Improving footwear to prevent ulcer recurrence in diabetes: Analysis of adherence and pressure reduction
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Chapter 7

PROGNOSTIC FACTORS OF PLANTAR FOOT ULCER RECURRENCE IN NEUROPATHIC DIABETIC PATIENTS

In preparation

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ABSTRACT

Background: Plantar foot ulcer recurrence in patients with diabetes mellitus and peripheral neuropathy is common and its risk factors are not well understood. A comprehensive analysis of biomechanical, behavioural, and disease-related factors was conducted to assess prognostic determinants of plantar foot ulcer recurrence.

Methods: 171 neuropathic diabetic patients with prior plantar foot ulceration and prescription therapeutic footwear were followed for 18 months or until ulceration. Demographic data, disease parameters, barefoot and in-shoe plantar peak pressures, footwear adherence, and daily ambulatory activity were entered in multivariate logistic regression models of ulcer recurrence: one model for all recurrences and one for recurrences at the prior ulcer location with a non-traumatic cause, to isolate those ulcers suggestive of a pressure-related aetiology (model 2).

Findings: Significant determinants for all 71 recurrences were: minor lesion at study entry (OR 5.24, 95%CI[2.83-9.68]), day-to-day variation in stride count (0.92[0.88-0.95]), and past cumulative ulcer months (1.04[1.01-1.06]), predicting 68% of ulcers correctly. Significant determinants for the 41 recurrences at the prior ulcer location were: minor lesion at study entry (9.12[4.14-20.09]), in-shoe peak pressure <200kPa + adherence >80% (0.40[0.18-0.90]), barefoot peak pressure (1.10[1.00-1.21]), day-to-day variation in stride count (0.92[0.87-0.97]), and past cumulative ulcer months (1.02[1.00-1.05]), predicting 76% of ulcers correctly.

Interpretation: Prediction of plantar foot ulcer recurrence was moderately successful. Minor lesion was the most dominant predictor, while sustained adequate offloading was protective against pressure-related recurrence. These findings suggest that to reduce ulcer recurrence risk, minor lesions should be adequately managed, barefoot walking prevented, and adequate offloading and adherence guaranteed.
INTRODUCTION
In patients with diabetes mellitus, foot ulcers are a serious risk for infection and amputation. The prevention of foot ulcers is paramount to avoid these devastating outcomes. Several studies have identified risk factors for diabetic foot ulceration, which include, among others, peripheral neuropathy, peripheral arterial disease, and foot deformity. The strongest predictors of ulceration are peripheral neuropathy and a history of ulceration, which illustrates that ulcers often recur, up to 40% annually.

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. This suggests that barefoot plantar peak pressure, although important, is a moderate predictor. Adding in-shoe plantar peak pressure may improve prediction since patients, in particular those with healed foot ulcers, often have prescription therapeutic footwear with the goal to prevent ulcer recurrence. Controversy still exists on the effectiveness of this footwear, but none of these studies measured in-shoe plantar pressures. Therefore the role of this parameter in ulcer development is so far unknown.

Factors that may further contribute to ulceration are ambulatory weight-bearing activity and adherence to wearing adequately offloading footwear. More steps taken presumes a higher cumulative load on the foot during the day, which may increase the risk of ulceration, although to date a clear association between activity and ulceration has not been found. Adherence to wearing prescription footwear is a behavioural parameter that also influences the amount of biomechanical stress that the foot experiences since we know that barefoot peak pressures are generally much higher than in-shoe peak pressures. Combining pressure, activity, and adherence data best represents the cumulative load on the foot and may prove valuable in understanding ulcer recurrence in diabetes.

To the best of our knowledge, a prospective study that integrates disease-related, biomechanical, and behavioural factors into a model of plantar foot ulcer recurrence does not exist. Such a model may support clinicians to decide on potentially preventative measures. The aim of this prospective study was to assess the prognostic value of disease-related, biomechanical, and behavioural factors in plantar foot ulcer recurrence in diabetic patients who are at high risk for foot ulceration.

METHODS

Subjects
One hundred seventy-one patients with diagnosed diabetes mellitus, peripheral neuropathy, a recently healed plantar foot ulcer (<18 months prior to study entry) and new prescription footwear were included in the study. These were patients who participated in a randomized controlled trial on therapeutic footwear effectiveness (Dutch trial reg...
ister, NTR1091) and who were consecutively recruited from 10 participating centres. Loss of protective sensation due to peripheral neuropathy was confirmed present by 10-g Semmes Weinstein monofilament and vibration perception threshold testing. The exclusion criteria were an active plantar foot ulcer, bilateral amputation proximal to the tarso-metatarsal level, severe illness that would make 18-months survival unlikely, and the inability to walk unaided. Written informed consent was obtained from each patient prior to inclusion of the study, which was approved by the local Research Ethics Committee of each participating centre.

**Outcome**

The outcome in this study was plantar foot ulcer recurrence in 18 months. A plantar foot ulcer was defined as a full-thickness lesion of the skin, i.e. a wound penetrating through the dermis at the plantar side of the foot, without reference to time present. Photographs of the plantar foot, taken at each study visit or in-between visits when an ulcer occurred, were assessed for outcome by 3 independent diabetic foot experts who were blinded to patient identity and characteristics. When agreement on outcome was not present, 2 additional foot experts assessed the photographs to obtain a clear (4 against 1) majority on outcome.

Two outcomes of plantar foot ulcer recurrence were considered: all ulcer recurrences, and only those recurrences with a suggested pressure-related aetiology (model 2), because of our specific interest in biomechanical determinants. A pressure-related aetiology was suggested for those plantar foot ulcers of which patients did not report trauma as cause (e.g. bumping the foot, stepping into a nail) and which developed at the location where the prior ulcer healed.

**Procedures**

Patients were prospectively evaluated every 3 months until a plantar foot ulcer occurred or until 18 months follow-up, whichever came first. At study entry, demographic and disease-related data were collected, a foot examination was performed, and new custom-made therapeutic footwear was delivered to the patient. Footwear consisted of custom-made insoles either in custom-made shoes or in extra-depth shoes. Photographs of the foot taken at each study visit using a standardized protocol were assessed for presence of foot deformities and minor lesions, which were defined as the presence of abundant callus, haemorrhage, or a blister on the plantar aspect of the foot. Two observers independently scored foot deformity and minor lesions and reached consensus on outcome. Furthermore, at each visit, the frequency of treatment by a foot care provider was assessed.

Barefoot dynamic plantar foot pressures were measured at study entry using an EMED-X system (Novel, Munich, Germany) with sensors arranged in a spatial resolution of 4 sensors per cm², sampling at 50 Hz. Data was collected using a two step gait approach to the platform. At each study visit, in-shoe dynamic plantar foot pressures were measured in a maximum two pair of prescription footwear per patient, including the newly delivered footwear. In-shoe plantar pressures were measured at 50Hz sampling frequency using the Pedar-X system (Novel, Munich, Germany). This system includes wide-sized
pressure measurement insoles with a sensor resolution of approximately one sensor per cm$^2$. Patients walked forth and back along a 10-meter long walkway assuring that a minimum 12 midgait steps per foot were collected. Each Pedar insole was calibrated each 3 months using a calibration device and protocol from the manufacturer.

Use of prescription footwear was objectively assessed once during the study over a 7-day period using a shoe-worn monitor (@monitor; Academic Medical Center, Amsterdam) that accurately and reliably distinguished periods that shoes were on and off. Over the same 7-day period, daily stride count was measured using an ankle-worn step activity monitor (StepWatch$^{TM}$, Orthocare Innovations LLC, Oklahoma, United States). Patients were asked to keep a daily log of the time periods that they were away from home.

**Data analysis**

In the barefoot and in-shoe plantar pressure distribution pictures, regions of interest were masked, including the plantar foot region distal to the heel (named ‘plantar foot’), the prior ulcer location, and the new ulcer location in those patients who ulcerated. Mean peak pressure and pressure-time integral over the steps taken were calculated for each mask using Novel multimask software (version 20.3.32). Pressure data was averaged over two consecutive study visits to reflect as adequate as possible the loading condition over the 3-month period in-between visits.

To calculate adherence to wearing prescription footwear, the @monitor and StepWatch data were synchronized and analysed using Matlab R2011a software (MathWorks, Natick, MA). Adherence was calculated as the percentage of foot strides over the measurement period that the patient wore their prescribed footwear. Using the daily log data, adherence and stride count were calculated for the periods that patients were at home and away from home.

Data on plantar foot pressure, adherence, and stride count were combined to define two new parameters that represented the actual load on the foot in daily life: weighted pressure (WP) and cumulative plantar tissue stress (CPTS):

\[
WP = \text{inshoe PP} \times \text{adherence} + \text{barefoot PP} \times (1 - \text{adherence}) \quad [\text{kPa}]
\]

\[
CPTS = (\text{inshoe PTI} \times \text{adherence} + \text{barefoot PTI} \times (1 - \text{adherence})) \times \text{strides} \quad [\text{MPa.s/day}]
\]

where PP = peak pressure; PTI = pressure time integral and strides = daily stride count

**Independent factors**

Multiple patient and disease-related factors were included in the analysis: age, gender, diabetes type and duration, body-mass index, HbA1c, vibration perception threshold, cumulative duration of past foot ulcers, history of amputation, presence of peripheral arterial disease, smoking, alcohol consumption (>2 units/day), living alone, being employed, highest education level, and time between healing of the prior ulcer and study entry. Foot deformity was also included and was classified as “absent”, “mild” (i.e.
pes planus, pes cavus, hallux valgus or limitus, hammer toes, and lesser toe amputation), “moderate” (i.e. hallux rigidus, hallux or ray amputation, prominent metatarsal heads, and claw toes), or “severe” (i.e. Charcot deformity, (fore)foot amputation and pes equines). For minor lesions, presence of a minor lesion at study entry was included, as well as the ratio of the first two visits (entry and first follow-up) that a minor lesion was present (“minor lesion index”, [0, 0.5, 1]).

Biomechanical factors included in the analysis were barefoot plantar peak pressure at the plantar foot, the prior ulcer location, and the new ulcer location, and in-shoe peak plantar pressure at the plantar foot, prior ulcer location, and the new ulcer location (for each pair of shoes included in the study). Additionally, patients were categorized into two groups based on an in-shoe peak pressure cut-off level of 200 kPa at the plantar foot and the prior ulcer location, as this was indicated to be potentially discriminative for ulcers remaining healed.26

Behavioural factors included in the analysis were: average daily stride count, day-to-day variation in stride count (calculated as the standard deviation in daily stride count over the 7-day measurement period),27 footwear adherence, adherence at home, adherence away from home, and the average number of visits per month to a foot care provider. Additionally, patients were categorized into two groups based on the combined presence, or absence, of an in-shoe peak pressure <200kPa and adherence ≥80%. This parameter, together with weighted pressure and cumulative plantar tissue stress were included in the analysis.

**Statistical analysis**

Descriptive statistics were performed using SPSS Statistics 19 (IBM Corporation, NY, USA). To combine patient-related data (one patient) and foot related data (two feet) in the analysis, we selected the foot with the new ulcer for those patients who re-ulcerated and the foot with the prior ulcer for those patients who survived ulceration in 18 months.

Including all independent factors, univariate and multivariate multi-level logistic regression models were developed of all plantar foot ulcer recurrences (model 1) and all recurrences with pressure-related aetiology (model 2) using MLWIN software, version 2.23 (Institute of Education, University of London, London, UK). Foot ulcer recurrence was nested at four levels – participating centre (fourth level), patient (third), footwear (second) and follow-up period (first) – and a random intercept at patient level or footwear level was calculated, whichever fitted the model best. A significance level of $P < .10$ was used. Significant factors from the univariate analysis were entered in a multivariate multi-level logistic regression model of plantar foot ulcer recurrence (with backward selection, significance at $P < .10$). To assess the fit of the model, the percentage of correctly classified ulcer recurrences was calculated.

Pearson correlation coefficients were calculated between selected factors, to explore associations between these factors.
RESULTS

Baseline patient characteristics and descriptive statistics for all factors in the study are shown in table 1. Seventy-one patients developed a plantar foot ulcer, in a mean±SD 28±22 weeks. Forty-one of the 71 ulcers developed at the prior ulcer location and had a suggested pressure-related aetiology. These 41 ulcers developed in a mean±SD 25±19 weeks. In 23 of the 71 patients with ulcer recurrence, a minor lesion directly preceded the ulcer, meaning that a minor lesion was present at the last follow-up visit before ulceration. Of all 135 minor lesions that were identified during the study, 17% developed into a foot ulcer.

Results of the univariate and multivariate multi-level logistic regression analysis for all 71 recurrences (model 1) are shown in table 2. The univariate analysis showed that having a severe foot deformity, a higher minor lesion index, a minor lesion at entry, increased weighted pressure, increased barefoot peak pressure, and a longer cumulative duration of past foot ulceration increased the odds of developing ulcer recurrence. A combination of in-shoe peak pressure <200kPa with adherence >80%, and more day-to-day variation in stride count decreased the odds of developing ulcer recurrence. In multivariate analysis, a minor lesion at entry, cumulative duration of past foot ulceration in months, and day-to-day variation in stride count remained independently significant prognostic factors. With this model, 68% of the ulcer recurrences were correctly classified.

The results for the 41 ‘pressure-related’ recurrences (model 2) are shown in table 2. The univariate analysis showed that having a higher minor lesions index, a minor lesion at entry, increased in-shoe peak pressures at the (prior) ulcer location, increased weighted pressure, increased barefoot peak pressure, and a longer cumulative duration of past foot ulceration increased the odds of developing a recurrent ulcer. A combination of in-shoe peak pressure <200kPa with adherence >80%, longer time between prior ulcer healing and study entry, more day-to-day variation in stride count, and a longer diabetes duration decreased the odds for a recurrent ulcer. In the multivariate analysis, a minor lesion at entry, combination of in-shoe peak pressure <200kPa with adherence >80%, barefoot peak pressure, day-to-day variation in stride count, and cumulative months of past foot ulceration remained independent significant prognostic factors. With this model, 76% of the ulcer recurrences were correctly classified.

The correlation coefficient between minor lesion index and the time between prior ulceration and study entry was r = -0.23 (P < 0.01); and between minor lesion index and the cumulative number of months patients had a foot ulcer in the past was r = 0.18 (P < 0.05).
Table 1. Baseline and outcome data expressed as mean (SD), percentage (%), or as frequency (N) for all included patients, for the patients with and without ulcer recurrence in the analysis of all 71 plantar ulcers, and for the patients with and without ulcer recurrence in the analysis of the 41 non-traumatic plantar ulcers that developed at the previous ulcer location.

<table>
<thead>
<tr>
<th>Variable</th>
<th>All patients</th>
<th>Analysis of all ulcer recurrences (N=71)</th>
<th>Analysis of all non-traumatic ulcers at the prior ulcer location (N=41)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subjects (N)</td>
<td>171</td>
<td>100</td>
<td>71</td>
</tr>
<tr>
<td>Age (years)</td>
<td>63.3 (10.1)</td>
<td>63.6 (9.4)</td>
<td>62.8 (11.2)</td>
</tr>
<tr>
<td>Male gender (%)</td>
<td>82.5</td>
<td>80</td>
<td>85.9</td>
</tr>
<tr>
<td>Diabetes type 2 (%)</td>
<td>71.3</td>
<td>71.0</td>
<td>71.8</td>
</tr>
<tr>
<td>Diabetes duration (years)</td>
<td>17.3 (13.5)</td>
<td>17.7 (13.8)</td>
<td>16.7 (13.2)</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>30.7 (5.7)</td>
<td>30.7 (5.3)</td>
<td>30.6 (6.2)</td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td>7.6 (1.4)</td>
<td>7.5 (1.3)</td>
<td>7.7 (1.6)</td>
</tr>
<tr>
<td>Vibration Perception threshold (V)</td>
<td>45.4 (10.2)</td>
<td>46.2 (9.9)</td>
<td>44.3 (10.6)</td>
</tr>
<tr>
<td>Cumulative duration of past foot ulcers (months)</td>
<td>14.1 (19.0)</td>
<td>10.7 (12.5)</td>
<td>20.3 (26.2)</td>
</tr>
<tr>
<td>Smoker or history of smoking (%)</td>
<td>66.7</td>
<td>66.0</td>
<td>67.6</td>
</tr>
<tr>
<td>More than 2 units alcohol intake per day (%)</td>
<td>11.7</td>
<td>13.0</td>
<td>9.9</td>
</tr>
<tr>
<td>Living alone (%)</td>
<td>26.9</td>
<td>22.0</td>
<td>33.8</td>
</tr>
<tr>
<td>Employed (%)</td>
<td>21.6</td>
<td>20.0</td>
<td>23.9</td>
</tr>
<tr>
<td>Education level (Low / Medium / High %)</td>
<td>56 / 18 / 26</td>
<td>56 / 18 / 26</td>
<td>56 / 18 / 25</td>
</tr>
<tr>
<td>Peripheral arterial disease, grade II (%)</td>
<td>35.2</td>
<td>38.5</td>
<td>30.4</td>
</tr>
<tr>
<td>Visits per month to a foot care provider (N)</td>
<td>1.3 (0.8)</td>
<td>1.2 (0.7)</td>
<td>1.4 (0.8)</td>
</tr>
<tr>
<td>Minor lesion at entry (%)</td>
<td>29.2</td>
<td>18.0</td>
<td>45.1</td>
</tr>
<tr>
<td>Minor lesion index (0-1)</td>
<td>0.27 (0.38)</td>
<td>0.17 (0.31)</td>
<td>0.41 (0.43)</td>
</tr>
<tr>
<td>History of amputation (%)</td>
<td>29.8</td>
<td>28.0</td>
<td>32.4</td>
</tr>
<tr>
<td>Foot deformity (%)</td>
<td>9.9</td>
<td>13.0</td>
<td>5.6</td>
</tr>
</tbody>
</table>
### Prognostic factors of recurrent foot ulceration

<table>
<thead>
<tr>
<th>Variable</th>
<th>All patients</th>
<th>Analysis of all ulcer recurrences (N=71)</th>
<th>Analysis of all non-traumatic ulcers at the prior ulcer location (N=41)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No ulcer</td>
<td>Ulcer</td>
<td>No ulcer</td>
</tr>
<tr>
<td></td>
<td>Mild</td>
<td>36.8</td>
<td>38.0</td>
</tr>
<tr>
<td></td>
<td>Moderate</td>
<td>41.5</td>
<td>42.0</td>
</tr>
<tr>
<td></td>
<td>Severe</td>
<td>11.7</td>
<td>7.0</td>
</tr>
<tr>
<td>Months healed from ulceration before study entry</td>
<td>4.99 (5.50)</td>
<td>5.34 (5.71)</td>
<td>4.45 (5.19)</td>
</tr>
<tr>
<td>Daily stride count (N)</td>
<td>3359 (1749)</td>
<td>3437 (1990)</td>
<td>3238 (1287)</td>
</tr>
<tr>
<td>Variation in daily stride count (N)</td>
<td>1194 (713)</td>
<td>1276 (793)</td>
<td>1068 (549)</td>
</tr>
<tr>
<td>Adherence (%)</td>
<td>72.9 (24.3)</td>
<td>72.7 (24.1)</td>
<td>73.1 (24.7)</td>
</tr>
<tr>
<td>Adherence at home (%)</td>
<td>61.7 (32.3)</td>
<td>63.2 (32.3)</td>
<td>59.3 (32.6)</td>
</tr>
<tr>
<td>Adherence away from home (%)</td>
<td>87.6 (26.7)</td>
<td>84.9 (30.8)</td>
<td>91.7 (18.3)</td>
</tr>
<tr>
<td>In-shoe peak pressure @plantar foot (kPa)</td>
<td>254 (79)</td>
<td>249 (77)</td>
<td>261 (83)</td>
</tr>
<tr>
<td>In-shoe peak pressure @plantar foot &gt;200kPa at entry (%)</td>
<td>4.9</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Barefoot peak pressure @plantar foot (kPa)</td>
<td>979 (293)</td>
<td>935 (307)</td>
<td>1042 (260)</td>
</tr>
<tr>
<td>Weighted pressure @plantar foot (kPa)</td>
<td>445 (198)</td>
<td>429 (188)</td>
<td>472 (212)</td>
</tr>
<tr>
<td>Cum. tissue stress @plantar foot (MPa.s/day)</td>
<td>675 (475)</td>
<td>652 (436)</td>
<td>715 (538)</td>
</tr>
<tr>
<td>In-shoe peak pressure @plantar foot &lt;200kPa and adherence &gt;80% at entry (%)</td>
<td>24.8</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Presence of peripheral arterial disease (grade I=No, grade II =Yes) was assessed using the PEDIS classification.*

---

7
<table>
<thead>
<tr>
<th>Variable</th>
<th>Analysis of all ulcer recurrences (N=71)</th>
<th>Analysis of all non-traumatic ulcers at the prior ulcer location (N=41)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Univariate model</td>
<td>Multivariate model</td>
</tr>
<tr>
<td></td>
<td>ß [95% CI] P value</td>
<td>ß [95% CI] P value</td>
</tr>
<tr>
<td>Age (years)</td>
<td>0.99 [0.96-1.02] .678</td>
<td>1.00 [0.96-1.03] .779</td>
</tr>
<tr>
<td>Gender (M/F)</td>
<td>0.66 [0.3-1.47] .310</td>
<td>0.56 [0.22-1.44] .230</td>
</tr>
<tr>
<td>Diabetes type (1/2)</td>
<td>1.03 [0.52-2.01] .935</td>
<td>1.12 [0.52-2.44] .769</td>
</tr>
<tr>
<td>Diabetes duration (years)</td>
<td>1.00 [0.97-1.02] .705</td>
<td>0.97 [0.95-1.00] .041*</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>1.00 [0.95-1.05] .977</td>
<td>0.98 [0.93-1.05] .627</td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td>1.14 [0.91-1.41] .255</td>
<td>1.00 [0.77-1.29] .985</td>
</tr>
<tr>
<td>Vibration Perception threshold (V)</td>
<td>0.98 [0.95-1.01] .267</td>
<td>0.99 [0.96-1.03] .662</td>
</tr>
<tr>
<td>Cumulative duration of past foot ulcers (months)</td>
<td>1.04 [1.01-1.06] .006*</td>
<td>1.04 [1.02-1.06] .001*</td>
</tr>
<tr>
<td>Smoking (No / Yes or smoking history)</td>
<td>1.08 [0.56-2.08] .810</td>
<td>1.69 [0.79-3.62] .178</td>
</tr>
<tr>
<td>Alcohol intake &gt;2 units/day (No /Yes)</td>
<td>0.75 [0.29-1.93] .547</td>
<td>1.06 [0.36-3.15] .918</td>
</tr>
<tr>
<td>Living alone (No/Yes)</td>
<td>1.79 [0.89-3.57] .102</td>
<td>1.14 [0.52-2.53] .745</td>
</tr>
<tr>
<td>Employment (No/Yes)</td>
<td>1.26 [0.6-2.63] .545</td>
<td>1.24 [0.53-2.91] .616</td>
</tr>
<tr>
<td>Education level</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td>reference</td>
<td></td>
</tr>
<tr>
<td>Medium</td>
<td>0.99 [0.43-2.26] .983</td>
<td>1.36 [0.53-3.51] .528</td>
</tr>
<tr>
<td>High</td>
<td>0.95 [0.46-1.97] .898</td>
<td>1.00 [0.43-2.31] .993</td>
</tr>
<tr>
<td>PAD grade (I / II)a</td>
<td>0.78 [0.53-1.15] .206</td>
<td>0.79 [0.37-1.68] .540</td>
</tr>
<tr>
<td>Monthly visits to foot care provider (N)</td>
<td>1.35 [0.87-2.12] .185</td>
<td>1.44 [0.85-2.45] .179</td>
</tr>
<tr>
<td>Minor lesion index (0-1)</td>
<td>5.60 [2.39-13.13] .000*</td>
<td></td>
</tr>
<tr>
<td>Variable</td>
<td>Analysis of all ulcer recurrences (N=71)</td>
<td>Analysis of all non-traumatic ulcers at the prior ulcer location (N=41)</td>
</tr>
<tr>
<td>-------------------------------------------------------------------------</td>
<td>------------------------------------------</td>
<td>---------------------------------------------------------------------</td>
</tr>
<tr>
<td></td>
<td>Univariate model</td>
<td>Multivariate model</td>
</tr>
<tr>
<td></td>
<td>$\hat{\beta}$ [95% CI]</td>
<td>P value</td>
</tr>
<tr>
<td>History of amputation (No/Yes)</td>
<td>1.21 [0.62-2.37]</td>
<td>.567</td>
</tr>
<tr>
<td>Severity of deformity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Absent</td>
<td>reference</td>
<td></td>
</tr>
<tr>
<td>Mild</td>
<td>2.24 [0.73-6.87]</td>
<td>.158</td>
</tr>
<tr>
<td>Moderate</td>
<td>2.33 [0.77-7.05]</td>
<td>.135</td>
</tr>
<tr>
<td>Severe</td>
<td>6.10 [1.57-23.69]</td>
<td>.009*</td>
</tr>
<tr>
<td>Months healed before study entry</td>
<td>0.97 [0.92-1.03]</td>
<td>.334</td>
</tr>
<tr>
<td>Daily stride count (per 100 strides)</td>
<td>0.99 [0.97-1.01]</td>
<td>.360</td>
</tr>
<tr>
<td>Variation in daily stride count (per 100 strides)</td>
<td>0.95 [0.90-0.99]</td>
<td>.023*</td>
</tr>
<tr>
<td>Adherence (%)</td>
<td>1.00 [0.99-1.01]</td>
<td>.989</td>
</tr>
<tr>
<td>Adherence above 80%</td>
<td>0.98 [0.51-1.9]</td>
<td>.958</td>
</tr>
<tr>
<td>Adherence at home (%)</td>
<td>1.00 [0.98-1.01]</td>
<td>.495</td>
</tr>
<tr>
<td>Adherence away from home (%)</td>
<td>1.01 [1.00-1.03]</td>
<td>.114</td>
</tr>
<tr>
<td>In-shoe peak pressure @plantar foot (per 100 kPa)</td>
<td>1.21 [0.95-1.53]</td>
<td>.120</td>
</tr>
<tr>
<td>In-shoe peak pressure @plantar foot &gt;200kPa</td>
<td>1.24 [0.85-1.82]</td>
<td>.261</td>
</tr>
<tr>
<td>Barefoot peak pressure @plantar foot (per 100kPa)</td>
<td>1.18 [1.09-1.27]</td>
<td>.000*</td>
</tr>
<tr>
<td>Weighted pressure @plantar foot (per 100 kPa)</td>
<td>1.22 [1.08-1.38]</td>
<td>.001*</td>
</tr>
<tr>
<td>Cum. tissue stress @plantar foot (per MPa.s/day)</td>
<td>1.00 [1.00-1.00]</td>
<td>.453</td>
</tr>
</tbody>
</table>
### Analysis of all ulcer recurrences (N=71)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Univariate model</th>
<th>Multivariate model</th>
<th>Univariate model</th>
<th>Multivariate model</th>
</tr>
</thead>
<tbody>
<tr>
<td>In-shoe peak pressure @plantar foot &lt;200kPa and adherence &gt;80%</td>
<td>0.47 [0.26-0.85]</td>
<td>.012*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>In-shoe peak pressure @(prior)ulcer (per 100 kPa)</td>
<td>1.38 [1.05-1.81]</td>
<td>.023*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>In-shoe peak pressure @(prior)ulcer &gt;200kPa</td>
<td>1.43 [0.89-2.32]</td>
<td>.142</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Barefoot peak pressure @(prior)ulcer (per 100 kPa)</td>
<td>1.12 [1.05-1.21]</td>
<td>.001*</td>
<td>1.10 [1.00-1.21]</td>
<td>.053*</td>
</tr>
<tr>
<td>Weighted pressure @(prior) ulcer (per 100 kPa)</td>
<td>1.22 [1.06-1.40]</td>
<td>.005*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cum. tissue stress @(prior)ulcer (per MPa.s/day)</td>
<td>1.00 [1.00-1.00]</td>
<td>.162</td>
<td></td>
<td></td>
</tr>
<tr>
<td>In-shoe pressure @(prior)ulcer &lt;200kPa and adherence &gt;80%</td>
<td>0.5 [0.28-0.89]</td>
<td>.019*</td>
<td>0.40 [0.18-0.90]</td>
<td>.027*</td>
</tr>
</tbody>
</table>

*Data are mean (SD) values per factor, un-standardized linear regression coefficients (i.e. odds ratio's) with 95% confidence intervals, and P-values. * = significant association (P < 0.10); reference = reference category*
DISCUSSION

Taking into account a wide range of biomechanical and behavioural factors that are suggested to be important in causing plantar foot ulcer recurrence in diabetes, 68% of all recurrences and 76% of recurrences most supposed to be pressure-related were correctly classified. This is moderate given the large number of risk factors included and the fact that by chance alone, 50% of ulcers are correctly classified. Factors that could be expected to play a role in plantar foot ulcer recurrence proved to be the strongest determinants. The presence of a minor lesion (i.e. haemorrhage, abundant callus or blister) at study entry caused the largest increase in ulcer recurrence risk (odds ratio’s > 5). History of patient burden, expressed as the cumulative number of months that patients had a foot ulcer, could also be expected as significant factor. And for biomechanics and patient behaviour, the analyses showed that both peak pressure while walking barefoot (predictor) and continuous offloading in worn prescription footwear (protector) were associated with ulcer recurrence.

The strong association between minor lesions and foot ulceration has been long recognized in the aetiological pathways of foot ulceration in diabetes. A minor lesion directly preceded 32% of recurrences and 17% of minor lesions resulted in a foot ulcer. Both the minor lesion index and minor lesion at entry were strong univariate predictors of recurrence, but only lesions at entry remained independently significant in multivariate analysis. A shorter period between healing of the prior foot ulcer and entry in the study was positively correlated with minor lesion index. This suggests that the previous ulcer, although fully reepithelialised, had not yet fully recovered to intact skin making it more vulnerable for injury. Furthermore, minor lesion index was also significantly correlated with the cumulative number of months patients had a foot ulcer in the past. This may explain why a history of ulceration is one of the strongest predictors of new ulceration in diabetes.

For the first time, prospectively an association is found between pressures measured inside prescription footwear and ulcer recurrence in neuropathic diabetic patients. This accounted for the analysis of 'pressure-related' ulcer recurrence (model 2), not for the analysis of all recurrences (model 1), for which none biomechanical parameter was a prognostic factor in the multivariate analysis. This difference in outcome between the two models is understandable because for model 2 only recurrences were taken into account with a suggested pressure-related cause, not being the result of direct trauma acting on the foot. Although we only had data on ulcer cause from patient reports, we suggested that recurrence at the prior ulcer location would best represent a non-traumatic pressure-related cause. While both in-shoe peak pressure alone (OR 1.4) and low in-shoe peak pressure combined with high adherence (OR 0.50) were significant factors in the univariate analysis of model 2, only the latter remained a prognostic factor in multivariate analysis, thereby confirming earlier results from Chantelau et al. This stresses the importance of continuous offloading to lower risk of ulcer recurrence. High barefoot peak pressure also increased the risk of recurrence, which is in accordance with several previous studies. Predictive power was, however, small, both univariately and multivariately, compared to these previous analyses. This may be because we tested a selected group of high risk patients (all with a prior foot ulcer and peripheral neuropathy) which may weaken associations compared to studies that assess patients...
across a wider spectrum of complications. In any case, identification of a common bare-foot peak pressure threshold for ulcer recurrence remains an elusive goal.

Footwear adherence and ambulatory activity level were not independently predictive of ulcer recurrence. In combination with low in-shoe peak pressures, high adherence was, however, protective of ulcer recurrence. Weighted pressure also combined plantar peak pressures with adherence. This showed to be a significant factor in univariate, but not in multivariate analysis, maybe because it does not use specific cut-off levels for low pressure and high adherence like the first parameter does. No association was found with ulcer recurrence when combining pressure-time integral with adherence and daily stride count as cumulative plantar tissue stress parameter, despite that we defined cumulative stress in a more sophisticated way than others did. Maybe this is because the role of ambulatory activity level in ulcer risk is not straightforward. Further sophistication of the model, incorporating the measurement of all footwear that the patient wears (also non-prescription footwear), and, when possible, shear pressure as a parameter, may be needed to better predict plantar foot ulcer recurrence in high-risk diabetic patients.

Understanding which factors determine ulcer recurrence in this high-risk group of patients is important given the high prevalence of recurrence after an episode of ulceration. However, factors known to be the strongest predictors of ulceration, i.e. prior ulceration and presence of peripheral neuropathy, were conditions all patients already had, and could therefore not be included as dichotomous parameter in the regression analyses. Furthermore, all patients had prescription custom-made footwear, which prevented assessing the role of having prescription footwear or not on ulcer recurrence. These facts may explain the moderate success in correctly classifying ulcer recurrence with both models in this study. Measuring disease-related, biomechanical, and behavioural factors in a diabetic patient group ranging in complication level from non-neuropathic, to neuropathic without ulcer history, to neuropathic with ulcer history and without fixed types of footwear may better predict ulceration. Nevertheless, the results showed that changeable as well as non-changeable factors were associated with ulcer recurrence, and clinical practice should focus on managing the changeable factors.

For clinical practise the findings in this study implicate that to lower the risk of plantar foot ulcer recurrence in diabetes, the primary focus should be on frequently screening patients’ feet for presence of minor lesions as ‘warning signs’ of ulceration. It can be questioned whether current recommendations for foot screening suffice; more frequent screening may be required. If minor lesions are present, they should be managed in a timely fashion to prevent further complications. The findings on minor lesions also suggest that patients may benefit from continued offloading with a healing device after re-epithelialisation of the ulcer and before transferring to preventative footwear to allow the skin to regenerate and regain strength. Regarding biomechanics and patient behaviour, the predictive effect of barefoot peak pressures and the protective effect of adequate footwear offloading and adherence stresses the importance for patients to avoid walking barefoot and to wear adequately offloaded footwear at all times.
CONCLUSION

In conclusion, the study showed that prediction of plantar foot ulcer recurrence in diabetes was moderately successful from disease-related, biomechanical and behavioural factors. The presence of minor lesions most strongly increases the odds to develop ulcer recurrence. High barefoot peak pressure increases the risk, while continuous effective offloading in worn prescription footwear reduces the risk for ulcer recurrences with a suggested pressure-related aetiology. Therefore, to prevent ulcer recurrence in diabetes, the focus should be on managing the changeable prognostic factors, which means reducing risk and improving early recognition of minor lesions, urging patients not to walk barefoot, guaranteeing adequate offloading in prescription footwear, and improving adherence to prescription footwear.

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REFERENCES


