Risk Factors for Plantar Foot Ulcer Recurrence in Neuropathic Diabetic Patients

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PATHOPHYSIOLOGY/COMPLICATIONS

OBJECTIVE

Recurrence of plantar foot ulcers is a common and major problem in diabetes but not well understood. Foot biomechanics and patient behavior may be important. The aim was to identify risk factors for ulcer recurrence and to establish targets for ulcer prevention.

RESEARCH DESIGN AND METHODS

As part of a footwear trial, 171 neuropathic diabetic patients with a recently healed plantar foot ulcer and custom-made footwear were followed for 18 months or until ulceration. Demographic data, disease-related parameters, presence of minor lesions, barefoot and in-shoe plantar peak pressures, footwear adherence, and daily stride count were entered in a multivariate multilevel logistic regression model of plantar foot ulcer recurrence.

RESULTS

A total of 71 patients had a recurrent ulcer. Significant independent predictors were presence of minor lesions (odds ratio 9.06 [95% CI 2.98–27.57]), day-to-day variation in stride count (0.93 [0.89–0.99]), and cumulative duration of past foot ulcers (1.03 [1.00–1.06]). Significant independent predictors for those 41 recurrences suggested to be the result of unrecognized repetitive trauma were presence of minor lesions (10.95 [5.01–23.96]), in-shoe peak pressure <200 kPa with footwear adherence >80% (0.43 [0.20–0.94]), barefoot peak pressure (1.11 [1.00–1.22]), and day-to-day variation in stride count (0.91 [0.86–0.96]).

CONCLUSIONS

The presence of a minor lesion was clearly the strongest predictor, while recommended use of adequately offloading footwear was a strong protector against ulcer recurrence from unrecognized repetitive trauma. These outcomes define clear targets for diabetic foot screening and ulcer prevention.

In patients with diabetes, foot ulcers are a serious risk for infection and amputation (1). The prevention of foot ulcers is important 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 (2–7). The strongest predictors of ulceration are presence of peripheral neuropathy and a history of ulceration, which shows that ulcers often recur—up to 40% annually (8). Ulcer recurrence significantly increases long-term costs for diabetic foot care (9) and further increases risk for amputation and deterioration of

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patient's health and well-being (10). Apart from the role of ulcer history, ulcer recurrence is not well understood.

In the presence of neuropathy, elevated plantar pressure during walking is another predictor of diabetic foot ulceration (11–13). However, studies on the sensitivity and specificity of barefoot plantar pressure to predict ulceration show that barefoot pressure, although important, is only a moderate predictor (12,14). This is probably because patients do not only walk barefoot in daily life but also wear shoes, in which the biomechanical conditions are different. Peak plantar pressures while walking barefoot are generally much higher than while wearing protective footwear that patients often get prescribed after healing of a plantar foot ulcer (15). Therefore, adherence to wearing such footwear influences the cumulative amount of mechanical load on the foot and may be an important mediator in risk for ulcer recurrence.

Recent data from our multicenter trial on custom-made footwear effectiveness suggest that the combination of improved plantar pressure distribution inside custom-made footwear and high footwear adherence is important to prevent ulcer recurrence (16). However, being an intervention study, the trial was not designed to establish clear threshold targets for peak pressure reduction and adherence that would facilitate prescribers and orthotists/shoe technicians in their footwear practice. The trial was also not designed to assess the relative importance of pressure and adherence in ulcer recurrence or the role of footwear in association with demographic, disease-related, and other factors that may be important in ulcer recurrence.

One factor could be the amount of ambulatory weight-bearing activity of the patient. More steps taken presumes a higher cumulative load on the foot (17), and more day-to-day variation in the patient's step activity may precede ulceration (18), although a clear association between step activity and ulceration has not been found to date (17,19). Combining in-shoe and barefoot pressure, footwear adherence, and step activity data best represents the actual load on the foot and may improve our understanding of ulcer recurrence in diabetes (20). A prospective risk factor analysis of plantar foot ulcer recurrence that includes these parameters and also demographic and disease-related data in the same model does not exist. Therefore, we used the data from our footwear trial and aimed to identify independent risk factors of plantar foot ulcer recurrence and targets for prevention.

RESEARCH DESIGN AND METHODS

Subjects

One hundred seventy-one patients with diabetes, peripheral neuropathy, a recently healed plantar foot ulcer (<18 months prior to study entry), and new prescription custom-made footwear were included in the study. Data were obtained from a randomized controlled trial on footwear effectiveness to prevent ulcer recurrence for which patients were consecutively recruited from 10 participating centers (16). Loss of protective sensation due to peripheral neuropathy was confirmed to be present by 10-g Semmes-Weinstein monofilament and vibration perception threshold testing (4). The exclusion criteria were an active plantar foot ulcer, bilateral amputation proximal to the tarso-metatarsal level, severe illness that would make 18-month 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 center.

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 (21,22). Photographs of the plantar foot, taken at each study visit or in between visits when an ulcer occurred, were assessed for outcome by three independent diabetic foot experts and by two additional foot experts when unanimous agreement on outcome was not initially reached.

Two models in the analysis of risk factors of plantar foot ulcer recurrence were considered: model 1, including all ulcer recurrences, and model 2, including those recurrences suggested to be the result of unrecognized repetitive trauma (i.e., stress related). We considered model 2 owing to our specific interest in biomechanical determinants of ulcer recurrence and the effect of custom-made footwear that aims to reduce repetitive stress on the foot. Ulcers were suggested to be the result of unrecognized repetitive trauma when they developed at the location where the most recent ulcer healed (from here on denoted as "previous ulcer location") and were reported by patients not to be the result of acute trauma (e.g., bumping the foot, stepping onto a nail) (23).

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 prescription custom-made footwear was delivered to the patient. Footwear consisted of custom-made insoles worn in custom-made shoes or in extradepth shoes. Patients could have an additional pair of custom-made footwear from an earlier prescription or from a new prescription later in the study. Photographs of the foot were taken at each study visit using a standardized protocol. Two independent observers assessed these photographs for presence of foot deformities and presence of minor lesions and reached consensus on outcome. Minor lesions were defined as nonulcerative lesions of the skin on the plantar aspect of the foot and included abundant callus, hemorrhage, or a blister. Furthermore, at each study visit, patients were asked about the number of visits to a foot care provider since the last study visit (e.g., podiatric care).

Barefoot dynamic plantar foot pressures were measured at study entry using an Emed-X pressure platform (Novel, Munich, Germany), which has sensors arranged in a spatial resolution of 4 sensors/cm^2, sampling at 50 Hz. Data were collected using a two-step gait approach to the platform, and at least four steps per foot on the platform were collected (24). At each 3-month study visit, in-shoe dynamic plantar foot pressures were measured in the patient's prescription footwear. In-shoe plantar pressures were measured at a 50-Hz sampling frequency using the

Pedar-X system (Novel). This system includes wide-sized pressure measurement insoles with a sensor resolution of ~1 sensor/cm^2. Patients walked along a 10-m-long walkway assuring that a minimum of 12 midgait steps per foot were collected (25). Each Pedar insole was calibrated each 3 months using a calibration device and protocol from the manufacturer.

Use of prescription footwear was objectively assessed at least 3 months after study entry over a 7-day period using a shoe-worn monitor (@monitor, Academic Medical Centre, Amsterdam, the Netherlands). The @monitor accurately and reliably distinguishes periods that shoes are worn from periods that shoes are not worn (26). Over the same 7-day period, daily stride count was measured using an ankle-worn step activity monitor (StepWatch; Orthocare Innovations, LLC, Oklahoma City, OK). Patients were asked to keep a daily log of the time periods that they were away from home.

Data Analysis

Regions of interest were masked in the barefoot and in-shoe plantar pressure distribution plots. These regions included the foot region distal to the heel (named "plantar foot") and the previous ulcer location. Mean peak pressure and pressure-time integral over the steps taken were calculated for each mask using Novel multimask software (version 20.3.32). In-shoe pressure data were averaged over two consecutive study visits to reflect the loading of the foot over the 3-month period in between study visits.

For calculation of adherence to wearing prescription footwear, the @monitor and StepWatch data were synchronized and analyzed 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 prescription footwear. With use of data from the daily kept log, 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 represent the cumulative load on the foot: weighted pressure (WP) and cumulative plantar tissue stress (CPTS):

$$\begin{aligned} \text{WP} = {} & \text{in-shoe PP} \times \text{adherence} \\ & + \text{barefoot PP} \times (1 - \text{adherence})\ [\text{kPa}] \end{aligned}$$

$$\begin{aligned} \text{CPTS} = {} & [\text{in-shoe PTI} \times \text{adherence} \\ & + \text{barefoot PTI} \times (1 - \text{adherence})] \\ & \times \text{stride count}\quad [\text{MPa/day}] \end{aligned}$$

where WP is weighted pressure, PP is peak pressure, CPTS is cumulative plantar tissue stress, and PTI is pressure time integral.

Independent Risk Factors

Demographic and disease-related factors collected at baseline were included in the risk factor analysis: age, sex, diabetes type and duration, BMI, HbA_{1c}, vibration perception threshold, cumulative duration of past foot ulcers, history of amputation, presence of peripheral arterial disease (21), smoking, alcohol consumption (>2 units/day), living alone, being employed, highest education level, and time between healing of the previous ulcer and study entry. Presence of foot deformity was also included and was classified as "absent," "mild" (i.e., presence of pes planus, pes cavus, hallux valgus or limitus, hammer toes, and/or lesser toe amputation), "moderate" (i.e., presence of hallux rigidus, hallux or ray amputation, prominent metatarsal heads, and/or claw toes), or "severe" (i.e., presence of Charcot deformity, [fore]foot amputation, and/or pes equines). For presence of minor lesions, we included in the analysis the presence of a minor lesion at study entry and the fraction of study visits at which a minor lesion was present (named "minor lesion index" and representing the burden of minor lesions over time).

Biomechanical factors included in the analysis were barefoot peak plantar pressure and, for each follow-up visit and pair of study footwear, the in-shoe peak plantar pressure. For model 1 (i.e., all plantar foot ulcer recurrences), we included the peak pressure measured at the plantar foot, i.e., distal to the heel. For model 2 (i.e., recurrences from unrecognized repetitive trauma), we included the peak pressure measured at the previous ulcer location because of our special interest in this region within this model. Additionally, based on indications of what may be a protective in-shoe plantar pressure threshold (15), patients were classified based on a measured in-shoe peak pressure <200 or >200 kPa at the plantar foot and at the previous ulcer location and as such entered into the analysis.

Behavioral factors included in the analysis were average daily stride count, day-to-day variation in stride count (i.e., SD in daily stride count over a 7-day period) (18), 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 classified based on a measured in-shoe peak pressure <200 kPa (15,27,28) and adherence >80% (29). This parameter, WP, and CPTS were included in the analysis.

Statistical Analysis

Descriptive statistics were performed using SPSS Statistics, version 19 (IBM Corporation, Armonk, NY). For combination of patient-related data (one patient) and foot-related data (two feet) and avoidance of dependent observations in the analysis, one foot per patient was selected for analysis: the foot with the new ulcer for those patients who reulcerated and the foot with the previous ulcer for those patients who survived ulcer recurrence in 18 months.

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

Univariate and multivariate multilevel logistic regression models were developed for model 1 (all plantar foot ulcer recurrences) and model 2 (recurrences from unrecognized repetitive trauma). Models were developed using MLwiN software, version 2.23 (Institute of Education, University of London, London, U.K.) (30). Foot ulcer recurrence was nested at four levels: participating center (fourth level), patient (third), footwear (second), and follow-up visit (first). A random intercept at patient level or footwear level was calculated—whichever fitted the model best. A significance level of $P < 0.10$ was used. Significant factors from the univariate analysis were entered in the multivariate model using backward selection. Also, for the multivariate analysis a significance level $P < 0.10$ applied. The multivariate model was calculated from the estimated logistic regression equation: $\text{logit}(P) = \alpha + \beta_i \times x_i$, where x_i is the explanatory variable,

β_i the estimated logistic regression coefficient, α the constant term, and logit (P) the predicted value of logit(p), where p is the probability of ulcer recurrence [logit(p) = ln(p/(1 − p))]. To assess the fit of the multivariate model, we calculated the percentage of correct prediction of patients with ulcer recurrence (sensitivity) and without ulcer recurrence (specificity). Optimal fit was obtained by adjusting the probability p in such a manner that the highest sensitivity was reached, under the condition that specificity was ≥0.5.

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 median 5.1 months (25–75% quartile 2.8–9.4). Forty-one of the 71 ulcers were suggested to be the result of unrecognized repetitive trauma. These 41 ulcers developed in a median 3.9 months (2.5–8.9). Timing of ulcer recurrence over 18 months' follow-up is presented in Fig. 1.

Of patients who developed an ulcer, 45% had a minor lesion at study entry, and the mean minor lesion index was 0.42. Of patients who did not develop an ulcer, 18% had a minor lesion at entry and mean minor lesion index was 0.17. For the group of 41 patients with recurrence from unrecognized repetitive trauma, these values were 63% and 0.58, respectively, compared with 15% and 0.17, respectively, for patients without recurrence. 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 ulcer diagnosis. Of all 135 minor lesions that were identified during the study, 17% developed into a foot ulcer. The correlation coefficient between minor lesion index and the time that elapsed between healing of the previous ulcer and study entry was $r = -0.23$ ($P < 0.01$). The correlation coefficient between minor lesion index and the cumulative duration of past foot ulcers was $r = 0.18$ ($P < 0.05$).

Results of the univariate and multivariate multilevel logistic regression analysis for all 71 ulcer recurrences (model 1) are shown in Table 2. The univariate analysis showed that having severe foot deformity, a higher minor lesion index, a minor lesion at study entry, increased WP, increased barefoot peak pressure, and a longer cumulative duration of past foot ulcers significantly increased the odds for ulcer recurrence. A combination of in-shoe peak pressure <200 kPa with adherence >80% and more day-to-day variation in stride count significantly decreased the odds for ulcer recurrence. In the multivariate analysis, a higher minor lesion index (odds ratio [OR] 9.06 [95%CI 2.98–27.57]), longer cumulative duration of past foot ulcers (1.03 [1.00–1.06]), and more day-to-day variation in stride count (0.93 [0.89–0.99]) remained independently significantly related to ulcer recurrence. Based on these results, the estimated logistic regression equation was defined as: logit(p) = −0.62 + 0.03 × cumulative duration of past foot ulcers + 2.20 × minor lesion index − 0.07 × variation in daily stride count. The optimal probability cutoff point of $P = 0.275$ yielded an 81% sensitivity (correctly classifying the group with ulcer recurrence) and 50% specificity (correctly classifying the group without ulcer recurrence) for this model.

The results of the regressions analysis for the 41 ulcer recurrences suggested to be the result of unrecognized repetitive trauma (model 2) are also shown in Table 2. The univariate analysis showed that having a higher minor lesion index, a minor lesion at entry, higher in-shoe peak pressures at the previous ulcer location, higher WP, higher barefoot peak pressure, and a longer cumulative duration of past foot ulcers significantly increased the odds for ulcer recurrence. A combination of in-shoe peak pressure <200 kPa with adherence >80%, longer time between the healing of the previous ulcer and study entry, more day-to-day variation in stride count, and a longer diabetes duration significantly decreased the odds for ulcer recurrence. In the multivariate analysis, having a minor lesion at entry (OR 10.95 [95% CI 5.01–23.96]), a combination of in-shoe peak pressure <200 kPa and adherence >80% (0.43 [0.20–0.94]), a higher barefoot peak pressure (1.11 [1.00–1.22]), and more day-to-day variation in stride count (0.91 [0.86–0.96]) remained independently significantly related to ulcer recurrence. Based on these results, the estimated logistic regression equation was defined as: logit(p) = −1.98 + 2.39 × minor lesion at entry − 0.09 × variation in daily stride count + 0.10 × barefoot peak pressure − 0.84 × in-shoe pressure <200 kPa and adherence >80%. The optimal probability cutoff point of $P = 0.063$ yielded a 76% sensitivity and 51% specificity for this model.

CONCLUSIONS

Based on an analysis of a wide range of biomechanical, behavioral, and disease-related factors that were studied as part of a multicenter trial on footwear effectiveness (16) and that have been suggested to be important in diabetic foot ulceration, the prediction of plantar foot ulcer recurrence was 81% sensitive and 50% specific. The prediction of ulcer recurrence suggested to be the result of unrecognized repetitive trauma was 76% sensitive and 51% specific. These findings suggest a good classification of patients who develop ulcer recurrence and a moderate classification of patients who do not develop ulcer recurrence. A high sensitivity is preferred in programs aimed at preventing plantar foot ulcer recurrence in diabetes.

Incidence of ulcer recurrence was high at 42% in 18 months, and therefore a good understanding of risk factors is important. This extends from what we have learned about the role of footwear and adherence from our footwear trial (16), since the presence of a minor lesion was clearly the strongest determinant of ulcer recurrence in both risk models (ORs >9). It has been recognized before that ulcers often develop from lesions such as tissue hemorrhage and blisters or underneath callosities (22), but now we have proven this in the context of ulcer recurrence and based on a comprehensive analysis of factors that shows that minor lesions are most dominant. A minor lesion directly preceded 32% of all ulcer recurrences, and both percentage minor lesion at study entry (>45%) and minor lesion index (>0.42) were high in patients who ulcerated. A shorter period between healing of the previous foot ulcer and entry in the study was positively correlated with the minor lesion index. This may mean that the previous ulcer, although reepithelialized, was not fully recovered to intact skin and underlying tissue, increasing the risk for injury. Furthermore, the minor lesion index was significantly correlated with

Table 1—Baseline and outcome data

Variable	All patients	All ulcer recurrences (model 1)		Ulcer recurrences from unrecognized repetitive trauma (model 2)	
		Patients with no ulcer	Patients with ulcer	Patients with no ulcer	Patients with ulcer
Subjects (*N*)	171	100	71	130	41
Age (years)	63.3 (10.1)	63.6 (9.4)	62.8 (11.2)	63.4 (9.8)	62.9 (11.3)
Male sex (%)	82.5	80	85.9	80.8	87.8
Type 2 diabetes (%)	71.3	71.0	71.8	70.8	73.2
Diabetes duration (years)	17.3 (13.5)	17.7 (13.8)	16.7 (13.2)	18.2 (14.2)	14.3 (10.5)
BMI (kg/m^2)	30.7 (5.7)	30.7 (5.3)	30.6 (6.2)	30.8 (5.7)	30.3 (5.7)
HbA_{1c}					
mmol/mol	60.0 (15.3)	58.0 (14.2)	61.0 (17.5)	60.0 (15.3)	60.0 (16.4)
%	7.6 (1.4)	7.5 (1.3)	7.7 (1.6)	7.6 (1.4)	7.6 (1.5)
Vibration perception threshold (volt)†	50.0 (6.2)	50.0 (3.3)	50.0 (13.5)	50.0 (4.9)	50.0 (11.2)
Cumulative duration of past foot ulcers (months)	14.1 (19.0)	10.7 (12.5)	20.3 (26.2)	13.3 (17.9)	16.9 (22.5)
Smoker or history of smoking (%)	66.7	66.0	67.6	63.8	75.6
>2 units alcohol intake/day (%)	11.7	13.0	9.9	11.5	12.2
Living alone (%)	26.9	22.0	33.8	26.2	29.3
Employed (%)	21.6	20.0	23.9	20.8	24.4
Education level (low/medium/high [%])	56/18/26	56/18/26	56/18/25	57/17/26	54/22/24
Grade II peripheral arterial disease (%)‡	35.2	38.5	30.4	36.5	30.8
Visits per month to a foot care provider (*N*)	1.3 (0.8)	1.2 (0.7)	1.4 (0.8)	1.2 (0.8)	1.5 (8.3)
Minor lesion at entry (%)	29.2	18.0	45.1	15.4	63.4
Minor lesion index (0–1)	0.27 (0.36)	0.17 (0.25)	0.42 (0.42)	0.17 (0.27)	0.58 (0.41)
History of amputation (%)	29.8	28.0	32.4	31.5	24.4
Foot deformity (%)					
Absent	9.9	13.0	5.6	11.5	4.9
Mild	36.8	38.0	35.2	36.2	39.0
Moderate	41.5	42.0	40.8	40.8	43.9
Severe	11.7	7.0	18.3	11.5	12.2
Months healed from ulceration before study entry	5.0 (5.5)	5.3 (5.7)	4.5 (5.2)	5.5 (5.7)	3.5 (4.7)
Daily stride count (*N*)	3,359 (1,749)	3,437 (1,990)	3,238 (1,287)	3,404 (1,857)	3,209 (1,331)
Variation in daily stride count (*N*)	1,194 (713)	1,276 (793)	1,068 (549)	1,234 (747)	1,062 (578)
Adherence (%)	72.9 (24.3)	72.7 (24.1)	73.1 (24.7)	73.1 (23.7)	72.2 (26.2)
Adherence at home (%)	61.7 (32.3)	63.2 (32.3)	59.3 (32.6)	64.4 (31.2)	53.7 (34.7)
Adherence away from home (%)	87.6 (26.7)	84.9 (30.8)	91.7 (18.3)	86.1 (28.8)	91.9 (19.1)
In-shoe peak pressure @plantar foot (kPa)	254 (79)	249 (77)	261 (83)	—	—
In-shoe peak pressure @plantar foot >200kPa at entry (%)	76.6	76.0	77.5	—	—
Barefoot peak pressure @plantar foot (kPa)	979 (293)	935 (307)	1,042 (260)	—	—
WP @plantar foot (kPa)	445 (198)	429 (188)	472 (212)	—	—
CPTS @plantar foot (MPa/day)	675 (475)	652 (436)	715 (538)	—	—
In-shoe peak pressure @plantar foot <200 kPa and adherence >80% at entry (%)	9.7	10.2	9.0	—	—
In-shoe peak pressure @previous ulcer (kPa)	187 (88)	—	—	178 (82)	212 (99)
In-shoe peak pressure @previous ulcer >200 kPa at entry (%)	40.1	—	—	36.2	51.2
Barefoot peak pressure @previous ulcer (kPa)	738 (393)	—	—	699 (393)	849 (375)
WP @previous ulcer (kPa)	329 (192)	—	—	314 (188)	372 (200)
CPTS @previous ulcer (MPa/day)	377 (283)	—	—	361 (279)	423 (292)
In-shoe peak pressure @previous ulcer <200 kPa and adherence >80% at entry (%)	24.8	—	—	27.3	17.9

Data are mean (SD) unless otherwise indicated. For model 1, we included the peak pressure measured at the plantar foot, distal to the heel, because we did not specify the region where ulcers developed. For model 2, which specified ulcer recurrences at the prior ulcer site from unrecognized repetitive trauma, we included the peak pressure measured at the prior ulcer location because of our special interest in this region within this model. †Maximum measured value of the vibration threshold at the hallux from a Biothesiometer was 50 volts. ‡Presence of peripheral arterial disease (grade I = no; grade II = yes) was assessed using the Perfusion Extent Depth Infection Sensation classification (21).

the cumulative number of months patients had a foot ulcer in the past. This provides indirect support for why a history of ulceration is one of the strongest predictors of new ulceration in diabetes (2,3).

For the first time, the role of in-shoe plantar pressures in foot ulcer recurrence has been demonstrated in a prospective risk factor analysis. In-shoe peak pressure was a significant risk factor of ulcer recurrences from unrecognized repetitive trauma, but only in univariate analysis (OR 1.43). More importantly, the combination of a low in-shoe peak pressure (<200 kPa) and high adherence (>80%) was a significant determinant in the multivariate analysis of recurrences from unrecognized repetitive trauma (OR 0.43) and confirms earlier indications from Chantelau and Haage (31). Thus, effective offloading below target pressures in footwear that is worn as recommended (above target adherence) protects the foot and can reduce risk of ulcer recurrence with more than 50%. This finding is unprecedented in diabetic foot research and demonstrates the clinical importance of continuous and adequate offloading.

Only few risk factors were found to be independently significantly associated with ulcer recurrence. While high barefoot peak pressure was an independent risk factor of ulcer recurrence from unrecognized repetitive trauma, which confirms earlier data (4,11,12), the OR was small (1.1 per 100 kPa increase in pressure). The reason for this is not quite clear but may be the result of testing a selected group of only the highest-risk patients (i.e., with ulcer history), which the other studies (4,11,12) did not do. Footwear adherence was by itself not associated with ulcer recurrence (only in combination with pressure it was), and daily step count was not either (only variation in step count was). This suggests that the role of these behavioral parameters is not straightforward in ulcer recurrence. The variable WP combined plantar pressures with adherence but was only significant in univariate analysis, maybe because it does not specify cutoff levels for low pressure and high adherence. Maluf and Mueller (17) found lower CPTSs in patients with ulcer history compared with those without. We found no significant association with ulcer recurrence, even though we defined cumulative stress in a more sophisticated way than Maluf and Mueller did. The indistinct role of ambulatory weight-bearing activity in ulcer risk may potentially explain this outcome (18,19). Further sophistication of the cumulative stress model, including all worn footwear (also nonprescriptive) and shear pressure, may improve ulcer prediction based on cumulative stress.

Outcomes generally depend on which variables are entered in the regression model and are likely affected by how narrow or broad the risk spectrum of selected patients is. For example, Dubský et al. (6) showed that plantar location of the ulcer, presence of underlying osteomyelitis during healing of the prior ulcer, poor glycemic control, and increased C-reactive protein levels at time of ulcer diagnosis were the independent predictors of diabetic foot ulcer recurrence. Their results are difficult to compare with ours because of the different input variables (more disease-related parameters in their study) and because they assessed parameters at ulcer diagnosis—not after ulcer healing. Of the disease-related parameters that we assessed, none were independently associated with ulcer recurrence. All patients had neuropathy and as a result already a high vibration perception threshold, which limits its potential to discriminate in logistic regression analysis. The inclusion of a selected group of only high-risk patients may also have been the reason that other parameters such as peripheral vascular disease and diabetes control were not associated with ulcer recurrence. Studies that show these associations generally select patients across a wider risk spectrum.

The study findings have several important implications, which extend beyond those from our footwear trial (16), since we assessed the role of pressure and adherence with respect to many other patient and disease-related parameters. An important result is that most significant risk factors in the study are amendable and can therefore be targeted by health care providers in preventative foot care. First, patients should be screened frequently for minor lesions as "warning signs" of ulceration, and probably more frequently than current guidelines recommend (22). This could take place in the podiatrist's office but may also mean monitoring foot status more closely in the patient's home. When a minor lesion occurs, it should be managed promptly to prevent more

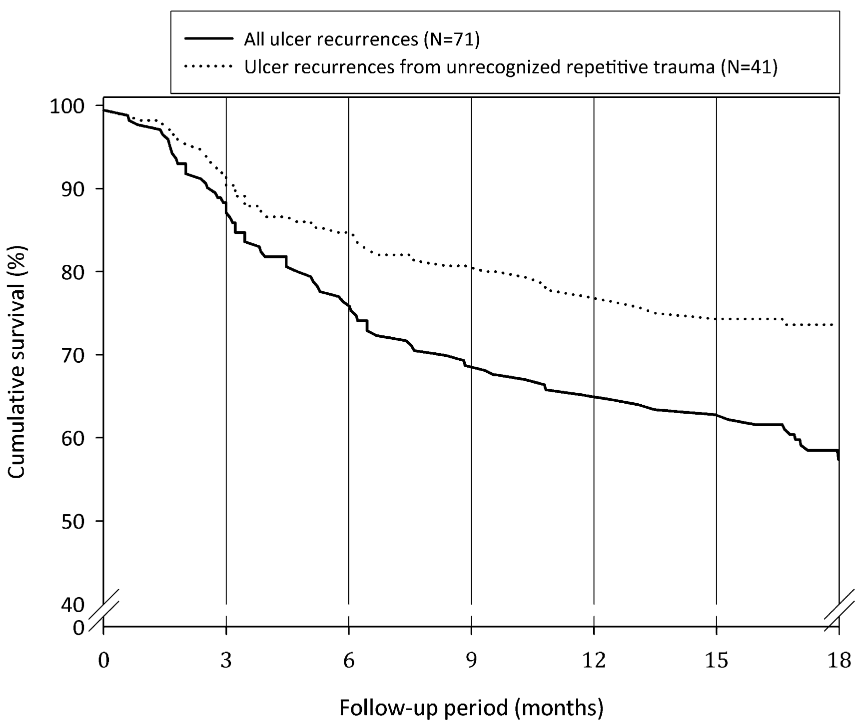

Figure 1—Timing of plantar foot ulcer recurrence over 18 months of follow-up.

Table 2—Univariate and multivariate multilevel logistic regression analysis of plantar foot ulcer recurrence

Variable	All ulcer recurrences (model 1)				Ulcer recurrences from unrecognized repetitive trauma (model 2)			
	Univariate model		Multivariate model		Univariate model		Multivariate model	
	OR (95% CI)	*P*	OR (95% CI)	*P*	OR (95% CI)	*P*	OR (95% CI)	*P*
Age (years)	0.99 (0.96–1.02)	0.678			1.00 (0.96–1.03)	0.779		
Female sex	0.66 (0.3–1.47)	0.310			0.56 (0.22–1.44)	0.230		
Type 2 diabetes (vs. type 1 diabetes)	1.03 (0.52–2.01)	0.935			1.12 (0.52–2.44)	0.769		
Diabetes duration (years)	1.00 (0.97–1.02)	0.705			0.97 (0.95–1.00)	0.041*		
BMI (kg/m^2)	1.00 (0.95–1.05)	0.977			0.98 (0.93–1.05)	0.627		
HbA_{1c}								
mmol/mol	1.01 (0.99–1.03)	0.255			1.00 (0.98–1.02)	0.985		
%	1.14 (0.91–1.41)	0.255			1.00 (0.77–1.29)	0.985		
Vibration perception threshold (volt)	0.98 (0.95–1.01)	0.267			0.99 (0.96–1.03)	0.662		
Cumulative duration of past foot ulcers (months)	1.04 (1.01–1.06)	0.006*	1.03 (1.00–1.06)	0.053*	1.04 (1.01–1.07)	0.012*		
Smoking or history of smoking	1.08 (0.56–2.08)	0.810			1.69 (0.79–3.62)	0.178		
Alcohol intake >2 units/day	0.75 (0.29–1.93)	0.547			1.06 (0.36–3.15)	0.918		
Living alone	1.79 (0.89–3.57)	0.102			1.14 (0.52–2.53)	0.745		
Employment	1.26 (0.6–2.63)	0.545			1.24 (0.53–2.91)	0.616		
Education level								
Low	Reference‡				Reference‡			
Medium	0.99 (0.43–2.26)	0.983			1.36 (0.53–3.51)	0.528		
High	0.95 (0.46–1.97)	0.898			1.00 (0.43–2.31)	0.993		
Peripheral arterial disease, grade II (vs. grade I)†	0.78 (0.53–1.15)	0.206			0.79 (0.37–1.68)	0.540		
Monthly visits to a foot care provider (*N*)	1.35 (0.87–2.12)	0.185			1.44 (0.85–2.45)	0.179		
Minor lesion at entry	3.80 (1.88–7.65)	0.000*			9.75 (3.81–24.91)	0.000*	10.95 (5.01–23.96)	0.000*
Minor lesion index (0–1)	8.62 (3.40–21.85)	0.000*	9.06 (2.98–27.57)	0.000*	23.82 (9.11–62.25)	0.000*		
History of amputation	1.21 (0.62–2.37)	0.567			0.69 (0.32–1.51)	0.355		
Severity of deformity								
Absent	Reference‡				Reference‡			
Mild	2.24 (0.73–6.87)	0.158			2.69 (0.73–9.9)	0.136		
Moderate	2.33 (0.77–7.05)	0.135			2.66 (0.73–9.66)	0.136		
Severe	6.10 (1.57–23.69)	0.009*			2.69 (0.56–12.91)	0.217		
Months prior ulcer was healed before study entry	0.97 (0.92–1.03)	0.334			0.94 (0.88–1.01)	0.081*		
Daily stride count (per 100 strides)	0.99 (0.97–1.01)	0.360			0.99 (0.97–1.01)	0.404		
Variation in daily stride count (per 100 strides)	0.95 (0.90–0.99)	0.023*	0.93 (0.89–0.99)	0.012*	0.96 (0.91–1.01)	0.096*	0.91 (0.86–0.96)	0.001*
Adherence (%)	1.00 (0.99–1.01)	0.989			1.00 (0.98–1.01)	0.823		

Continued on p. 1704

Table 2—Continued

Variable	All ulcer recurrences (model 1)				Ulcer recurrences from unrecognized repetitive trauma (model 2)			
	Univariate model		Multivariate model		Univariate model		Multivariate model	
	OR (95% CI)	*P*	OR (95% CI)	*P*	OR (95% CI)	*P*	OR (95% CI)	*P*
Adherence >80%	0.98 (0.51–1.9)	0.958			1.06 (0.5–2.23)	0.883		
Adherence at home (%)	1.00 (0.98–1.01)	0.495			0.99 (0.98–1.00)	0.146		
Adherence away from home (%)	1.01 (1.00–1.03)	0.114			1.01 (0.99–1.03)	0.216		
In-shoe peak pressure @plantar foot (per 100 kPa)	1.21 (0.95–1.53)	0.120			—	—	—	—
In-shoe peak pressure @plantar foot >200 kPa	1.24 (0.85–1.82)	0.261			—	—	—	—
Barefoot peak pressure @plantar foot (per 100 kPa)	1.18 (1.09–1.27)	0.000*			—	—	—	—
WP @plantar foot (per 100 kPa)	1.22 (1.08–1.38)	0.001*			—	—	—	—
CPTS @plantar foot (per MPa/day)	1.00 (1.00–1.00)	0.453			—	—	—	—
In-shoe peak pressure @plantar foot <200 kPa and adherence >80%	0.47 (0.26–0.85)	0.012*			—	—	—	—
In-shoe peak pressure @previous ulcer (per 100 kPa)	—	—	—	—	1.38 (1.05–1.81)	0.023*		
In-shoe peak pressure @previous ulcer >200 kPa	—	—	—	—	1.43 (0.89–2.32)	0.142		
Barefoot peak pressure @previous ulcer (per 100 kPa)	—	—	—	—	1.12 (1.05–1.21)	0.001*	1.11 (1.00–1.22)	0.040*
WP @previous ulcer (per 100 kPa)	—	—	—	—	1.22 (1.06–1.40)	0.005*		
CPTS @previous ulcer (per MPa/day)	—	—	—	—	1.00 (1.00–1.00)	0.162		
In-shoe pressure @previous ulcer <200 kPa and adherence >80%	—	—	—	—	0.5 (0.28–0.89)	0.019*	0.43 (0.20–0.94)	0.033*

Data are unstandardized logistic regression coefficients. For model 1, we included the peak pressure measured at the plantar foot, distal to the heel, because we did not specify the region where ulcers developed. For model 2, which specified ulcer recurrences at the prior ulcer site from unrecognized repetitive trauma, we included the peak pressure measured at the prior ulcer location because of our special interest in this region within this model. *Significant association ($P < 0.10$) †Presence of peripheral arterial disease (grade I = no; grade II = yes) was assessed using the Perfusion Extent Depth Infection Sensation classification (21). ‡Reference = reference category with which the other categories were compared.

severe complications. Second, patients may benefit from continued treatment with an offloading healing device after reepithelialization of the ulcer and before transferring to preventative footwear to allow the skin to regain strength and resiliency and avoid having a break in the skin (minor lesion) still present when footwear is delivered. Third, the data provide clear target threshold levels for offloading and adherence, where peak pressures inside prescription footwear should be <200 kPa, and this footwear should be worn for >80% of the steps taken. Finally, patients should avoid barefoot walking. When implemented in diabetic foot care, these recommendations are expected to significantly improve patient outcome.

In conclusion, the study showed that diabetic patients with plantar foot ulcer recurrence can be properly classified based on a combination of disease-related, biomechanical, and behavioral risk factors. Furthermore, clear targets for prevention of ulcer recurrence have been obtained. Minor lesions most strongly increase the odds for ulcer recurrence. High barefoot peak pressure increases the risk, while effective offloading in footwear that is worn as recommended protects the foot against ulcer recurrence from unrecognized repetitive trauma. The focus in preventative foot care should be on managing these amendable risk factors. This means preventing minor lesions or improving their early recognition and prompt treatment, urging patients not to walk barefoot, guaranteeing adequate footwear offloading (i.e., in-shoe peak pressure <200 kPa), and improving adherence to footwear use (i.e., to >80% of the steps taken).

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