Moisture Status of the Skin of the Feet Assessed by the Visual Test Neuropad Correlates With Foot Ulceration in Diabetes

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OBJECTIVE — To examine the association between the moisture status of the skin of the feet with foot ulceration in subjects with diabetes.

RESEARCH DESIGN AND METHODS — A total of 379 subjects with diabetes were examined. Assessment of peripheral neuropathy was based on neuropathy symptom score, neuropathy disability score, vibration perception threshold, and the 10-g monofilament perception. The moisture status of the skin of the feet was assessed using the visual test Neuropad.

RESULTS — Patients with foot ulceration had more severe peripheral neuropathy and more often an abnormal Neuropad response. Multivariate logistic regression analysis demonstrated that the odds of foot ulceration increased with measures of neuropathy but increased also with an abnormal Neuropad response.

CONCLUSIONS — An abnormal Neuropad response correlates with foot ulceration in subjects with diabetes. This finding, if confirmed prospectively, suggests that the Neuropad test may be included in the screening tests for the prediction of foot ulceration.

Diabetes Care **33:1112–1114, 2010**

Damage of the peripheral sympathetic nerves results in sudomotor dysfunction, which manifests as dry skin of the feet and may result in callus and/or fissure formation and eventually in foot ulceration (1,2). The American Diabetes Association recommends examination of sudomotor function for the detection of diabetic neuropathies (3); however, the lack of specific equipment has restricted the study of sudomotor function and its contribution to foot ulceration. The Neuropad test (miro Verbandstoffe, Wiehl-Drabenderhöhe, Germany) is a novel visual test for the assessment of the moisture status of the skin of the feet (4,5). The research hypothesis we tested herein was that an abnormal Neuropad response may be associated with foot ulceration in subjects with diabetes.

RESEARCH DESIGN AND METHODS

— A total of 379 adult subjects were recruited in this study. Exclusion criteria were age >75 years, ankle-brachial pressure index <0.5, estimated creatinine clearance rate using the formula of Cockcroft-Gault <30 ml/min, amputation, significant foot swelling or infection, and causes of neuropathy other than diabetes. The demographic and clinical characteristics of the participants are shown in Table 1.

Assessment for peripheral neuropathy was based on symptoms (neuropathy symptom score [NSS]) and signs (neuropathy disability score [NDS]), as described previously (6). Moreover, we assessed vibration perception threshold (VPT) using a biothesiometer (Biomedical Instruments, Newbury, OH) and the 10-g Semmes-Weinstein monofilament (Bailey Instruments, Manchester, U.K.) perception. Monofilament was applied three times on three plantar sites (under the great toe and first and fifth metatarsal heads) (7,8). Inability to perceive the monofilament at any site was considered abnormal. The Neuropad was applied for 10 min under the first metatarsal head in the sitting position at both feet and evaluated as normal (pink color) or abnormal (blue color or any other combination of colors) (4,5). Peripheral artery disease was diagnosed in the presence of any of the following: history of intermittent claudication or revascularization procedure at the leg arteries, diminished or nonpalpable pedal pulses, and ankle-brachial pressure index <0.9.

Differences between the studied groups were tested using parametric or nonparametric methods according to the specific indications, whereas a χ^2 test was used to compare categorical data. Univariate and multivariate logistic regression analyses (stepwise backward method) were performed to look for associations between the studied parameters with foot ulceration. The area under the receiver operating characteristic (ROC) curve of various established risk factors for foot ulceration and of the Neuropad test was calculated. The area under the ROC curve indicates how informative a test for the prediction of foot ulceration is. *P* values <0.05 were considered statistically significant.

RESULTS

— Subjects with foot ulceration were mostly men and had longer diabetes duration, worse glycemic control, and more often peripheral neuropathy and peripheral artery disease than subjects without foot ulceration. The values of the NSS, NDS, and VPT were higher, whereas monofilament insensation and an abnormal Neuropad result were more often documented in patients

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Received 1 November 2009 and accepted 28 January 2010. Published ahead of print at http://care.diabetesjournals.org on 2 February 2010. DOI: 10.2337/dc09-2027.

Table 1—*Demographic and clinical characteristics as well as the association [odds ratio (95% CI)] between the studied parameters with foot ulceration*

	Without foot ulceration	With foot ulceration	*P*
n	258	121	—
Age (years)	60.0 ± 11.7	63.2 ± 10.2	0.86
Male/female [*n* (%)]	130 (50.4)/128 (49.6)	84 (69.4)/37 (30.6)	0.001
Type 1/type 2 diabetes [*n* (%)]	15 (5.8)/243 (94.2)	8 (6.6)/113 (93.4)	0.46
Duration of diabetes (years) [median value (IQR)]	10.0 (5.0–16.0)	18.0 (10.0–25.0)	<0.001
A1C (%)	7.4 ± 1.6	9.2 ± 2.4	<0.001
VPT (V)	21.5 ± 11.6	37.4 ± 12.2	<0.001
VPT ≥25 V [*n* (%)]	85 (32.9)	101 (83.5)	<0.001
NSS [median value (IQR)]	4.5 (0.0–6.0)	6.0 (4.0–7.0)	<0.001
NDS [median value (IQR)]	2.0 (0.0–5.0)	7.0 (6.0–10.0)	<0.001
NDS ≥6 [*n* (%)]	62 (24.0)	92 (76.0)	<0.001
Monofilament insensation [*n* (%)]	36 (14.0)	70 (57.9)	<0.001
Neuropathy [*n* (%)]	114 (44.2)	114 (94.2)	<0.001
Ankle-brachial pressure index	1.00 ± 0.22	0.98 ± 0.22	0.050
Peripheral artery disease [*n* (%)]	42 (16.3)	31 (25.6)	0.09
Abnormal Neuropad result [*n* (%)]	135 (52.3)	115 (95.0)	<0.001
Univariate analysis	OR	95% CI	
Age (1 year)	1.00	0.98–1.02	0.56
Sex (male vs. female)	1.83	1.14–2.95	0.01
Duration of diabetes (1 year)	1.08	1.05–1.11	<0.001
A1C (1%)	1.32	1.18–1.74	0.002
NSS (1 unit)	1.24	1.13–1.36	<0.001
NDS (1 unit)	1.61	1.45–1.79	<0.001
NDS ≥6 vs. <6	10.7	6.25–18.40	<0.001
VPT (1 V)	1.10	1.08–1.13	<0.001
VPT ≥25 vs. <25 V	12.23	6.20–22.68	<0.001
Monofilament result (insensation vs. sensation)	8.33	4.18–16.59	<0.001
Neuropad result (abnormal vs. normal)	17.3	7.36–40.8	<0.001
Peripheral artery disease (yes vs. no)	1.84	1.07–3.10	0.02
Multivariate analysis*			
Model 1			
NDS ≥6 vs. <6	6.70	3.31–13.35	<0.001
Model 2			
VPT ≥25 vs. <25 V	11.91	6.03–21.86	<0.001
Model 3			
Monofilament result (insensation vs. sensation)	6.40	3.09–13.28	<0.001
Model 4			
Neuropad result (abnormal vs. normal)	16.28	6.27–38.24	<0.001

Data are means ± SD unless otherwise indicated. IQR, interquartile range. Sex, NDS ≥6 vs. <6, VPT ≥25 vs. <25 V, monofilament result (insensation vs. sensation), Neuropad result (abnormal vs. normal), and peripheral artery disease (yes vs. no) were analyzed as categorical variables; all the other variables were analyzed as continuous variables in both univariate and multivariate analysis. *Each one of the models 1–4 were adjusted in addition for age, sex, duration of diabetes, A1C, NSS, and peripheral artery disease status.

with foot ulceration (Table 1). The Neuropad result was not different between patients with neuropathic and neuroischemic ulcers ($P = 0.30$).

Univariate logistic regression analysis showed that the odds of foot ulceration increased with male sex; longer duration of diabetes; worse diabetes control; increasing NSS, NDS, and VPT; monofilament insensation; presence of peripheral artery disease; and abnormal Neuropad response. Multivariate logistic regression analysis after adjustment for age, sex, duration of diabetes, A1C, NSS, and peripheral artery disease status demonstrated that the odds of foot ulceration increased with higher NDS, VPT, and monofilament insensation as well as with an abnormal Neuropad result (Table 1).

The area (± SE) under the ROC curve for the identification of patients with foot ulceration of VPT ≥25 vs. <25 V was 0.76 ± 0.02 ($P < 0.001$; sensitivity 85.4%; specificity 67.6%), of NDS ≥6 vs. <6 was 0.76 ± 0.02 ($P < 0.001$; sensitivity 75.7%; specificity 77.8%), of monofilament result (insensation vs. sensation) was 0.72 ± 0.03 ($P < 0.001$; sensitivity 57.4%; specificity 86.3%), and of the Neuropad result (abnormal vs. normal) was 0.71 ± 0.03 ($P < 0.001$; sensitivity 97.1%; specificity 49.3%). The area under the ROC curve of Neuropad testing did not differ significantly from that of VPT, NDS, and monofilament examination. No adverse events were observed from the Neuropad use.

CONCLUSIONS — This study has shown that dryness of the skin of the feet correlates with foot ulceration. Subclinical sudomotor dysfunction can be de-

tected early in diabetes, even in subjects with normal nerve conduction velocities (9). We showed that dryness of the skin of the feet was detected in 95% of the patients with foot ulceration using the Neuropad test. These findings agree with previous data showing sudomotor dysfunction assessed with the sympathetic skin response in the vast majority of patients with foot ulceration (10).

Noteworthy, the comparison of the values of the areas under the ROC curves demonstrated that the results obtained by Neuropad testing are as informative as those obtained by determination of other neurological modalities commonly used for the prediction of foot ulceration such as VPT, NDS, and monofilament testing.

Identification of patients at risk for foot ulceration using simple and reliable methods is of clinical relevance. The American Diabetes Association recommends the combined use of simple tests including pinprick, temperature, vibration, and 10-g monofilament perception as well as ankle reflexes for this purpose (11). Our findings suggest that the Neuropad can be included in the screening tests for the prediction of foot ulceration. Advantages of the Neuropad are its simplicity, wide availability, high performance for the diagnosis of peripheral neuropathy, and high reproducibility (5,12). Moreover, the test can be self-performed and evaluated safely by the patients (13).

This is a cross-sectional study and a casual relationship between the moisture status of the skin of the feet, and foot ulceration cannot be established. Moreover, although the odds ratio is large, suggesting that there is an association between an abnormal Neuropad response and foot ulceration, the CIs are wide, and it is necessary to be cautious about the interpretation of the finding.

In summary, dryness of the skin of the feet assessed by the Neuropad test correlates with foot ulceration. This finding, if confirmed prospectively, suggests that the Neuropad may be included in the screening tests for the prediction of foot ulceration in subjects with diabetes.

Acknowledgments— Neuropad tests were supplied by miro Verbandstoffe.

No potential conflicts of interest relevant to this article were reported.

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