Risk Factors for Diabetic Peripheral Sensory Neuropathy

Results of the Seattle Prospective Diabetic Foot Study

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OBJECTIVE — To identify risk factors for diabetic lower-extremity peripheral sensory neuropathy prospectively in a cohort of U.S. veterans with diabetes.

RESEARCH DESIGN AND METHODS — General medicine clinic outpatients with diabetes were followed prospectively for the development of insensitivity to the 5.07 monofilament on the foot.

RESULTS — Of 775 subjects, 388 (50%) had neuropathy at baseline. Of the 387 subjects without neuropathy at baseline, 288 were followed up, and of these, 58 (20%) developed neuropathy. Multivariate logistic regression modeling of prevalent neuropathy controlling for sex and race revealed independent and significant associations with age, duration of diabetes, glycohemoglobin level, height, history of lower-extremity ulceration, callus, and edema; an independent and inverse correlation was noted with ankle-arm index. Risk factors for incident neuropathy in multivariate logistic regression included age, baseline glycohemoglobin level, height, history of ulcer, and CAGE screening instrument alcohol score; current smoking and albumin level were inversely associated with risk.

CONCLUSIONS — Poorer glycemic control increases the risk of neuropathy and is amenable to intervention. Height and age directly increase risk of neuropathy and may help identify patients at risk. A proportion of neuropathy in diabetic veterans is probably due to or worsened by alcohol ingestion. Neuropathy was less common in current smokers than subjects not currently smoking.

Peripheral sensory neuropathy is a common complication of diabetes, as demonstrated in part by the observation that over one-third of Americans with diabetes, estimated at 16 million, acknowledged symptoms of peripheral neuropathy (1,2). Peripheral neuropathy complicates diabetes, yet the relationship between diabetes, per se, and other causes is not yet clear.

Treatments to reduce or control symptoms of peripheral sensory neuropathy, which tends to follow an inexorable course, frequently fail. Neuropathy increases the risk for other complications of diabetes including amputations (3) and foot ulcers (4). Thus, identification of risk factors for neuropathy might provide a means to identify patients at high risk for lower-limb complications, as well as lead to interventions or treatments.

Studies that have attempted to define risk factors for neuropathy are inevitably difficult to compare owing to a lack of standardized definitions. In a prospective study of 133 patients with NIDDM, where neuropathy was defined as the presence of pain or parathesias and poor nerve conduction velocity, those patients developing polyneuropathy had higher fasting blood glucose levels throughout the study, but were not older than those without polyneuropathy (5). Using information of self-reported symptoms of neuropathy (that is, numbness, painful sensations or tingling, or decreased ability to feel hot or cold) from the National Health Interview Survey, the authors found independent associations between these symptoms and longer duration of diabetes, hypertension, and hyperglycemia (2). In Colorado, a study of neuropathy prevalence defined by the presence of two of three criteria (symptoms, decreased Achilles reflexes, and decreased thermal sensation) showed that age, glycohemoglobin levels, insulin use, male sex, and duration of diabetes independently increased risk (6). The Diabetes Control and Complications Trial (DCCT), comprised exclusively of patients with IDDM, defined clinical neuropathy as the presence of two of three findings (neuropathic symptoms, sensory deficits, or impaired reflexes) in the absence of other known causes of neuropathy and showed an inverse association between intensity of treatment and risk of neuropathy (7). Height has been associated with slowed nerve conduction, decreased vibration sense, and abnormal biothesiometry (8). A large Belgian cohort study of 4,440 subjects with diabetes attempted to define risk factors for neuropathy, but the vague definition of neuropathy employed makes interpretation difficult (9).

This study sought to identify risk factors for diabetic peripheral sensory neuropathy in a cohort of U.S. veterans with diabetes using monofilament testing to detect neuropathy.

RESEARCH DESIGN AND METHODS

— The Seattle Diabetic Foot Study is an ongoing prospective investigation designed to identify risk factors for diabetic foot complications. Eligible subjects were U.S. veterans followed in an outpatient general medicine clinic. The clinic population numbered 4,211 of whom 1,042 (25%) had diabetes, defined as diagnosis by a physician or current treatment

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CAGE, cut down, annoyed by criticism, guilty about drinking, eye-opener drinks; DCCT, Diabetes Control and Complications Trial; OR, odds ratio.

with oral hypoglycemic agents or insulin. Excluded from the study were subjects who were deemed too ill to participate in research (40), who could not walk 50 feet (71), who were unable to consent (10), or who declined (143). We included in the study the remaining 778 subjects, of whom 775 underwent screening for neuropathy.

At baseline, we obtained information by interview, physical examination, and laboratory testing. Demographic information included age, sex, and race. The interview sought information on age at diagnosis of diabetes, type of diabetes, and treatment of diabetes. The interview also included the history of symptoms, signs, and previous self-reported physician diagnoses of diabetic and vascular complications. We obtained information related to smoking and to alcohol using the CAGE screening instrument (acronym for "cut down, annoyed by criticism, guilty about drinking, eye-opener drinks") designed to assess alcohol dependence (10). The physical examination concentrated on the lower extremities and included monofilament testing, segmental Doppler blood pressures (11), transcutaneous P_{O_2} (Radiometer, Copenhagen) (12), reflexes, pulses, foot deformities, calluses, edema, height, and weight. A nurse practitioner performed the examinations and a trained neurovascular technician performed the blood pressures and transcutaneous P_{O_2} determinations. Laboratory analyses of blood included measurements of glycohemoglobin, albumin, leukocytes, hematocrit, and creatinine. Diabetes type (IDDM vs. NIDDM) was based on an algorithm, taking into account treatment, age at onset of symptoms, family history, BMI, and history of ketoacidosis. Total follow-up was 1,860 person-years.

We defined two study outcomes: prevalent sensory neuropathy at baseline, and peripheral sensory neuropathy at the latest follow-up examination in those free of neuropathy at baseline. We defined peripheral sensory neuropathy as insensitivity to the 5.07-g monofilament at one or more of nine sites on either foot. The monofilament examination was performed using the interval comparison method (13) as follows: The examiner requested that the patient not watch the exam and then said, "I will touch this plastic wire to your foot. Tell me if you feel it when I say 'one' or 'two' or not at all." The examiner then counted aloud to two and touched the monofilament to the foot either while saying "one" or "two". Monofilament testing was performed by either of two trained examiners who were not blinded to the medical history of the patient. To measure reliability, a subset of 153 patients were examined by two examiners.

We used χ^2 test to compare proportions and Student's t test to compare the means of continuous variables (14). The κ statistic was used to assess interobserver variability. Unless otherwise noted, variables were measured at the time of study entry; current smoking, for example, indicates smoking current to the time of study entry. Variables chosen for univariate analysis were those previously identified in the literature, or deemed potential risk factors on the basis of pathophysiology, or potential confounders. Variables chosen for further multivariate modeling were significant at the $P = 0.10$ level in univariate analysis and were retained in the multivariate model if significant at the $P = 0.05$ level following backward elimination. Potential confounders were included in multivariate modeling when justified by biological plausibility. To assess for the presence of interaction, first-order interaction terms between all variables in the multivariate model were tested for significance at $P < 0.05$. Multivariate modeling was performed using logistic regression (15).

Table 1—*Demographic and clinical variables related to prevalent neuropathy*

Variables	Prevalent neuropathy	No neuropathy	*P* value
n	388	387	
Age (years)	64.7	61.7	<0.001
White race (%)	82.8	73.4	0.002
Male (%)	99.7	96.4	<0.001
Age at diagnosis (years)	51.7	51.4	0.785
Duration diabetes (years)	13.1	9.8	<0.001
Glycohemoglobin (%)	11.6	10.9	0.006
NIDDM (%)	94.3	92.4	0.292
IDDM (%)	54.0	40.9	<0.001
Height (cm)	179.7	176.7	<0.001
BMI (kg/m^2)	28.7	28.4	0.509
Systolic pressure (mmHg)	124	121	0.395
Diastolic pressure (mmHg)	70	68	0.443
Callus history (%)	48.1	37.3	0.003
Ulcer history (%)	41.6	25.3	<0.001
Lower-extremity edema history (%)	46.1	27.3	<0.001
Multivitamin use (%)	23.5	22.7	0.900
Ankle-arm index	0.94	1.00	0.004
Transcutaneous P_{O_2} (mmHg)*	53.5	55.4	0.060
Albumin (SU)	4.27	4.34	0.013
CAGE alcohol score (%)			
0	49.7	50.3	Reference
1	50.0	50.0	0.964
2	58.2	41.8	0.232
3	52.1	47.9	0.754
4	45.1	54.3	0.646
History of alcohol treatment (%)	17.9	19.1	0.657
Current alcohol use (%)	29	27	0.590
Smoked ever (%)	85.6	82.7	0.266
Current smoker (%)	19.3	25.3	0.043

Continuous data are mean values. Lower-extremity edema was for 1 year before study. *Transcutaneous P_{O_2} on dorsum of foot at 44°C.

RESULTS — Of the 778 subjects, 92% had NIDDM, the mean duration of diabetes was ~11 years, and 47% were treated with insulin at baseline. The mean age was 62 years. Subjects were mainly white (78%) and male (98%). Of 775 subjects for whom neuropathy testing was available, 388 (50%) had neuropathy at baseline. Of the 387 subjects without neuropathy at baseline, 288 (74%) had follow-up, and of these, 58 (20%) developed neuropathy. The average length of time from study enrollment to last neuropathy exam was

Table 2—*Mean duration of diabetes in years by presence or absence of neuropathy and age

Age at entry into study	Prevalent neuropathy	No neuropathy
<57.9 years	11.5	8.8
58.0–64.9 years	14.1	11.7
65.0–69.9 years	12.7	8.2
>70.0 years	13.6	10.6

*Quartiles based on age distribution in subjects without neuropathy at baseline.

2.6 years for those who did develop neuropathy, compared with 2.3 years for those who never developed neuropathy. With respect to interobserver agreement, the two examiners participating in the reliability study agreed 78% of the time as to the presence or absence of sensation among 153 tested; the κ statistic was 0.53. Of the initial 778 subjects, 188 (15%) died, 103 (13%) withdrew, 33 (4%) moved, and none were lost to follow-up.

Univariate analysis of factors related to prevalence of neuropathy is presented in Table 1. Compared with subjects without neuropathy at baseline, those with neuropathy were more likely to be older, taller, white, and male. They were also more likely to be treated with insulin, have had diabetes of longer duration, and have a higher glycohemoglobin levels at baseline. Subjects with neuropathy, compared with subjects without neuropathy, had lower albumin levels and ankle-arm indexes, and were more likely to have a history of lower-extremity edema, ulcer, or callus, but were less likely to be current smokers at study onset. Subjects with neuropathy were also more likely to have edema involving the foot or lower leg by exam ($P = 0.0009$). Table 2 shows that for every age stratum, the duration of diabetes in subjects with prevalent neuropathy exceeds that for subjects without neuropathy.

Multiple logistic regression modeling of prevalent neuropathy, controlling for sex and race, revealed independent and significant associations with age, duration of diabetes, glycohemoglobin level, and height, histories of lower-extremity ulceration, callus, or edema, and an independent and inverse correlation with ankle-arm index. (Table 3). As markers of renal function, albumin, plasma creatinine, and history of end-stage renal disease neither confounded the observed effect measures nor independently predicted prevalent neuropathy.

Patients who developed neuropathy during follow-up who were originally free of neuropathy at study onset, compared with those who remained free of neuropathy, were more likely to be taller, have higher baseline glycohemoglobin, have a history of lower-extremity edema or ulcer, have lower albumin levels, and were less likely to be current smokers (Table 4). These factors were in common with the analysis of prevalent versus nonprevalent subjects. Patients who developed new neuropathy also had lower glycohemoglobin values at follow-up ($P = 0.065$).

The multivariate model for incident neuropathy had a number of variables in common with the model for prevalent neuropathy. These were height, history of ulcer before study onset, age at entry into the study, and glycohemoglobin level at entry. Adjustment for time to development of neuropathy did not appreciably change the magnitude of these associations. Also, the CAGE alcohol score was independently predictive of risk. Albumin level (controlling for creatinine, which was significantly inversely correlated with albumin) was inversely associated with risk, as was current, but not former, smoking at study onset (Table 5). Because of the possibility that history of ulcer was a marker for subclinical neuropathy, a model was developed excluding the 98 subjects who had no evidence of neuropathy at baseline but had a history of ulcer in the previous year. Using the 208 subjects for whom follow-up data was available, three factors remained in the model: height (per 2.54 cm or 1 inch) (odds ratio [OR] 1.19; 95% CI 1.04–1.37), glycohemoglobin at baseline (OR 1.13; CI 1.00–1.29), and smoking at baseline (OR 0.23; CI 0.07–0.81).

CONCLUSIONS — Half of the diabetic subjects in this study had peripheral sensory neuropathy at baseline. For comparison, acknowledging that the course of diabetes may vary by population, Plummer and Albert (16), using similar methods (the inability to feel the 5.07 monofilament at any one of 10 sites on each foot), found a prevalence of 43% in patients with diabetes and a mean age of 70 years in a university clinic (16). In a population-based study from Australia, neuropathy (defined by bilateral diminution of pinprick perception in the feet) was present in 18.2% of 433 men with NIDDM (17). In the National Health Interview Survey, 38% of the population with diabetes had at least one symptom of neuropathy (2); in this study, 81% of subjects at baseline had either lower-extremity pain or numbness or tingling.

We identified numerous clinical and historical variables associated with an increased risk of diabetic peripheral sensory neuropathy. Significant and common to both multivariate analyses of prevalent and incident neuropathy were height, age at entry into the study, glycohemoglobin level, and history of lower-extremity ulceration. Of these, only

Table 3—*Risk factors for prevalent neuropathy in multivariate modeling using logistic regression

Variable	Beta	SE	*P* value	OR	95% CI
Age at entry into study (per year)	0.0469	0.0094	0.000	1.05	1.03–1.07
Duration of diabetes (per year)	0.0273	0.0093	0.003	1.03	1.01–1.05
Glycohemoglobin (per %)	0.0541	0.0250	0.031	1.06	1.01–1.11
Treatment with insulin at study entry	0.3504	0.1837	0.057	1.42	0.99–2.03
Height (per 2.54 cm)	0.1531	0.0306	0.000	1.17	1.10–1.24
History of lower-extremity edema	0.7324	0.1721	0.000	2.08	1.48–2.91
Ankle-arm index <0.8	0.3657	0.1705	0.032	1.44	1.03–2.01
History of foot callus	0.4268	0.1673	0.011	1.53	1.10–2.13
History of lower-extremity ulceration	0.5017	0.1764	0.004	1.65	1.17–2.33

*Controlling for race and sex.

Table 4—*Demographic and clinical variables related to incident neuropathy*

Variable	Incident neuropathy	No neuropathy during course of study	*P* value
n	58	230	
Age (years)	64.0	61.5	0.099
White race (%)	79.3	77.4	0.753
Male (%)	98.3	95.2	0.470
Age at diagnosis (years)	54.0	51.5	0.240
Duration diabetes (years)	10.3	9.5	0.568
Diabetes type			
NIDDM (%)	92.9	92.5	0.923
IDDM (%)	44.8	38.0	0.341
Glycohemoglobin at baseline (%)	11.9	10.6	0.005
Glycohemoglobin at follow-up (%)	8.8	8.3	0.065
Height (cm)	178.5	176.2	0.037
BMI (kg/m^2)	28.5	28.6	0.927
Systolic pressure (mmHg)	138	133	0.273
Callus history (%)	41.4	36.7	0.514
Ulcer history (%)	39.7	24.3	0.020
Lower-extremity edema history (%)	31.6	25.8	0.376
Diastolic pressure (mmHg)	78.9	75.1	0.194
Ankle-arm index	0.99	1.00	0.765
Transcutaneous Po_2 (mmHg)*	54.1	56.1	0.279
Multivitamin use (%)	42.9	18.2	0.034
Albumin (mg/dl)	4.2	4.4	0.008
History of alcohol treatment (%)	24.1	14.8	0.088
CAGE alcohol score (%)			
0	17.2	82.8	Reference
1	28.6	71.4	0.146
2	17.6	82.4	0.963
3	26.7	73.3	0.315
4	41.7	58.3	0.049
Current alcohol use (%)	35.1	22.7	0.054
Smoked ever (%)	75.9	84.3	0.127
Current smoker (%)	10.3	26.1	0.011

Continuous data are mean values. *Transcutaneous Po_2 on dorsum of foot at 44°C.

Table 5—*Risk factors for incident neuropathy in multivariate modeling using logistic regression***

Variable	Beta	SE	*P* value	OR	95% CI
Height (per 2.54 cm)	0.2136	0.0669	0.001	1.24	1.09–1.41
History of ulcer before study onset	0.7170	0.3531	0.042	2.05	1.03–4.09
Age at entry into study (per year)	0.0380	0.0177	0.027	1.04	1.00–1.08
Baseline glycohemoglobin (per %)	0.1386	0.0522	0.008	1.15	1.04–1.27
CAGE alcohol score					
0				1.00	Reference
1	0.4937	0.5115	0.335	1.64	0.60–4.45
2	0.17	0.7421	0.814	1.19	0.28–5.10
3	1.24	0.6989	0.076	3.46	0.88–13.60
4	1.94	0.7281	0.008	6.96	1.67–28.99
Current smoker	−1.52	0.5635	0.007	0.22	0.07–0.66
Albumin (per mg/dl)*	−1.1916	0.4583	0.009	0.31	0.12–0.75

*Controlling for serum creatinine.

the last two may be amenable to intervention, yet high glycohemoglobin levels may represent diabetes that is more severe or more difficult to control, and the association with previous ulcer may be a manifestation of neuropathy that was not detected by monofilament testing. Higher glycohemoglobin may reflect inadequate treatment since aggressive therapy in the DCCT markedly diminished the risk of polyneuropathy (7). In this study, subjects initially free of neuropathy at study entry, who later tested positive for neuropathy at last follow-up, had both higher mean glycohemoglobin at baseline and at follow-up, although only the baseline value achieved significance. Each percentage increase in baseline glycohemoglobin was associated with an ~15% increase in risk of neuropathy.

Duration of diabetes was a risk factor in this study as in other reports (2,18). Aging is frequently associated with neuropathy and is a potential confounder of the relationship between duration of diabetes and neuropathy (19). In general, for a duration of diabetes up to 10 years, the majority of patients did not have neuropathy; for durations between 10 and 15 years, ~0.5 of patients had neuropathy; and for durations ≥15 years, the majority of patients had neuropathy. Duration of diabetes as measured in this study does not reflect the true duration of the disease, but instead reflects the time since diagnosis, as NIDDM onset may precede its diagnosis by several years (20).

Ischemia, which has been suggested as a cause (21) and a result (22) of neuropathy, is independently associated with neuropathy in this study as measured by low (<0.8) ankle-arm index, a marker for arterial disease. Transcutaneous Po_2, which has been suggested as a marker for vascular perfusion in subjects with diabetic foot disease (23), was lower in those who had or developed neuropathy, but not to a statistically significant degree (Table 4). Edema, which independently predicted prevalent neuropathy (Table 3), may reflect additional vascular factors not accounted for in the measurement of ankle-arm index or transcutaneous Po_2, or may produce local changes that render the skin insensitive to monofilament testing.

History of foot callus in the year before the study was associated with prevalent neuropathy and may be a result of change in foot shape owing to muscle atrophy from motor neuropathy or, conversely, the presence of a callus may have led to a false-positive result of monofilament test-

ing. However, examiners in this study did not place the monofilament over a callus.

The finding of a protective effect of smoking at study entry for incident neuropathy seems implausible. One explanation for this association may be that current smoking is a marker for better, rather than worse, health on the assumption that very ill patients are more strongly encouraged to stop smoking than are less ill patients. Indeed, subjects with a history of myocardial infarction were less likely to be current smokers (19.1%) than were subjects without a history of myocardial infarction (23.1%). This was also true for those with histories of angina (20.6 vs. 23.1%). Possibly, patients with sensory neuropathy may have diminished mobility and access to cigarettes.

The explanation for the inverse association between albumin and incident neuropathy in the multivariate model is not accounted for wholly by renal disease (resulting in urinary protein loss) because neither creatinine, with which albumin is significantly inversely correlated, nor history of end-stage renal disease confound the association between albumin and risk of neuropathy. Low albumin may be a marker for poor nutrition with which neuropathy may be associated (24).

Height as a risk factor has been previously observed and has been interpreted to be a marker for neuronal length (25). Among Japanese-American men with diabetes, height was inversely correlated to peroneal sensory nerve action potential amplitudes (26). Height was not associated with neuropathy in a study of NIDDM in Japan (27). Height may act in concert with poor glycemic control, which is postulated to contribute to capillary basement membrane thickening (26) because height is associated with greater pressure in lower extremities, which has been shown to decrease capillary blood flow (28). Clinicians can easily measure or estimate height and therefore can identify patients at increased risk for neuropathy.

Our choice of the 5.07 monofilament to diagnose neuropathy is based on a number of factors. It has been recommended in the literature (29). Some epidemiologists feel more than one test should be used (30), while others recommend testing that incorporates 26 diagnostic categories (31), compared with the use of monofilament alone, which is clearly more efficient. Use of the 5.07 monofilament, which delivers a pressure of 10 g, has been shown in a prospective study to predict lower-extremity ulceration (OR 9.9) (32,33). This evidence, rather than any correlation of monofilament testing with other, possibly complicated, neurological measures, supports its use in this study. The κ value associated with interobserver agreement in this study is considered between fair and substantial (34). It is generally agreed that monofilament testing is easy to perform, takes relatively little time, and is inexpensive. The implication of false-positive findings from monofilament testing would appear to be low, since labeling a diabetic patient as having neuropathy is unlikely to place the patient at risk for deleterious treatments or social stigmatization. Nor do false-negative findings have serious implications, as no truly effective treatments exist. With respect to this study, false-positive results could have occurred, since of the 280 subjects who had neuropathy at baseline and who underwent follow-up examination, 55 (19.6%) tested negative. Yet, clinical improvement of neuropathy could account for these findings, as could false-negative findings at follow-up.

With respect to possible biases, alcohol, a known risk for peripheral neuropathy, may have caused some of the neuropathy identified in this study leading to misclassification of the outcome of diabetic neuropathy, particularly since CAGE score independently correlated with risk. A subject with incident neuropathy compared with a subject not developing neuropathy was more likely (21 vs. 14%) to have a CAGE score ≥ 2, a conventional cutoff for alcoholism (35). It is plausible that an individual with occult alcoholism could have more poorly controlled diabetes, yet multivariate analysis revealed an independent effect of CAGE score while adjusting for glycosylated hemoglobin. Analyses of an interaction term incorporating glycohemoglobin level and CAGE score did not contribute to the model, suggesting that poor glycemic control does not exert a stronger or weaker effect depending on the presence or absence of alcoholism, or if it does, then this study did not identify it. Similarly, some neuropathy related to malnutrition may have led to misclassification, since low albumin, which may reflect poor dietary intake of protein, was associated with higher risk. It is likely that the cause of neuropathy in patients with diabetes is multifactorial as suggested by the absence of neuropathy in some patients with long-standing diabetes (36).

Whereas the examiners in this study were not blinded, the resulting potential biases were likely to have been lessened both by the objectivity of monofilament testing, and because many of the risk factors we report have not been previously published, making a priori knowledge of an association unlikely. Insofar as we studied few women, nonwhites, or young patients, we do not know if our findings can be generalized to other populations.

In summary, this study confirms that many easily measured factors independently predict diabetic peripheral neuropathy and that height, age, glycohemoglobin level, and history of lower-extremity ulceration are independently associated with both prevalent and incident neuropathy. We have observed that these factors, in addition to current smoking, low albumin, and an elevated CAGE score, preceded the clinical development of neuropathy as defined by monofilament testing. This study also supports efforts aimed at improving glycemic control and reducing alcohol intake as potential means to reduce the incidence of sensory neuropathy in diabetic patients.

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