good communication and collaboration between the patient and the healthcare providers involved, and between the healthcare providers from different disciplines, are important in the management of RA-related foot problems [1, 4, 5]. All disciplines involved can play a role in the detection of inflammation, biomechanical and dermatological foot impairments. Early diagnosis and treatment of these foot problems is important, because (i) long-term synovitis may lead to pain and joint damage and deformities [6, 7], (ii) malalignment of the feet may result in biomechanical alterations in foot function (e.g. the loading pattern of the foot resulting in high plantar pressure) and pain [8-11], and (iii) biomechanical alterations may lead to dermatological problems such as excessive hyperkeratotic lesions, which can cause pain, corns and wounds/ulcers [12, 13]. Access to multidisciplinary consultation and collaboration is nessecary to provide treatment with sufficient content and timing for the individual patient [4, 14, 15]. The frameworks for diagnosis and treatment in **Chapter 2** may offer guidance in providing foot care and collaboration between different disciplines. In addition, patients can play an important role in their own foot-related health, provided that they are sufficiently coached and trained by the healthcare providers involved [16]. Good communication, shared descision-making and patient education improve knowledge about the disease, involvement in the treatment process and self-management by the patient [12, 17-19].

Adequate organization of RA-related foot care in which several disciplines are involved is complex but essential for accessibility of timely foot care with sufficient content [20]. Healthcare providers from different disciplines often work in different departments or settings (e.g. hospitals, outpatient clinics and private practices) with different processes, IT infrastructure and financing structures. This may lead to barriers for structural and integral collaboration [21, 22]. The development of the recommendations in **Chapter 2** was a first step in guiding a multidisciplinary approach and a better organization of RA-related foot care. However, the recommendations do not have the status of a practice guideline and were not issued by a professional organization with the involvement of all stakeholders. In order to be able to provide the right foot care in the right place, a national guideline with support of all the stakeholders involved and official ratification is needed [23]. Such a guideline should include a foot care pathway for the guidance of timely referral for diagnosis and treatment by various disciplines. Treatment of inflammation in the foot will primarily be managed by a medical doctor, while biomechanical and dermatological impairments can be managed with the involvement of different medical and non-medical disciplines, based on a stepped-care approach. Furthermore, the development of international multidisciplinary recommendations could be considered to improve the knowledge and uniformity of RA-related foot care [24], for example by using EULAR standardised operational procedures [25].

Implementation of the recommendations in **Chapter 2** is needed to improve foot care for the individual patient [26]. Ideally, the implementation is based on a structured analysis of the current situation and barriers and facilitators for implementation [26]. Using the results of such an analysis, an implementation plan must be developed [26]. This can consist of improving insight and knowledge among healthcare providers from different disciplines, e.g. by developing an educational programme. Furthermore, the application of the recommendations in clinical practice can be facilitated by the development of an interactive digital platform for patients and healthcare providers, whereby information can be exchanged at various levels; a) general information (open access), b) geographical network of cooperating healthcare providers, and c) individual patient and treating healthcare providers. Moreover, a patient education programme could be developed and provided as e-Health to improve self-management [17, 26-28]. Besides implementation of knowledge transfer, implementation strategies can be aimed at dissolving financial barriers (e.g. compensation of costs for foot orthoses or therapeutic shoes), or barriers concerning timely referrals (e.g. a referral pathway for foot care by the different involved disciplines).

The role of plantar pressure in treatment with FOs

In **Chapter 5** a protocol for optimizing foot orthoses by using the feedback of in-shoe plantar pressure measurements was evaluated. In this proof of concept study 43 patients with foot pain were treated with usual care foot orthoses. Based on the protocol 70% of these usual-care foot

orthoses (in 30 patients) were adapted. In these patients, usual care foot orthoses resulted in a mean 9% plantar pressure reduction (PTI) compared to no foot orthoses. Adaptation of usual care foot orthoses led to an additional mean 3% PTI reduction. The protocol was considered feasible by patients. Podiatrists considered the protocol more useful to achieve individual rather than general treatment goals. A final protocol was proposed. In **Chapter 6** the outcomes on pain, physical function and forefoot plantar pressure three months after foot orthoses delivery (follow-up) were presented. A statistically significant within-group improvement on pain (medium effect size), physical functioning (large effect size) and forefoot plantar pressure (small effect size) was found. Furthermore, the relationship between change in forefoot plantar pressure and change in pain or physical functioning was investigated in **Chapter 6**. Analysis in a subgroup of 23 patients with combined forefoot pain and high forefoot plantar pressure showed non-significant relations between change in plantar pressure and changes in pain or physical functioning. In **Chapter 7** we investigated the relationship of forefoot disease activity (inflammation) and forefoot deformity (biomechanical impairment) with plantar pressure in 172 patients from the Amsterdam Foot (AMS-foot) cohort. Statistically significantly higher plantar pressures were found in forefoot regions with deformities, compared to forefoot regions without forefoot pathology. No significant differences in plantar pressures were found when solely forefoot disease activity was present in forefoot regions.

The primary goal of the foot orthoses optimization protocol was to reduce plantar pressure in painful foot areas, since high forefoot plantar pressure is associated with forefoot pain [11]. However, in a part of the patients included in the proof of concept study in **Chapter 5** a relatively low plantar pressure in the painful foot area was detected. This may possibly be due to an offloading strategy caused by inflammation [7, 29]. This implies that the treatment strategy in patients with a biomechanical impairment should be different from that for forefoot problems caused by inflammation. In patients with a biomechanical impairment, foot deformity may lead to high plantar pressure in the painful foot region. Because of the deformity, the patient cannot apply an offloading strategy, therefore the main goal of foot orthoses treatment is reduction of plantar pressure in the painful foot region. Patients with foot problems caused by inflammation, without a deformity, in the painful foot region may use an offloading strategy leading to low plantar pressure and pain avoidance. In these patients, medical treatment of disease activity should have treatment priority. In addition, foot orthoses treatment could be prescribed aimed at normalizing the loading pattern of the foot. A final foot orthoses optimization protocol has been proposed in which individual treatment goals are set aimed at redistribution of plantar pressure in painful foot regions.

The concept of biomechanical impairments versus foot problems caused by inflammation was partly supported by the findings in **Chapter 7**. With regard to biomechanical foot impairments, a relation was found between forefoot deformity and high forefoot plantar pressure. However, in **Chapter 6** no relation between change in plantar pressure and change in pain could be proven. This could possibly be explained by the small sample size or a threshold for plantar pressure. The hypothesis that in patients with foot problems caused by inflammation, pain is related to low plantar pressures could not be confirmed in **Chapter 7**. In contrast, such an association was found in previous research from Bowen et al. [7]. In

that study, inflammation in the forefoot was detected by ultrasonography, while we only used palpation. The use of ultrasonography to detect inflammation should be considered in clinical practice and future research [30-32]. Furthermore, the reduction of disease activity should be given priority in the treatment through the use of systemic medication or local steroid injections [33]. In addition, foot orthoses can be used to redistribute plantar pressure.

In patients with diabetes mellitus (DM) a comparable protocol with the use of sequential in-shoe plantar pressure measurements for the adaptation of therapeutic shoes resulted in shoes with better plantar pressure-distributing properties, as shown by previous research by Bus et al. [34, 35]. Because both the intervention and the study populations differed between the protocol for DM and ours, different treatment criteria were established in both protocols [34]. In patients with diabetic neuropathy, offloading of foot regions with high plantar pressures is necessary to prevent ulceration [36]. The diagnosis and treatment of DM and foot problems is guided by guidelines [37-39]. An annual foot screening is recommended [37]. In the event of foot problems, the patient is referred for an extensive foot examination, including barefoot plantar pressure measurements for early detection of regions with high plantar pressure [39]. In-shoe plantar pressure measurements are recommended as diagnostic tool to evaluate the plantar pressure distribution properties of shoes in order to prevent (re)ulceration [38]. A similar approach might also be useful in the detection and diagnosis of foot problems in RA. A yearly check-up of the feet can lead to early detection of foot problems, especially as the most frequently used instrument to detect disease activity (with a 28-joint count [40]) excludes examination of the feet. When foot problems are identified, barefoot plantar pressure measurements can be considered to support the distinction between foot problems caused by inflammation or a biomechanical impairment. In the case of complex biomechanical foot problems, in-shoe plantar pressure measurements can be used to guide the optimization of foot orthoses or therapeutic shoes.

The final protocol, as proposed in **Chapter 5**, may also, in addition to daily clinical care for patients with RA-related foot problems, be useful in other contexts. In the first place, the protocol may be applicable for the optimization of foot orthoses in patients with foot problems due to rheumatic disorders other than RA, such as spondylarthritis, (pseudo) gout, tendonitis/fasciitis/enthesitis and osteoarthritis. Secondly, the protocol can be used in podiatry education, as feedback from in-shoe plantar pressure measurements provides insight into the relationship between foot pain and plantar pressure. It can provide guidance in the student's clinical reasoning process to determine and evaluate treatment goals. Thirdly, the protocol can be used in research when investigating the plantar pressure outcomes of different types of foot orthoses or therapeutic shoes.

Innovations in real-time in-shoe plantar pressure measurements and direct communication of data, to an application that is accessible to both the patient and the healthcare professional involved, may lead to early detection of abnormal plantar pressures to support the management of foot problems. Smart textiles with integrated pressure sensors and antimicrobial properties can possibly be used to develop an innovative cover layer for foot orthoses or inner lining for therapeutic shoes [41, 42]. In addition, integration of temperature sensors could be considered to monitor compliance with foot orthoses or therapeutic

shoes [43-45]. Moreover, localized temperature measurements can also be used to detect and monitor inflammation (caused by RA or by infection) and therefore may be supportive in the management of local disease activity and wounds/ulcers [46-48].

Methodological aspects

The studies in this thesis have methodological strengths and limitations. To highlight some strengths, the methodology used to develop the recommendations (**Chapter 2**) is based on published strategies for the development of practice recommendations [25, 49]. Second, these are the first recommendations on the management of RA-related foot problems with the involvement of several disciplines. Third, both systematic reviews (**Chapter 3 and 4**) were prepared in accordance with the PRISMA statement (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) [50]. Fourth, the multi-level analyses used in the second part of this thesis (**Chapter 6 and 7**) enabled us to use different areas of both feet of the same patient, apart from the dependency within a person. Important limitations in the studies that were included in the systematic reviews (**Chapter 3 and 4**) were the small sample sizes, the methodological quality and the limited between-group results. With regard to the proof of concept study (**Chapter 5**) as performed by our research group, a limitation is the lack of a control group that did not receive the protocol to adapt foot orthoses based on in-shoe plantar pressure measurements. Therefore, we could only report within-group results and no established effects of benefit of the protocol over usual care regarding the manufacturing of foot orthoses (**Chapter 6**).

Directions for future research

Based on the study findings in this thesis, the following directions for future research are suggested.

Overall, more research is needed to strengthen the evidence on diagnosis and treatment of RA-related foot problems. Research on the value of (yearly) check-up of the feet for the prevention or delay of progression of RA-related foot problems is indicated. For the treatment of RA-related foot problems definitive, high-quality RCTs are needed to investigate the effectiveness of corticosteroid injections in the foot, different types of (fore-)foot surgery, treatment of nails and hyperkeratotic lesions. Furthermore, definitive high-quality RCTs are needed to investigate the (cost) effectiveness of different types of foot orthoses and therapeutic shoes.

Implementation of the recommendations (**Chapter 2**) could be the next step in improving multidisciplinary foot care in RA. First, a strategy and plan for implementation should be developed based on a structured analysis of the current situation and barriers and facilitators for implementation. Implementation could be aimed at knowledge transfer among healthcare providers and patients, or dissolving barriers e.g. concerning timely referrals, cooperation between healthcare providers, or (financial) organization of foot care. Development, evaluation and implementation of a referral- and foot care pathway based on a stepped-care approach with the involvement of multiple disciplines is needed. This could be part of a multidisciplinary practice guideline developed and issued by a professional organization with the involvement of all stakeholders in the management of foot problems in patients with RA. An official ratified guideline is necessary to improve (i) uniformity, (ii) adequate timing and content, (iii) communication and organization of multidisciplinary foot care. Furthermore, development, evaluation and implementation of a foot-specific education program for patients with RA seems mandatory.

Whether treatment with foot orthoses developed according to the final foot orthoses optimization protocol (**Chapter 5**) is (cost) effective, warrants further investigation. A definitive RCT with stratification in order to control for confounding of pain and function driven by biomechanical impairments and/or foot problems caused by inflammation could be considered. Furthermore, development and evaluation of an educational program for the implementation of the foot orthoses optimization protocol in podiatry practice and education is needed.

Lastly, to better understand how foot orthoses work in the treatment of RA-related foot problems, studies exploring the potential mechanisms underlying the observed effects on pain and physical functioning are warranted. Besides further research into the role of plantar pressure, the relationship between the change in foot position by wearing foot orthoses and the change in clinical outcomes could be quantified. Furthermore, the role of shearing forces and patients' expectations from treatment with FOs could be investigated.

Conclusions

In summary, the following conclusions can be drawn from this thesis:

Multidisciplinary foot care

- We developed multidisciplinary recommendations for diagnosis and treatment of foot problems in patients with RA. These recommendations may contribute to uniformity and adequate timing of diagnosis and treatment of RA-related foot problems. They may also contribute to adequate communication and improved organization of RA-related foot care.
- Therapeutic shoes are likely to be effective in patients with RA, based on within-group results. Treatment with custom-made and ready-made therapeutic shoes leads to a reduction of foot pain and improvement in physical functioning.
- In the treatment of RA-related foot problems different kinds of foot orthoses can be used. Evidence was found that foot orthoses made of soft material may lead to more (immediate) forefoot plantar pressure reduction compared to foot orthoses constructed of semi-rigid materials. For other characteristics (such as type of foot orthoses, construction techniques and applied modifications) inconclusive evidence was found, necessitating more research in this area.

The role of plantar pressure in treatment with FOs

- The immediate feedback of in-shoe plantar pressure measurements leads to small additional pressure reduction, and offers guidance in the clinical reasoning process of the podiatrist. It can be helpful in setting individual treatment goals, and in evaluating and adapting foot orthoses.
- Foot orthoses developed according to a protocol for optimizing the plantar pressure reduction lead to clinically relevant outcomes. Within-group comparisons after three months of foot orthoses treatment resulted in medium to large improvements in pain and physical function and a significant reduction of forefoot plantar pressure. The hypothesis that more plantar pressure reduction would lead to better clinical outcomes could not be proven.
- Deformities of foot joints in the medial, central and lateral forefoot regions were related to higher plantar pressures measured in these regions. The expected association between local disease activity (as detected by palpation) and plantar pressure could not be established. In future research, the use of ultrasonography in the detection of local inflammation should be considered.

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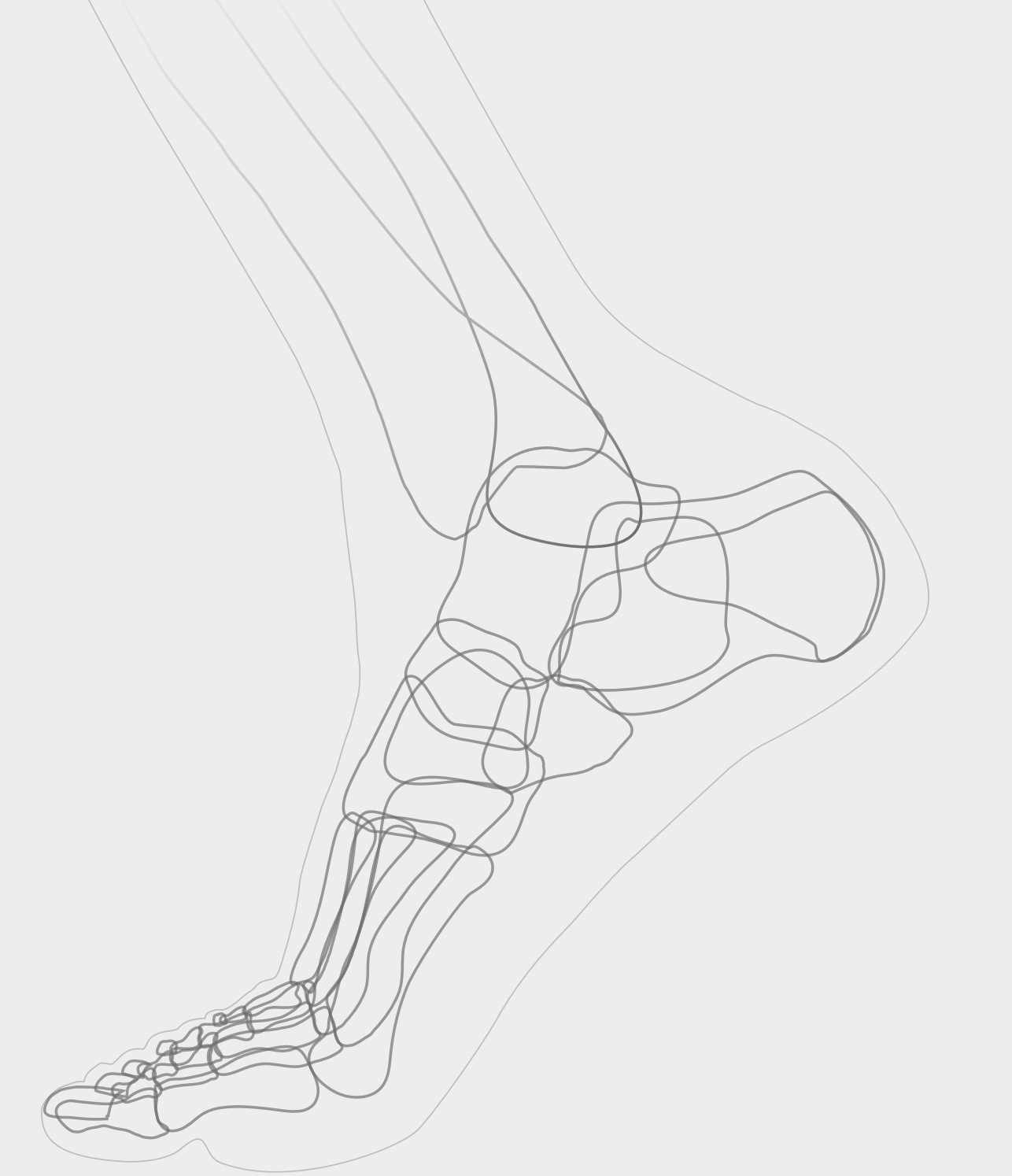


Management of foot problems in patients with rheumatoid arthritis

Summary

Summary

Foot problems are highly prevalent in patients with rheumatoid arthritis (RA). These foot problems often start with pain, swelling and stiffness caused by inflammation of joints and soft tissues. Long-term inflammation can have a destructive impact on the quality and structure of the joints and surrounding soft tissues. This may lead to structural malalignment of the feet due to damage and deformities of foot joints. Malalignment of the feet may result in pain and biomechanical alterations in foot function, i.e. the loading pattern of the foot, resulting in high plantar pressure. In addition to inflammation and biomechanical impairments, dermatological and neurovascular impairments, and external and personal factors can also play a role in RA-related foot problems. These foot problems may lead to restrictions in daily activities and participation, and a reduced quality of life.

Management of foot problems in an early disease stage seems important to reduce pain and activity limitations, and to prevent deterioration of foot function. Also in a more advanced disease stage, treatment of foot problems is often necessary. However, underuse of foot care seems apparent. Among patients there is limited knowledge of the possibilities of, and access to, foot care. Among healthcare providers, there is often limited attention and expertise in the management of RA-related foot problems. Various disciplines can be involved in the management of RA-related foot problems. However, healthcare providers from these different disciplines often lack insight into the specific skills of professionals from another discipline. In order to improve foot care for patients, an overview of the multidisciplinary diagnosis and treatment of foot problems in RA is first necessary. This is needed to provide guidance to healthcare providers and patients in the organisation of timely, appropriate and evidence-based foot care. The objective of the first part of this thesis was to provide an overview of multidisciplinary foot care for patients with rheumatoid arthritis (RA) **(Chapter 2-4)**.

Foot orthoses are frequently used in the treatment of RA-related foot problems. The general aims of prescribing foot orthoses are reducing foot pain and improving physical functioning by influencing biomechanical factors, such as plantar pressure, to an optimum. However, the reported treatment effect of foot orthoses on foot pain in RA is small to medium (effect size 0.40 – 0.45). Efforts to increase the effectiveness of foot orthoses are needed. Plantar pressure measurements can provide a better insight into the loading of the foot during gait. Improving the effects of foot orthoses by using the immediate feedback from in-shoe plantar pressure measurements seems promising. Since high plantar pressures are related to foot pain in RA it is hypothesized that a reduction of forefoot plantar pressure leads to reduction of pain and subsequent disability. Nevertheless, there is a lack of evidence supporting this hypothesis. The objective of the second part of this thesis was to investigate the role of plantar pressure measurements in the management with foot orthoses **(Chapter 5-7)**.

Chapter 1 provides a general introduction of the research topics of this thesis. Insights in the cause and course of RA-related foot problems were described. The factors of influence on these foot problems were depicted in an overview by using the International Classification of Functioning, Disability and Health (ICF) of the World Health Organization. Furthermore, the current management of RA-related foot problems and the role of plantar pressure in the treatment with foot orthoses were addressed. At the end of this chapter, the aim and outline of this thesis was presented.

In **Chapter 2** multidisciplinary recommendations for the management of foot problems in patients with RA were developed. The recommendations were based on research evidence and consensus among experts, following published strategies for the development of practice recommendations. The expert group was composed of 2 patients and 22 experienced professionals (rheumatologists, rehabilitation physicians, orthopaedic surgeons, specialized nurses, podiatrists, orthopaedic shoe technicians, pedicurists, and researchers) in the Netherlands. In total, 41 recommendations were developed. Two recommendations concerned a framework for diagnosis and treatment. Thirty-nine recommendations addressed foot care: seven on diagnosis (including check-ups of feet and shoes and diagnostic imaging), 27 on treatment (including corticosteroid injections, foot surgery, therapeutic shoes, foot orthoses, exercise therapy, toe-orthoses and toenail-braces, treatment of toenails and skin), four on communication, and one on organisation of RA-related foot care. These multidisciplinary recommendations can provide guidance in the organisation of timely, appropriate and evidence-based foot care. Implementation of the recommendations, based on a strategy and plan addressing barriers and facilitators for implementation, is needed to improve foot care for the individual patient.

In **Chapter 3** the literature was systematically summarized on the effectiveness of therapeutic shoes in patients with RA on the outcomes foot function, foot pain, physical functioning, health-related quality of life, adherence, adverse events and patient satisfaction. Therapeutic shoes include custom-made and ready-made shoes. Custom-made shoes are developed for the individual patient based on specific measures and specifications, whereby a variety of technical adaptations can be incorporated. Ready-made shoes are serial-produced shoes with extra depth, support, incorporated inlays or technical adaptations. Eleven studies were identified, with a total number of 429 participants, of which three were of high quality. Two studies investigated custom-made therapeutic shoes, eight studies ready-made therapeutic shoes, and one study investigated both. For custom-made shoes, a best evidence syntheses showed weak evidence for the reduction of foot pain and improvement of physical functioning. For ready-made shoes, meta-analysis showed a medium to large effect for the reduction of foot pain and a small to medium effect for the improvement of physical functioning. All results were based on within-group differences, since insufficient studies reporting between-group differences were available. The results of this chapter implicate that treatment with therapeutic shoes is effective in patients with RA. However, definitive high-quality RCTs to investigate whether patients with RA benefit more from therapeutic shoes than from non-therapeutic shoes (i.e. the patient's own shoes or standardized conventional shoes) are needed.

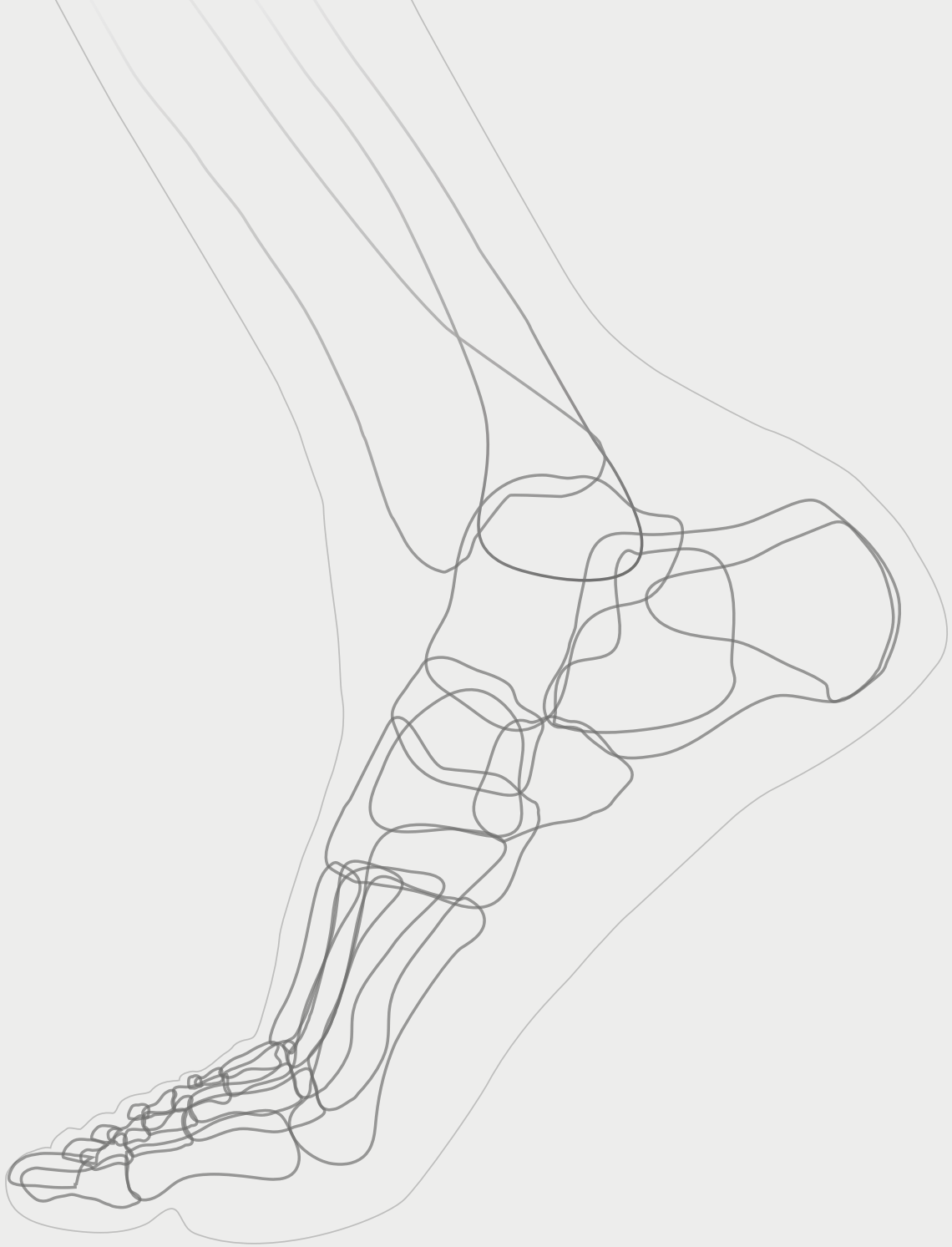
In **Chapter 4** the literature was systematically summarized on the comparative effectiveness of foot orthoses in the treatment of various foot problems in patients with rheumatoid arthritis on the primary outcomes foot function and foot pain, and the secondary outcomes physical functioning, health related quality of life, compliance, adverse events, the costs of foot orthoses and patient satisfaction. Ten studies, with a total number of 235 patients, were identified of which three were of high quality. These studies made a comparison between different materials used (soft versus semi-rigid), types of foot orthoses (custom-made versus ready-made; total contact versus non-total contact), or modifications applied (metatarsal bars versus domes). Also, different techniques to construct custom-made foot orthoses were compared (standard custom-moulding techniques versus more sophisticated techniques). Meta-analysis showed a medium effect for (immediate) reduction of forefoot plantar pressure in favour of treatment with soft foot orthoses compared to semi-rigid foot orthoses. Other comparisons between foot orthoses resulted in non-significant effects or inconclusive evidence for one kind of foot orthoses over the other. Based on the results of this chapter, it can be concluded that there is still limited insight into the effectiveness of one kind of foot orthoses compared to another. Therefore, definitive high quality RCTs are needed to investigate the comparative (cost-) effectiveness of different kinds of foot orthoses for the treatment of specific RA-related foot problems.

In **Chapter 5** a protocol for optimizing the plantar pressure reduction achieved with foot orthoses treatment by using the feedback of in-shoe plantar pressure measurements was evaluated. Forty-five RA patients with foot problems were included in this observational proof-of concept study. Custom-made foot orthoses were made by a podiatrist according to usual care. In 43 patients usual care foot orthoses were evaluated using in-shoe plantar pressure measurements and, if necessary, adapted. Adapted foot orthoses were developed in 70% of the patients. In these patients, usual care foot orthoses showed a mean 9% reduction in forefoot plantar pressure compared to no-foot orthoses. Foot orthoses adaptation led to an additional mean 3% plantar pressure reduction. Semi-structured interviews were held with patients and podiatrists to evaluate the feasibility of the protocol. The protocol was considered feasible by patients. Podiatrists considered the protocol more useful to achieve individual rather than general treatment goals. A final foot orthoses optimization protocol has been proposed in which individual treatment goals are set aimed at redistribution of plantar pressure in painful foot regions. The results of this chapter may have several implications for both clinical practice and podiatry education. First, in-shoe plantar pressure measurements can be used as an additional diagnostic tool in RA patients with foot problems; it provides insight in the relation between foot pain and plantar pressure during walking with shoes. Second, the immediate feedback of in-shoe plantar pressure measurements may offer guidance to the process of evaluation and adaptation of foot orthoses.

In **Chapter 6** the developed foot orthoses according to the 'foot orthoses optimization protocol' (as described in **Chapter 5**) were evaluated on pain, physical functioning and plantar pressure of the forefoot after three months of wearing foot orthoses in 38 patients. The within-group change scores showed a medium effect on pain reduction, a large effect on improvement of physical functioning and a small effect on forefoot plantar pressure reduction. Whether foot orthoses developed according to the 'foot orthoses optimization protocol' may lead to better clinical outcomes compared to foot orthoses developed without this protocol is unclear. Further investigation on the clinical relevance of using the protocol is required. Furthermore, the relationship between change in forefoot plantar pressure and change in pain and physical functioning was determined in a subgroup of 23 patients. In these patients no statistically significant relations were found between change in plantar pressure and change in pain or physical functioning. Therefore, the hypothesis that more pressure reduction would lead to better clinical outcomes could not be proven.

In **Chapter 7** the association of plantar pressure with disease activity and deformity in the forefoot was investigated in a cross sectional study, using data of 172 RA patients with forefoot problems from the Amsterdam Foot (AMS-foot) cohort. Plantar pressure in the forefoot was measured with a pressure platform. Forefoot deformity was assessed using the Platto score. Forefoot disease activity was defined as swelling and/or pain assessed by palpation of the metatarsophalangeal joints. Higher plantar pressures were found in forefoot regions with deformities compared to forefoot regions without forefoot pathology. This confirms our hypothesis and findings of previous research that forefoot deformities are related to higher plantar pressures. No association between local disease activity and lower plantar pressure could confirmed. Future research with sensitive imaging measures to detect disease activity is recommended to reveal the effect of forefoot disease activity on plantar pressure.

Finally, in **Chapter 8** the main results of this thesis are summarized and discussed and directions for future research are provided.



Management of foot problems in patients with rheumatoid arthritis

Nederlandse samenvatting

Samenvatting

Voetproblemen komen veel voor bij patiënten met reumatoïde artritis (RA). Deze voetproblemen beginnen vaak met pijn, zwelling en stijfheid veroorzaakt door ontsteking van gewrichten en weke delen. Langdurige ontsteking kan leiden tot schade in deze structuren, met deformiteiten van gewrichten en standsafwijkingen van de voeten als gevolg. Hierdoor kunnen biomechanische veranderingen tijdens het belasten van de voet ontstaan, zoals een hoge druk onder de (voor)voet. Naast ontstekingen en biomechanische stoornissen kunnen ook dermatologische en neurovasculaire stoornissen en externe en persoonlijke factoren een rol spelen bij RA-gerelateerde voetproblemen. Deze voetproblemen hebben vaak pijn, beperkingen in dagelijkse activiteiten, restricties in participatie en een verminderde kwaliteit van leven als gevolg.

Diagnostiek en behandeling van voetproblemen in een vroeg stadium van de ziekte lijkt van belang om pijn en beperkingen in activiteiten te verminderen en om een verslechtering van voetfunctie te voorkomen. In een verder gevorderd ziektestadium is de behandeling van voetproblemen ook vaak noodzakelijk. Er lijkt echter sprake te zijn van ondergebruik van voetzorg. Bij patiënten is de kennis over de mogelijkheden van en de toegang tot voetzorg beperkt. Bij zorgverleners is er vaak beperkte aandacht voor en expertise in het behandelen van RA-gerelateerde voetproblemen. Daarnaast hebben zij vaak onvoldoende inzicht in de specifieke vaardigheden van zorgverleners van andere disciplines die betrokken kunnen zijn. Om de voetzorg voor patiënten te verbeteren is allereerst een overzicht van de multidisciplinaire diagnostiek en behandeling van voetklachten bij RA noodzakelijk. Dit is nodig om zorgverleners en patiënten handvatten te bieden voor het organiseren van tijdige, passende en evidence-based voetzorg. In het eerste deel van dit proefschrift is een overzicht gegeven van de verschillende opties voor multidisciplinaire voetzorg bij patiënten met reumatoïde artritis (RA) (**Hoofdstuk 2-4**).

Plantaire voetorthesen (zolen) worden vaak voorgeschreven in de behandeling van RA-gerelateerde voetproblemen. Het algemene doel van zooltherapie is het verminderen van voetpijn en het verbeteren van fysiek functioneren door het beïnvloeden van biomechanische factoren, zoals plantaire druk. Het gerapporteerde effect van zooltherapie op voetpijn bij RA is echter klein tot middelgroot (effectgrootte 0,40 - 0,45). Het verbeteren van de effecten van zooltherapie door gebruik te maken van de directe feedback van plantaire drukmetingen in de schoenen lijkt veelbelovend. Plantaire drukmetingen kunnen een beter inzicht geven in de belasting van de voet tijdens het lopen. Aangezien hoge druk onder de voorvoet gerelateerd is aan voetpijn bij RA, wordt verondersteld dat meer verlaging van de plantaire druk leidt tot meer pijnvermindering. Voor deze hypothese is echter nog geen wetenschappelijk bewijs. Het doel van het tweede deel van dit proefschrift was om de rol van plantaire drukmetingen in de behandeling met zolen in kaart te brengen (**Hoofdstuk 5-7**).

Hoofdstuk 1 geeft een algemene inleiding op de onderzoeksthema's van dit proefschrift. Inzichten in de oorzaak en het beloop van RA-gerelateerde voetproblemen zijn beschreven. De factoren die van invloed zijn op deze voetproblemen zijn weergegeven in een overzicht aan de hand van de International Classification of Functioning, Disability and Health (ICF) van de World Health Organization. Daarnaast is de huidige aanpak van RA-gerelateerde voetproblemen en de rol van plantaire druk in de behandeling met zolen beschreven. Aan het eind van dit hoofdstuk zijn het doel en de hoofdlijnen van dit proefschrift weergegeven.

Hoofdstuk 2 beschrijft een project waarin multidisciplinaire aanbevelingen zijn ontwikkeld voor de diagnostiek en behandeling van voetproblemen bij patiënten met RA. De aanbevelingen zijn ontwikkeld op basis van wetenschappelijk bewijs en de opinie van experts, waarbij gepubliceerde strategieën voor de ontwikkeling van praktijk aanbevelingen zijn gevolgd. De expertgroep bestond uit twee patiënten en 22 ervaren professionals (reumatologen, revalidatieartsen, orthopedisch chirurgen, gespecialiseerde verpleegkundigen, podotherapeuten, orthopedisch schoentechnici, pedicures en onderzoekers) in Nederland. In totaal werden 41 aanbevelingen ontwikkeld. Twee aanbevelingen hadden betrekking op een kader voor diagnostiek en behandeling. Negenendertig aanbevelingen gingen over voetzorg: zeven over diagnose (inclusief controle van voeten en schoenen en diagnostische beeldvormende technieken), 27 over behandeling (inclusief corticosteroïdeninjecties, voetchirurgie, therapeutische schoenen, zolen, oefentherapie, teenortheses en teennagelbeugels, en de behandeling van teennagels en huid), vier over communicatie en één over de organisatie van de RA-gerelateerde voetzorg. Deze multidisciplinaire aanbevelingen kunnen een leidraad zijn voor het organiseren van tijdige, passende en evidence-based voetzorg. Implementatie van de aanbevelingen, gebaseerd op een strategie en plan voor het aanpakken van bevorderende en belemmerende factoren voor implementatie, is nodig om de voetzorg voor de individuele patiënt te verbeteren.

In **Hoofdstuk 3** is de literatuur over de effectiviteit van orthopedische schoenen bij patiënten met RA systematisch samengevat op de uitkomsten voetfunctie, voetpijn, fysiek functioneren, gezondheid-gerelateerde kwaliteit van leven, naleving van de behandeling, bijwerkingen en patiënttevredenheid. Orthopedische schoenen kunnen bestaan uit volledig op-maat-gemaakte schoenen (in Nederland: orthopedische schoenen A) en semi op-maat-gemaakte schoenen (orthopedische schoenen B). Orthopedische schoenen A worden op basis van specifieke maatnames en specificaties voor de individuele patiënt ontwikkeld, waarbij verschillende technische aanpassingen kunnen worden geïntegreerd. Orthopedische schoenen B zijn in serie geproduceerde schoenen met extra diepte, ondersteuning, ingebouwde inlays of technische aanpassingen. Elf studies zijn geïdentificeerd, met een totaal aantal van 429 patiënten, waarvan drie van hoge kwaliteit. Twee studies onderzochten orthopedische schoenen A, acht studies orthopedische schoenen B en één studie onderzocht beide. Voor orthopedische schoenen A toonden best-evidence-syntheses een zwak bewijs voor de vermindering van voetpijn en verbetering van fysiek functioneren. Voor orthopedische schoenen B toonden meta-analyses een middelgroot tot groot effect voor de vermindering van voetpijn en een klein tot middelgroot effect voor de verbetering van fysiek functioneren. Alle resultaten zijn gebaseerd op verschillen binnen de groep, aangezien er onvoldoende studies beschikbaar waren die verschillen tussen de groepen rapporteerden. De resultaten van dit hoofdstuk impliceren dat behandeling met orthopedische schoenen effectief is bij patiënten met RA. Definitieve RCT's van hoge kwaliteit zijn noodzakelijk om te onderzoeken wat de meerwaarde is van orthopedische schoenen ten opzichte van confectieschoenen.

In **Hoofdstuk 4** is de literatuur over de effectiviteit van verschillende soorten zolen in de behandeling van voetproblemen bij RA patiënten systematisch samengevat. In deze studie zijn de primaire uitkomsten voetfunctie en voetpijn en de secundaire uitkomsten fysiek functioneren, gezondheid-gerelateerde kwaliteit van leven, naleving van de behandeling, bijwerkingen, kosten van zolen en patiënttevredenheid. Tien studies, met een totaal aantal van 235 patiënten, zijn geïdentificeerd, waarvan drie van hoge kwaliteit. Deze studies maakten een vergelijking tussen verschillende gebruikte materialen (zacht *versus* semi-rigide), typen zolen (op-maat-gemaakt *versus* kant-en-klaar; total contact *versus* niet-total contact) of uitgevoerde aanpassingen (metatarsale balk *versus* pelotte). Ook werden verschillende technieken om op-maat-gemaakte zolen te construeren met elkaar vergeleken (standaard custom-moulding technieken *versus* meer geavanceerde technieken). Meta-analyses toonden een middelgroot effect aan voor (directe) vermindering van de druk onder de voorvoet in het voordeel van een behandeling met zachte zolen (in vergelijking met semi-rigide zolen). Andere vergelijkingen tussen de zolen resulteerden in niet-significante verschillen of niet sluitend bewijs voor het ene soort zolen in vergelijking met het andere. Op basis van de resultaten van dit hoofdstuk kan geconcludeerd worden dat er nog beperkt inzicht is in het verschil in effectiviteit tussen verschillende soorten zolen. Daarom zijn definitieve RCT's van hoge kwaliteit nodig om de (kosten-)effectiviteit van verschillende soorten zolen met elkaar te vergelijken.

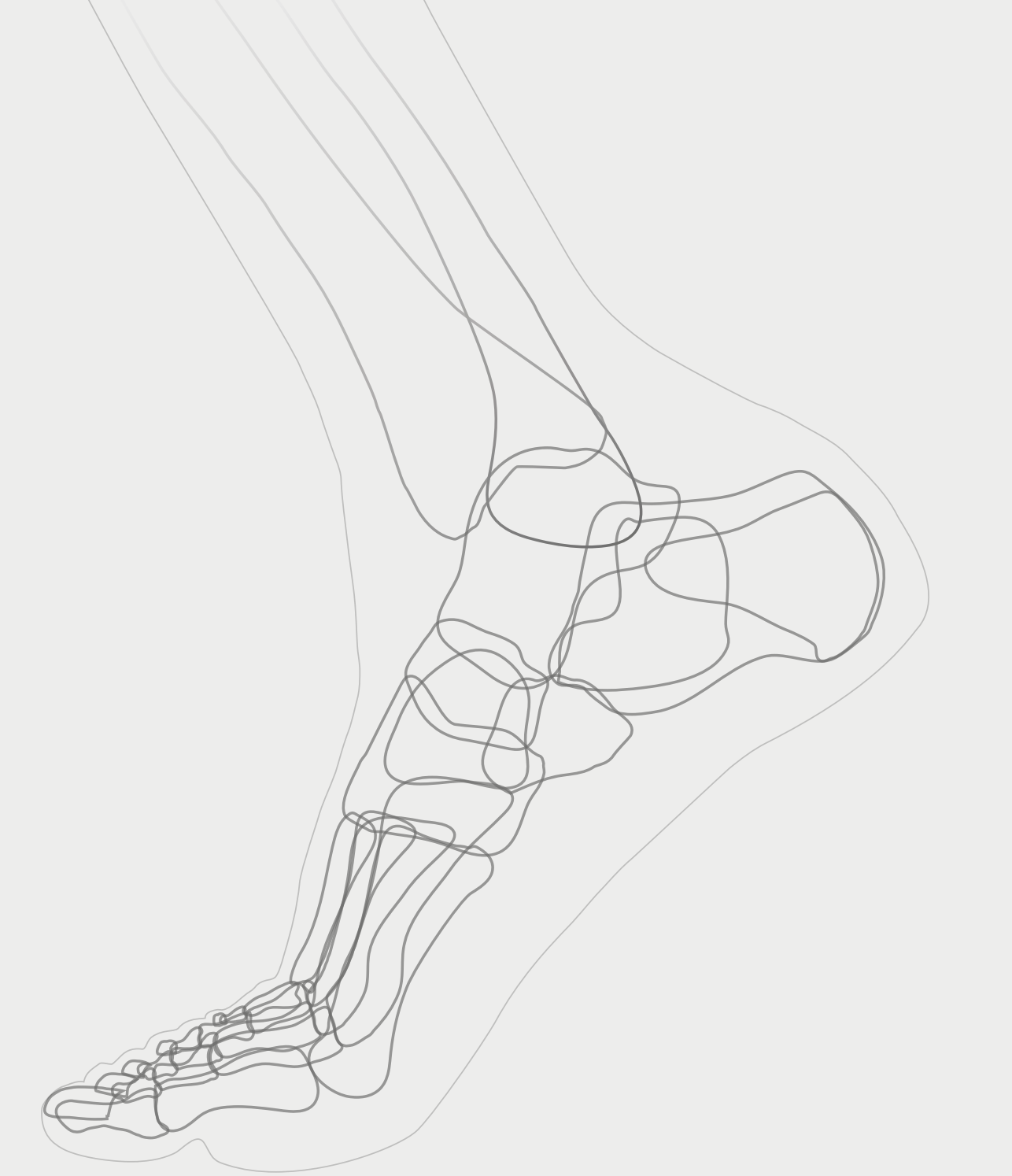
In **Hoofdstuk 5** is een protocol geëvalueerd voor het optimaliseren van plantaire drukreductie door zooltherapie, waarbij gebruik gemaakt wordt van de directe feedback van drukmetingen in de schoenen. Vijfenveertig RA-patiënten met voetproblemen zijn geïncludeerd in deze observationele proof-of-concept studie. De op-maat-gemaakte zolen zijn door een podotherapeut vervaardigd volgens usual-care. Bij 43 patiënten zijn deze usual-care zolen geëvalueerd met behulp van drukmetingen in de schoenen en, indien nodig, aangepast. Bij 70% van de patiënten is aanpassing van de zolen uitgevoerd. Bij deze patiënten werd een gemiddelde plantaire voorvoet drukreductie van 9% gevonden tijdens het dragen van usual-care zolen ten opzichte van het niet dragen van zolen. De aanpassingen van de zolen leidden tot een extra gemiddelde plantaire drukverlaging van 3%. Semigestructureerde interviews zijn gehouden met patiënten en podotherapeuten om de haalbaarheid van het protocol te evalueren. Het protocol werd haalbaar geacht door patiënten. Podotherapeuten vonden het protocol bruikbaarder om individuele behandeldoelen te bereiken dan vooraf vastgestelde, algemene behandeldoelen. Er is een definitief optimalisatieprotocol voor zooltherapie voorgesteld, waarin individuele behandeldoelen worden vastgesteld die gericht zijn op herverdeling van de plantaire druk in pijnlijke voetgebieden. De resultaten van dit hoofdstuk

hebben verschillende implicaties voor zowel de klinische praktijk als voor onderwijs en scholingsprogramma's gericht op (toekomstige) podotherapeuten. Ten eerste kunnen plantaire drukmetingen in de schoenen worden gebruikt als extra diagnostisch middel bij RA-patiënten met voetproblemen; het geeft inzicht in de relatie tussen voetpijn en plantaire druk tijdens het lopen met schoenen. Ten tweede kan de directe feedback van drukmetingen in de schoenen een leidraad bieden voor het proces van evaluatie en aanpassing van zolen.

In **Hoofdstuk 6** zijn de ontwikkelde zolen volgens het 'zolen optimalisatieprotocol' (zoals beschreven in **Hoofdstuk 5**) geëvalueerd op pijn, fysiek functioneren en druk onder de voorvoet na drie maanden dragen van zolen bij 38 patiënten. De scores voor de verandering binnen de groep lieten een middelgroot effect zien op pijnvermindering, een groot effect op verbetering van fysiek functioneren en een klein effect op vermindering van plantaire voorvoet druk. Of zolen ontwikkeld volgens het 'zolen optimalisatieprotocol' kunnen leiden tot betere klinische resultaten in vergelijking met zolen ontwikkeld zonder dit protocol is onduidelijk. Verder onderzoek naar de klinische relevantie van het gebruik van het protocol is nodig. Tevens is de relatie tussen verandering in de plantaire voorvoetdruk en verandering in pijn en fysiek functioneren onderzocht in een subgroep van 23 patiënten. Bij deze patiënten zijn geen statistisch significante relaties gevonden tussen de verandering in plantaire druk en de verandering in pijn of fysiek functioneren. Daarom kon de hypothese dat meer drukverlaging zou leiden tot betere klinische resultaten niet worden bevestigd.

In **Hoofdstuk 7** is de associatie van plantaire druk met ziekteactiviteit en deformiteiten in de voorvoet onderzocht in een cross-sectionele studie, waarbij gebruik is gemaakt van gegevens van 172 RA-patiënten met voorvoetproblemen uit het Amsterdam Foot (AMS-voet) cohort. Plantaire druk in de voorvoet is gemeten met een drukplatform. De mate van deformiteit van de voorvoet is beoordeeld aan de hand van de Platto-score. Ziekteactiviteit in de voorvoet is gedefinieerd als zwelling en/of pijn, welke is beoordeeld door palpatie van de metatarso-falangeale gewrichten. Hogere plantaire druk is gevonden in gebieden met deformiteit in de voorvoet ten opzichte van gebieden zonder voorvoetpathologie (ziekteactiviteit of deformiteit). Dit bevestigt onze hypothese en bevindingen uit eerder onderzoek, dat deformiteiten van de voorvoet zijn gerelateerd aan hogere plantaire drukken. Er werd geen associatie tussen lokale ziekteactiviteit en lagere plantaire druk gevonden. Toekomstig onderzoek met sensitieve beeldvormende metingen, om ziekteactiviteit te detecteren, is aanbevolen om het effect van ziekteactiviteit in de voorvoet op de plantaire druk inzichtelijk te maken.

Tot slot zijn in **Hoofdstuk 8** de belangrijkste resultaten van dit proefschrift samengevat en bediscussieerd en zijn suggesties gedaan voor toekomstig onderzoek.



Dankwoord

Dankwoord

Het is zover, mijn proefschrift is klaar! In de afgelopen jaren heb ik met veel plezier gewerkt aan de verschillende onderzoeksprojecten die terug te vinden zijn in dit boek. Ik ben trots op het eindresultaat en ben tot de ontdekking gekomen dat ik onderzoeken echt leuk vind. Toch ben ik ook blij dat mijn PHD-traject nu tot een einde is gekomen. Het was soms best zwaar om dit te combineren met het runnen van een podotherapiepraktijk, het krijgen van twee prachtige kinderen, een verbouwing en een verhuizing. Door de hulp van veel verschillende mensen is het toch gelukt. Daarom wil ik deze mensen hier heel hartelijk danken.

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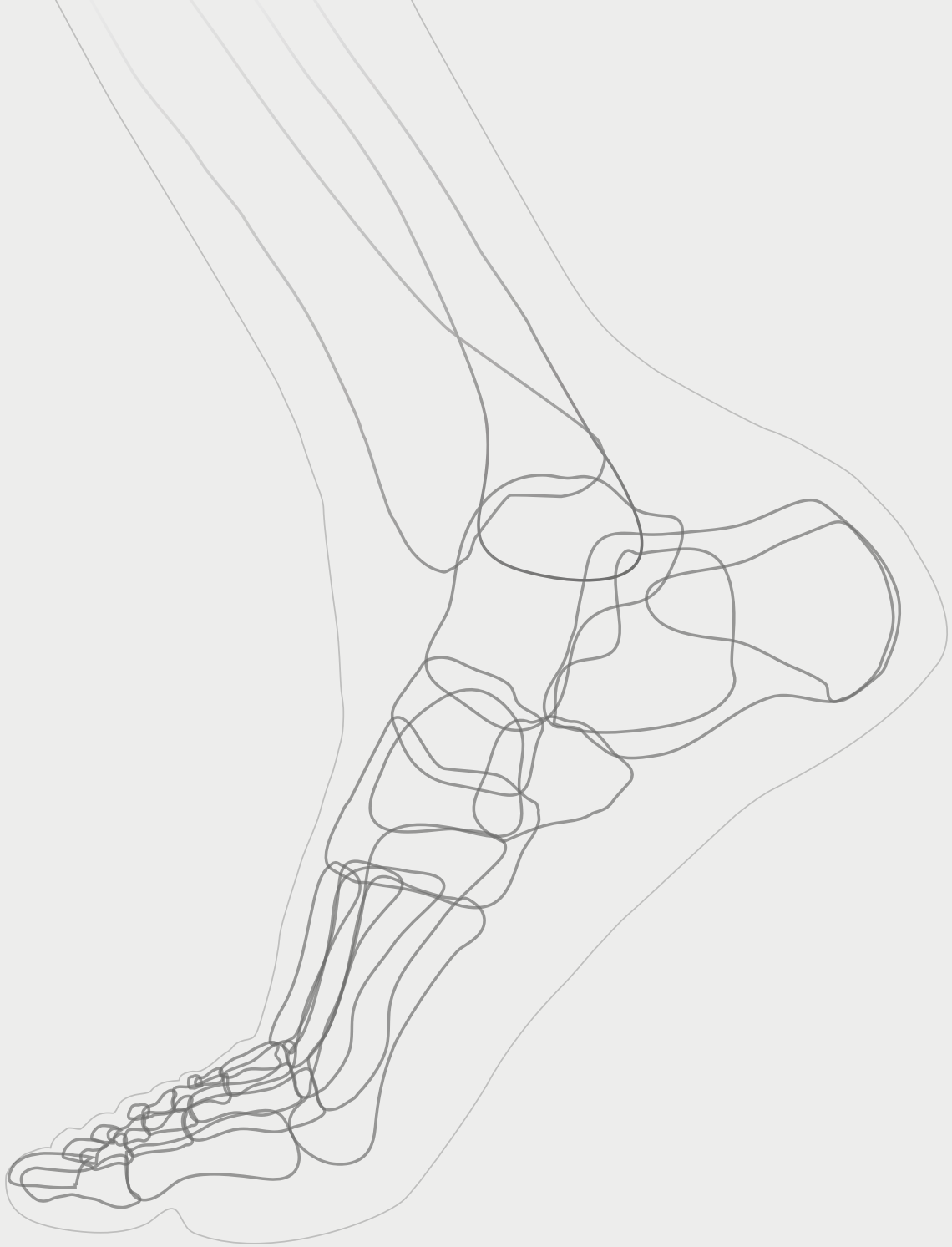

Over de auteur

Over de auteur

Marloes Tenten-Diepenmaat werd geboren op 4 september 1981 te Enschede. In 1998 haalde ze haar HAVO diploma aan Scholencentrum Het Assink in Haaksbergen. In 2002 studeerde ze af als podotherapeut aan Fontys Hogescholen in Eindhoven. Tussen 2002 en 2005 was ze werkzaam als podotherapeut bij verschillende praktijken in Oost-, Zuid- en West-Nederland. Van 2005 tot 2020 werkte ze binnen haar eigen podotherapie-onderneming met vestigingen in verschillende gezondheidszorgsettingen, in de regio Rotterdam en Gouda. Tussen 2012 en 2017 werkte ze als onderzoeker bij Reade, centrum voor revalidatiegeneeskunde en reumatologie, in Amsterdam. Hier heeft zij gewerkt aan de onderzoeksprojecten die beschreven zijn in dit proefschrift. In 2013 haalde ze het masterdiploma Epidemiologie aan de Vrije Universiteit van Amsterdam. Sinds 2019 werkt Marloes als hoofddocent/ onderzoeker binnen de opleiding Podotherapie van hogeschool Saxion in Enschede. Haar doel is om haar kennis en kunde in te zetten op het snijvlak van onderzoek, onderwijs en praktijk.

List of publications

International journals

Tenten-Diepenmaat M, Dekker J, Steenbergen M, Huybrechts E, Roorda LD, van Schaardenburg D, et al. In-shoe plantar pressure measurements for the evaluation and adaptation of foot orthoses in patients with rheumatoid arthritis: A proof of concept study. Gait & posture. 2016;45:45-50.

Tenten-Diepenmaat M, van der Leeden M, Vliet Vlieland TPM, Roorda LD, Dekker J. The effectiveness of therapeutic shoes in patients with rheumatoid arthritis: a systematic review and meta-analysis. *Rheumatology international* 2018;38(5):749-762. doi: 10.1007/s00296-018-4014-4.

Tenten-Diepenmaat M, van der Leeden M, Vliet Vlieland TPM, Dekker J. Multidisciplinary recommendations for diagnosis and treatment of foot problems in people with rheumatoid arthritis. *Journal of foot and ankle research* 2018;11:37. doi: 10.1186/s13047-018-0276-z.

Konings-Pijnappels APM, **Tenten-Diepenmaat M**, Dahmen R, et al. Forefoot pathology in relation to plantar pressure distribution in patients with rheumatoid arthritis: A cross-sectional study in the Amsterdam Foot cohort. *Gait & posture* 2019;68:317-322. doi: 10.1016/j.gaitpost.2018.12.015.

Tenten-Diepenmaat M, Dekker J, Heymans MW, Roorda LD, Vliet Vlieland TPM, van der Leeden M. Systematic review on the comparative effectiveness of foot orthoses in patients with rheumatoid arthritis. *Journal of foot and ankle research* 2019;12:32. doi: 10.1186/s13047-019-0338-x.

Tenten-Diepenmaat M, Dekker J, Twisk JWR, Huijbrechts E, Roorda LD, van der Leeden M. Outcomes and potential mechanism of a protocol to optimize foot orthoses in patients with rheumatoid arthritis. *Submitted for publication*.

National journals

Tenten-Diepenmaat M, Protocollarie in-shoe drukmeting effectief bij reumatoïde artritis. Podosophia > uitgave 2 /2017; 11 mei 2017. Bohn Stafleu van Loghum - Uitgeverij voor de gezondheidszorg.

Tenten-Diepenmaat M, Aanbevelingen voor de diagnostiek en behandeling van voetklachten bij patiënten met reumatoïde artritis. Orthopedisch schoentechniek > uitgave november 2017. NVOS-Orthobanda.

Contribution to books

E.J. Huijbrechts, M. van der Leeden en **M. Tenten-Diepenmaat**. Chapter 10: Voetbehandeling en educatie voor mensen met een reumatische aandoening. Third edition. Voeten en Reuma. Bohn Stafleu van Loghum. October 2019.

Online publications

Tenten-Diepenmaat M, van der Leeden M, Vliet Vlieland TPM, Dekker J. Aanbevelingen voor de diagnostiek en behandeling van voetklachten bij patiënten met reumatoïde artritis; hoofddocument, toelichting en samenvatting. Website: Nederlandse Health Professionals in de Reumatologie (NHPR). [Available from: https://www.nhpr.nl/richtlijnen-en-literatuur/]

PhD portfolio

PhD training	Year	Workload
Education		
Scientific meetings – in company, Reade, Amsterdam	2012-2016	7 ECTS
Systematic reviews and meta-analysis – EpidM, VUmc, Amsterdam	2012	1
Multilevel analysis – EpidM, VUmc, Amsterdam	2012	1
Scientific writing – in company course, Reade, Amsterdam	2012	1
Master Epidemiology – EpidM, VUmc, Amsterdam	2009-2013	60
Total European credit transfer system		**70 ECTS**
Congresses and presentations		
International		
EULAR[1], Madrid (Spain) – poster presentation	2017	1 ECTS
FIP[2] Podiatry World Congress, Rome (Italy) – oral presentation	2013	1
EULAR[1] visiting Fellowship, Glasgow (Scotland) – oral presentation	2012	0.6
Novel Expert Scientific Meeting, Aalborg (Denmark) – oral presentation	2012	0.6
National		
NVR[3], Arnhem – oral presentation	2019	10 hours
ASWS[4] Pedicurecongres, Nieuwegein – oral presentation	2018	10
NVR[3], Arnhem – oral presentation	2017	10
NVvP[5] Autumn congress, Nieuwegein – oral presentation	2017	10
NERASS[6] Autumn Congress, Woerden – oral presentation	2014	10
NVvP[5] Autumn congress, Nieuwegein – oral presentation	2014	10
Total European credit transfer system		**6 ECTS**
Teaching activities and other oral presentations		
Saxion, Enschede – oral presentation and clinical lesson	2019	8 hours
Tutor for pedicurists, Rotterdam	2017	16
Fontys, Eindhoven – oral presentation and clinical lesson	2017	8
Tutor for pedicurists, Rotterdam	2016	16
PHD-students meeting, VUmc, Amsterdam – oral presentation	2016	4
Fontys, Eindhoven – oral presentation and clinical lesson	2014	8
Reade, multidisciplinary RA-team meeting, Amsterdam – oral presentation	2014	4
Reade, scientific meeting – oral presentation	2012	4
Total European credit transfer system		**6 ECTS**
Other		
Contribution to KNGF[6]-Guideline Rheumatoid Arthritis	2018	16 hours
Member of the foot care-section of the NHPR[7]	2017-2019	24
Member of the Committee on Science and Innovation of the NVvP[5]	2012-2019	80
Total European credit transfer system		**5 ECTS**
	Total	**87 ECTS**

[1]Annual congress European League Against Rheumatism, [2]International Federation of Podiatrists, [3]Jaarcongres Nederlandse Vereniging voor Reumatologie, [4]ASWS Uitgeverij &Beursorganisatie, [5]Nederlanse Vereniging van Podotherapeuten, [6]Netherlands Rheumatoid Arthritis Surgical Society, [7]Dutch Health Professionals in Rheumatology