Hypertension as a Risk Factor for Diabetic Neuropathy

A Prospective Study

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The pathogeneses of diabetic neuropathy is still unclear. This study prospectively investigated the risk factors for distal symmetrical polyneuropathy (DSP) in a cohort of childhood-onset IDDM patients. Subjects from the Epidemiology of Diabetes Complications (EDC) Study were clinically examined at baseline and then biennially. DSP was diagnosed by a combination of clinical criteria, symptoms and signs (Diabetes Control and Complications Trial [DCCT] exam), and quantitative sensory threshold (QST). Among the 463 (70.4%) subjects who were free of DSP at baseline, 453 (97.8%) participated in at least one biennial reexamination during the first 6 years of follow-up and were included in the current analysis. A total of 68 (15.0%) subjects developed DSP in 6 years, giving a cumulative probability of 0.29. The Cox proportional hazards model shows that longer IDDM duration, hypertension, poor glycemic control, height, and smoking were all independent predictors of the incidence of DSP (all $P < 0.0001$, except for smoking for which $P = 0.03$). Hypertension showed the greatest impact on the development of DSP for individuals with either short or long IDDM duration. This study confirms some risk factors for DSP found in cross-sectional studies and suggests a strong relationship between hypertension and DSP. The results indicate that in addition to good glycemic control, avoidance of smoking and good blood pressure control may be helpful in preventing or delaying the onset of DSP in IDDM patients. *Diabetes* 46:665–670, 1997

The pathogenesis of distal symmetrical polyneuropathy (DSP) remains elusive despite extensive research (1). A close linkage with hyperglycemia, long suspected (2,2a), has recently been confirmed by the dramatic results of the Diabetes Control and Complications Trial (DCCT), showing a 60% lower incidence of clinically detected neuropathy (CDN) in the intensive therapy group (3). One biochemical mechanism for relating hyperglycemia with diabetic neuropathy is excessive sorbitol pathway activity leading to depletion of myoinositol and impaired neurological function (4). However, knowledge of other risk factors is limited, and clearly identifying additional risk factors would be helpful in preventing this common and disabling component of diabetes complications, which may afflict 70% of those with the disease for >30 years (5). Previous studies of DSP and its risk factors, which have been cross-sectional, have suggested possible additional associations with smoking (6–8), HDL cholesterol (6), height (9–11), and blood pressure (6,12). In this study, we aim to determine more definitely the role of these factors by examining their predictive power in incidence analyses. The quest for additional preventive strategies derived from knowledge of nonglycemic risk factors is especially important, for this may help prevent neuropathy in those with good glycemic control (12% of those in the intensive therapy group of the DCCT developed CDN over 5 years) and add to the general preventive potential of the DCCT in terms of glycemic control.

A particular concern in studying diabetic neuropathy is the multiple and diverse approaches to diagnoses. The different approaches include symptoms, clinical signs, quantitative sensory threshold (QST) testing, electrophysiological diagnosis, and autonomic function testing. The San Antonio Workshop developed a series of criteria for diagnosing and staging diabetic neuropathy, which recommended, in general, at least one test from each of the above categories be included in the diagnosis (13). This approach was later extended in a subsequent workshop (14). Such multifaceted criteria are not easily adaptable to epidemiological studies, and the recommendations postdated the start of the current study. Nonetheless, in the current study population, four of these five modalities are assessed (i.e., clinical symptoms and signs [DCCT clinical exam], QST [vibratory threshold], and autonomic neuropathy [expiration:inhalation ratio]). Because our focus in this analysis is with DSP, only the QST and clinical assessments are used, as described later.

RESEARCH DESIGN AND METHODS

Study population. This report is from the Epidemiology of Diabetes Complications (EDC) Study, which is based on a cohort of childhood-onset IDDM subjects diagnosed between 1950 and 1980. This cohort is being followed

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CDN, clinically detected neuropathy; DCCT, Diabetes Control and Complications Trial; DSP, distal symmetrical polyneuropathy; EDC, Epidemiology of Diabetes Complications; QST, quantitative sensory threshold; RR, relative risk.

with biennial examinations, and the data to be presented come from the first four cycles of exams, that is, baseline, 2-, 4-, and 6-year follow-up. The nature, derivation, and representativeness of the cohort have been previously described in detail (5,15). Briefly, 658 individuals were examined at baseline, with 555 (84.3%) attending at least one of the three reexaminations, and 95% have been followed up with questionnaires.

At cycle 1 (baseline), a clinical examination for neuropathy was performed according to the DCCT protocol (16). In addition, 168 individuals, aged 25–34 years, took part in a special neuropathy substudy that involved QST (both thermal and vibratory), three tests for autonomic neuropathy, and nerve conduction studies. On the basis of the results of this substudy, R-R variation (expiration:inspiration ratio) was added to cycle 2 for all subjects and vibratory threshold testing for all subjects at cycles 3 and 4. The DCCT clinical exam was maintained at all four cycles. Results presented in this report are based on the 6-year incidence of DSP (between cycles 1 and 4). Incidence of DSP is defined as "clinical" DSP (DCCT exam) at cycle 2 and "confirmed" DSP (clinical DSP plus abnormal age-specific vibratory threshold) at cycles 3 and 4. As reported previously, the sensitivity of abnormal vibratory threshold for DSP is virtually 100% in this population (17); therefore, the absence of vibratory thresholds at cycle 2 should have a minimal effect on this classification. This is confirmed by the observation that at cycles 3 and 4, only 12 subjects with clinical DSP had normal vibratory thresholds.

Clinical DSP. The clinical neurological evaluation, performed by a trained internist, was based on that used for the DCCT (16). A standard clinical history was taken regarding any concurrent disease processes that could cause neuropathy, exposure to known neurotoxins, and family history of neuromuscular disorders. Participants were questioned about sensory, motor, and autonomic symptoms. Positive responses were recorded; for example, numbness, dysesthesia and/or paresthesia, hypersensitivity to touch, burning, aching, or stabbing pain in the hands and/or feet. A standard neurological examination included evaluation of reflex activity and sensation to light touch (cotton wool), pain (pinprick), vibration (tuning fork), and proprioception. Muscle weakness, coordination, and gait were also assessed. DSP was defined as the presence of two or more of the following: symptoms, sensory and/or motor signs, and/or absent (or present only with reinforcement) tendon reflexes.

Confirmed DSP neuropathy. This measure was available at cycles 3 and 4 for all examined subjects and comprised the combination of DSP (as defined above) and the presence of a vibratory threshold above the age-specific normal range using the Vibatron II tester (Physitemp Instruments, Clifton, NJ). The criteria for an abnormal vibratory threshold are >2.39, >2.56, and >2.89 vibration units for ages ≤35, 36–50, and >50 years, respectively (18). Vibratory sensory thresholds were measured on the plantar aspect of the great toe on the dominant side of the body and gave an assessment of large sensory nerve fibers. A forced-choice procedure for the determination of vibratory threshold was used. Precision (repeatability) data previously have been reported in detail (17). The coefficient of variation for the great toe was 8%.

Potential risk factors. Blood pressure was measured with a random zero sphygmomanometer, according to the Hypertension Detection and Follow-up Program protocol, after a 5-min rest (19). Subjects were considered hypertensive if they were taking blood pressure medication and/or had systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg. Height was measured with the clinic stadiometer. Stable glycosylated hemoglobin (HbA_1) was initially measured in saline-incubated samples with microcolumn cation-exchange chromatography (Isolab, Akron, OH) and subsequently by automated high-performance liquid chromatography (Diamat, BioRad, Hercules, CA). Readings with the two methods are almost identical ($r = 0.95$; Diamat [HbA_1] = –0.18 + 1.00 Isolab [HbA_1]). HDL cholesterol was determined by a precipitation technique (heparin and manganese chloride) with a modification (20) of the Lipid Research Clinics method (21). Cholesterol and triglycerides were measured enzymatically (22,23). LDL cholesterol levels were calculated from measurements of the levels of total cholesterol, triglycerides, and HDL (24). Serum fibrinogen levels were determined via a biuret colormetric procedure and a clotting method. Urinary albumin was determined by immunonephelometry. Smoking history (ever or never smoked and number of packs per year) and alcohol status (drinker or nondrinker and number of drinks per week) were ascertained by questionnaire.

Other complications. Coronary artery disease was diagnosed based on history of myocardial infarction, confirmed by Q waves on electrocardiogram and/or hospital chart review that met standard criteria (25), and on angina, diagnosed by the clinic physician or by angiographic evidence of coronary artery disease >50% or more stenosis. Lower-extremity arterial disease was defined as ankle-to-brachial blood pressure ratio <0.9 in any one of the four distal arteries (left or right anterior tibial and dorsalis pedis arteries) or by amputation for vascular insufficiency. Medial-wall calcification was classified as ankle pressure >75 mmHg above arm pressure (26). Retinopathy was determined in stereoscopic color fundus photographs of three (one, two, and four) standardized fields. Photographs were evaluated and graded at the Wisconsin Reading Center, using the Wisconsin Epidemiologic Study of Diabetic Retinopathy Classification and Grading System, a modification of the Airlie House classification (27). Overt nephropathy was defined as albumin excretion rate >200 μg/min in at least two of three timed urine collections (24 h, overnight, postclinic) or as end-stage renal disease (kidney dialysis or transplant or serum creatinine >5.0 mg/dl). Microalbuminuria was defined as an albumin excretion rate of 20–200 μg/min in at least two of the three timed urine collections.

Statistical analyses. To examine the differences between neuropathic and nonneuropathic individuals, several univariate and multivariate analyses were performed. The χ^2 test was used for dichotomous variables, and Student's t test was used for continuous variables. Owing to a skewed distribution, triglycerides were log-transformed before analyses. Subjects with HbA_1 values above the median (≥10.0) were classified as having poor glycemic control, and subjects with HbA_1 values below the median (HbA_1 <10.0) as having fair glycemic control. In some analyses, the study population was divided into two groups based on the median value of IDDM duration, LDL, or height. In addition, Kaplan-Meier lifetables and Cox proportional hazards modeling were used to examine the prospective relationship of predictor variables to neuropathic outcome. All variables that were significant in univariate analyses were evaluated for their individual relative risk (RR) of developing DSP (adjusting for duration) and for their independent relationship with DSP in multivariate analyses. All statistical analyses were performed using SAS software (version 6.08) for VMS/VAX (SAS Institute, Cary, NC). The significance level was set at 0.05.

RESULTS

At baseline, 463 subjects were free of DSP. During the first 6 years of follow-up, 453 (97.8%) subjects returned for at least one biennial examination and were included in these analyses. The average length of follow-up was 5.3 years (or 2,418 person-years). Of the study subjects, 70% attended the 6-year clinical exam or were followed up to the development of DSP. A total of 68 (15.0%) subjects developed DSP by the end of the follow-up, giving an incidence rate of 2.8 per 100 person-years or a cumulative probability of 0.29. The baseline characteristics by DSP status at the end of 6-years of follow-up are shown in Table 1. Cases are individuals who developed DSP after baseline, while noncases are those who were still free of DSP at the end of the follow-up. Compared with noncases, cases were taller ($P < 0.01$) and older, and had a longer IDDM duration ($P < 0.0001$) and a later mean age of IDDM onset ($P < 0.01$). HbA_1 level, LDL, and blood pressure were also significantly higher in cases than in noncases ($P < 0.01$), while no differences were observed for other lipids or apolipoproteins. Cases were more likely to have hypertension, overt nephropathy (with or without microalbuminuria), or proliferative retinopathy and to have a smoking history (all $P < 0.003$). However, the prevalence of macrovascular disease (i.e., coronary heart disease, lower-extremity arterial disease, and medial-wall calcification) did not differ between cases and noncases. Although women and those who had a college education were more likely to develop neuropathy, the differences were not statistically different.

The cumulative probabilities and IDDM-duration–adjusted relative risk of developing DSP for several baseline risk factors are shown in Table 2. Subjects with values above median for duration, LDL, or HbA_1 or subjects with hypertension, overt nephropathy, microalbuminuria/overt nephropathy, proliferative retinopathy, or history of smoking all experienced increased risk for the development of DSP (all log-rank test P values <0.0038). After adjusting for duration, relative risks remained significant for HbA_1, LDL, smoking, and hypertension. The results were almost identical when adjustment was

Table 1
Baseline characteristics by DSP status at the end of follow-up

	68 cases	385 noncases	*P* value
Mean ± SD			
Age (years)	30.2 ± 6.7	24.2 ± 6.9	0.000
Age at IDDM onset (years)	9.4 ± 3.9	8.0 ± 4.1	0.01
Duration of IDDM (years)	20.9 ± 7.0	16.2 ± 6.4	0.000
Height (cm)	168.3 ± 9.8	165.0 ± 9.9	0.01
HbA_1 (%)	10.8 ± 2.0	10.2 ± 1.8	0.01
LDL (mmol/l)	3.13 ± 0.83	2.79 ± 0.80	0.002
HDL (mmol/l)	1.45 ± 0.33	1.42 ± 0.31	0.57
Triglycerides (mmol/l)	1.01 ± 0.02	0.92 ± 0.02	0.19
Fibrinogen (mg/dl)	297.1 ± 94.8	276.7 ± 85.8	0.08
$ApoA_1$ (mg/dl)	137.5 ± 22.1	137.7 ± 19.0	0.95
$ApoA_2$ (mg/dl)	46.1 ± 11.7	45.0 ± 9.3	0.39
ApoB (mg/dl)	102.8 ± 27.0	97.1 ± 28.5	0.13
SBP (mmHg)	116.6 ± 11.7	109.8 ± 11.7	0.003
DBP (mmHg)	75.7 ± 11.3	70.9 ± 9.7	0.001
Percentage			
Male	44.1	50.1	0.36
Smokers	45.6	26.1	0.001
Alcohol users	42.4	38.8	0.24
Hypertension	27.9	5.5	0.000
Overt nephropathy	27.9	13.5	0.003
Microalbuminuria/overt nephropathy	20.3	12.2	0.02
Proliferative retinopathy	33.8	15.4	0.000
Macrovascular disease	11.8	12.0	0.97
College education	69.6	57.9	0.07

Data are means ± SD or % from the Pittsburgh EDC Study.

made for age instead of duration (data not shown), reflecting the high correlation between age and duration in this cohort.

To examine the independent association between the risk factors and DSP, a multivariate Cox proportional hazards model was developed, using a stepwise mode with all significant risk factors in the Table 1 available for selection. Baseline IDDM duration, HbA_1, LDL, and height were entered into model as continuous variables. Table 3 presents the final model. IDDM duration, height, HbA_1 levels, smoking, and hypertension were all independent positive predictors of neuropathy in the first 6 years of follow-up. The independence of hypertension as a DSP predictor was further examined by excluding subjects with overt nephropathy. Hypertension remained an independent predictor along with HbA_1, duration, and height.

Hypertension at baseline showed an important impact on the risk of developing DSP. Figure 1 shows the estimated survival function by hypertension status derived from the Cox proportional hazards model. When the study population was stratified by the median IDDM duration at baseline (<16 years vs. ≥16 years), the impact of hypertension on the risk of developing DSP was similar in both short- and long-duration groups (data not shown). Although the interaction between hypertension and glycemic control was not significant, it was noted that the magnitude of the significant effect of hyperglycemia on the risk of developing DSP is somewhat greater in subjects with hypertension than in subjects without hypertension.

When blood pressure (particularly diastolic blood pressure) instead of hypertension was used in analysis, similar but weaker results were observed (data not shown). However, among hypertensive people, there was no gradient of increased risk of DSP with increased blood pressure. Also, the use of antihypertensive medication did not have a significant effect on the development of DSP.

DISCUSSION

The current study prospectively followed a cohort of childhood-onset IDDM patients without diabetic neuropathy at baseline. During the first 6 years of follow-up, 15% of the study population developed DSP, giving an incidence rate of 2.8 per 100 person-years and a cumulative probability of 0.29. The main finding of this prospective analysis is that hypertension, in addition to the established risk factors of IDDM duration, poor glycemic control (increased HbA_1 level), and recently reported associations with cigarette smoking and height, is a strong independent predictor of incident DSP. Indeed, in this cohort, it is the strongest predictor. The strength of this finding is particularly striking when one considers the considerable variability in both blood pressure measurement (19) and clinical assessment of neuropathy, as we have previously described (17). In this cohort, ~25% of those with DSP at one cycle will no longer be positive at the next.

The finding that duration and degree of glycemic control were important predictors for DSP is consistent with our previous results from a cross-sectional study of the prevalence of neuropathy at EDC baseline, in which longer duration and poor glycemic control were found to be associated with the presence of neuropathy in both the younger and older age-groups (6). Our recent 4-year incidence analysis also confirms this association (28). Similar findings have also been reported from other studies (2,12,29,30), though a Swedish study found that despite modern multiple insulin injection therapy, with reasonably good metabolic control, nerve dysfunction was still common in child and adolescent IDDM patients (11). Definitive evidence comes from the DCCT, which reported that intensive therapy reduced the appearance of clinical neuropathy (using the same clinical protocol used in the current study) at 5 years by 69% (3 vs. 10% in the conventional therapy group, $P = 0.006$) in the primary prevention cohort, and by 57% (7 vs. 16%, $P < 0.001$) in the secondary intervention cohort (3). There is little doubt about the relationship of glycemic control to diabetic polyneuropathy.

The current study also confirms the previous findings that increased height is associated with increased risk of diabetic neuropathy (9–11). The underlying reason for the association with height is unclear, but it is likely that longer neurons are at greater risk for metabolic and/or ischemic insults. Robinson et al. (31) found that although height predisposes to sensory nerve dysfunction, it does not predispose to motor fiber dysfunction in diabetic subjects. Thus, height as a risk factor for DSP may be limited to sensory axons, which were the predominant type examined in this study.

Smoking was correlated with prevalence of diabetic neuropathy in our previous cross-sectional analysis (6) and was found again as an independent risk factor for incident DSP in this prospective analysis. These findings confirm earlier studies that smoking increased the risk of neuropathy in IDDM patients (7,8). Interestingly, smoking was not found to be associated with diabetic neuropathy in DCCT (16) or with the

TABLE 2
Relative risks of developing DSP for risk factors at baseline

Risk factors	*n*	Cases	Cumulative probability	*P* value*	RR (95% CI)†
IDDM duration (years)‡					
<15.8	226	19	0.18		1
≥15.8	227	50	0.41	0.0001	2.86 (1.68–4.87)
Height (centimeters)‡					
<166	226	26	0.25		1
≥166	227	42	0.33	0.0919	1.63 (0.99–2.65)
LDL (mg/dl)‡					
<107.6	204	23	0.21		1
≥107.6	204	42	0.42	0.0036	1.88 (1.12–3.17)
HbA_1 (%)‡					
<10.0	212	23	0.24		1
≥10.0	241	45	0.35	0.0038	2.6 (1.6–4.3)
Ever smokers					
No	306	37	0.20		1
Yes	126	31	0.61	0.0023	1.74 (1.07–2.83)
Hypertension					
No	413	49	0.26		1
Yes	40	19	0.58	0.0001	3.92 (2.23–6.91)
Overt nephropathy					
No	382	49	0.19		1
Yes	71	19	0.33	0.0031	1.67 (0.97–2.87)
Microalbuminuria/overt nephropathy					
No	295	32	0.18		1
Yes	158	36	0.34	0.008	1.52 (0.94–2.48)
Proliferative retinopathy					
No	364	45	0.18		1
Yes	81	23	0.37	0.0003	1.39 (0.78–2.46)

Data are from the Pittsburgh Epidemiology of Diabetes Complications Study. *Derived from log-rank test of equality over strata. †RR adjusted for duration. ‡Categories determined by median value.

studies of risk factors for neuropathy in NIDDM patients (12,29). Whether smoking contributes to DSP via an ischemic mechanism is unclear. Another potential mechanism would be the effect of smoking on advanced glycation end product (AGE) formation (32).

Hypertension has been shown to relate to the development of nephropathy and retinopathy in IDDM patients, but a relationship to diabetic neuropathy has not been widely reported. Although hypertension was found to be associated with symptoms of sensory neuropathy in people with NIDDM (12), we have been unable to find another similar report in IDDM. The current study found that the hypertensive individual has a significantly increased risk of developing DSP in 6 years of follow-up, which confirmed our previous finding that hypertension was associated with the prevalence of neuropathy in young IDDM patients (aged 18–29 years) (6). Although hypertension was more common in the subjects with long IDDM duration, our study found that the impact of hypertension on the risk of developing DSP was independent of duration and other complications, including microalbuminuria and overt nephropathy. Indeed, our analyses would suggest that hypertension is the strongest risk factor we have identified to date. This study also observed that the effect of hyperglycemia on the development of DSP was somewhat increased in IDDM patients with hypertension than those without hypertension.

The underlying mechanism by which hypertension may lead to DSP is obscure. However, the concept that it poten-

TABLE 3
Final Cox proportional hazards model for DSP

Independent variables	Coefficient	RR (95% CI)	*P* value
IDDM duration (1 SD increase)	0.09	1.82 (1.41–2.33)	0.0001
Height (1 SD increase)	0.05	2.04 (1.57–2.66)	0.0001
HbA_1 (1 SD increase)	0.37	1.64 (1.27–2.11)	0.0001
Smoking (yes vs. no)	0.55	1.73 (1.06–2.82)	0.03
Hypertension (yes vs. no)	1.41	4.10 (2.33–7.24)	0.0001

Data are from the Pittsburgh Epidemiology of Diabetes Complications Study. 1 SD of IDDM duration = 6.7 (years); 1 SD of height = 9.2 (cm); 1 SD of HbA_1 = 1.9 (%).

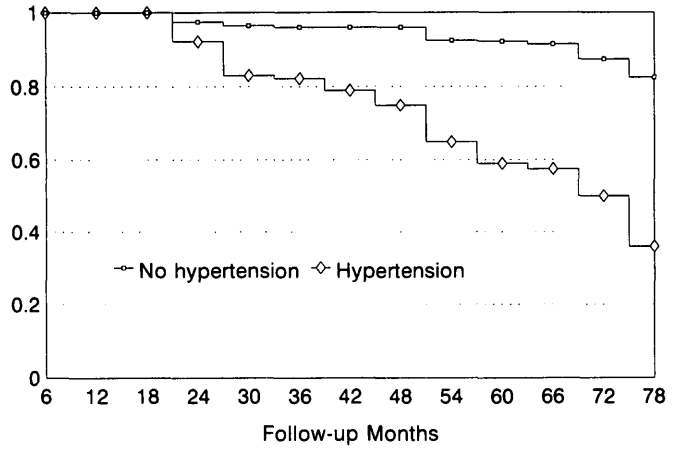

FIG. 1. Lifetable: survival function estimates by hypertension status derived from Cox proportional hazards model.

tiates the effect of glycemia (suggested by the interrelationship between hypertension and glycemic control) suggests that a shared abnormality may underlie the association. Reduced Na^+-K^+-ATPase activity may be a likely candidate for such a link. Hypertensive individuals, who may have decreased Na^+-K^+-ATPase (33,34), may thus be at particular risk for neuropathy because low Na^+-K^+-ATPase activity may further exacerbate the derangement of the polyolpathway commonly seen in hyperglycemia (35), leading to decreased intracellular myoinositol and disturbed neurological function. Interestingly, another recent paper also suggests that erythrocyte Na^+-K^+-ATPase activity was significantly lower in diabetic patients with neuropathy, an effect that was independent of glycemic control (4). Na^+-K^+-ATPase was also positively correlated with nerve conduction velocity. An alternative explanation might relate to a direct blood pressure load or hemodynamic stress effect. That an association of hypertension and diabetic neuropathy is likely to be real gains further credence from a report of improved nerve function after 12 weeks of treatment with an ACE inhibitor (36), although it is not clear whether the benefit seen reflects vasodilation alone or reduced pressure effects. If improved perfusion was the mechanism responsible for the benefit, this would support a third explanation, i.e., that hypertension is acting purely as an ischemic risk factor. It has also recently been shown that among traditional cardiovascular disease risk factors, hypertension is the strongest predictor of coronary heart disease in this population (37). Another possibility is that hypertension predicts DSP not because of a direct pathogenetic mechanism, but rather as a matter for the etiology of hypertension itself. In IDDM, the major etiological factor underlying the higher prevalence of hypertension is renal disease. As reported, we reanalyzed the data, excluding subjects with nephropathy, and found that hypertension was still predictive. This therefore suggests that it was not acting as a marker for renal disease and further confirms its true independence.

Macrovascular disease, including coronary artery disease and lower-extremity arterial disease, did not differ between those who subsequently developed DSP and those who did not. A lack of any true association cannot be ruled out, however, because of the relatively young age of the study cohort (30 and 24 year olds, cases and noncases, respectively) and relatively low incidence of events. This age difference may also explain some of the inconsistency between studies of NIDDM and IDDM; for example, in the San Luis Valley study of NIDDM, cigarette smoking and blood pressure were not risk factors for DSP (38).

In summary, this prospective study confirms well-known associations between duration and glycemic control with DSP and provides further evidence that smoking may be a risk factor. It also raises the strong possibility that hypertension may have a major pathogenetic role. Thus, if these findings are confirmed, smoking cessation and blood pressure control should be added to intensive glycemic therapy as potential preventive strategies for this sometimes devastating complication.

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