Improving footwear to prevent ulcer recurrence in diabetes: Analysis of adherence and pressure reduction
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Chapter 8

GENERAL DISCUSSION
The main aims of this thesis were to expand the body of knowledge on the effectiveness of offloading-improved custom-made footwear in lowering risk of plantar foot ulcer recurrence, and on the predictive value of biomechanical, behavioural, and disease-related factors on plantar foot ulcer recurrence in diabetic patients with peripheral neuropathy and a previous plantar foot ulcer.

Additional supportive aims were to select the most appropriate biomechanical stress parameter to use for in-shoe plantar pressure studies on the diabetic foot, to evaluate the value and effect of using in-shoe plantar pressure measurements to modify footwear and improve offloading, to develop a method to objectively measure adherence, and to assess adherence to wearing custom-made footwear in these patients.

These aims led to several specific research objectives, as described in chapter 1, which can be summarized into four themes, which are a) biomechanical stress parameter, b) adherence to wearing custom-made footwear, c) effectiveness of offloading-improved footwear and d) prognostic factors of ulcer recurrence. In perspective of these four themes, the main findings of the studies in this thesis will be discussed. Furthermore, in this chapter methodological issues of the studies performed will be considered as well as the implications of the findings for clinical practise. Finally, recommendations for future research will be given.

**MAIN FINDINGS**

**Biomechanical stress parameter**

Many parameters can be calculated to express the mechanical stress on the plantar side of the foot. Previous diabetic foot studies focused mainly on maximal peak pressure (hereafter referred to as peak pressure) and pressure time integral. In chapter 2 we showed that peak pressure and peak pressure-time integral were highly interdependent and lead to the same conclusions when measured in neuropathic diabetic patients wearing different types of commonly prescribed footwear. This interdependency was strongest in the foot regions that were most prone to develop pressure-related ulcers and was independent of the type of footwear tested. These results confirmed earlier findings in non-diabetic subjects\(^1\) and suggest that both parameters can be used interchangeably in pressure studies on the diabetic foot.

However, peak pressure has to date been used more frequently than the pressure time integral\(^2,7\), it is the only parameter of the two that has been associated prospectively with diabetic foot ulceration\(^8\), is easier to interpret due to the lack of time dimension involved, and can be obtained directly from measurements while the calculation of the pressure time integral requires post-processing of data. Therefore, we consider peak pressure as the most appropriate parameter and the findings support our choice to use peak pressure as primary parameter throughout this thesis.

**Adherence to wearing custom-made footwear**

Adherence to wearing prescription footwear is likely an important factor in footwear
effectiveness, and therefore it is important to measure this parameter accurately and reliably. Most previous studies assessed adherence expressed in wearing time by using questionnaires and interviews. The accuracy of these subjective methods has been debated and may lead to response bias and missing data. Furthermore, these methods fail to assess adherence while patients are ambulatory, which is the most important period considering the stress on the foot. A more valid outcome would be adherence expressed as the percentage of steps the footwear is worn. In chapter 3, we described a method that combines data from a shoe-worn temperature-based monitor with data from an ankle-worn step activity monitor, and demonstrated that this is an accurate, reliable and feasible method to assess footwear adherence in diabetic patients.

Using this measurement setup, we showed that diabetic patients at high risk for ulcer recurrence wore their prescribed footwear in 71% of the steps taken as described in chapter 4. There was a large variability in adherence during ambulation between patients ranging from 10-100%. Around half of the patients wore their footwear more than 80% of the steps taken, which we classified as high adherence. Moreover, around one third of the patients wore their footwear less than 60% of the steps, which we classified as low adherence. Adherence at home was much lower than away from home. In particular in patients showing an overall low adherence, adherence at home was poor (28% of the steps compared with 69% away from home). Furthermore, patients were more active while being at home than away from home. This combination of low adherence with high ambulant activity at home is worrisome as more steps are taken on an inadequately protected foot.

**Benefit of offloading-improved footwear**

In chapter 5, we demonstrated that in-shoe peak pressure measurements could be used as guidance tool for footwear modifications to improve and maintain offloading in custom-made footwear. With this method, peak pressures could be reduced substantially at high risk areas with pressures above 200kPa, which was in accordance with previous data. These lowered peak pressures could be maintained or further reduced over time using this approach at each 3-monthly follow-up visit. Furthermore, the peak pressure in this improved footwear was significantly lower than in non-improved custom-made footwear (usual care). Such a method to warrant adequate offloading in footwear is suggested to be of high clinical relevance, because lower peak pressure reduces the risk for ulcer recurrence.

As the multicenter randomized trial described in chapter 6, offloading-improved custom-made footwear was not significantly more effective over usual care (i.e. conventional custom-made footwear) in reducing plantar foot ulcer recurrence in diabetes. This unexpected outcome showed that offloading-improved custom-made footwear by itself was not clinically beneficial. This result may indicate that the 20% improvement in peak pressure reduction achieved, compared to usual care, is insufficient to reduce ulcer recurrence. To understand (lack of) clinical success, we assessed the influence of footwear adherence, since walking barefoot or wearing non-prescribed footwear might counteract the beneficial effect of offloading-improved footwear. Offloading-improved custom-made footwear significantly reduced plantar foot ulcer recurrence risk with 46% compared to usual care in a subgroup of patients that wore their footwear more
than 80% of the steps. This difference suggests that offloading-improved custom-made footwear can be more effective in preventing ulcer recurrence than conventional custom-made footwear, when this footwear is worn consistently.

**Prognostic factors of ulcer recurrence**

To assess the prognostic value of a broad range of biomechanical, behavioural and disease related factors on plantar foot ulcer recurrence (chapter 7) we developed two logistic regression models. In the first model, we assessed determinants of all plantar ulcer recurrences that developed during the study period. In the second model, we assessed only the ulcer recurrences with a non-traumatic cause occurring at the same location as the prior ulcer, to isolate those ulcers that most likely had a pressure-related aetiology. The multivariate logistic regression showed that 68% of all recurrences (model 1) and 76% of pressure-related recurrences (model 2) were correctly predicted. This is moderate given the large number of factors that were assessed, and the fact that change alone, will 'predict' 50% of the ulcers correctly.

Some expected risk factors prevailed from the models. We found in both models the presence of minor lesions (abundant callus, haemorrhage or a blister) at entry of the study to be the strongest predictor, with patients having a minor lesion being over five to ten times more at risk to re-ulcerate. For the biomechanical and behavioural parameters analysed we found that patients were less likely to develop an ulcer at the prior ulcer location when they wore properly offloaded footwear (in-shoe peak pressure below 200kPa) more than 80% of the daily steps. Furthermore, having a higher barefoot peak pressure increased the risk for non-traumatic ulcer recurrence at the prior ulcer location. These results suggest that overall plantar foot ulcer recurrence is moderately predicted from the many disease-related, biomechanical and behavioural factors, but with an important role for minor lesions, adherence, barefoot- and in-shoe peak pressures.

**METHODOLOGICAL CONSIDERATIONS**

In this section, a number of methodological issues, strengths and limitations of the studies described in this thesis will be discussed.

**Study population**

The population studied in this thesis concerned patients with type 1 or 2 diabetes mellitus, peripheral neuropathy, and a recent history of plantar foot ulceration. For this patient population special diabetic footwear is recommended according to the international consensus on the diabetic foot (2011)²³, and these patients are typically prescribed with custom-made footwear to prevent ulcer recurrence. Exclusion criteria in this study were bilateral amputation proximal to the tarsometatarsal joint, the use of walking aids that offload the foot, inability to follow study instructions, and the unlikelihood to survive 18 months of follow-up. This implied that our study population comprised high-risk patients with severe foot deformity such as partial foot amputation, Charcot deformity, and rigid claw toe deformity, deformities that have often been a reason for exclusion in other footwear studies²⁴-²⁷. Furthermore, these patients were recruited in ten diabetic foot clinics throughout the Netherlands, in both urban and rural
regions. Therefore, we assume that the results of this study have large external validity for patients that are typically prescribed with therapeutic footwear in Dutch diabetic foot clinics.

**Patient recruitment rate**

In the DIAFOS trial, patient inclusion was difficult due to a limited number of eligible patients. Based on a power calculation, a required sample size of 240 patients was anticipated. According to a priori estimates of recruitment rates by the care providers in each participating centre, we estimated that this number of patients could be included in two years time in eight participating centres. However, despite a prolonged inclusion period of one year and the addition of two participating centres, financial and time constraints forced us to stop inclusion at 171 participants.

Fortunately, the lower inclusion rate and statistical power was partly compensated by a low dropout rate of only 6% in 18 months. This low dropout rate was suggested to be the result of the intensive contact between the patients and researchers, who were centrally appointed in the AMC and therefore had a large interest in low dropout rates. A 6% dropout rate is much lower compared to other studies showing dropout rates ranging from 14-36%.

In combination with the intention-to-treat analysis in which all patients including the dropouts were analysed, the inclusion of 171 patients still yielded a (one-sided) power of 0.76. Despite this slightly underpowered analysis, we do not expect that inclusion of the originally anticipated number of patients would have given different outcomes.

Many randomized controlled trials face the problem of overrating the number of eligible patients, referred to as Lasagna’s Law. A better prognosis of recruitment rates based on more detailed analyses of medical files in participating centres is required to improve project and time management of trials like the DIAFOS trial.

**Randomization**

To ensure balanced treatment allocation within centres and within gender groups, we used a non-deterministic minimization method incorporating the factors centre and gender to randomize the patients. Especially when there are many subgroups (centres (10) x gender (2)) with small sample sizes, the minimization method is preferred above other forms of randomization. We found no significant differences between the study groups at baseline of the study for in-shoe peak pressures and baseline characteristics except diabetes duration, which we assume to be as a result of chance. We conclude that this minimization method was successful and that results of this trial were not biased by factors within diabetic foot clinics.

**The offloading intervention**

One of the aims in the DIAFOS trial was to improve pressure offloading in custom-made footwear, using in-shoe peak pressure measurements as guidance tool for footwear modifications. This offloading intervention was based on a previous efficacy study from our group that showed that offloading could be improved in a session that lasted on
average 53 minutes\(^{17}\). We confirmed these findings in a larger group of patients as described in chapter 5. In our trial, in-shoe peak pressures were measured by the researcher. Guided by these measurements, the shoe technician modified the footwear. The shoe technician chose the footwear modification and was not enforced by any protocol. Together with the fact that nearly all patients were measured and footwear modifications were made during regular outpatient clinic visits, this routine facilitated implementation in clinical practice.

With this intervention, we aimed to reduce peak pressure under an absolute level of 200kPa or to achieve a reduction of minimal 25% in a maximum of three rounds of footwear modifications at each 3-monthly follow-up. We showed that peak pressure at high-risk locations could be improved on average with about 20% (chapter 6). The lack of clinical benefit of this intervention as shown in the RCT suggests that the 20% improvement in offloading might not be sufficient to reduce ulcer recurrence. Several factors may play a role here. Of all footwear delivered to the patient at baseline, 24% of the footwear showed already peak pressures below 200kPa. This includes patients in the usual care group. According to our study protocol, this footwear was qualified as properly offloaded and consequently no major modifications were made to improve offloading, which reduces the contrast between study groups. Furthermore, we were not always able to reduce the peak pressure successfully in patients showing peak pressures above 200kPa. This, because for example the maximum number of three footwear modifications rounds was achieved, or due to time constrains in a busy clinic, or when the shoe technician feared that further modification of the shoe would increase pressure in an already offloaded region. Another factor is that in the intervention group peak pressure relief followed a “saw-tooth” pattern (Figure 2, chapter 6, page 87), with increase in peak pressure in-between study visits. This affected the sustained effect of pressure relief in the intervention group and also reduced the contrast between study groups. A final explanation could be that due to a learning effect knowledge on effective footwear modifications was transferred to the control condition, diminishing the difference in peak pressure between both study groups. This, however, seems unlikely, since in the control group hardly any footwear modifications were done during follow-up.

**Blinding**

In the randomized controlled trial, we compared the intervention group with the control group on in-shoe peak pressure and ulcer outcome (chapter 6). The patients, researchers and care providers should ideally be blinded to prevent bias. Our study, however, was an open-label trial in which the researchers as well as care providers were necessarily involved in the treatment of the intervention group patients, i.e. modification of the footwear. Therefore blinding of the researcher and care provider was not possible. We attempted to blind the patients by not informing them to which study group they were allocated. To assess whether patient blinding was successful, we surveyed 77 patients at the final visit. Of these patients, 74 did not know there were two study groups or to which study group they were allocated. Therefore, we assumed that blinding of the patients was successful. It should however be taken into account that patients at the final visit (18 months after baseline) might not remember that there were two study groups about which they were informed only at the start of the study.
In the studies wherein we assessed adherence with the in-shoe temperature-based adherence monitor in combination with the activity monitor (chapter 4, 6 and 7) we tried to blind patients by not mentioning the purpose of the measurement. This because patients might change their behaviour if they know that adherence was measured. Therefore, we told patients that we measured the temperature in the shoe and ambulant activity, without mentioning that we intended to measure adherence. Unfortunately, we did not collect data on the success of this blinding.

Although the researchers and care providers were not blinded, we were able to blind the assessors of the primary outcome (chapter 6 and 7). At each three-monthly follow-up or when a wound was detected, photographs of the plantar side of the foot were taken. These photographs and additional descriptions of the care provider were scored by three (or five in case of disagreement) independent diabetic foot experts, that were blinded to treatment allocation, on ulcer outcome. In most studies on (prevention of) ulcer recurrence, the outcome assessor(s) were not blinded or the method of assessment was not mentioned in these publications\(^{5, 25, 27, 33-36}\). Therefore, we assume that the risk for observer bias in our study was low compared to other studies.

**Primary outcome measure**

In our trial, a plantar ulcer was defined as ‘a full-thickness lesion through the skin’\(^{23, 37}\), and was additionally classified using the University of Texas system\(^{38}\). The ulcer recurrence rate in our trial (42% of all patients over 18 months) was higher than in previous footwear studies that found recurrence rates between 15% and 28%\(^{26, 27, 33}\). This discrepancy could be explained by differences in ulcer definition and population between the studies. For example, the study of Reiber and colleagues (15% ulcer recurrence over two years), might have underestimated ulcer recurrence rate because their classification of ulceration was “overly conservative”\(^{39}\). They defined an ulcer as ‘a cutaneous erosion extending into or through the dermis to deeper tissue or other cuts that did not heal in 30 days’, which is inconsistent with the international guidelines that do not consider an arbitrary time cut-off for ulcer classification\(^{26}\). In addition, only around half of their patients had peripheral neuropathy and patients with severe foot deformities were excluded. This makes their population at lower risk to re-ulcerate\(^{39}\) than our population. Also the study of Rizzo and colleagues (18% recurrence rate over three years)\(^{33}\) and Uccioli et al. (28% recurrence rate over 12 months)\(^{27}\) included few patients with prior ulcers\(^{33}\), neuropathy\(^{27, 33}\) or deformities\(^{27, 33}\). This makes their study population at lower risk for ulcer recurrence compared to our population in which all patients had prior plantar ulcers, neuropathy and most of them foot deformities. The recurrence rate of the study performed by Uccioli and colleagues\(^{27}\) seems comparable to ours, however, they included all ulcers, whereas we assessed plantar foot ulcers only.

**CLINICAL IMPLICATIONS AND RECOMMENDATIONS**

The studies in this thesis were based on a multicenter RCT (DIAFOS, trial register NTR1091) that aimed to expand the body of knowledge on the effectiveness of offloading-improved custom-made footwear on ulcer recurrence in diabetic patients with neuropathy and a previous ulcer. Several main findings are important for clinical practice.
These are:

- Offloading-improved custom-made footwear is by itself not more effective than non-improved custom-made footwear in reducing plantar foot ulcer recurrence.
- When offloading-improved custom-made footwear was worn more than 80% of the steps, offloading-improved footwear significantly reduced ulcer recurrence.
- Offloading in custom-made footwear could be improved and maintained by using in-shoe peak pressure measurements to guide footwear modifications.
- Adherence was low, in particular at home, where patients were more active than away from home.
- Having abundant callus, a hematoma or a blister was found to be the strongest predictor of ulcer recurrence.

Overall, the findings of the trial suggest that custom-made footwear, in which in-shoe peak pressures are measured regularly to evaluate and guide footwear modifications, improve offloading. Since we executed this study in a clinical setting, mostly during normal outpatient clinic visit hours, we assume that this approach is feasible and implementable in clinical practice.

Offloading-improved footwear was by itself not effective in preventing ulcer recurrence. However, when adherence to footwear use was high, lower ulcer recurrence rates were found in patients that wore offloading-improved custom-made footwear. These results suggest that besides proper offloading, adherence is an important factor. Therefore, adherence to wearing custom-made footwear needs to be measured in patients at high risk for ulceration to evaluate footwear use. This information helps the care provider to explore causes of non-adherence, which might be valuable for interventions aimed at increasing adherence.

A possible intervention that might be successful in increasing adherence is the prescription of custom-made footwear for indoor use. We found that adherence at home was lower than away from home. Providing custom-made indoor footwear might result in an increase in adherence at home.

Although the aetiology of ulcer recurrence is multifactorial and the prediction of recurrence was moderately successful, the results show that having abundant callus, hematoma or blisters was the strongest predictor for ulcer recurrence. Therefore, the following recommendations are given for clinical practise:

- Custom-made footwear of which proper offloading is guaranteed should be prescribed.
- To improve offloading in custom-made footwear, the use in-shoe pressure measurements to guide footwear modifications is advised.
- Assess adherence and if found to be low, apply interventions to increase adherence. Prescribing indoor footwear might be such an intervention.
- Frequently screen patients’ feet for presence of abundant callus, hematoma or blisters and if present manage them in a timely fashion.
- Increase frequency of screening patients who are at high risk of plantar ulceration.

To summarize, besides guaranteeing adequate offloading at risk locations and increas-
Discussion

ing adherence to wear this footwear the focus should be on the early recognition and treatment of minor lesions. These preventative strategies may lead to a reduced risk for ulcer recurrence, and therefore lower the risk of infection and amputation\textsuperscript{40}, give reduced treatment costs\textsuperscript{41}, and preserve patient quality of life\textsuperscript{42}.

SOME RECOMMENDATIONS FOR FUTURE RESEARCH

The intervention of the DIAFOS trial aimed to reduce ulcer recurrence by improving offloading in prescribed custom-made footwear (chapter 6). Previous studies showed that the pressure offloading of footwear was not optimal at delivery, probably due to the lack of available evidence-based guidelines for footwear prescription\textsuperscript{17, 43}. Providing better offloaded footwear at delivery, might save footwear modifications sessions after delivery, resulting in less time investment. Furthermore, due to the lack of evidence-based guidelines about effective footwear modifications, shoe technicians mainly based their modifications on clinical expertise. Therefore, further research should be aimed at developing and implementing evidence-based guidelines for both proper footwear prescription and footwear modifications that may lead to better offloading footwear and effective modifications to offload the footwear.

Only half of the patients wore their footwear more than 80% of the steps (chapter 5). Because high adherence to wearing prescribed custom-made footwear in combination with improved-pressure offloading seems to reduce the risk for ulcer recurrence (chapter 6 and 7), more research is needed that aims to explore reasons for low adherence, especially at home. Possible reasons might be a lack of patient’s knowledge on the relevance to adhere to footwear, their motivation to wear the footwear or the availability of custom-made footwear. Subsequently, research should focus on assessing the effects of interventions that aim to improve adherence. These intervention may include patient education and motivational interviewing to target patients’ knowledge and motivation or it may involve providing custom-made footwear for indoor use. In these studies, adherence could be accurately determined with the use of objective adherence measurements. In addition, research is needed that determines which groups are at high risk for low adherence by exploring the influence of social-economic and cultural backgrounds, ethnicity, or experiences with foot complications.

Peak pressure was measured by collecting multiple barefoot steps on a pressure platform and multiple steps with in-shoe pressure measurements along a ten meter walkway. This method is found valid and reliable\textsuperscript{44, 45}. Despite that we measured this barefoot and in two pairs of custom-made footwear each three months, we missed information about experienced plantar tissue stress at home. Further exploration of pressure measurements in all used footwear during daily living in at home situations, including stair walking, turning and standing might add information on the relation between peak pressure and ulcer recurrence. With this data, the cumulative stress can be calculated more precisely during daily life and might improve prediction of ulcer recurrence.

We improved footwear based on plantar foot pressure measurements. Another biomechanical factor that is suggested to play an important role in ulcer recurrence is shear\textsuperscript{46}. Currently it is not possible to measure in-shoe shear with commercial available sys-
tems. In order to study the influence of shear in ulcer occurrence, techniques should be
developed to measure shear in the footwear.

GENERAL CONCLUSION
This thesis aimed to expand the body of knowledge on the effectiveness of offloading-improved custom-made footwear in lowering risk of plantar foot ulcer recurrence, and on the predictive value of biomechanical, behavioural, and disease-related factors on plantar foot ulcer recurrence in diabetic patients with peripheral neuropathy and a previous plantar foot ulcer. It was shown that offloading-improved custom-made footwear was not more effective than usual care (i.e. conventional custom-made footwear) in reducing plantar foot ulcer recurrence in these patients. However, the data suggests that a favorable and important clinical effect of offloading-improved custom-made footwear can be achieved when adherence to wearing this footwear is assured. Although future trials should confirm the positive effect of continuously worn offloading-improved custom-made footwear, these findings stress the importance of a combined improvement of footwear offloading and adherence to footwear use to reduce plantar foot ulcer recurrence in high-risk diabetic patients. To achieve and preserve better offloading, in-shoe peak pressure measurements were a useful and objective tool to guide footwear modifications. Adherence to wearing custom-made footwear was found to be insufficient in half of the patients. Especially at home, where patients were more active, adherence was low. Therefore, more research is necessary on interventions that aim to improve adherence in this population. Furthermore, our prognostic study showed that prediction of ulcer recurrence was moderately successful. Minor lesions (abundant callosus, a hematoma or a blister) was the strongest risk factor for ulcer recurrence. Early detection of these minor lesions seems important and these lesions should be treated in a timely manner, to prevent further complications. This thesis resulted in several recommendations that could be implemented in clinical practise. Additionally, further research is needed that continues to explore prognostic factors of ulcer recurrence that will hopefully result in interventions that prove to be effective in reducing ulcer recurrence in patients with diabetes mellitus.
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