A Prospective Study of Risk Factors for Diabetic Foot Ulcer

The Seattle Diabetic Foot Study

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OBJECTIVE — Little prospective research exists on risk factors for diabetic foot ulcer that considers the independent effects of multiple potential etiologic agents. We prospectively studied the effects of diabetes characteristics, foot deformity, behavioral factors, and neurovascular function on foot ulcer risk among 749 diabetic veterans with 1,483 lower limbs.

RESEARCH DESIGN AND METHODS — Eligible subjects included all diabetic enrollees of a general internal medicine clinic without foot ulcer, of whom 83% agreed to participate. Baseline assessment included history and lower-limb physical examination, tests for sensory and autonomic neuropathy, and measurements of macro- and microvascular perfusion in the foot. Subjects were followed for the occurrence of a full thickness skin defect on the foot that took >14 days to heal, with a mean follow-up of 3.7 years.

RESULTS — Using stepwise Cox regression analysis, the following factors were independently related to foot ulcer risk: foot insensitivity to the 5.07 monofilament (relative risk [95% CI]) 2.2 (1.5–3.1), past history of amputation 2.8 (1.8–4.3) or foot ulcer 1.6 (1.2–2.3), insulin use 1.6 (1.1–2.2), Charcot deformity 3.5 (1.2–9.9), 15 mmHg higher dorsal foot transcutaneous Po_2 0.8 (0.7– 0.9), 20 kg higher body weight 1.2 (1.1– 1.4), 0.3 higher ankle-arm index 0.8 (0.7–1.0), poor vision 1.9 (1.4–2.6), and 13 mmHg orthostatic blood pressure fall 1.2 (1.1–1.5). Higher ulcer risk was associated with hammer/claw toe deformity and history of laser photocoagulation in certain subgroups. Unrelated to foot ulcer risk in multivariate models were diabetes duration and type, race, smoking status, diabetes education, joint mobility, hallux blood pressure, and other foot deformities.

CONCLUSIONS — Certain foot deformities, reduced skin oxygenation and foot perfusion, poor vision, greater body mass, and both sensory and autonomic neuropathy independently influence foot ulcer risk, thereby providing support for a multifactorial etiology for diabetic foot ulceration.

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Lower-limb amputation and foot ulcer account for considerable morbidity, mortality, and health care expenditures among patients with diabetes. More than half of lower-limb amputations in the U.S. occur in patients with diagnosed diabetes, who comprise only 3% of the U.S. population (1). In one study, nonhealing foot ulcer preceded 85% of diabetic lower-limb amputations (2). Prevention of diabetic foot ulcer, which has been estimated to occur in 15% of diabetic patients at some time over the course of their disease, has been proposed as a method to decrease the high incidence of lower-limb amputation (3). Effective prevention of diabetic foot ulcer requires detailed knowledge of the pathogenesis and correlates of this complication, neither of which is well understood.

Despite the magnitude of the problem of diabetic foot ulcer and its consequences, little research has been performed to investigate the independent roles of multiple potential etiologic factors for this complication. We performed a prospective study among U.S. veterans to assess the contributions of multiple factors to the risk of developing a diabetic foot ulcer, including sensory and autonomic neuropathy, micro- and macrovascular perfusion, foot deformity and joint mobility, diabetes characteristics, and self-care behavior.

RESEARCH DESIGN AND METHODS

Study subjects

All ambulatory general internal medicine clinic patients at a Veterans Affairs medical center with diabetes were eligible for enrollment. Informed consent was obtained from all subjects after the procedures involved were fully explained. Exclusion criteria included current foot ulcer, bilateral foot amputations, wheelchair bound or unable to walk, too sick to participate, and psychiatric illness that prevented informed consent. Subjects with clinically apparent diabetes were identified by review of hospital computerized pharmacy data for receipt of insulin, oral hypoglycemic medication, or blood or urine glucose test strips, review of laboratory data, and review of medical record problem lists for the diagnosis of diabetes. The diagnosis was then confirmed by communication with clinical providers or medical record review.

Baseline data collection

Subjects were interviewed to collect data on demographics; diabetes type, duration, and treatment; smoking history; self-care behaviors; neuropathic symptoms; and past history of foot or leg ulcer and amputation. History of several clinical provider (clinician)-diagnosed conditions was assessed by inter-

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Abbreviations: AAI, ankle-arm index; RR, relative risk; $TcPo_2$, transcutaneous O_2 tension.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

view, including "poor circulation in the legs" (peripheral vascular disease), "kidney disease" (nephropathy), and "nerve problems in the feet" (neuropathy). A physical exam with emphasis on the lower limbs was performed by research nurse practitioners, who assessed presence of the following characteristics: hammer/claw toe, Charcot deformity, hallux limitus, prominent metatarsal heads, hallux valgus, bony prominences, and ankle and hallux mobility measured with a goniometer. The bulk of the extensor digitorum brevis muscle, thought to reflect the presence of diabetic neuropathy, was assessed and recorded as normal, diminished, or absent (4). Visual acuity was assessed with a Snellen chart, and defined as poor if worse than 20/40 in both eyes. Weight in kilograms was measured with a balance beam scale.

Patients whose diabetes was treated with diet or oral hypoglycemic agents were considered to have type 2 diabetes. Diabetes type for patients taking insulin was determined using a clinically based algorithm that considered age at onset, presenting weight and symptoms, family history, onset of insulin treatment, and history of ketoacidosis.

Laboratory and neurovascular measurements

Sensory testing was performed at nine locations on each foot using the Semmes-Weinstein monofilament (5). Inability to perceive the 5.07 monofilament at one or more sites on a foot was considered to represent peripheral sensory neuropathy in that foot. Vibration sensation was measured on the plantar hallux using a 128-Hz tuning fork, and was graded as absent if the subject reported no vibration while the examiner could still sense vibration. Achilles tendon reflex was elicited with the subject in a seated position.

Two measures of cardiovascular autonomic neuropathy were obtained: *1*) mean heart rate variability on a continuous electrocardiogram tracing during deep breathing at 6 breaths/min and *2*) immediate systolic blood pressure response to standing from a supine position (6).

Measurements of lower-limb transcutaneous O_2 tension ($TcPO_2$) were performed at 44°C with TCM-3 monitors (Radiometer, Copenhagen) under uniform conditions on the dorsal foot just proximal to the second toe and the plantar hallux (7). Laser Doppler flowmetry (Perimed, Stockholm) was performed on the dorsal foot after 10 min of cutaneous warming at 44°C, with flow measured in terms of perfusion units. Brachial and lower-limb arterial blood pressures in both limbs over the posterior tibialis and dorsalis pedis arteries were measured by standard Doppler techniques (Medasonics, Fremont, CA) (8). Foot arteries were considered incompressible when the Doppler blood pressure was ≥200 mmHg. Hallux blood pressure was measured on the plantar surface using a penile cuff and handheld Doppler (Medasonics). The ankle-arm index (AAI) was calculated as the ratio of the ankle systolic pressure (defined as the higher of the dorsalis pedis or posterior tibialis measurements) divided by the higher brachial systolic pressure. A random blood sample was drawn for measurement of plasma glucose (glucose oxidase method), serum glycosylated hemoglobin (Isolab, Akron, OH), serum creatinine (Hitachi 917 autoanalyzer; Boehringer Mannheim, Indianapolis, IN), and the erythrocyte sedimentation rate (Westergren method; Polymedco, Cortlandt Manor, NY).

Follow-up data collection

Foot ulcer was defined as a full thickness skin defect that required >14 days to heal. Subjects were reexamined at 12- to 18-month intervals (mean interval = 13 months) to assess whether the outcome had occurred. Also, subjects were contacted quarterly by mail and were encouraged to call study staff or drop by the research clinic if they suspected that they had a foot ulcer. Subjects who did not return mailed questionnaires were contacted whenever possible in person at their next scheduled clinic visit at this medical center. To assure capture of incident foot ulcers that were not detected by the above means, study staff publicized the project throughout the medical center and emphasized the need for clinical providers to notify them of all incident ulcers seen in ambulatory, urgent care, surgical specialty clinics, and other clinical settings. Fluorescent orange labels were affixed to the medical record problem list reminding providers to check their patients' feet. As an incentive for this reporting, study staff offered to expedite triage of patients with foot lesions, thereby reducing provider workload.

Statistical analysis

Each lower limb was considered a subject in the analysis. The outcome was defined as the first ulcer occurrence on the foot. Follow-up on both limbs was terminated when the first ulcer occurred on either during the follow-up period. Limb-specific measurements (e.g., AAI) were analyzed in relation to ulcer occurrence on the same foot. Since the two legs of a given patient do not constitute independent observations, Huber's robust variance estimation method, which takes into account the dependence of observations, was used to calculate confidence limits and *P* values in all statistical comparisons (9,10). Univariate analyses of potential risk factors in relation to ulcer occurrence were performed using Cox regression analysis (11). Continuous variables were entered into these analyses as linear terms. Stepwise Cox proportional hazards regression was used to identify independent risk factors for foot ulcer occurrence while controlling for potential confounding factors (11). Only variables with a *P* value <0.20 in univariate analyses were considered to be potential candidates for inclusion in the Cox model. Cox regression relative risks (RRs) for continuous variables were calculated for a 1 SD (based on all subjects) increase in the value of a continuous variable.

RESULTS — Of the 900 patients eligible for the study, 749 agreed to participate (83.2%). Subjects were elderly (mean age 63.2 years) men (98.0%) with type 2 diabetes (93.6%) and an average diabetes duration of 11.4 years. Of the total, 734 subjects contributed two lower limbs each, while 15 amputee subjects contributed only one, for a total of 1,483 limbs available for analysis. Complete follow-up to the time of this analysis was available for 77% of patients. During follow-up, 162 ulcers developed over 5,442.6 cumulative person-years (3.0/100 person-years). Mean follow-up duration was 3.7 years.

Baseline characteristics of study limbs by whether an ulcer developed during follow-up are shown in Table 1 for all comparisons with $P \leq 0.1$. Of the 47 characteristics examined, 32 were significantly related ($P < 0.05$) to the risk of foot ulcer. The following characteristics were related to a significantly higher risk of developing foot ulcer: greater height and weight; longer diabetes duration; insulin use; greater random plasma glucose, HbA_{1c}, erythrocyte sedimentation rate, and serum creatinine; lower ankle blood pressure, AAI and foot $TcPO_2$; claudication with walking less than one block; self-reported clinician-diagnosed peripheral vascular disease; history of vascular bypass surgery; greater

Table 1—*Characteristics of study subjects at baseline by whether a foot ulcer developed during follow-up*

Baseline characteristic	Incident ulcer	No incident ulcer	RR (95% CI)	*P* value
n	162	1,321	—	—
Weight (kg)	98.5 ± 21.3	94.2 ± 19.9	1.21 (1.05–1.39)	0.009
Height (m)	1.82 ± 0.08	1.80 ± 0.08	1.29 (1.11–1.51)	0.001
Diabetes duration (years)	12.9 ± 9.6	11.3 ± 9.7	1.18 (1.05–1.32)	0.005
Type 2 diabetes	90.1	94.0	0.68 (0.44–1.04)	0.072
Insulin use	64.2	45.1	2.23 (1.64–3.04)	<0.001
Random glucose (mmol/l)	14.3 ± 5.7	12.7 ± 5.8	1.26 (1.11–1.44)	<0.001
HbA_{1c} (%)	12.1 ± 3.2	11.1 ± 3.3	1.26 (1.11–1.43)	<0.001
Erythrocyte sedimentation rate	24.0 ± 26.6	20.0 ± 18.7	1.28 (1.14–1.43)	<0.001
Serum creatinine (μmol/l)	128.8 ± 59.5	123.4 ± 50.7	1.16 (1.04–1.29)	0.008
Ankle blood pressure (mmHg)	123.4 ± 39.9	130.9 ± 34.3	0.74 (0.62–0.89)	0.001
AAI	0.94 ± 0.29	0.98 ± 0.25	0.80 (0.68–0.95)	0.008
$TcPO_2$ dorsal foot (mmHg)	50.4 ± 14.5	54.9 ± 14.7	0.74 (0.64–0.85)	<0.001
Claudication <1 block	22.2	16.2	1.57 (1.09–2.25)	0.015
Clinician diagnosed peripheral vascular disease	49.1	31.2	2.12 (1.58–2.83)	<0.001
Past history of vascular bypass surgery	10.5	5.9	2.51 (1.53–4.10)	<0.001
Change in heart rate with timed breathing (beats/min)	4.9 ± 4.7	5.2 ± 5.5	0.85 (0.72–1.00)	0.052
Mean orthostatic blood pressure drop (mmHg)	10.1 ± 14.6	6.8 ± 12.7	1.36 (1.17–1.58)	<0.001
Sensory neuropathy by 5.07 monofilament	67.9	38.6	3.37 (2.45–4.63)	<0.001
Absent hallux vibration sensation	60.9	40.7	2.33 (1.66–3.28)	<0.001
Absent Achilles tendon reflex	60.4	52.9	1.40 (1.03–1.90)	0.030
Foot numbness	74.1	62.6	1.66 (1.19–2.30)	<0.001
Foot pain	66.1	53.2	1.69 (1.24–2.31)	0.001
Clinician-diagnosed neuropathy	38.9	26.0	1.74 (1.29–2.33)	<0.001
History of foot ulcer	54.9	30.8	2.46 (1.84–3.29)	<0.001
History of amputation	16.7	5.4	3.99 (2.71–5.87)	<0.001
Special footwear	25.9	15.3	1.82 (1.31–2.53)	<0.001
Hallux limitus	27.2	20.5	1.65 (1.18–2.29)	0.003
Severe hammer/claw toe deformity	29.5	20.3	1.75 (1.23–2.48)	0.002
Charcot deformity	2.5	0.6	3.62 (1.59–8.23)	0.002
Total hallux dorsal and plantar joint mobility (degrees)	68.2 ± 18.7	72.6 ± 18.3	0.77 (0.65–0.90)	0.001
Extensor digitorum brevis test (absent vs. normal)	38.2	25.7	2.85 (1.80–4.49)	<0.001
Chronic lower-limb edema	36.3	27.5	1.52 (1.12–2.06)	0.007
History of laser photocoagulation treatment	29.4	17.3	2.25 (1.66–3.05)	<0.001
Vision <20/40	50.6	33.4	2.31 (1.72–3.09)	<0.001

Data are means ± SD or %. RR are shown for a 1 SD increase in the value of continuous variables for the entire group of subjects.

orthostatic blood pressure drop; sensory neuropathy assessed by monofilament or tuning fork; absent Achilles tendon reflexes; symptoms of neuropathy in the feet (numbness, pain); history of foot ulcer and lower-limb amputation; wearing special footwear; hallux limitus; hammer/claw toe and Charcot deformities; hallux joint mobility; chronic lower-limb edema; history of laser photocoagulation treatment; and poor vision. Of note, type 2 diabetes and higher mean change in heart rate with timed breathing were related to a borderline lower risk of foot ulcer ($P < 0.1$). No significant association was seen between foot ulcer risk and the following characteristics: age, race, pack-years of cigarettes smoked, history or number of hours of diabetes education, hallux blood pressure, laser Doppler measured foot perfusion, hallux $TcPO_2$, prominent metatarsal heads, bony foot prominences, hallux valgus, ankle joint mobility, and self-reported physician-diagnosed nephropathy.

Results of the Cox proportional hazards stepwise model are shown in Table 2. The log-transformed AAI fit the model better than the linear variable and so was used in its place in these analyses. For the remaining continuous variables in Table 2, the linear form fit better than logarithmic or exponential transformations. Two different models are shown, since the inclusion of orthostatic blood pressure drop resulted in a reduction in sample size by 41 limbs due to a greater number of missing observations associated with this measurement. Model 1 did not consider orthostatic blood pressure drop as a potential predictor, while model 2 did consider this variable. Both models have in common the following variables that were independently associated with higher foot ulcer risk: neuropathy by 5.07 monofilament testing, history of foot ulcer and amputation, insulin use, lower foot $TcPO_2$ and log(AAI), higher weight, Charcot deformity, and poor vision. In model 2, orthostatic blood pressure drop enters the model, but Charcot deformity does not. Charcot deformity remains in the model, however, because this diminution of significance was due to the limbs excluded from the analysis that were missing orthostatic blood pressure data.

Removal of orthostatic blood pressure from model 2 results in a similar level of statistical significance ($P = 0.110$) and value for the RR for Charcot deformity (2.76). No statistically significant first-order interactions were observed between pairs of the following variables: body weight, $TcPO_2$ of the foot, log(AAI), neuropathy by monofilament testing, insulin use, and orthostatic blood pressure drop. AAI was entered into model 1, Table 2, as a categorical variable (≤ 0.5, >0.5 to ≤ 0.8, >0.8) in place of log(AAI), with the following foot ulcer RR and 95% CIs estimated: ≤ 0.5, 1.94 (1.07–3.52), >0.5 to ≤ 0.8, 1.68 (1.14–2.48), >0.8, 1 (reference category).

The RRs for the variables shown in Table 1 that were related to foot ulcer risk at $P < 0.1$ are shown in Table 3 adjusted for the nine variables from model 1, Table 2. Adjustment for these nine variables results in a substantial diminution of the RR toward one for nearly all of these factors. The only factors that remain related to foot ulcer risk at $P < 0.1$ are random plasma glucose, HbA_{1c}, and the erythrocyte sedimentation rate. Also, two interactions were observed involving variables that were not included in the final models shown in Table 2. A significant negative interaction (coefficient = -1.03, $P = 0.006$) was observed between past history of foot ulcer and hammer/claw toe deformity, resulting in an elevation in risk associated with this deformity only among patients who responded negatively to the question regarding past history of foot or leg ulcer (Table 3). A significant negative interaction (coefficient = -0.63, $P = 0.049$) was seen between poor vision and laser photocoagulation history. In patients with vision $\geq$20/40, a significant increase in foot ulcer risk was observed in relation to having received this ophthalmologic treatment, whereas the risk was not significantly different from 1 in patients with poor vision (Table 3).

Table 2—*Final results of the Cox model developed as described in the text*

Model variables	RR (95% CI)	*P* value
Model 1		
Sensory neuropathy by 5.07 monofilament	2.17 (1.52–3.08)	<0.001
History of foot ulcer	1.63 (1.17–2.26)	0.004
History of amputation	2.81 (1.84–4.29)	<0.001
Insulin use	1.59 (1.14–2.22)	0.006
$TcPO_2$ dorsal foot (mmHg)	0.80 (0.69–0.93)	0.004
Weight (kg)	1.23 (1.06–1.43)	0.006
Log(AAI)	0.83 (0.73–0.96)	0.011
Charcot deformity	3.49 (1.22–9.92)	0.019
Vision <20/40	1.93 (1.42–2.63)	<0.001
Model 2		
Sensory neuropathy by 5.07 monofilament	1.96 (1.36–2.83)	<0.001
History of foot ulcer	1.55 (1.10–2.18)	0.011
History of amputation	2.82 (1.78–4.47)	<0.001
Insulin use	1.58 (1.11–2.24)	0.010
$TcPO_2$ dorsal foot (mmHg)	0.77 (0.66–0.90)	0.001
Weight (kg)	1.19 (1.02–1.39)	0.030
Log(AAI)	0.84 (0.73–0.97)	0.018
Charcot deformity	2.74 (0.77–9.76)	0.121
Vision <20/40	1.92 (1.39–2.64)	<0.001
Orthostatic blood pressure drop (mmHg)	1.23 (1.05–1.45)	0.013

Models are shown with and without the inclusion of orthostatic blood pressure drop.

CONCLUSIONS — These data confirm that foot ulcers in diabetes result from multiple pathophysiologic mechanisms. Support for many of the theories of ulcer development can be found in these data, including roles for neuropathy, diminished vascular perfusion, foot deformity and higher foot pressure, and diabetes severity reflected by type of treatment and preexisting diabetic complications. A major strength of this study is its prospective design, which permits the demonstration of potential etiologic factors before the appearance of ulcer. This advantage is not available in cross-sectional or case-control designs for many exposures.

To our knowledge, this study is the first prospective demonstration of an effect of autonomic neuropathy on foot ulcer risk independent of other measures of sensory neuropathy. Several other investigators have previously shown a cross-sectional association between presence of foot ulcer and autonomic dysfunction measured using the skin galvanic response, power spectral analysis, or cardiovascular reflexes (12–15). Of the two measures of autonomic neuropathy examined, only orthostatic blood pressure drop, which reflects late-stage autonomic neuropathy and sympathetic dysfunction, was independently related to ulcer risk (16). Autonomic neuropathy may result in functional microvascular disorders including increased arteriovenous shunting, impaired cutaneous hyperemic response to injury, and impaired vasoregulatory response to temperature change (17). Additionally, autonomic dysfunction may cause dry feet through decreased sweat production, with risk of cracks developing in the skin that might serve as the nidus for infection and/or ulceration. Researchers, though, have not been able to identify consistent micro- or macrocirculatory abnormalities in diabetic patients with autonomic neuropathy (18–21). It should be noted that cardiovascular reflexes were used in this study as a measure of peripheral autonomic neuropathy. Confirmation of these findings with direct measurements of autonomic function in the feet would be desirable.

Foot sensory neuropathy as measured by the 5.07 monofilament emerged as the test of peripheral neuropathy most predictive of foot ulcer risk in our population. Several case-control and prospective studies have demonstrated higher foot ulcer risk in association with insensitivity to the 5.07 monofilament, absent Achilles tendon reflex, and diminished vibration sensation as reflected by a hallux vibration perception threshold >25 measured using the biothesiometer (22–24). In contrast to a previous case-control report of independent associations between foot ulcer risk and both sensory neuropathy as assessed by monofilament testing and absent Achilles tendon reflex, our data did not support an independent role for the latter (22). Similarly, vibration sensation as assessed with a 128-Hz tuning fork or the extensor digitorum brevis test in our population did not provide additional predictive power with regard to foot ulcer risk over and above that available from monofilament testing. Biothesiometer assessment of sensory neu-

ropathy was not available at the start of our study, but has since been incorporated and will be available for future analyses. Historical information concerning neuropathy (foot pain and numbness), although related to ulcer risk in univariate analyses, did not provide additional information on ulcer risk after adjustment (Table 3).

Measures of both diminished large vessel perfusion (AAI) and skin oxygenation ($TcPO_2$) were related to higher risk of foot ulcer, confirming an important role for oxygen delivery in the development of this complication. This study demonstrates that skin oxygenation plays an important role not only in predicting the healing of diabetic foot ulcers (25), but also in the development of these lesions. One might speculate that this higher risk is due to diminished cutaneous capacity for repair of foot trauma due to lower skin oxygenation, leading to a chronic nonhealing ulcer. Previous case-control studies have also demonstrated an association between lower-limb $TcPO_2$ and risk of foot ulcer and amputation, but it was not possible to conclude in these studies that lower skin oxygenation preceded the occurrence of either type of event because $TcPO_2$ was measured in these studies after the ulcer had developed or the decision to operate had been made (22,26). In addition to $TcPO_2$, the AAI provided additional independent information regarding foot ulcer risk. The independent contributions of $TcPO_2$ and AAI to foot ulcer risk are not surprising, given the weak correlation between these measurements (27,28). These measurements may reflect different physiologic processes that separately influence foot ulcer risk. The natural log transformation of AAI was more strongly related to foot ulcer risk, indicating that a similar change in AAI had a greater effect on risk for AAI readings in the low compared with the normal range. Previous reports have noted the absence of an association between foot ulcer risk and the AAI, but it is possible that the greater sample size of our analysis permitted detection of a relationship that these smaller studies may have missed (22,29).

Other measures of limb perfusion and skin blood flow in this study were not related to ulcer risk in the univariate or multivariate analyses, except for ankle blood pressure in univariate analysis only. Hallux blood pressure was not significantly associated with foot ulcer risk even before adjustment for other factors in Table 2, despite the demonstrated value of these measurements in predicting foot ulcer outcome (30). Point-source laser Doppler flowmetry, which measures skin capillary blood flow, similarly showed little ability to predict ulcer occurrence. Several explanations for this negative finding are possible, including heterogeneity in skin perfusion and the inability of the laser Doppler to capture the determinants besides flow that affect skin oxygenation (variable diffusion and oxygen consumption due to metabolic processes) (31,32).

A number of clinically diagnosed foot deformities and joint mobility were considered as potential risk factors for foot ulcer, but of these, only Charcot deformity and hammer/claw toe among subjects with no ulcer history emerged as being independently related to this outcome. The reason for this ulcer–hammer/claw toe association only among previously nonulcerated patients is unclear. Although significantly related in univariate analysis, hallux limitus and directly measured hallux joint mobility were only weakly related to foot ulcer risk in adjusted models (Table 3), indicating that they serve primarily as markers for other foot ulcer etiologies. A similar finding comes from a case-control study by Boulton et al. (29), who detected a higher risk of diabetic foot ulcer in association with limited joint mobility, but this effect diminished after adjustment for abnormal vibration perception and diabetes duration. If hallux or ankle mobility or the foot deformities we studied other than Charcot deformity and hammer/claw toe have an effect on foot ulcer risk, it is likely to be small in magnitude.

Although the relationship between Charcot deformity and ulcer risk diminished in a model that included orthostatic blood pressure drop, it is most likely that this change resulted from an alteration in sample size and composition as opposed to confounding, due to the greater amount of missing data for this measure of autonomic function. The magnitude of the RR of foot ulcer for Charcot deformity was similar whether or not orthostatic blood pressure drop was included in this model with a reduced number of limbs.

Table 3—*Relative risks for variables from Table 1 not included in the multivariate models shown in Table 2, adjusted for the nine variables shown in Table 2 (final model)*

Baseline characteristic	RR (95% CI)	*P* value
Height (m)	1.12 (0.90–1.40)	0.302
Diabetes duration (years)	0.92 (0.79–1.08)	0.295
Type 2 diabetes	0.68 (0.40–1.14)	0.143
Random glucose (mmol/l)	1.13 (0.98–1.31)	0.092
HbA_{1c} (%)	1.13 (0.98–1.31)	0.096
Erythrocyte sedimentation rate	1.09 (0.99–1.21)	0.081
Serum creatinine (μmol/l)	0.99 (0.89–1.10)	0.804
Claudication <1 block	1.16 (0.77–1.75)	0.479
Clinician-diagnosed peripheral vascular disease	1.17 (0.83–1.65)	0.385
Past history of vascular bypass surgery	1.47 (0.80–2.73)	0.218
Change in heart rate with timed breathing (beats/min)	0.87 (0.72–1.05)	0.150
Absent hallux vibration sensation	1.28 (0.85–1.91)	0.239
Absent Achilles tendon reflex	1.16 (0.84–1.61)	0.361
Foot numbness	0.95 (0.67–1.34)	0.767
Foot pain	1.29 (0.93–1.78)	0.132
Special footwear	1.18 (0.75–1.84)	0.476
Hallux limitus	1.32 (0.92–1.88)	0.132
Hammer/claw toe		
No past ulcer history	2.11 (1.25–3.57)	0.005
Past ulcer history	0.76 (0.45–1.26)	0.283
Total hallux dorsal and plantar joint mobility (degrees)	0.89 (0.75–1.05)	0.153
Extensor digitorum brevis test (absent vs. normal)	1.13 (0.67–1.88)	0.652
Chronic lower limb edema	0.97 (0.68–1.39)	0.882
Laser photocoagulation		
Vision ≥20/40	1.79 (1.18–2.74)	0.007
Vision <20/40	0.95 (0.58–1.56)	0.849

For continuous variables, RRs reflect a 1 SD increase.

Body weight emerged as an independent risk factor for foot ulcer, with higher risk associated with greater weight. One potential mechanism for this association is through higher foot pressure in heavier subjects. A prospective study of 86 diabetic patients followed prospectively for a mean period of 30 months demonstrated a higher risk of foot ulcer among those patients with a peak plantar pressure of >12.3 kg/cm^2 measured using the optical pedobarograph (33). Several other cross-sectional reports have shown both higher weight and plantar pressure in diabetic subjects with ulcer compared with control subjects (34,35). Although a body weight–plantar pressure link has intuitive appeal as an explanation for the higher foot ulcer risk with increasing weight, the evidence to support an association between body weight and plantar pressure is not consistent. One report concluded that body mass was a poor predictor of peak plantar pressure, even though a correlation coefficient of 0.37 was observed between these two parameters (36). More research will be required to determine whether the association between body weight and foot ulcer risk is mediated by plantar pressure.

Insulin use and history of poor vision were independently related to higher ulcer risk. It is possible that both of these factors reflect diabetes severity. Also, poor vision may interfere with a patient's ability to detect early foot lesions that without attention might progress to nonhealing ulcer. Among subjects with better vision, laser photocoagulation was associated with a higher risk of foot ulcer, but this was not observed among subjects with poor vision. It is possible that laser photocoagulation is related to visual impairment not reflected completely by Snellen testing and that this accounts for the higher risk in patients with vision better than 20/40 in either eye. It is also possible that the underlying mechanism responsible for proliferative retinopathy is also implicated in foot ulcer pathogenesis, although why this association would not be seen in patients with poor vision is unclear. Previous cross-sectional research has demonstrated an association between diabetic foot ulcer and retinopathy (37).

Past history of amputation and ulcer were independently related to risk of ulcer during this prospective study. These histories probably represent underlying limb pathology, which placed the limb at higher risk for ulcer that was not otherwise captured by the measurements made in this study. Also, amputation may produce changes in gait or foot shape that influence risk of ulcer, as demonstrated in a study of past hallux amputation and ipsilateral foot deformities (38).

Although HbA_{1c} and random plasma glucose were associated with ulcer occurrence in the univariate analysis, these effects diminished in the multivariate model. This may have occurred because of adjustment for consequences and correlates of poorer diabetes control (e.g., neuropathy and insulin use). A trend remained for an association between random glucose and ulcer risk in the multivariate model. Thus, this analysis is consistent with higher ulcer risk associated with more severe hyperglycemia. In predicting foot ulcer occurrence, however, a more accurate classification results from a model that incorporates the complications of hyperglycemia (if this information is available). The absence of an association between foot ulcer risk and diabetes duration may be explained by the difficulty in establishing the onset of this condition in this predominantly type 2 population (39).

Although patients who developed foot ulcer more frequently wore special shoes and reported a history of diabetes education, this may reflect recognition of higher risk by clinical providers (or self-referral by patients who perceive their risk as high). Whether diabetes education or special footwear has any impact on ulcer incidence cannot be addressed by this observational study.

Foot ulcer does not appear to be related to amount smoked as measured in pack-years. Ulcer risk also did not differ in relation to current smoking (data not shown).

There are several potential limitations to this study. Bias could have resulted if loss to follow-up was associated with both ulcer risk and baseline risk factors. This problem is not likely to seriously bias this study's results because of the unlikely nature of this occurrence as well as the high proportion of subjects for whom complete follow-up information was available (77%). Bias might also have occurred if the occurrence of foot ulcer had been incompletely ascertained. This is unlikely because of several procedures designed to maximize our detection of incident foot ulcers in study patients. All study subjects underwent a detailed clinical examination by the study nurse practitioner and medical record review on the average of every 13 months after the baseline visit. To assure that providers promptly notified us of the occurrence of foot ulcer in study patients, this project maintained high visibility at our medical center and assisted clinicians with the development of a management plan for new foot ulcers, thereby providing them with a time-saving reward. Also, the study clinic was open daily during normal hospital business hours for drop-in visits or phone calls from patients regarding any foot concern. All study patients were taught about the outcomes of interest and were instructed to notify us immediately if they suspected that they had a foot ulcer. Finally, quarterly mailed questionnaires were sent to all patients asking about the occurrence of foot ulcer or other foot complications since the last study exam. Subjects who indicated on the returned questionnaire that they had a foot problem were telephoned and interviewed regarding the occurrence of possible study outcomes. With regard to study generalizability, these results apply to U.S. veterans, but could be extrapolated with caution to similar populations.

In conclusion, this study demonstrated that multiple mechanisms contribute to the development of diabetic foot ulcer. Because of the interrelatedness of many diabetic complications and associated factors, it may be misleading to consider individual potential risk factors for foot ulcer in future research, since, as demonstrated in this study, many predictors in univariate analysis will not be shown to have independent effects on ulcer risk. This study confirms important roles for neuropathy, Charcot deformity, skin oxygenation, larger vessel perfusion, body weight, past history of lower-limb complications, and poor vision in the etiology of diabetic foot ulcer. The important potential role of plantar foot pressure in foot ulcer risk was not directly addressed by this study. These findings support regular foot examinations as a strategy for prevention of foot ulcer, since most of the independent risk factors could be identified without the need for specialized training or equipment. None of the independent risk factors are potentially reversible, except for weight through caloric restriction, limb perfusion through revascularization, and improvement of visual acuity where feasible. These findings emphasize the prevention of diabetic neuropathic and vascular complications as the ultimate method to reduce the incidence of this frequent and costly complication.

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