The Independent Contributions of Diabetic Neuropathy and Vasculopathy in Foot Ulceration

How great are the risks?

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OBJECTIVE — To describe the relative contributions of neurological and vascular abnormalities to the overall risk of diabetic foot ulceration.

RESEARCH DESIGN AND METHODS — A case-control study of diabetic veterans from the Seattle Veterans Affairs Medical Center was conducted using data collected from 46 patients with diabetic foot ulcers and 322 control subjects. Neuropathy was determined by vibratory, monofilament, and tendon reflex testing. Macrovascular disease was measured by ankle-arm blood pressure index, and cutaneous perfusion was measured by transcutaneous oxygen tension ($TcPO_2$) on the dorsal foot. A multivariate logistic regression model was used to adjust for confounding variables and to calculate the odds ratios (ORs) for each independent risk factor.

RESULTS — Three variables were significant independent predictors of foot ulceration: absence of Achilles tendon reflexes (adjusted OR 6.48, 95% confidence interval [CI] 2.37–18.06), insensate to the 5.07 monofilament (adjusted OR 18.42, 95% CI 3.83–88.47), and $TcPO_2$ <30 mmHg (adjusted OR 57.87, 95% CI 5.08–658.96). Absent vibratory sensation and low ankle-arm blood pressure index were not significant independent risk factors.

CONCLUSIONS — Both neuropathy and vasculopathy are strong independent risk factors for the development of diabetic foot ulcers. In our model, the strongest risk factor is impaired cutaneous oxygenation. However, in the clinical setting, sensory examination with a 5.07 monofilament probably remains the single most practical measure of risk assessment.

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$TcPO_2$, transcutaneous oxygen tension; CI, confidence interval; OR, odds ratio.

About 2.5% of diabetic men and women will develop a foot ulcer each year (1). Foot ulcers that become complicated by healing failure or infection are a major cause of lower extremity amputations in this population (2). It is thought that meticulous foot care and patient education strategies can reduce lower extremity amputation rates by 40–50%, largely by reducing the frequency and severity of foot ulcers (3). However, educational interventions and evaluation for special foot wear requires some additional effort, time, and cost. Therefore, predicting which patients are at the greatest risk for foot ulceration could lead to more efficient use of resources.

It is well accepted that peripheral neuropathy is an important pathophysiological risk factor for developing foot ulcers (4,5). The majority of foot ulcers appear to result from minor trauma in the presence of sensory neuropathy (2,3,6). Vasculopathy is also presumed to play a role in some individuals, but it remains unclear whether this is primarily due to impaired cutaneous circulation, peripheral macrovascular disease, or both (7). To our knowledge, there is no published controlled study that describes the relative contribution of neurological and vascular abnormalities to the overall risk of foot ulceration. The purpose of this study was to identify and quantify neurovascular risk factors for diabetic foot ulcers using multivariate techniques.

RESEARCH DESIGN AND METHODS

— Participants in this case-control study were diabetic veterans at the Seattle Veterans Affairs Medical Center. Cases included 46 veterans evaluated in the Diabetic Foot Clinic between October 1987 and November 1992 with a documented foot ulcer graded as Seattle Wound Class 2.0 through 6.0 (8) who received a complete neurovascular foot examination.

The control group comprised 322 veterans enrolled in a prospective study

Table 1—*Characteristics of subjects in the case-control study of risk factors for diabetic foot ulcer*

Characteristics	Patients	Control subjects	*P* value
n	46	322	
Demographics			
Men	93.5	97.8	0.117
Age (years)	60.4 ± 10.1	64.2 ± 10.2	0.021
Caucasian	84.4	79.8	0.464
Body mass index (kg/m^2)	27.9 ± 4.9	29.6 ± 6.0	0.048
Married	47.6	58.4	0.185
Education (years)	12.0 ± 2.8	12.3 ± 3.6	0.561
Cigarette use (pack/year)	42.7 ± 50.9	44.7 ± 44.5	0.820
Alcohol use	25.6	15.5	0.263
Diabetes Profile			
IDDM	13.0	8.7	0.341
Current treatment			0.640
Diet only	13.0	12.4	
Oral agent	32.6	39.8	
Insulin	54.3	47.8	
Years of known diabetes	13.2 ± 10.3	12.7 ± 11.9	0.753
Any formal diabetes education	60.5	56.7	0.639
Random serum glucose (mmol/l)	14.4 ± 6.0	13.4 ± 5.9	0.288
Medical history			
Ischemic heart disease	47.6	50.3	0.743
Stroke	25.0	20.4	0.498
Diabetic retinopathy	60.5	57.8	0.736
Diabetic nephropathy	19.0	11.3	0.151
Serum creatinine (μmol/l)	113 ± 37	123 ± 54	0.115
Arterial bypass to leg	11.9	6.5	0.203
Lower extremity amputation	23.9	5.6	0.00002

Data are means ± SD, %, or otherwise marked. Ischemic heart disease defined as history of angina, myocardial infarction, or coronary artery bypass surgery. Diabetic retinopathy defined as history of eye changes due to diabetes, prior retinal laser treatment, or blindness. Diabetic nephropathy defined as history of renal disease due to diabetes or requiring dialysis. IDDM, insulin-dependent diabetes mellitus.

designed to identify risk factors for foot ulceration between October 1990 and October 1992. This group represents the diabetic patients followed in the General Internal Medicine Clinic. Exclusion criteria included: active foot ulcer at the time of enrollment, nonambulatory status, inability to participate due to medical or psychiatric reasons, inability to provide informed consent, previous enrollment in the case group, or incomplete neurovascular foot examination. Subjects who were excluded as control subjects because of an active foot ulcer were recruited for the case group.

A nurse practitioner interviewed each subject to obtain medical history information. Distal vibratory sensation was measured by placing of the end of a vibrating 128-Hz tuning fork on the examiner's distal index finger, overlying the subject's hallux, medial malleolus, and lateral malleolus. If the subject was unable to perceive vibration at any of the three sites on either foot, then vibratory sensation was considered absent. Aesthesiometry was measured using Semmes-Weinstein monofilaments (9) on eight standardized plantar sites and one mid-dorsal site of each foot. Inability to perceive the 5.07 monofilament at any of the nine sites on either foot was classified as insensate. Achilles tendon reflexes were graded as present or absent for each ankle. The ankle-arm blood pressure index was computed as the highest ankle (dorsalis pedis or posterior tibial) blood pressure divided by the highest brachial blood pressure (right or left) for each side. Cutaneous circulation was estimated by measuring transcutaneous oxygen tension ($TcPO_2$) on the mid-dorsum of each foot (10). For all variables measured bilaterally, the lower of the two readings (right or left) was used in the analysis.

Statistical comparisons between groups for individual variables were made using the chi-squared test for categorical variables or the Student's *t* test (two-tailed) for continuous variables. Logistic regression analysis was used to identify significant independent neurovascular risk factors for foot ulceration, including absent vibratory sensation, insensate to the 5.07 monofilament, absent Achilles tendon reflex, ankle-arm blood pressure index, and $TcPO_2$, to test for significant first-order interaction and to adjust for potential confounding variables.

RESULTS— Control subjects were significantly older, heavier, and less likely to have had a lower extremity amputation than case group participants ($P < 0.05$; Table 1). Control subjects also tended to be male, tended to have higher serum creatinine levels, were more likely to be living with a spouse, and were less likely to report diabetic nephropathy or prior lower extremity arterial bypass surgery ($P < 0.2$). The groups were similar with respect to other characteristics shown in Table 1. Sixty-seven percent of the foot ulcers were located on the plantar surface or heel.

Considered individually, each of the neurovascular measures was a significant risk factor for foot ulceration except for ankle-arm blood pressure index (Table 2). However, in the multivariate analysis, only three variables were significant independent predictors of foot ulcer-

Table 2—*Neurovascular measurements: univariate analysis*

Neurovascular measure	Patients	Control subjects	OR for foot ulceration (95% CI)
n	46	322	
Absent vibratory sensation	84.8	64.0	3.14 (1.36–7.23)
Absent ankle reflex	76.1	40.7	4.63 (2.27–9.45)
Insensate to 5.07 monofilament	91.3	51.2	9.99 (3.50–28.49)
$TcPO_2$ ≤30 mmHg	41.3	13.4	23.37 (3.01–181.38)*
$TcPO_2$ 31–60 mmHg	56.5	70.2	6.09 (0.81–45.78)*
Ankle-arm index	0.89 ± 0.37	0.90 ± 0.28	0.86 (0.30–2.51)

Data are % or mean ± SD. Continuous variable: OR interpreted as change in odds per one unit change in scale. *OR is relative to $TcPO_2$ > 60 mmHg.

ation: absent Achilles tendon reflexes, insensate to the 5.07 monofilament, and low $TcPO_2$. No significant interaction was found between $TcPO_2$ and tendon reflex or monofilament sensation or between tendon reflex and monofilament sensation.

The results of the logistic regression model before and after adjustment for confounding variables are shown in Table 3. There were small to moderate differences in the magnitude of the adjusted and unadjusted odds ratios (ORs), but the order of variables from strongest to weakest predictors of foot ulceration remained unchanged.

CONCLUSIONS — This study demonstrates that both neurological and vascular abnormalities are independently associated with increased risk for diabetic foot ulceration. While our study does not rule out a neurological mechanism for abnormal cutaneous perfusion, it appears that any neuropathy affecting the cutaneous vasculature is largely independent of traditional clinical markers for neuropathy (i.e., loss of monofilament or vibratory sensation and absent tendon reflexes).

One limitation of the study is our inability to establish with certainty that the neurovascular abnormalities identified as risk factors preceded the foot ulcer event. For example, it is conceivable that the presence of the ulcer affected the cutaneous perfusion measures, possibly through a mechanism such as edema or infection. We think this is unlikely for several reasons. First, $TcPO_2$ measurements reflect the perfusion status of the cutaneous compartment only within the region of the probe. In no instance was the $TcPO_2$ measurement site in close proximity to an ulcer. Second, all measurements were made 1 week after any initial debridement or antibiotic therapy. Third, the foot with the lowest $TcPO_2$ measurement was not consistently the ulcerated foot in a given patient. The ulcerated foot had a reading equal to or greater than the unaffected foot in 43% of ulcer patients. Finally, only four patients had asymmetric pedal edema associated with a lower $TcPO_2$ on the side of the ulcerated foot. Therefore, we consider it very unlikely that the markedly elevated relative risk estimates we found can be attributed to the presence of an ulcer at the time the measurements were made. However, the case-control design is unable to definitively address these temporal issues, and a prospective cohort study will be needed to confirm our results.

Although our results demonstrate that impaired cutaneous oxygenation is associated with a very high risk of foot ulceration, $TcPO_2$ measurement may not be indicated for routine risk assessment. The goal in the clinical setting is to identify which patients are at enough increased risk to warrant special precautions. A precise quantification of their risk is not usually necessary. Because sensory neuropathy is such a strong risk factor for foot ulceration and it is more common than severely impaired cutaneous perfusion, it is not clear that $TcPO_2$ measurements would provide additional clinically meaningful information in a screening situation beyond that obtained from monofilament and Achilles tendon reflex testing. Therefore, we do not feel that our results justify the use of routine screening $TcPO_2$ measurements in people with diabetes.

In summary, this study shows that both neuropathy and vasculopathy are strong independent risk factors for the development of diabetic foot ulcers. The strongest risk factor is impaired cutaneous circulation, whereas macrovascular disease was not a significant predictor. Impaired cutaneous oxygen delivery should be further studied to elucidate the mechanisms by which this phenomenon alters foot ulcer risk. In the clinical setting, sensory examination with a 5.07 monofilament probably remains the sin-

Table 3—*Neurovascular risk factors for diabetic foot ulceration with and without adjustment for confounding variables using logistic regression*

Neurovascular measures in the model	Unadjusted OR (95% CI)	Adjusted OR (95% CI)
Absent ankle reflex	4.58 (2.11–9.94)	6.48 (2.37–18.06)
Insensate to 5.07 monofilament	7.38 (2.52–21.66)	18.42 (3.83–88.47)
$TcPO_2$ ≤ 30 mmHg	26.9 (3.30–218.99)	57.87 (5.08–658.96)
$TcPO_2$ 31–60 mmHg	7.2 (0.93–55.67)	8.70 (0.84–89.92)

Adjusted OR is adjusted for age, sex, body mass index, serum creatinine, random serum glucose, marital status, history of treatment for alcohol abuse, prior lower extremity amputation, and prior lower extremity vascular bypass graft. OR is relative to $TcPO_2$ > 60 mmHg.

gle most practical measure of foot ulcer risk assessment.

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