Risk Factors for Distal Symmetric Neuropathy in NIDDM

The San Luis Valley Diabetes Study

GARY M. FRANKLIN, MD, MPH
SUSAN M. SHETTERLY, MS
JEFFREY A. COHEN, MD
JUDITH BAXTER, MA
RICHARD F. HAMMAN, MD, DRPH

OBJECTIVE — To investigate risk factors for distal symmetric (sensory) neuropathy among prevalent cases of non-insulin-dependent diabetes mellitus (NIDDM) in a population-based study in southern Colorado.

RESEARCH DESIGN AND METHODS — Prevalent neuropathy was identified in 77 of 277 people with NIDDM by a standardized history and neurologic examination. Fifteen known or suspected risk factors for neuropathy were determined without knowledge of neuropathy status.

RESULTS — Older age at examination, longer duration of diabetes, higher glycohemoglobin percentage, lower fasting C-peptide, insulin use, and presence of retinopathy and nephropathy (microalbumin ≥200 μg/ml) were all significantly associated with neuropathy. Sex, ethnicity (Hispanic versus non-Hispanic white), height, systolic blood pressure, peripheral vascular disease, cigarette and alcohol use, and serum lipid levels were not significantly associated with neuropathy. In a multivariate logistic model, increasing age (odds ratio [OR] = 1.3, 95% confidence interval [CI] = 1.1–1.6), longer duration of diabetes (OR = 1.3, CI = 1.0–1.6), increased glycohemoglobin percentage (OR = 1.5, CI = 1.1–2.1), and insulin use (OR = 2.8, CI = 1.3–6.1) were associated with neuropathy. Retinopathy (OR = 3.0, CI = 1.2–7.7), but not nephropathy, was important when added to this model.

CONCLUSIONS — Worse glycemic control and insulin use were independently associated with neuropathy in people with NIDDM. Whether insulin use represents another marker for severity of the metabolic disturbance or is an independent risk factor for neuropathy requires further study. We could not confirm associations of neuropathy with height, with nephropathy, or with retinopathy, independent of duration of diabetes.

From the Departments of Environmental Health and Medicine (Neurology) (G.M.F.), University of Washington School of Public Health and Community Medicine, and School of Medicine, Seattle, Washington; the San Luis Valley Diabetes Study Department of Preventive Medicine and Biometrics (S.M.S., J.B., R.F.H.), University of Colorado School of Medicine; and the Department of Neurology (J.A.C.), Kaiser Permanente, Denver, Colorado.

Address correspondence and reprint requests to Gary M. Franklin, MD, MPH, University of Washington, Occupational Epidemiology and Health Outcomes Program, 1914 North 34 Street, Suite 101, Seattle, WA 98103.

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NIDDM, non-insulin-dependent diabetes mellitus; IDDM, insulin-dependent diabetes mellitus; SLVDS, San Luis Valley Diabetes Study; sBP, systolic blood pressure; HDL, high-density lipoprotein; OR, odds ratio; CI, confidence interval.

Risk factors for the development of distal symmetric (sensory) neuropathy in people with non-insulin-dependent diabetes mellitus (NIDDM) have not been well investigated in population-based studies. Worse glycemic control, longer duration of diabetes, and hypertension were significantly associated with sensory neuropathy symptoms among people with NIDDM reported from the 1989 National Health Interview Survey (1). Previous hospital- or clinic-based studies reported significant associations of poorer glycemic control (2), increased age (3), longer duration of diabetes (4), alcohol intake (5), and increased height (6) with neuropathy in NIDDM. In addition, hypertension (7), smoking (7,8), and lipid status (7) have been reported to be associated with neuropathy in insulin-dependent diabetes mellitus (IDDM). Age and duration of diabetes were independently associated with neuropathy in a large multicenter study of both IDDM and NIDDM in the U.K. (9).

We identified neuropathy by a standardized neurologic examination in 77 of 277 prevalent cases of NIDDM in two rural bi-ethnic counties in Colorado between 1984 and 1986 (10). Earlier analyses of risk factors for neuropathy revealed significant univariate associations for increased age, longer duration of diabetes, male gender, and poorer glycemic control (10). No significant association with neuropathy was found for ethnic status (Hispanic versus non-Hispanic white) or alcohol intake (ever/never). This study is an investigation of 15 known or suspected risk factors using multivariate models to determine if *1*) the association with neuropathy appears to be stronger for metabolic compared with vascular risk factors, 2) the presence of retinopathy or nephropathy, independent of diabetes duration, is associated with neuropathy, and 3) the previously reported association of height with neuropathy could be replicated.

RESEARCH DESIGN AND METHODS

Classification of distal symmetric (sensory) neuropathy

Methods related to sampling and case ascertainment in the prevalence portion of the San Luis Valley Diabetes Study (SLVDS) have been previously described (11). The SLVDS was designed as a geographically based prevalent case-control study, identifying all people with NIDDM in the Alamosa and Conejos counties of Colorado during 1984–1986. Previously diagnosed diabetic patients 20–74 years of age were identified through review of medical records in all health-care facilities, radio and newspaper advertisements, and local presentations inviting diabetic patients to contact the clinic. Eighty-two percent of eligible diabetic patients completed a 4-h clinic examination. Two hundred seventy-nine were confirmed as diabetic subjects by current use of insulin or oral hypoglycemic medications or by World Health Organization standards (12) using a 75-g oral glucose tolerance test. Two subjects had incomplete neurological exam data and were excluded from these analyses.

Of 277 people with NIDDM, 77 (27.7%) were classified with neuropathy when two of three criteria were present in both feet: *1*) pain, burning, or tingling, 2) decreased or absent ankle reflexes, and 3) decreased or absent response to an iced tuning fork in the dorsum of the feet (10). Ninety-six percent of patients with neuropathy were so classified on the basis of both a positive history of neuropathic pain and at least one of the neurologic examination criteria. The history of neuropathic symptoms (criterion 1) and findings on examination (criteria 2 and 3) were determined by independent examiners, both blinded to diabetes status. The classification of neuropathy using these criteria demonstrated 90% agreement with a standard neurologic examination and was validated by a psychophysical measurement (Optacon vibration instrument) (10).

Exposure variables

Age, sex, ethnicity, duration of diabetes, insulin use, cigarette use, prior alcohol use, height, and blood pressure were determined as part of a 4-h clinic interview and examination (11). Glycated hemoglobin (glycohemoglobin), a marker of glucose control over the previous 60–90 days, was measured by a commercial microcolumn method (13). Presence of preproliferative or proliferative retinopathy was measured by examination of fundus photographs (14), independent of neuropathy status, by the University of Wisconsin retinal photograph reading center. Presence of nephropathy was determined from urinary microalbumin determination by radioimmunoassay (15). Presence of peripheral vascular disease was determined by Doppler ultrasound using ankle/arm systolic blood pressure (sBP) ratios (16). Serum lipids (cholesterol, total high-density lipoprotein [HDL], triglycerides) were measured in the University of Colorado Clinical Research Center laboratory. Fasting C-peptide was measured by radioimmunoassay in the laboratory of Dr. A. Rubenstein at the University of Chicago (17).

Statistical analysis

Univariate differences in all exposure variables are described for those with and without neuropathy. Student's *t* test was used where appropriate as a test of significance for means, and the χ^2 test was used for categorical variables (18). Unconditional logistic regression was used (19) to explore associations with the exposure variables of interest, and full models that included all known or suspected variables were developed. A more parsimonious, stepped-down model was also developed to evaluate the stability of parameter estimates once nonsignificant variables (at $P > 0.05$) were excluded from the full model. Logistic regression model *P* values are based on likelihood ratio tests of the model with and without the variable of interest.

RESULTS — A univariate comparison of characteristics in people with diabetes with and without neuropathy are presented in Table 1. Older age at examination, longer duration of diabetes, increased glycohemoglobin, insulin use, presence of (preproliferative or proliferative) retinopathy or nephropathy (urinary microalbumin $\geq$200 μg/ml), and decreased fasting C-peptide were associated with neuropathy. Male sex, Hispanic ethnicity, sBP, height, presence of peripheral vascular disease, cigarette use (pack-years), prior alcohol use (g/week), and serum lipids (cholesterol, HDL, triglycerides) had no univariate association with neuropathy.

In a logistic regression model that simultaneously included 15 previously reported or suspected risk factors for neuropathy (Table 2), only older age (odds ration [OR] = 1.29 per 5-year increase; 95% confidence interval [CI] 1.08–1.55), longer duration of diabetes (OR = 1.29 per 5-year increase; 95% CI 1.02–1.62), higher glycohemoglobin (OR = 1.49 per 2.5% increase; 95% CI 1.07–2.08), and insulin use (OR = 2.78; 95% CI 1.26–6.12) remained independently associated with neuropathy.

Retinopathy (Table 3) was a significant factor when added to the regression model shown in Table 2 (OR = 3.04; 95% CI 1.20–7.71). Because duration became nonsignificant in this model and retinopathy is strongly duration-dependent (14), retinopathy is most likely only a comorbid condition. Nephropathy was nonsignificant when added to the full model.

A more parsimonious, stepped-down model (Table 4) was developed to analyze the effect of removing variables that were nonsignificant in the full logistic model and of removing retinopathy, which is likely comorbid. Male gender became significant when height was removed from the model. The high correlation between height and male gender (r = 0.72, $P < 0.0001$) probably accounts for the lack of significance of gender in the full model (Table 2). Analysis of height

Table 1—*Baseline characteristics in people with diabetes by neuropathy status, Alamosa and Conejos counties, Colorado, 1984–1986*

	Neuropathy status		
	Present	Absent	*P* value
n	77	200	
Age (years)	61.7	58.6	0.026
Sex (% male)	49.4	41.0	(0.21)
Diabetes duration (years)	13.4	8.3	<0.0001
Ethnicity (% Hispanic)	64.9	68.0	(0.63)
sBP (mean mmHg)	140.2	140.2	(0.99)
Height (cm)	163.2	161.7	(0.34)
Glycohemoglobin (%)	11.2	10.2	0.003
Insulin use (%)	73.0	42.4	<0.001
Peripheral vascular disease (%)	19.0	21.0	(0.78)
Retinopathy (% with preproliferative or proliferative)	36.0	13.0	<0.001
Nephropathy (% with microalbumin ≥200 μg/ml)	17.6	8.5	0.04
Cigarette use (%)			
Never	41.6	44.0	(0.91)
<20 pack-years	36.4	33.0	
≥20 pack-years	22.1	23.0	
Prior alcohol use (%)			
Never	59.1	57.7	(0.37)
<20 g/week	13.6	20.6	
>20 g/week	27.3	21.7	
Serum lipids (%)			
Cholesterol (mg)	222.1	225.5	(0.60)
Total HDL (mg)	43.4	44.2	(0.67)
Triglycerides (mg)	225.0	240.6	(0.39)
Fasting C-peptide (nmol/l)	0.78	0.88	<0.03

P values were determined using Student's *t* test or the χ^2 test. *P* values in parentheses are nonsignificant.

relationships within gender showed no evidence for an independent effect of height. Insulin use remained strongly and independently associated with neuropathy in this model, as did older age at examination and longer duration of diabetes. In this model, glycohemoglobin fell to borderline significance (OR = 1.33; 95% CI 0.98–1.80; *P* = 0.06).

CONCLUSIONS— This study extends the findings of our earlier preliminary analysis of risk factors related to diabetic neuropathy (10) and tests additional hypotheses related to other suspected risk factors for neuropathy. The principal findings are that increased age, increased duration of diabetes, poorer glucose control (increased glycohemoglobin), and insulin use are significantly associated with distal, symmetric (sensory) neuropathy in people with NIDDM. Male gender was also strongly associated with neuropathy when height was removed from the logistic regression model. Vascular risk factors (hypertension, smoking, lipid status, presence of peripheral vascular disease), comorbid complications (retinopathy, nephropathy), and height were not significantly associated with the presence of neuropathy.

Much current scientific and clinical investigation has focused on metabolic and biochemical factors as primary events in the development of distal, symmetric (sensory) neuropathy in diabetes. These data have led to an era of tighter glucose control and to pharmacological trials aimed at the putative biochemical causes of neuropathy (2,20). Moreover, restoration of the euglycemic state by pancreatic transplantation in IDDM patients was associated with objective improvement in nerve function only 12 months after transplantation (21).

The strong association of insulin use and glycosylated hemoglobin with neuropathy in the full logistic model (Table 2) lends epidemiological support to the importance of metabolic factors in the pathogenesis of distal, symmetric (sensory) neuropathy in subjects with NIDDM. Although the role of poor glycemic control in the pathogenesis of neuropathy has been extensively studied (2), few prior reports have suggested that insulin use per se may be associated with development of neuropathy in diabetes (22). Possible explanations for an association of insulin use with neuropathy may include: *1*) insulin use may be a surrogate marker for other endogenous metabolic factors associated with neuropathy, 2) insulin use per se, or associated hypoglycemia from insulin use, may be injurious to peripheral nerves, or 3) this association results from the cross-sectional design of this study.

Insulin use may be a surrogate marker for the severity of the metabolic derangement in NIDDM. Decreased production of endogenous insulin, as measured by plasma or urinary C-peptide, is one abnormality that has been associated with the presence of both neuropathy (23) and retinopathy (24). Significantly less C-peptide immunoreactivity was excreted in urine from diabetic patients with neuropathy compared with those without neuropathy (23). In the current study, fasting plasma C-peptide was also significantly reduced in those with neuropathy (Table 1), but neither C-peptide (Table 2) nor an interaction between C-peptide and insulin use were significant predictors of neuropathy in the full logistic model. Insulin use remained signifi-

Table 2—*Logistic regression model without retinopathy or nephropathy*

	OR	95% CI	*P* value	Δ for continuous variables
Age	1.29	1.08–1.55	0.004	5 years
Sex	1.70	0.55–5.21	(0.35)	
Diabetes duration	1.29	1.02–1.62	0.03	5 years
Ethnicity	1.07	0.44–2.60	(0.88)	—
sBP	0.94	0.88–1.01	(0.06)	5 mmHg
Height	1.02	0.97–1.07	(0.53)	1 cm
Glycohemoglobin	1.49	1.07–2.08	0.02	2.5%
Insulin use	2.78	1.26–6.12	0.01	—
Smoking				
≤20 pack-years	1.49	0.69–3.22	(0.29)	—
>20 pack-years	0.74	0.29–1.84	—	—
Prior alcohol use				
<20 g/week	0.71	0.29–1.72	(0.69)	—
≥20 g/week	1.03	0.40–2.62	—	—
Serum lipids				
Cholesterol	1.00	0.93–1.08	—	10 mg/dl
HDL	0.93	0.82–1.06	(0.95)	5 mg/dl
Triglycerides	0.99	0.96–1.02	(0.32)	10 mg/dl
Peripheral vascular disease	0.71	0.31–1.64	(0.43)	—
Fasting C-peptide	1.20	0.57–2.51	(0.63)	1 nmol/l %

n = 256. All variables are in the model simultaneously. Δ for continuous variables is the amount of change (Δ) in a continuous variable that gives the OR shown. *P* values in parentheses are nonsignificant.

cantly associated with neuropathy even after adjustment for recent glucose control. However, a valid marker of longer-term glucose control (e.g., hair protein glycation [25]) might more accurately reflect longer-term metabolic balance.

A direct toxic effect of exogenous insulin or attendant hypoglycemia, although unlikely, should be considered. Human insulinoma has long been known to be associated with a predominantly motor neuropathy, particularly following several episodes of hypoglycemia (26). Although this hypoglycemia-related neuronopathy appears to be quite different experimentally from the distal symmetric (sensory) axonopathy of diabetes (27), some nerve damage in diabetic patients under tight insulin control could result from even moderate levels of hypoglycemia (28). Although frank hypoglycemia is probably rare in NIDDM, recent cases of acute painful neuropathy have been reported in IDDM patients in whom strict glycemic control was undertaken (29, 30). Also, some researchers have postulated that in patients with severe insulin resistance, hyperinsulinemia resulting from overzealous attempts at strict control could theoretically lead to microvascular as well as macrovascular complications (31).

A final potential explanation for the strong association of insulin use with diabetic neuropathy is methodological. Our study is a cross-sectional study of prevalent cases of neuropathy. It is not known whether insulin was added after neuropathy onset or before. A prospective cohort study would be necessary to fully validate these findings. However, the nearly complete ascertainment of diabetic patients (90%) in the SLVDS (11) and the use of a validated case definition for distal symmetric neuropathy (10) are clear advantages of this study over many studies of diabetic neuropathy that have not been population-based.

Other factors found to be associated with neuropathy in NIDDM in this study include increased age (3), longer duration of diabetes (4), and poorer glycemic control (2), which have been well corroborated in the literature. Male gender, a recently reported risk factor for neuropathy in IDDM (32), was also associated with neuropathy in our study. Other previously reported risk factors for neuropathy in IDDM, including increased alcohol intake (5) and increased height (6), could not be corroborated here. In biological terms, one would expect alcohol to have a detrimental effect on peripheral nerves; however, the population of the San Luis Valley has a high proportion of nondrinkers (52%). With a decreased range in exposure to alcohol in our study population, a real effect of alcohol on neuropathy may have been difficult to detect. Our study and results from the Pittsburgh study (7) and the National Health Interview Survey (1) did not find an effect of height (or axonal length) on neuropathy. Sosenko et al. (6), in three separate studies, found a significant relationship between increased height and absent vibratory perception threshold, slower nerve conduction velocity (33), and symptomatic sensory neuropathy (34). Robinson et al. (35), however, could not confirm the relationship between height and nerve conduction velocity among Japanese-American men. Although retinopathy, but not nephropathy, was significant when added to the

Table 3—*Full logistic regression model with retinopathy*

	OR	95% CI	*P* value
Age	1.32	1.08–1.61	0.01
Diabetes duration	1.14	0.89–1.47	(0.34)
Glycohemoglobin	1.54	1.08–2.19	0.04
Insulin use	2.44	1.04–5.71	0.05
Retinopathy	3.04	1.20–7.71	0.04

n = 230. Nonsignificant variables included in the model but not shown: sex, ethnicity, BP, height, smoking, prior alcohol use, serum lipids, and peripheral vascular disease. Changes in units are the same as shown in Table 2. *P* values in parentheses are nonsignificant.

Table 4—*Parsimonious logistic regression model*

	OR	95% CI	*P* value
Age	1.19	1.02–1.39	0.03
Sex	2.24	1.22–4.12	0.01
Diabetes duration	1.28	1.04–1.56	0.02
Glycohemoglobin	1.33	0.98–1.80	(0.06)
Insulin use	2.67	1.37–5.21	0.004

n = 275. Changes in units are the same as shown in Table 2. *P* values in parentheses are nonsignificant.

full logistic model, both conditions appear to simply be comorbid with neuropathy and dependent on disease duration.

We were not able to confirm previously reported associations with neuropathy of hypertension (1,7), smoking (7,8), or lipid status (7). Other investigators reported that smoking was specifically not associated with neuropathy in NIDDM, and we could find no association between neuropathy and smoking even at >30 pack-years exposure. The lack of association between exposure variables related to vascular disease (hypertension, smoking, lipid status, and peripheral vascular disease) and neuropathy in this study does not necessarily weaken the argument that the pathogenesis of diabetic neuropathy is principally related to microvascular, rather than metabolic, factors (36,37). Some neuropathological studies suggest, however, that the microvascular changes in diabetic neuropathy may not be as specific as previously suggested (38). Experimental models that evaluate the interaction of metabolic and ischemic factors in diabetic neuropathy represent a reasonable approach to sorting out the relative importance of these factors (39). Results of the Diabetes Control and Complications Trial of tight control in IDDM were recently reported with a 60% reduction in risk of developing retinopathy, nephropathy, and neuropathy, as well as delayed onset and slowing of progression of these complications with intensive treatment (40). These promising results must be balanced by cost/benefit considerations (41) and the possibility that overuse of insulin in NIDDM patients may be associated with neuropathy or other adverse outcomes (31).

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