

Symptoms of Sensory Neuropathy in Adults with NIDDM in the U.S. Population

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OBJECTIVE— To ascertain the prevalence and determinants of sensory neuropathy symptoms through structured interview of a representative sample of people with diabetes in the U.S. population.

RESEARCH DESIGN AND METHODS— The 1989 National Health Interview Survey consisted of a representative sample of 84,572 persons in the U.S. ≥ 18 yr of age. A household respondent identified all people in the household believed to have diabetes ($n = 2829$). Subjects who could not be personally interviewed ($n = 129$) and individuals who stated they did not have diabetes ($n = 295$) were excluded. A detailed questionnaire was administered to 99.3% of the remaining 2405 subjects. Questions on symptoms of sensory neuropathy included whether during the past 3 mo the subjects had experienced numbness or loss of feeling, pain or tingling, or decreased ability to feel hot or cold. The neuropathy questions were also administered to a representative sample of 20,037 subjects who were not known to have diabetes.

RESULTS— Prevalence of symptoms of sensory neuropathy was 30.2% among people with IDDM. This prevalence was 36.0% for men with NIDDM and 39.8% for women with NIDDM, compared with 9.8 and 11.8% for nondiabetic men and women, respectively. In logistic regression, factors independently related to symptoms of sensory neuropathy in people with NIDDM included duration of diabetes, hypertension, hyperglycemia, and glycosuria. Long duration of NIDDM (≥ 20 yr) was associated with a twofold increased risk of symptoms of sensory neuropathy compared with those with 0–4 yr of diabetes. Hypertension was associated with a 60% higher likelihood of symptoms. Diabetic individuals whose blood glucose was high all or most of the time or whose urine tests showed glucose all of the time were >2 times as likely to have symptoms of sensory neuropathy than those who did not report hyperglycemia or glycosuria. Age, sex, ethnicity, cigarette smoking, and height were not determinants of sensory neuropathy.

CONCLUSIONS— Symptoms of sensory neuropathy affect 30–40% of diabetic patients in the U.S. Men and women are affected equally. Prevalence of these symptoms increases with longer duration of diabetes; hypertension and hyperglycemia predispose to symptoms of sensory neuropathy.

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IDDM, insulin-dependent diabetes mellitus; NIDDM, non-insulin-dependent diabetes mellitus; NHIS, National Health Interview Survey; BMI, body mass index; OR, odds ratio; CI, confidence interval.

Diabetic neuropathy is believed to be one of the most common complications of diabetes, but no studies have measured its frequency in representative samples of the U.S. population. In addition, it is unknown whether certain groups of diabetic patients are at particular risk for neuropathy, for example blacks or men. To explore these issues, we analyzed data from the 1989 NHIS. A detailed questionnaire on diabetes, including questions on symptoms of sensory neuropathy, was administered to a representative sample of people with diagnosed diabetes in the U.S. population ≥ 18 yr of age. The questions on sensory neuropathy were also administered to a representative sample of people who were not known to have diabetes.

RESEARCH DESIGN AND METHODS

The NHIS is a cross-sectional nationwide survey of a representative sample of the U.S. civilian, noninstitutionalized population (1). Conducted annually since 1957, the NHIS includes a basic questionnaire, which remains virtually unchanged from year to year, and a series of questions on special health topics, which vary annually. Trained interviewers from the U.S. Bureau of the Census conduct the personal household interviews and make repeated visits to the home when respondents are not immediately available. Quality assurance is ongoing via supervised observation of interviewers, reinterviewing a sample of the subjects, and statistical studies of data. The response rate has been 95–98% over the years.

In 1989, the total interviewed sample age ≥ 18 yr for the basic questionnaire was 84,572 people. A screening question was administered to a household respondent to identify all household members ≥ 18 yr of age who were known to have diabetes. Of the 2829 diabetic subjects identified, 4.6% were not interviewed and 10.4% stated they did not have diabetes or had only pre-, potential, borderline, or gestational dia-

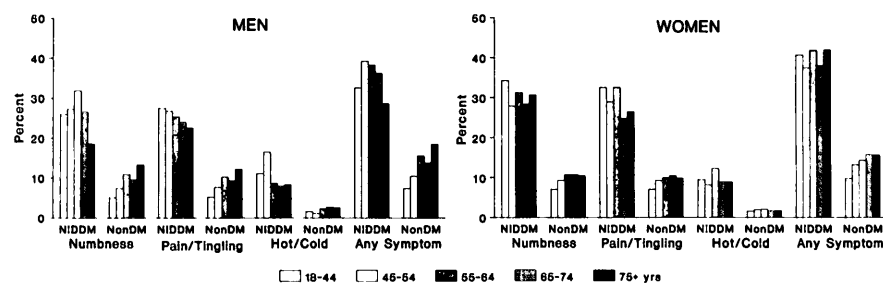


Figure 1—Prevalence of numbness or loss of feeling in hands or feet, painful sensation or tingling in hands or feet, decreased ability to feel hot or cold, and any of these symptoms of sensory neuropathy among men and women during the past 3 mo, according to age ≥ 18 yr in the U.S. population. The subjects included NIDDM diagnosed subjects and nondiabetic (NonDM) subjects with no medical history of diabetes.

betes (2). Of the remaining 2405 diabetic subjects, 99.3% completed a special questionnaire on diabetes with detailed questions about diagnosis of the disease, medical care received, comorbid conditions including symptoms of neuropathy, and personal health practices. A probability sample of subjects unidentified by the household respondent as having diabetes was selected to receive a separate questionnaire. Of 22,592 nondiabetic subjects, 89.1% completed the questionnaire. Questions related to sensory neuropathy were identical in both questionnaires and were phrased as "During the past three months have you had a) Numbness or loss of feeling in your hands or feet other than from your hands or feet falling asleep; b) A painful sensation or tingling in your hands or feet? Do not include normal foot aches from standing or walking for long periods; c) Decreased ability to feel hot or cold in things you touch?" These questions were analyzed individually, and if any question was answered positively the person was considered to have symptoms of sensory neuropathy.

Diabetic subjects were classified as having IDDM ($n = 124$, 5% of the diabetic population) if all of the following criteria were met: 1) BMI (weight [kg] divided by height squared [m^2], calculated from self-reported height and weight) < 27 kg/ m^2 for men and < 25

kg/ m^2 for women; 2) age at diagnosis of diabetes < 30 yr; and 3) continuous insulin use since diagnosis. Of the subjects, 13 could not be assigned to IDDM or NIDDM because of missing data on height, weight, age at diagnosis, or insulin use. The remaining 2268 subjects were considered to have NIDDM. To assess the extent of hyperglycemia and glycosuria, subjects were asked how frequently they were checked for blood and urine glucose by health professionals and by self-monitoring and, based on these tests, how often their blood and urine glucose levels had been too high.

Statistical analysis

All analyses were performed using SAS (SAS, Cary, NC) with appropriate sampling weights to provide estimates that were representative of the U.S. population. SE of means and proportions were estimated using the Taylor Series linearization method (3) and were calculated by the SESUDAAN computer program developed for complex sample surveys (4). Two-tailed, large sample z -tests were used to test for statistically significant differences in means and proportions. Logistic regression was used to estimate the association of independent variables with the presence of sensory neuropathy in NIDDM subjects. Small sample size precluded this analysis in IDDM subjects. The regressions were performed

using the RTILOGIT program for complex sample surveys (5).

Variables included in the regression were age, sex, race (non-Hispanic white, black, Mexican American), insulin treatment, duration of diabetes since diagnosis, medical history of hypertension, cigarette smoking, height, hyperglycemia, and glycosuria. All variables except age and height were entered as categorical variables and coded as 0,1. Age was entered as a continuous variable and was standardized by subtracting the mean and dividing the resultant quantity by the SD to control rounding errors, which could introduce imprecision in point and variance estimates (6). Both linear and squared terms for age were included to examine the possibility of a nonlinear association. Height (in feet) was entered as a continuous variable. In preparation for the regression analyses, correlation matrices of all independent variables were examined. When strong collinearity was present ($r \geq |0.60|$), variables were eliminated individually during model reduction. To arrive at a reduced model, variables were eliminated using a backwards stepwise procedure, while examining sequentially the statistical significance of coefficients ($P < 0.05$), changes in the overall model fit by comparing log likelihood statistics, and effects on OR estimates. To illustrate trends with duration of diabetes and frequency of hyperglycemia and glycosuria, nonsignificant terms representing lower levels of these variables were re-entered into the reduced model to obtain OR estimates across the entire spectrum of the variable. This had little or no effect on the coefficients and SEs of the significant independent variables of the final reduced model.

RESULTS— Among all individuals with diabetes, 28.2% reported numbness, 26.8% reported pain or tingling, and 9.8% reported decreased ability to feel hot or cold. Of these symptoms ≥ 1 was reported by 37.9%, including 35.6 and 39.6% of men and women, respec-

tively. Of IDDM subjects, 15.7% reported numbness, 22.8% reported pain or tingling, and 9.9% reported decreased ability to feel hot or cold; ≥ 1 of these symptoms was reported by 30.2%. The prevalence of symptoms of neuropathy for men and women with NIDDM and for nondiabetic subjects is shown in Fig. 1 according to age.

For NIDDM men, prevalence of numbness, decreased ability to feel hot or cold, and any symptom of neuropathy appeared to initially increase with age and then decline with older age. However, this was statistically significant only for the declines with age ($P < 0.05$). For the symptom of pain or tingling, prevalence decreased throughout the whole age range for NIDDM men. For nondiabetic men, prevalence of all three neuropathy symptoms increased consistently with age. Within each age-group, prevalence of neuropathy symptoms among NIDDM men was often 3–4 times the prevalence among nondiabetic men.

Little effect of age on prevalence of neuropathy symptoms was observed in NIDDM women, whereas prevalence increased with age among nondiabetic women. Similarly to men, prevalence of neuropathy symptoms was 3–4 times greater in NIDDM women compared with nondiabetic women. For all age-groups combined, prevalence of any neuropathy symptom was 36.0 and 39.8% for NIDDM men and women ($P = 0.10$), respectively, compared with 9.8 and 11.8% for nondiabetic men and women, respectively (Fig. 2). The difference in neuropathy prevalence between NIDDM and nondiabetic subjects was highly significant ($P < 0.001$).

Prevalence of any symptom of neuropathy increased with longer time since NIDDM diagnosis for both men and women (Fig. 3). Although a higher prevalence was detected among men diagnosed 0–1 yr previously compared with men diagnosed 2–4 yr previously, this was not statistically significant ($P = 0.13$). Prevalence was 29.0 and 31.1% for men and women, respectively,

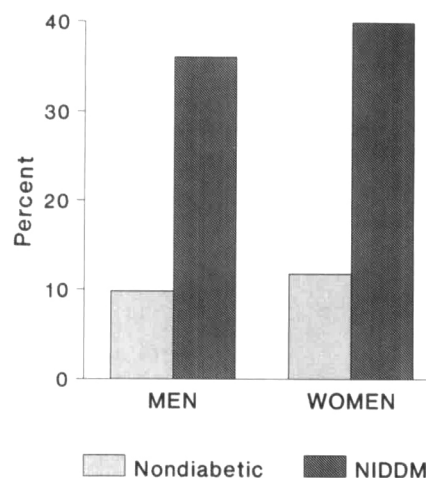


Figure 2—Prevalence of any symptom of sensory neuropathy among men and women, according to diabetes status in the U.S. population ≥ 18 yr of age. $P < 0.001$, NIDDM versus nondiabetic subjects; and $P = 0.10$, diabetic men versus diabetic women.

at 2–4 yr after diagnosis and increased to 45.7 and 53.2% for men and women, respectively, at ≥ 20 yr after diabetes diagnosis. The lowest prevalence for NIDDM subjects (29–31% at 2–4 yr after diagnosis) was substantially higher than the highest prevalence for nondiabetic subjects (Fig. 1, 16–19% at ≥ 75 yr of age).

The prevalence of any neuropathy symptom according to ethnicity and duration of NIDDM is shown in Fig. 4. Blacks and Mexican Americans had a higher frequency of neuropathy symp-

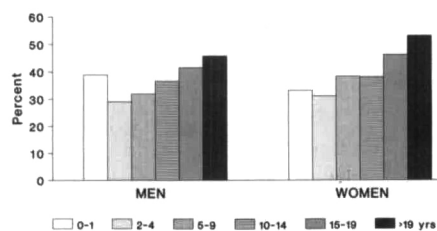


Figure 3—Prevalence of any sensory neuropathy symptom among men and women with NIDDM, according to year since diagnosis of diabetes in the U.S. population ≥ 18 yr of age.

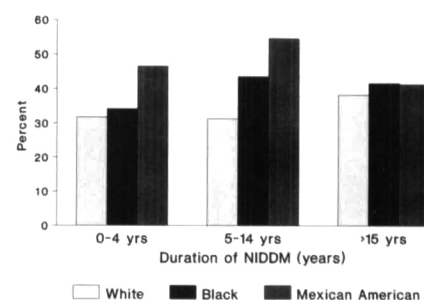


Figure 4—Prevalence of any symptom of sensory neuropathy among non-Hispanic whites, blacks, and Mexican Americans with NIDDM, according to diabetes duration in the U.S. population ≥ 18 yr of age.

toms at 0–14 yr after diabetes diagnosis compared with non-Hispanic whites, but these differences were not statistically significant ($P > 0.10$). The three ethnic groups had similar rates of neuropathy symptoms after 15 yr of diabetes.

The characteristics of NIDDM subjects are shown in Table 1 according to the presence or absence of symptoms of neuropathy. Those with neuropathy were of similar age, sex, ethnicity, and educational level compared with subjects without neuropathy but had lower family income. Individuals with neuropathy had a longer duration of diabetes and were more frequently treated with insulin. Subjects with neuropathy were $\sim 50\%$ more likely to report that their blood glucose was high always or most of the time, based on the results of blood glucose tests done by their physicians and by themselves. They also reported glycosuria more frequently. These subjects were more likely to have complications related to diabetes, including both microvascular disease (retinopathy, proteinuria, or kidney disease) and macrovascular disease (angina/heart disease, stroke, or hypertension). Subjects with neuropathy reported more frequently that they had sores that did not heal on their feet or ankles and periodontal disease. Cigarette smoking was not more common among subjects with neuropathy.

Table 1—Characteristics of NIDDM subjects with and without neuropathy

| Subject characteristics | Subjects with symptoms of neuropathy | Subjects with no symptoms of neuropathy |
|--|--------------------------------------|---|
| Demographic | | |
| Mean age (yr) | 61.8 | 61.7 |
| Male (%) | 39.2 | 43.1 |
| Non-hispanic white (%) | 67.0 | 71.4 |
| Black (%) | 22.3 | 18.7 |
| Mexican American (%) | 5.2 | 4.5 |
| More than high school education (%) | 20.5 | 21.5 |
| Family income >\$25,000 (%) | 27.4 | 37.2* |
| Clinical | | |
| Mean age at diabetes diagnosis (yr) | 49.7 | 51.9 |
| Mean diabetes duration since diagnosis (yr) | 12.0 | 9.6* |
| Treated with insulin (%) | 44.0 | 36.5* |
| Mean height (ft) | 5.5 | 5.5 |
| Obese (%)† | 63.2 | 59.1 |
| High blood glucose always/most of the time (%)‡ | 32.4 | 22.7* |
| Glucose in urine always/most of the time (%)‡ | 34.3 | 23.6* |
| Retinopathy (%) | 33.2 | 20.2* |
| Proteinuria (%) | 11.7 | 6.2* |
| Kidney disease (%) | 11.4 | 4.9* |
| Angina or heart trouble (%) | 42.1 | 27.4* |
| Stroke (%) | 15.4 | 6.1* |
| Hypertension (%) | 67.5 | 57.5* |
| Amputation (%) | 3.2 | 2.4 |
| Foot/ankle sores (%) | 15.2 | 5.1* |
| Periodontal disease (%) | 19.1 | 9.7* |
| Smoke cigarettes (%) | 20.0 | 19.5 |
| Medical care | | |
| ≥4 visits to diabetes physician in past yr (%) | 64.5 | 57.5 |
| Test their urine glucose ≥1 time/wk (%) | 26.6 | 23.7 |
| Test their blood glucose ≥1 time/day (%) | 14.3 | 12.8 |
| Urine glucose checked by health professional ≥2 times in past 6 mo (%) | 51.6 | 48.1 |
| Blood glucose checked by health professional ≥2 times in past 6 mo (%) | 69.9 | 67.2 |
| Feet checked by subject ≥1 time/wk (%) | 78.8 | 67.4* |
| Feet checked by health professional ≥2 times in past 6 mo (%) | 36.8 | 26.5* |
| Visited podiatrist in past yr (%) | 20.7 | 15.3* |
| Had dilated eye exam in past yr (%) | 50.2 | 46.8 |
| BP checked by health professional ≥2 times in past yr (%) | 89.1 | 87.9 |

*P < 0.001, subjects with neuropathy vs. subjects with no neuropathy.

†Percentage desirable weight ≥120.

‡Reported by subjects whose urine/blood glucose was tested either by a health professional or by themselves.

thy. Medical care was somewhat more intensive for subjects with neuropathy compared with those without neuropathy. In particular, those with neuropathy checked their own feet more frequently

and had a health professional check their feet for sores and irritations, and a higher proportion had seen a podiatrist in the past year.

Figures 5 and 6 illustrate the re-

sults of logistic regression to assess the independent effects of risk factors on the presence of sensory neuropathy symptoms in NIDDM individuals. NIDDM duration, hypertension, and high blood

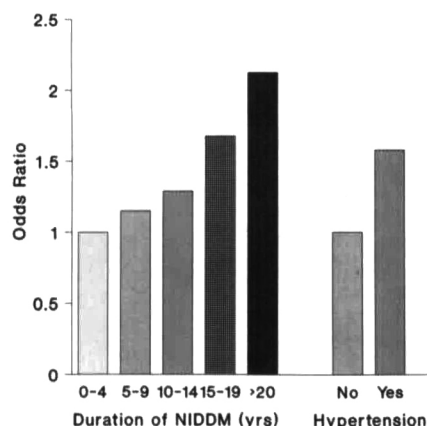


Figure 5—ORs for the effects of NIDDM duration and hypertension on the presence of symptoms of sensory neuropathy among NIDDM subjects.

glucose were statistically significant predictors ($P < 0.01$). In a separate model in which glycosuria replaced hyperglycemia, glycosuria was also a significant predictor ($P < 0.01$). The odds of having neuropathy increased with longer NIDDM duration and, for example, diabetic individuals with ≥ 20 yr of NIDDM had >2 times the likelihood of having neuropathy symptoms compared with those with 0–4 yr of duration (OR 2.13, 95% CI 1.60–2.84). The presence of a

medical history of physician-diagnosed hypertension was associated with a 60% higher likelihood of symptoms of sensory neuropathy (OR 1.58, [1.31–1.90]) compared with subjects without hypertension. Diabetic individuals who reported that the blood tests performed by themselves or by a health professional showed high glucose levels always or most of the time were 2.5 times more likely to have neuropathy compared with individuals who reported never having high blood glucose tests (OR 2.51, 95% CI 1.81–3.49). Those who had reported glycosuria in all of their urine glucose tests were >2 times as likely to have symptoms of neuropathy compared with diabetic individuals who reported never having glycosuria (OR 2.31, 95% CI 1.54–3.47).

No statistically significant effect of age ($P = 0.5$) or sex ($P = 0.3$) was observed after adjusting for NIDDM duration, hypertension, and high blood glucose. Blacks were at slightly higher risk of neuropathy compared with whites (OR 1.2), but this difference was of only borderline significance ($P = 0.09$). Mexican Americans had a similarly elevated risk compared with whites (OR 1.2), but this was not statistically significant ($P = 0.4$). Insulin treatment, cigarette

smoking, and height were not related to neuropathy after adjustment for the significant logistic regression variables ($P > 0.3$).

CONCLUSIONS—Neuropathy is believed to be one of the most common complications of diabetes, but few studies have been based on representative samples of diabetic people (7). The 1989 NHIS included a population-based probability sample of U.S. adults (1). Using NHIS data, we estimate that, in the U.S. population ≥ 18 yr of age, 37.9% of people with known diabetes have symptoms of sensory neuropathy; this includes 35.6 and 39.6% of men and women, respectively. Factors independently related to having symptoms of neuropathy in people with NIDDM included duration of diabetes, hypertension, hyperglycemia, and glycosuria. Age, sex, ethnicity, insulin treatment, cigarette smoking, and height were not determinants of neuropathy.

These results, based on self-reported sensory symptoms, must be interpreted cautiously with respect to the true prevalence of neuropathy in the diabetic population. Diabetic subjects compared with nondiabetic subjects are more likely to be informed about symptoms of neuropathy through interactions with health-care providers, and this could partly contribute to the higher prevalence of sensory neuropathy symptoms in diabetic subjects. It could also contribute to the increase in symptoms of neuropathy with longer diabetes duration (Fig. 3). The prevalence of neuropathy may also be overestimated because diabetic subjects reported symptoms caused by either transient nerve ischemia from compression or by musculoskeletal symptoms. NHIS participants were instructed to ignore symptoms of this nature, but the high prevalence of sensory symptoms in nondiabetics in our study (Fig. 1) is consistent with some over-reporting.

On the other hand, the true prevalence of neuropathy may be underesti-

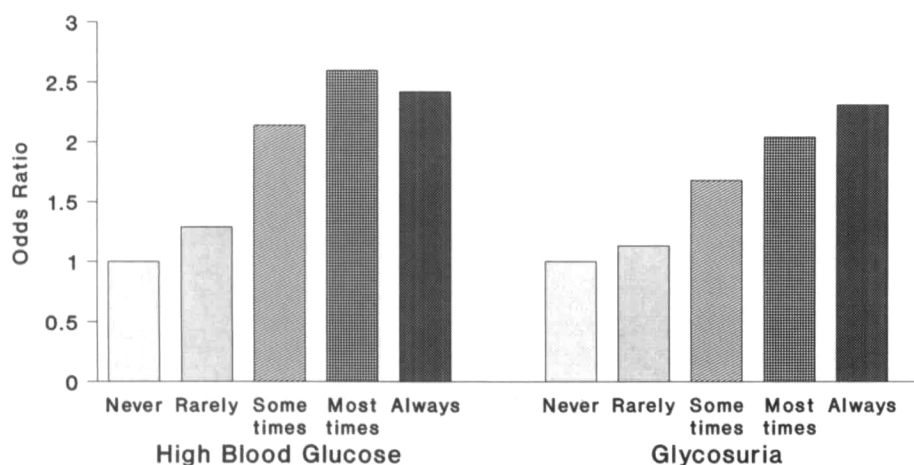


Figure 6—ORs for the effects of self-reported frequency of high blood glucose and glycosuria on the presence of sensory neuropathy symptoms among NIDDM subjects.

mated by our survey because subjects were questioned only about sensory symptoms and altered touch and temperature sense affecting the hands and feet. They were not questioned about symptoms of autonomic neuropathy or focal neuropathy. The prevalence of these neuropathies cannot be determined from this survey, but it is probably low (7). Distal, symmetric, sensorimotor polyneuropathy is the type of neuropathy potentially identified by our survey (7). However, patients with this neuropathy may be asymptomatic despite having decreased vibration sense or absent deep tendon reflexes; these are signs caused by large myelinated nerve fiber loss (7,8). The frequency with which patients with asymptomatic distal neuropathy note altered touch and temperature sensation is not known, but may be high. Thus, some neuropathy may not have been detected in the NHIS because subjects failed to note these changes, particularly changes of the feet, which are most commonly affected. Insensate patients are at particularly high risk for neuropathic ulcers, infections, and lower-extremity amputations. Thus, clinically significant neuropathy in insensate patients may have been underestimated in our study.

Very few population-based studies of distal sensory-motor neuropathy have been conducted, and none using the criteria used in this survey. Despite these limitations and lack of standard criteria for neuropathy, comparison of our results with other studies of neuropathy prevalence is of interest. The prevalence of neuropathy in several population-based surveys is ~30% (9), somewhat lower than the prevalence of sensory symptoms observed in our data. Prevalence of neuropathy is even lower in studies using more restrictive definitions (7,10,11). For example, in a study of newly diagnosed NIDDM patients, 80% had decreased vibration sense, whereas only 17% had neuropathy defined as symptoms plus 1 or 2 abnormal tests (12). Clinic-based studies show

prevalence of neuropathy ranging from 0–93% (7,10,13).

Diabetes duration, hypertension, and glycemic control measures were independent predictors of sensory symptoms in our study. In some respects these findings are similar to other studies. In a large clinic-based study, 8% of patients had neuropathy at the time of diagnosis; this increased to 50% after 25 yr of diabetes (10). In the San Luis Valley Study, a population-based study of Hispanics and Anglos, duration of diabetes predicted neuropathy (11). In contrast to our findings, however, age and male sex were also independent predictors. The different population in the San Luis Valley Study may explain this difference, although other studies have shown significant associations with age (14,15). We did not find any association between sensory symptoms and height, in contrast with two studies (16,17). These studies found no relationship between neuropathy and glycemic control, in contrast with our findings and those of others (11,18). In our survey, hypertension was an independent predictor of neuropathy, a finding that was reported for IDDM subjects 18–29 yr of age but not for all IDDM subjects ≥ 18 yr of age (19).

We found a sex difference in the relationship of diabetes duration to neuropathy. Sensory symptoms were present in 39% of diabetic men with diabetes duration of 0–1 yr, decreasing to 29% with diabetes duration of 2–4 yr (Fig. 3; $P = 0.13$). This pattern was observed for each of the three symptoms of neuropathy (data not shown). No increase was observed in women at 0–1 yr versus 2–4 yr of diabetes duration. A sex difference in reporting sensory symptoms is one possible explanation. Alternatively, it is possible that men experience small nerve fiber injury early in the course of diabetes, leading to the observed early increase in sensory symptoms. Male sex was a risk factor for neuropathy in IDDM patients enrolled in the Diabetes Control and

Complications Trial (15). This question needs further study.

We observed no significant effect of ethnicity on the prevalence of symptoms of neuropathy. This lack of ethnicity effect is different than for nephropathy and macrovascular disease, where striking ethnic and racial differences have been found (20–23). The absence of this effect in our survey is consistent with other studies. No effect of Hispanic heritage on neuropathy prevalence was seen in the San Luis Valley Study (11), nor was any effect of Indian heritage observed in the Fort Totten Study of neuropathy prevalence (24). The higher prevalence of neuropathy in blacks and Mexican Americans with shorter diabetes duration (0–14 yr), although not statistically significant, could reflect a longer duration of undiagnosed diabetes, a greater degree of hypertension, socioeconomic status, or more severe hyperglycemia caused by the natural history of the disease or intensity of the treatment. Further study is needed of this observation.

Distal polyneuropathy is known to predispose to ulceration, infection, and lower-extremity amputation. Of the nontraumatic amputations in this country >50% might be prevented by patient education, regular foot examinations, and early and aggressive treatment of ulcers and infection (25). Our data indicate that this important message is reaching diabetic patients, because those with sensory symptoms were more likely to have had a foot examination and to have seen a podiatrist in the preceding 12 mo (Table 1).

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