Short Reports

Cigarette Smoking and Neuropathy in Diabetic Patients

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We studied whether lifetime cigarette smoking is associated with the presence of diabetic neuropathy. The research design consisted of a case-control study conducted from a referral-based diabetes clinic at a major medical center. The patients were a 65% sample (163 insulin-dependent diabetes mellitus [IDDM] and 166 non-insulin-dependent diabetes mellitus [NIDDM] patients) of all patients admitted during a 26-mo period. Neuropathy was diagnosed on the basis of signs and symptoms. Smoking history was obtained by mailed questionnaire (66% response rate). Diabetes duration, HbA_1, age, sex, peripheral vascular disease, hypertension history, and lifetime alcohol consumption were measured as covariates. The prevalence of neuropathy was 49 and 38% in IDDM (n = 113) and NIDDM (n = 104) patients, respectively. In IDDM, but not NIDDM, current or ex-smokers were significantly more likely to have neuropathy than individuals who had never smoked (odds ratio 2.46, P = 0.02), and the prevalence of neuropathy increased with increasing number of pack-years smoked ($P < 0.001$). After adjustment for covariates, IDDM patients smoking ≥30 pack-yr were 3.32 times more likely to have neuropathy than patients smoking less than this amount (95% confidence interval 1.15–9.58, P = 0.026). Cigarette smoking was associated with the presence of neuropathy in this clinic-based population of IDDM patients. The hypothesis that cigarette smoking is associated with diabetic neuropathy should be investigated further, both prospectively and in a more representative population. *Diabetes Care* 13:434–37, 1990

Neuropathy is among the more common and often the most troublesome of the complications affecting individuals with diabetes. The risk factors for neuropathy, however, are largely unknown. Although the best evidence indicates that neuropathy is associated with both diabetes duration and level of hyperglycemia (1), these factors account for a relatively small portion of the observed variation in neuropathy prevalence. Clearly, other pathogenic factors must be operative.

The effect of personal health behaviors on susceptibility to neuropathy is not known. Two studies have examined the relationship between cigarette smoking and neuropathy in insulin-dependent diabetes mellitus (IDDM) subjects. In one study, which was clinic based, smoking was not statistically associated with neuropathy (2), whereas a second study, which was population based, found that adolescent smokers were more likely to report neuropathy symptoms than nonsmokers (3). Neither study, however, considered lifetime smoking habits. We therefore conducted a retrospective case-control study to examine the relationship between lifetime cigarette smoking and neuropathy. We hypothesized that diabetic individuals with neuropathy smoked more cigarettes during their lifetime than diabetic individuals without neuropathy.

RESEARCH DESIGN AND METHODS

Study subjects were selected from among all patients admitted to the inpatient diabetes clinic of the University of Michigan Medical Center between 1 July 1983 and 1 September 1985 (n = 538). The sample consisted of patients on whom a diabetes complications screening examination was performed at the time of admission (n = 351), representing 65.2% of all clinic admissions. Patients were classified according to type of diabetes by the clinic diabetologist on the basis of all available clinical information. IDDM was diagnosed by the clinic diabetologist in 163 of these patients, and non-insulin-dependent diabetes mellitus (NIDDM) was diagnosed in 166 patients. Twenty-two patients were excluded from analysis because the type of diabetes could not be determined (n = 16) or the diabetes was considered secondary to pancreatitis or alcohol abuse (n = 6).

Neuropathy was diagnosed by the clinic diabetologist if the patient reported at least one of the following symptoms: pain, tingling, burning, or loss of sensation; and, if on examination, at least one of the following abnormalities was present: impaired or absent tendon reflexes, decreased vibratory sensation, decreased sensitivity to pinprick, or impaired position sense. The diagnosis was not made if signs were present without symptoms or vice versa or if, in the diabetologist's judgment, either the symptoms or the signs could be attributable to other causes. In four patients (3 IDDM, 1 NIDDM) the diagnosis of neuropathy was questionable; these patients were therefore excluded from further analyses.

Patients' smoking habits were obtained by a mailed questionnaire, which was used previously to ascertain smoking habits in the Tecumseh Community Health Study (4). The response rates to this questionnaire for IDDM and NIDDM patients were 69.3% (113 of 163) and 63.2% (105 of 166), respectively. The percentage of questionnaire respondents and nonrespondents with neuropathy was nearly identical (42.3 vs. 39.0%, P = 0.63). Because of the few cigar and pipe smokers, only cigarette smoking was considered. Smokers were defined as individuals who reported smoking ≥100 cigarettes in their lifetime. All smokers were asked to indicate the age they started smoking, whether they currently smoked, and the average number of cigarettes smoked per day. Ex-smokers were asked to indicate the age at which they quit smoking. Patients were assured that their questionnaire responses would be kept confidential and would not be made a part of the medical record.

Duration of diabetes, hypertension history, and clinical assessment of peripheral vascular disease were determined at the clinic visit. Diabetes control was assessed by glycosylated hemoglobin (HbA_1) measured by ion-exchange chromatography with a normal range of 6.0–8.5%. A cumulative measure of lifetime alcohol consumption was estimated for each individual in a manner analogous to that of lifetime smoking habits. This measure is expressed as drink-years, in which 1 drink-yr equals one bottle of beer, one glass of wine, or one shot of hard liquor consumed each day for 1 yr.

The relationship between clinical neuropathy and smoking patterns was first evaluated with the χ^2-test (and test for trend). The multiple logistic regression model was then used to control for the effects of potential confounding variables (5).

TABLE 1
Selected clinical characteristics of study population according to presence or absence of neuropathy

	Insulin-dependent diabetes mellitus		Non-insulin-dependent diabetes mellitus	
	Neuropathy present	Neuropathy absent	Neuropathy present	Neuropathy absent
n	54	56	39	65
Age (yr)	36.1	32.7	59.4	57.7
Duration of diabetes (yr)	20.2	14.2*	13.3	11.4
HbA_1 (%)	10.7	9.7	9.8	9.5
Men (%)	42.6	37.5	35.9	32.3
Insulin therapy (%)	100	100	82.0	83.1
Peripheral vascular disease (%)	11.3	1.8	20.5	11.1
History of hypertension (%)	37.7	19.6†	65.8	69.2
Median drink-years	996	485	0	14
Smokers				
Ever smoked (%)	64.8	42.8†	48.7	60.6
Median pack-years	40	0*	0	14

*P < 0.001 (by one-way analysis of variance for duration of diabetes and by Mann-Whitney test for median pack-years).
†P < 0.05 (by χ^2-test).

TABLE 2
Insulin-dependent diabetic patients with neuropathy according to lifetime smoking level and duration of diabetes

Duration of diabetes (yr)	Tobacco exposure: ≥30 pack-yr *n*	≥30 pack-yr Percentage with neuropathy	<30 pack-yr *n*	<30 pack-yr Percentage with neuropathy
0–9	6	16.7	18	0.0
10–19	18	88.9	33	42.4
≥20	19	73.7	16	56.2
Total	43	72.1	67	34.3

Mantel-Haenszel odds ratio (95% confidence interval) = 5.18 (1.91–14.1).

RESULTS

Selected clinical characteristics of the study population are presented according to neuropathy status (Table 1). The prevalence of neuropathy was 49.1% in IDDM patients and 37.5% in NIDDM patients. In IDDM patients, the prevalence of neuropathy was associated with longer duration of diabetes ($P < 0.001$) and with a history of hypertension ($P < 0.05$) but not significantly with age, sex, level of HbA_1, or cumulative drink-years. None of these variables was associated with the presence of neuropathy in NIDDM patients.

In IDDM patients, current and ex-smokers were significantly more likely to have neuropathy than patients who had never smoked (64.8 vs. 42.8%, $P = 0.02$). Furthermore, neuropathy prevalence increased in stepwise fashion across five categories of cumulative pack-years of smoking (0 pack-yr and quartiles of pack-years; $P < 0.001$, χ^2-test for trend). There was no association of neuropathy with smoking measured on either the dichotomous or the ordinal scale in NIDDM patients.

The relationship between neuropathy and level of tobacco exposure was stratified by duration of diabetes. For these analyses, pack-years of smoking was dichotomized into two groups: 0–29 and ≥30 pack-yr. Patients smoking ≥30 pack-yr consistently had more neuropathy than patients smoking less than this amount, with an adjusted odds ratio of 5.18 (Table 2; Mantel-Haenszel $\chi^2 = 11.97$, $P = 0.001$).

The multiple logistic regression model was then used to examine the independent effects of smoking (≥30 vs. <30 pack-yr) while controlling for the effects of other factors. Variables selected for possible inclusion into the logistic model as covariates were age, sex, duration of diabetes, HbA_1, peripheral vascular disease, hypertension history, and cumulative lifetime alcohol consumption. A duration-squared term was entered into the model to allow for a nonlinear effect of duration. In the final model, duration ($P < 0.01$), duration squared ($P = 0.06$), and HbA_1 ($P = 0.06$) were retained in the model as covariates, and smoking remained highly significantly associated with the presence of neuropathy ($P = 0.026$; Table 3). The odds ratio corresponding to ≥30 pack-yr of smoking is 3.32 (1.15–9.58).

DISCUSSION

Among IDDM patients, a strong dose-response relationship was observed between lifetime cigarette smoking and the presence of neuropathy. Patients smoking ≥30 pack-yr in a lifetime were 3.32 times more likely to have neuropathy than patients smoking less than this amount. The actual smoking levels at which risk of neuropathy increases, however, cannot be discerned from this type of study design because the time of neuropathy onset is unknown. Many affected patients developed their neuropathy before 30 pack-yr of smoking, although how long before is unknown.

We used lifetime smoking history rather than current smoking status to assess tobacco exposure to minimize biases arising from the fact that patients may change their smoking habits over time. In fact, to the extent that patients may reduce their smoking after the onset of neuropathy, the use of lifetime smoking history will underestimate the true association between neuropathy and smoking. IDDM patients with neuropathy in this sample were, in fact, nearly twice as likely to be ex-smokers as IDDM patients without neuropathy (26 vs. 14%).

These findings must be considered preliminary because the patients included in this study are not repre-

TABLE 3
Coefficients for multiple logistic regression analysis of neuropathy versus pack-years of smoking in insulin-dependent diabetic patients

Variable	β (means ± SE)	*P*	Odds ratio	95% Confidence interval
Constant	−5.5564 ± 1.6497			
Smoker (≥30 pack-yr)	1.2015 ± 0.5397	0.026	3.32	1.15–9.58
Duration (yr)	0.2774 ± 0.1025	0.007		
Duration squared	−0.0040 ± 0.0021	0.063		
HbA_1*	0.1767 ± 0.0959	0.065	1.42	0.98–2.07

*Odds ratio corresponds to a 2-unit difference in HbA_1.

sentative of all IDDM individuals. This diabetes clinic is a major referral center for diabetes, and patients admitted to this unit tend to have more severe cases of diabetes. Moreover, only 65% of all clinic patients admitted during the study period were screened for neuropathy, and smoking information was obtained on only 69% of these patients.

In recent years, there has been renewed interest in the potential role of vascular factors in the pathogenesis of diabetic neuropathy (6,7). It may be speculated that cigarette smoking may contribute to tissue hypoxia and subsequent injury to the neural microvasculature. The association between smoking and neuropathy, however, was restricted to subjects with IDDM. This may be due to the much lower overall level of smoking in the NIDDM patients in this sample. Alternatively, the pathogenic features of neuropathy may differ between IDDM and NIDDM.

In summary, a strong association was observed between cigarette smoking and diabetic neuropathy among these IDDM clinic patients. The hypothesis that cigarette smoking is a risk factor for neuropathy should be investigated both prospectively and in a more representative population of diabetic individuals.

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Hyperphosphaturia and Hypermagnesuria in Children With IDDM

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Urinary excretion of calcium, inorganic phosphorus, magnesium, glucose, and creatinine was measured in first-void spot urine samples collected 4 days apart in 220 insulin-dependent diabetic (IDDM) children (mean age 11.9 yr) attending a summer camp. A single control urine sample was obtained from 33 healthy nondiabetic siblings (mean age 11.2 yr). Mean ± SD urinary calcium-creatinine ratios ($U_{Ca/Cr}$) did not significantly differ between IDDM and control subjects (0.14 ± 0.09 vs. 0.12 ± 0.09, respectively, $P = 0.156$). Mean urinary magnesium-creatinine ratios ($U_{Mg/Cr}$) were elevated in IDDM compared with control subjects (0.15 ± 0.06 vs. 0.08 ± 0.03, respectively, $P = 0.0001$). Similarly, mean urinary phosphorus-creatinine ratios ($U_{P/Cr}$) were significantly increased over those in control subjects (1.12 ± 0.33 vs. 0.40 ± 0.22, respectively, $P = 0.0001$). $U_{Ca/Cr}$, $U_{Mg/Cr}$, and $U_{P/Cr}$ were correlated with increasing mean urine glucose content ($P = 0.0001$). No correlations were found when $U_{Ca/Cr}$, $U_{Mg/Cr}$, or $U_{P/Cr}$ were compared with patient age, duration of diabetes, glycosylated hemoglobin, or insulin dosage. Urine losses of phosphorus and magnesium were present even when glycemic control was considered good by several methods (glycosylated hemoglobin, short-term glycemic index, or urinary glucose content). Glomerular hyperfiltration was unable to account for increased urinary mineral content. In conclusion, the data indicate that urinary excretion of phosphorus and magnesium is elevated in children with IDDM, regardless of glycemic control. In the presence of glucosuria, this loss is further enhanced. Urinary calcium excretion is significantly higher only during periods of glucosuria. The data suggest that children with IDDM could be at risk for mineral deficiencies in the absence of intensive insulin management. *Diabetes Care* 13:437–41, 1990