Improving footwear to prevent ulcer recurrence in diabetes: Analysis of adherence and pressure reduction
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Chapter 1

GENERAL INTRODUCTION
Chapter 1

Diabetes mellitus affects more than 366 million people worldwide and its prevalence is expected to rise substantially in the next decade\(^1\). The lifetime incidence of developing an ulcer is as high as 25\% in patients with diabetes\(^2\). Ulcers can cause infections, amputations and emotional and physical loss\(^2, 3\). It is believed that every 30 seconds a lower limb is lost somewhere in the world\(^4\) due to diabetes of which 85\% is preceded by a foot ulcer\(^5\). Ulcers are a costly complication of diabetes, accounting for approximately one third of the direct healthcare costs associated with diabetes\(^6\). Therefore, diabetic foot ulcers are a major problem in patients with diabetes and the prevention of foot ulcers has a great potential in the individual well-being and public health gain.

Patients with a previous plantar foot ulcer often develop a recurrent ulcer\(^7-12\). It is suggested that the development of a foot ulcer reflects the presence of underlying pathologic conditions, such as micro- and macro-vascular dysfunction, and peripheral nerve damage. Therefore patients with previous ulcers are at high risk for ulcer recurrence\(^7, 9\). One of the strategies used to prevent ulcer recurrence is providing custom-made footwear. There are many studies on the effectiveness of custom-made footwear to prevent ulcer recurrence, but the evidence to support this approach is still meagre\(^13\). Since ulcer recurrence is found to be multi-factorial\(^14\), the effectiveness of custom-made footwear needs to be studied in a broader perspective of factors to determine prognostic factors of plantar foot ulcer recurrence. In this introduction, the causes of ulceration are described, followed by a description of the existing evidence on the effectiveness of custom-made footwear and a description of a broad range of possible risk factors for plantar foot ulcer recurrence. Thereafter the approach we took to study the effectiveness of custom-made footwear and prognostic factors of plantar foot ulcer recurrence is described and this chapter will be finalized with the aims and outline of this thesis.

CAUSES OF ULCER RECURRENTE

The current theory of foot ulcer pathogenesis is that ulcers are caused by a combination of interacting risk factors, the three most relevant being: 1) a previous ulcer; 2) peripheral neuropathy; and 3) increased plantar foot pressures\(^15\). Several studies found an association between having previous ulcers and ulcer recurrence with relative risks between 1.6 and 5.3 in patients with diabetes\(^7-9, 11\). Especially a previous ulcer on the plantar side of the foot increases the risk for ulcer recurrence\(^12\). Peripheral neuropathy is also associated with ulcer occurrence. Odds ratio’s of 18 were found in diabetic patients with the inability to sense a 10-gram SWF monofilament\(^11, 16\). Peripheral neuropathy results in loss of protective sensation and is present in half of the diabetic patients with an age above 60 years\(^17\). Due to this inability to sense pressure and pain, high pressures may not be detected and patients continue to walk, which could lead to damage of the skin\(^18\). Also, a more than twofold risk on ulcer recurrence was found in patients with high plantar pressures\(^11, 19\), which could account for the fact that half of the ulcers occur on the plantar side of the foot\(^20\). Thus, high plantar pressures to a neuropathic foot play an important contributing role in ulcer recurrence\(^11, 19-24\). Furthermore, foot deformities, limited joint mobility and reduced plantar soft tissue thickness result in higher plantar peak pressures\(^25, 26\). Since patients with diabetes and neuropathy often have these abnormalities, their feet often show high peak pressures and are therefore at high risk for ulcer recurrence.
PRESSURE, CUSTOM-MADE FOOTWEAR AND ULCER OCCURRENCE

Elevated plantar peak pressures are associated with ulcer recurrence\textsuperscript{11, 19, 24, 27}. To date, the association between plantar peak pressure and ulcer recurrence has only been assessed in barefoot studies. These peak pressures do not fully reflect the biomechanical stress that the patient experiences during the day, because patients do not walk barefoot all day but use footwear most of the time. Therefore, in-shoe peak pressures are also necessary to determine the biomechanical stress on the foot. For that reason, footwear that reduces biomechanical stress on the foot might prevent ulcer recurrence.

Custom-made footwear aims to reduce in-shoe plantar peak pressures as compared to confection footwear. Based on this assumption, diabetic foot care-providers currently prescribe patients at high risk for ulceration with custom-made footwear to prevent foot ulceration\textsuperscript{15, 28-30}. Despite custom-made footwear, a recent study showed that still 40\% of the patients with neuropathy and a previous ulcer developed a recurrent ulcer, in a median 126 days\textsuperscript{31}. This high recurrence rate indicates that besides foot care, footwear might not (sufficiently) target the relevant risk factors. Possible explanations for this high recurrence rate might be that relieving pressure (offloading) in custom-made footwear is variable\textsuperscript{32} or that the prescribed footwear is not worn sufficiently\textsuperscript{33}. In this regard the quality of the custom-made footwear and patient’s adherence to wearing the prescribed footwear are thought to be important prognostic factors.

The offloading effect of custom-made footwear is achieved by accommodating the insoles to the foot and the use of special materials and corrective elements in such a way that load from high pressure locations is redistributed to low pressure locations\textsuperscript{34}. Cross-sectional studies found that in-shoe plantar peak pressures is reduced in custom-made footwear and a longitudinal study demonstrated that the initial pressure reduction can be maintained in the first 6 months, but these studies did not follow-up the patients to evaluate ulcer outcome\textsuperscript{35-40}. Prospective studies show conflicting results regarding the effectiveness of custom-made footwear to prevent ulcer recurrence. Several non-randomized longitudinal studies have found that ulcer recurrence rates were much lower in patients wearing custom-made footwear compared to patients wearing their own shoes\textsuperscript{33, 41-43}. However, a randomized controlled trial found no beneficial effect of specialized footwear on foot ulcer recurrence rate\textsuperscript{44}. In none of these longitudinal studies on ulcer recurrence the in-shoe plantar pressures were measured, and therefore, the effectiveness of footwear in pressure relief is unknown. Therefore, it remains unclear if the conflicting results of these studies can be explained by differences in pressure-relieving quality of the different footwear used or by other factors. Furthermore, these longitudinal studies had several other limitations: 1) patients were not always representative of the appropriate high risk population: not all patients had neuropathy and often patients with amputations and major foot deformities were excluded; 2) not all studies randomized the patients to an intervention group, or there was cross-over between study groups; 3) the definition of the primary ulcer outcome was often unclear, unreliable or very conservative and only one study assessed adherence to wearing the studied footwear subjectively. In view of this, two systematic reviews concluded that there is still no compelling evidence on the effectiveness of therapeutic footwear in preventing ulcer recurrence\textsuperscript{13, 45}.  

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Chapter 1

PROGNOSTIC RISK FACTORS OF ULCER RECURRENT

Elevated dynamic barefoot plantar pressure during walking is, in the presence of neuropathy, an important predictor of diabetic foot ulceration. One biomechanical study found the most optimal barefoot peak pressure cut-off level, 700kPa, to be 70% sensitive and 65% specific for ulceration, while another study found a barefoot peak pressure of 875kPa to be 64% sensitive and 46% specific. These findings indicate that a significant number of patients develop a recurrent ulcer despite lower pressure than threshold and patients do not develop an ulcer despite higher pressures than threshold. These results suggest that ulcer recurrence can not be predicted solely based on barefoot pressure and predictions may be improved by taking other prognostic factors into account. Possible prognostic factors can be divided biomechanical, behavioural, and disease-related factors. The main factors of interest in this thesis are discussed below.

Biomechanical factors

Biomechanical stress parameter

One of the risk factors of ulcer recurrence is biomechanical stress on the plantar side of the foot. Often used indicators of biomechanical stress are plantar pressure and peak pressure-time integral. Maximum peak pressure represents the maximum measured pressure of a defined region during one step cycle. Peak pressure-time integral integrates the peak pressure to the time duration of one step cycle. Although both parameters are often reported, specific conclusions per parameter are not usually reported, suggesting that these parameters may be interchangeable. A study that explores the association between maximum peak pressure and pressure-time integral in the diabetic foot is needed to further explore whether or not these parameters are interchangeable.

Barefoot pressure

Foot deformities, minor amputation, limited joint mobility, major callus and reduced plantar soft tissue thickness frequently occur in diabetic patients and all result in increased plantar foot pressures. Several studies assessed the association between barefoot plantar peak pressure and ulcer occurrence and found that elevated barefoot plant peak pressure is predictive for ulcer occurrence in diabetic patients with neuropathy. As mentioned before, the defined pressure thresholds in these studies showed a low sensitivity and specificity. It is unlikely that these patients walk barefoot all day. Adherence determines the amount of steps the patient wears (protective) footwear. Furthermore, these patients show variation in the level of ambulant activity. Therefore, an approximation of the true biomechanical stress on the plantar side of the foot might be improved when in-shoe pressures, adherence and ambulant activity are taken into account in combination with barefoot pressures. This suggests that the prediction of plantar foot ulceration can be more precise when more factors are included to estimate the biomechanical stress.

In-shoe plantar pressure in custom-made footwear

Inappropriate footwear has been reported to be the root cause of 21-76% of diabetic foot ulcers and/or amputations. It is said, for example, that inappropriate footwear is too tight or that the insole is too stiff. With these facts in mind, many care-providers
in clinical practice prescribe custom-made footwear in the belief that such footwear reduces plantar peak pressures and thereby reduce the incidence of foot ulceration. However, the evidence base for such a view is unclear. Currently, prescription of custom-made footwear is primarily based on clinical expertise and the effectiveness of this footwear is most often evaluated on whether the patient remains free of ulceration. Regular objective evaluation of peak pressures in custom-made footwear is not being done. Due to the presence of peripheral neuropathy, the patient’s feedback on pressure, pain and comfort is limited. Therefore, variability exists in the offloading properties of this footwear. This variability in offloading may explain the high recurrence rates of ulceration. Offloading may be improved by modifying footwear after it has been delivered to the patient, using objective measurement tools. In-shoe plantar pressure analysis is such a tool that can efficiently guide footwear modification to create better offloading properties, although studied in a relatively small and heterogeneous group of patients. Furthermore, wear and tear of footwear or progress of foot deformities may alter the pressure offloading over time, requiring repeated footwear modifications over time. Therefore a study that explores the effect of improving offloading guided by in-shoe pressure analyses and the course of peak pressure over time in a large homogeneous group of high-risk patients and footwear conditions is needed.

**Behavioural factors**

**Adherence to footwear use**

To effectively contribute to the prevention of ulcer recurrence, custom-made footwear should be worn by the patient, in particular when being ambulant. An observational study reported that half of the ulcer recurrence can be prevented when therapeutic footwear was worn more than 60% of the daytime. But, studies in which footwear use was self-reported have shown that only 22-36% of patients with diabetes wear their prescribed footwear regularly (>80% of the day). This indicates that many patients do not wear their therapeutic footwear as intended, elevating the risk of ulcer recurrence. Furthermore, to date, footwear adherence has been measured subjectively and might therefore be less accurate and reliable than objective methods. Therefore, data on footwear adherence in patients who have diabetes and are at high risk for ulceration should be measured objectively, but these methods have until recently been unavailable. Having these data and knowing what determines footwear use is valuable in addressing issues of footwear effectiveness.

**Ambulant activity**

Apart from plantar foot pressure and adherence, other factors such as the type and intensity of daily ambulant activity might determine clinical outcome, since the amount of weight-bearing activity is likely to influence the amount of mechanical stress accumulated by plantar tissues. So far, evidence for the relation between ambulant activity and ulcer recurrence is unclear. Several studies assessed daily weight-bearing activity, but none found that increased activity was associated with ulcer occurrence. However, increased intra-individual day to day variability in activity was associated with ulcer recurrence. Furthermore, weight-bearing activity in combination with plantar pressures is suggested to predict ulcer recurrence. The number of steps taken during the day and the applied biomechanical stress during each step determines the accumu-
lated stress on the foot. This accumulated stress was surprisingly lower in patients who had previous ulcers. In these previous studies on accumulated stress, adherence to wearing footwear was not taken into account and accumulated stress was calculated as if the patients wore the footwear in each step, which seems unlikely. Therefore, as mentioned before, information on ambulant activity in relation to footwear adherence, barefoot peak pressures, and in-shoe peak pressures might result in an improved estimate of the accumulated stress, with improved prediction of ulcer recurrence.

**Patient and disease-related factors**

Besides the above mentioned biomechanical and behavioural factors, several studies have identified many significant patient and disease-related risk factors for diabetic foot ulceration. These factors include age, gender, BMI, degree of peripheral neuropathy, peripheral arterial disease, diabetes type and duration, history of ulceration, Hb1Ac, deformities and minor lesions (callus, hematoma, blisters). These patient and disease-related factors might mediate or moderate the relation between biomechanical and behavioural factors and ulcer outcome, and therefore they are important to examine. For that reason these parameters should be integrated in a broader perspective to study their influence on ulcer recurrence in relation to other risk factors.

**THE DIABETIC FOOT ORTHOPAEDIC SHOE TRIAL**

To increase knowledge on the effect of plantar foot pressure and custom-made footwear on plantar foot ulcer recurrence, the DIAFOS trial was conducted. DIAFOS (the DIAbetic Foot Orthopaedic Shoe trial; Dutch trial register NTR1091) is a multicenter randomized controlled trial, in which the effectiveness of offloading-improved custom-made footwear in comparison with non-improved custom-made footwear on plantar foot ulcer recurrence in diabetic patients with neuropathy and a previous ulcer was studied. In this study, the Academic Medical Centre in Amsterdam collaborated with 9 other multidisciplinary diabetic foot centres and 9 orthopaedic footwear companies in the Netherlands. Patients in the intervention group were provided with custom-made footwear that was improved in its offloading capacity using in-shoe plantar pressure measurements as guidance tool for footwear modifications. Since the offloading properties of this footwear might be affected over time due to wear and tear or an altered foot shape, each 3 months a follow-up visit was scheduled so that adjustments could be made to ensure improved offloading. In the control group, patients received custom-made footwear that was prescribed following normal clinical practice, in which in-shoe pressure measurements were not used to improve offloading of the footwear. This footwear was also monitored for pressure each 3 months. Additionally, we measured many other parameters in addition to foot pressure to gain further insight in prognostic risk factors of ulcer recurrence. These data provided us with more insight in the biomechanical stress applied to the foot in combination with adherence to wearing prescribed footwear use and ambulatory weight-bearing activity (e.g. walking).

In summary, the review of the literature shows that ulcer recurrence is a major problem in patients with a diabetic foot. Several studies have explored causal pathways and elaborated on prognostic factors of ulcer recurrence. These studies led to screening tools to identify patients at risk and interventions with the goal to prevent ulcer recurrence. One of the interventions that is often used is prescription of custom-made footwear.
because there is an almost universal clinical opinion that this intervention is effective\textsuperscript{52}. However, intervention studies show conflicting results in this matter. None of the prospective studies on ulcer recurrence measured the offloading properties of prescribed footwear and none of the studies measured adherence to wearing this footwear objectively. With the use of in-shoe pressure analysis we can evaluate, improve, and preserve pressure offloading of prescribed footwear. Furthermore, by applying new quantitative technologies, adherence to footwear use and ambulant activity can be measured in an objective way. With these technologies, a wide range of biomechanical, behavioural, and patient- and disease-related prognostic factors of ulcer recurrence can be assessed which so far have remained underexposed. Therefore, the goal of the DIAFOS project was to study the effectiveness of offloading-improved custom-made footwear in a longitudinal multicenter randomized controlled trial that includes objectively measured peak pressures, adherence to wearing custom-made footwear and ambulant activity.

**AIMS OF THIS THESIS**

The aims of this thesis were to select the most appropriate biomechanical stress parameter to use in pressure studies on the diabetic foot, to evaluate the use of foot pressure analysis to modify footwear, to develop a method to measure adherence and to assess adherence to wearing custom-made footwear objectively in these patients. These studies will form the basis of the main aims of this thesis, which are: assessing the effectiveness of pressure-improved custom-made footwear on plantar foot ulcer recurrence and to expand the body of knowledge on the predictive value of a broad range of biomechanical, behavioural, and patient and disease-related factors on plantar foot ulcer recurrence in diabetic patients with neuropathy and a previously healed plantar foot ulcer.

More specifically, the objectives of this thesis are:

1. To explore the interdependency of maximal peak pressure and pressure-time integral in diabetic patients wearing different types of footwear.
2. To assess the validity and feasibility of a new temperature-based adherence monitor to measure adherence of wearing different types of footwear.
3. To assess objectively measured adherence to wearing prescribed custom-made footwear during ambulant activity.
4. To assess the value of using in-shoe plantar pressure analysis for evaluating, improving and maintaining the offloading properties of newly prescribed custom-made footwear.
5. To assess if offloading-improved custom-made footwear reduces recurrence of plantar ulcers.
6. To assess the prognostic value of biomechanical, behavioural, and patient and disease-related factors on plantar foot ulcer recurrence.

**OUTLINE OF THIS THESIS**

Chapter 2 presents a study that explores the association between maximum peak pressure and pressure time integral. The results of this study guided us to select the most appropriate parameter to be used for the subsequent studies.
In chapter 3 a study in which the validity and feasibility of a new sensor that measures adherence to wearing footwear in an objective way, was tested. With this technology we assessed adherence to wearing prescribed custom-made footwear in diabetic patients with neuropathy and a previous ulcer. The study results are described in chapter 4.

Chapter 5 assesses the value of using in-shoe plantar pressure analysis to evaluate, improve and preserve the offloading properties of newly prescribed custom-made footwear. Whether this approach was effective in preventing plantar foot ulcer recurrence in diabetic patients was studied in a multicenter randomized controlled trial of which the results are described in chapter 6.

In chapter 7 a study is described in which the prognostic value of a broad range of biomechanical, behavioural, and patient- and disease-related factors on plantar diabetic foot ulcer recurrence was assessed in order to explore risk factors for ulcer recurrence.

Finally, in chapter 8 the main findings of this thesis are presented and some methodological considerations are discussed. Additionally, the clinical implications of these studies and some recommendations for further research together with an overall conclusion is described.
REFERENCES


