Factors in Development of Diabetic Neuropathy

Baseline Analysis of Neuropathy in Feasibility Phase of Diabetes Control and Complications Trial (DCCT)

THE DCCT RESEARCH GROUP

The Diabetes Control and Complications Trial (DCCT) is a multicenter randomized clinical trial studying the effect of intensive insulin therapy on the early vascular and neurological complications of insulin-dependent diabetes mellitus (IDDM). During the feasibility phase of the DCCT, baseline neurological histories, physical examinations, and laboratory measurements of somatic and autonomic nerve function were obtained in 278 well-characterized IDDM subjects. Subjects were free of advanced complications, including the presence of peripheral or autonomic neuropathy sufficiently severe to require treatment. Analyses of the cross-sectional data reveal that clinically detectable peripheral neuropathy was present in 39% of the subjects. The presence of clinical neuropathy correlated with greater age, longer duration of IDDM, and male gender. The somatic and autonomic test results confirm the relationship between age, diabetes duration, and male gender and diabetic neuropathy. These results support an effect of age and gender on the development of diabetic complications. *Diabetes* 37:476–81, 1988

The metabolic consequences of diabetes mellitus are thought to interact with as yet poorly defined environmental or genetic variables to cause the chronic complications of diabetes. Although some of the sequelae of diabetes are most aptly explored in animal models or in vitro, only clinical studies can define the factors that may influence the development, expression, and course of the chronic complications in diabetic patients. The Diabetes Control and Complications Trial (DCCT) is an NIH-sponsored multicenter randomized clinical trial comparing the effects of an intensive insulin treatment regimen, designed to achieve glucose levels as close to normal as possible while minimizing hypoglycemia, with standard diabetes treatment on the chronic complications of insulin-dependent diabetes mellitus (IDDM) (1). A feasibility phase, which studied 278 volunteers over a 1-yr period, preceded the ongoing full-scale clinical trial (2). The 278 patients underwent a comprehensive neurological examination as well as nerve conduction and autonomic nervous system testing at baseline. Analysis of the baseline results in this predominantly asymptomatic population has provided the opportunity to define more clearly the extent of neurological dysfunction early in the course of IDDM, determine how clinical signs and symptoms compare with electrophysiological measures, and examine the association of clinical and demographic factors with the prevalence of early neuropathic changes.

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MATERIALS AND METHODS

Patient population. Two hundred seventy-eight IDDM subjects who met the eligibility requirements and enrolled in the feasibility phase of the DCCT underwent complete neurological assessment. For inclusion in the DCCT, C-peptide–deficient (3) diabetic patients had to be 13–39 yr of age with duration of diabetes between 1 and 15 yr. A detailed description of the eligibility criteria and randomization has been published (1). In general, subjects had to be healthy except for the presence of diabetes. Subjects with renal impairment, hypertension, history of heavy alcohol consumption within the past 5 yr, or regular use of analgesics were excluded. Presence of diabetic somatic or autonomic neuropathy severe enough to require treatment in the view of either the patient or the physician was also grounds for exclusion. Subjects with minor clinical signs or symptoms of neuropathy (e.g., minor postural hypotension, paresthesias, occasional mild leg cramps or pain, or absent deep tendon reflexes) were not excluded from the trial.

Clinical neurological assessment. A complete neurological history and physical examination were performed on each subject by a DCCT neurologist at the 21 clinical centers. The DCCT neurologists established uniform criteria for the

TABLE 1
Criteria for diagnosis of neuropathy

	No. affected	Percent of total affected
Signs, symptoms, and reflexes	9	8
Signs and symptoms	2	2
Signs and reflexes	20	18
Symptoms and reflexes	0	0
Signs	40	37
Symptoms	7	6
Reflexes	31	28

diagnosis of diabetic somatic neuropathy before the clinical assessments. The criteria consisted of signs, symptoms (including dysesthesias, paresthesias, hypersensitivity to touch, or burning pain consistent with a distal symmetrical peripheral neuropathy), or decreased or absent deep tendon reflexes. These diagnoses were based, therefore, on the presence of neurologic deficits and the extent to which their anatomic distribution was consistent with a distal symmetrical neuropathy. For the purposes of this baseline analysis, subjects were classified as affected with clinical neuropathy if any one of the three criteria was met, based on the history and physical examination performed by the DCCT neurologist.

Nerve conduction studies. After the clinical neurological examination, nerve conduction studies were performed according to rigid standards specified in the DCCT manual of operations (4). Testing was performed 1–2 h after a regular meal, and outpatients were allowed at least 30 min for temperature equilibration before study. Temperature was recorded with a surface thermistor at specified times and locations during the study. Surface recording and stimulating electrodes were placed at specified locations for median motor conduction velocity from elbow to wrist, orthodromic median sensory conduction from digit II to wrist, median F-wave latency stimulating at the wrist, peroneal motor conduction velocity from knee to ankle, peroneal F-wave latency stimulating at the ankle, and antidromic sural sensory conduction stimulating 14 cm proximal to a recording electrode at the lateral malleolus. Averaging was used for sensory conduction studies.

Autonomic function testing. Autonomic nervous system (ANS) testing included three elements: postural blood pressure testing, beat-to-beat heart rate variation during deep breathing (R-R variation) (5), and heart rate variation during a standardized Valsalva maneuver (Valsalva ratio). ANS studies were performed on all subjects in a quiet setting after an overnight fast and only on days free of hypoglycemia. Studies were not performed if autonomic stimulants or depressants had been taken in the preceding 24 h. Each of the 21 clinics also performed the ANS studies on two or three nondiabetic subjects to generate nondiabetic values for comparison. Subjects were connected to an electrocardiographic recording device and maintained in the supine resting position for 30 min while taught to synchronize their breathing rate with a microprocessor-driven 5-s sine wave displayed on an oscilloscope. The sine wave and electrocardiogram were recorded on multichannel magnetic tape that was analyzed at the central reading unit. Beat-to-beat R-R variation was computed with circular mean vector analysis on 6 min of deep rhythmic breathing (6). This technique yields a unitless number between 0.0 and 1.0 that is multiplied by 1000. Supine blood pressure was recorded by a standardized technique with a conventional sphygmomanometer before and after the 6-min deep-breathing period. The subject then assumed an upright posture, and blood pressure was measured after 1, 2, 3, 4, 5, and 10 min. After the postural study, the subjects were returned to the supine position for 15 min before performing the Valsalva study with a calibrated manometer to ensure that a pressure of 40 mmHg was maintained for two separate 20-s intervals. The Valsalva ratio was the ratio of the longest R-R interval during the post-Valsalva reflex bradycardia to the shortest R-R interval during the Valsalva maneuver.

Statistical analysis. The two-sample *t* test was used to compare two groups with respect to a continuous variable (e.g., age). For comparing two groups on a dichotomous variable (e.g., gender), the continuity-adjusted χ^2-test for contingency tables was used (7). Logistic multiple regression (8) was used to develop a prediction model for clinical neuropathy with baseline characteristics, including peripheral nerve function and autonomic neuropathy tests. The R^2 was adjusted for the number of predictor variables in each model. Results are expressed as means ± SD unless stated otherwise.

RESULTS

Clinical assessment. Despite the exclusion of patients with severe symptomatic peripheral neuropathy during the eligibility screening, 109 (39%) of the 278 subjects had symptoms, signs, and/or abnormal reflexes of peripheral somatic neuropathy, and were thus considered affected with clinical neuropathy (Table 1). Most subjects were affected by clinical neuropathy on the basis of signs (37%), abnormal reflexes (28%), or signs and reflexes (18%), with relatively few subjects with symptoms alone (6%) or in combination with other findings (10%).

Patient characteristics associated with presence of neuropathy. Table 2 presents the differences between IDDM subjects affected and unaffected with neuropathy for vari-

TABLE 2
Characteristics of IDDM subjects unaffected and affected with neuropathy

	Unaffected	Affected
n	169	109
Age (yr)	23 ± 8	26 ± 8*
Gender (% male)	42	58*
IDDM duration (yr)	6 ± 4	8 ± 4*
Cigarette smoking (%)	17	22
Diabetes diagnosed after onset of puberty (%)	47	22
Height (cm)	168 ± 10	171 ± 10*
Body weight (% ideal)	101 ± 14	102 ± 13
Diastolic blood pressure (mmHg)	69 ± 10	68 ± 10
Presence of retinopathy (%)	57	72*
HbA_{1c}	9.0 ± 2	9.0 ± 2
Stimulated C-peptide (pmol/ml)	0.09 ± 0.11	0.06 ± 0.09*
Albumin excretion (mg/24 h)	21 ± 21	25 ± 38

Where range is indicated, values are means ± SD.
*$P < .05$ vs. unaffected subjects.

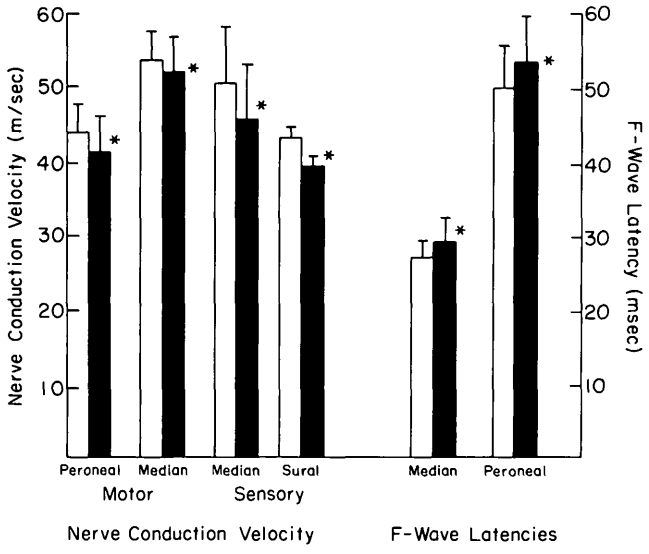

FIG. 1. Nerve conduction velocities and F-wave latencies (mean + SD) in subjects affected (*solid bars*) and unaffected (*open bars*) with clinical neuropathy. Adjusted differences in group means are differences in least-squares means for unaffected and affected subjects from analysis of covariance model (9). *$P < .05$ vs. unaffected subjects.

ables putatively associated with the development of neuropathy. Subjects with clinical neuropathy were older and more likely to be men than unaffected subjects. In addition, affected subjects were taller, had a longer duration of diabetes, higher prevalence of retinopathy, and lower stimulated C-peptide levels. We examined the putative association of pubertal status at the time of diagnosis of diabetes with the development of clinical neuropathy by calculating the percentage of subjects affected with clinical neuropathy depending on their duration of IDDM (≤5 yr vs. >5 yr) and their pubertal status at the time of diagnosis. Although subjects who developed diabetes before puberty tended to be affected less frequently with neuropathy (23% for duration ≤5 yr vs. 42% for duration >5 yr) than subjects who developed diabetes after puberty (35% for duration ≤5 yr vs. 54% for duration >5 yr), the odds ratios (1.85 and 1.60, respectively) did not reach significance.

Autonomic nerve functions. The 47 nondiabetic people who were assessed with the ANS protocol were similar in gender distribution, height, and weight, but were slightly older (31 ± 5 vs. 24 ± 8 yr) than the DCCT subjects. The R-R variation was significantly reduced in the IDDM subjects compared with the controls (45 ± 23 vs. 55 ± 24, $P < .05$), but the two groups were not significantly different with respect to Valsalva ratio (1.97 ± 0.42 vs. 2.04 ± 0.41). A comparison of IDDM subjects affected with peripheral somatic neuropathy with unaffected IDDM subjects revealed no significant difference in R-R variation (0.042 ± 0.022 vs. 0.046 ± 0.023). However, the Valsalva ratio was significantly reduced in the group affected with clinical neuropathy (1.91 ± 0.42 vs. 2.02 ± 0.41, $P < .05$).

Peripheral nerve function. In subjects affected with clinical peripheral neuropathy, motor and sensory nerve conduction velocities were significantly reduced and F-wave latencies were significantly prolonged (both measurements abnormal and indicative of peripheral somatic neuropathy) compared with unaffected subjects (Fig. 1). The differences between affected and unaffected subjects remained statistically significant, even after adjusting for the covariates in Table 2. Note that even in clinically unaffected diabetic subjects, mean median and peroneal motor and median sensory conduction velocities were less than the published reference values for normal populations. (10).

Intercorrelations among nerve tests. All four nerve conduction velocities (data not shown) were positively intercorrelated ($P < .05$) and were significantly negatively correlated with the F-wave latencies (decreased velocity and increased latency are abnormal). The absolute values of these correlation coefficients were .21–.64. The correlation between the R-R variation and the orthostatic blood pressure change was −.13 ($P < .05$) (smaller R-R variation and larger orthostatic change indicate autonomic neuropathy). No other significant correlations among the ANS tests were found. Although we observed several statistically significant correlations between nerve conduction velocities and autonomic testing results, the absolute values of these correlation coefficients were relatively low (.12–.21).

Association of neurophysiological tests with subject characteristics. Table 3 presents the correlations among peripheral and autonomic nerve tests and selected subject characteristics. Slower median and peroneal motor nerve conduction velocities were associated with greater age, higher HbA_{1c}, greater height, and lower stimulated C-peptide. Longer median and peroneal F-wave latencies (indicating slower conduction) confirmed these associations. In addition, longer latencies and slower peroneal motor nerve conduction velocities were associated with male gender. Slow nerve conduction velocities and longer F-wave latencies of several nerves were associated with longer duration of diabetes. Smaller R-R variation (indicating autonomic dysfunction) was associated with increased age, presence of retinopathy, greater body weight, and higher diastolic blood pressure. Smaller Valsalva ratio (indicating autonomic neuropathy) was associated with higher HbA_{1c}, lower C-peptide, greater height, and higher diastolic blood pressure. The partial correlations between the covariate and neurophysiological tests, adjusting for other covariates, were essentially the same as the simple correlations, with only a few exceptions.

In general, therefore, nerve conduction impairment and autonomic neuropathy were more evident in subjects who were older, taller, heavier, and had a higher supine diastolic blood pressure. Men had greater impairment than women. Subjects diagnosed after the onset of puberty were more impaired than subjects diagnosed earlier. Increased duration of diabetes and increased HbA_{1c} were also associated with electrophysiological impairment. These conclusions held consistently for nearly all the data, and even though statistically significant relationships were not found for all of the variables considered, the direction of the effects was in agreement.

Association of clinical neuropathy with subject characteristics and neurophysiological tests. Three logistic regression models were developed for the association of

TABLE 3
Simple and partial correlations between nerve function and subject characteristics

	Motor nerve conduction velocity		Sensory nerve conduction velocity		F-wave latency		Autonomic nervous system tests	
	Median	Peroneal	Median	Sural	Median	Peroneal	R-R variation	Valsalva maneuver
Age								
Simple	−.18*	−.15*	−.14*	−.07	.33*	.27*	−.17*	.06
Partial	−.08	−.03	−.14*	−.03	.12*	.06	−.19*	.05
Female gender								
Simple	.06	.21*	.11	.22*	−.41*	−.39*	.08	.27
Partial	.01	.02	.12*	.04	−.13*	.00	.02	.23*
Diabetes duration								
Simple	−.07	−.15*	−.16*	−.09	.13*	.09	−.06	−.04
Partial	−.03	−.09	−.01	−.02	.09	.03	.02	−.01
HbA_{1c}								
Simple	−.22*	−.25*	.05	−.03	.12*	.15*	−.07	−.16*
Partial	−.26*	−.31*	.00	−.05	.25*	.25*	−.10	−.15*
C-peptide								
Simple	.15*	.15*	.10	.08	−.08	−.08	.03	.16*
Partial	.12*	.07	.03	.04	−.04	−.04	.02	.14*
Presence of retinopathy								
Simple	−.10	−.21*	−.15*	−.11	.17*	.23*	−.05	−.07
Partial	−.01	−.02	−.07	−.02	.01	.07	.03	.02
Height								
Simple	−.13*	−.36*	−.06	−.28*	.54*	.64*	−.14*	−.13*
Partial	−.07	−.26*	.06	−.18*	.30*	.45*	.05	.01
Orthostatic blood pressure change								
Simple	−.09	−.11	−.06	−.15*	.15*	.12	−.23*	−.13*
Partial	−.03	.01	−.02	−.09	.00	.00	−.15*	−.05
Diagnosed after onset of puberty								
Simple	−.14*	−.09	−.03	−.01	.25*	.21*	−.03	.05
Partial	−.01	.01	.09	.05	−.01	−.03	.16*	.01

F-wave latencies were not corrected for differences in length of traversed neural pathway and therefore normally correlate with height. Partial correlation coefficients are from analysis of covariance model; simple correlation coefficients between 2 binary variables are point-biseral correlations (11).
*$P < .05$.

subject characteristics and neurophysiological tests (peripheral and autonomic) with the classification of neuropathy by clinical judgment in the 212 subjects for whom all data were available. Of the 212 subjects, 36% were judged to be affected with neuropathy. The first model included only subject characteristics as predictors of clinical neuropathy, and provided an adjusted R^2 of 3.5% ($P = .001$) with the presence or absence of neuropathy. The second model assessed the added association of the peripheral nerve tests above and beyond the association of the subject characteristics with neuropathy. In this model, adjusted R^2 increased to 6.7% ($P = .001$), a significant increase compared with the first model ($P < .005$). The third model assessed the added association of the autonomic tests above and beyond that of subject characteristics and peripheral nerve tests. In this model, the adjusted R^2 was 6.1% ($P = .001$), which represented a small decrease compared with the second model. A small R^2 for any of these models means that the factors included in the analyses only explain a small part of the variance between subjects with regard to clinical somatic neuropathy.

DISCUSSION

Microvascular complications of diabetes such as retinopathy and nephropathy appear to reflect a complex interplay between consequences of insulin deficiency and/or hyperglycemia and independent environmental, genetic, or developmental factors. Retrospective and prospective analyses have implicated gender, smoking, and hypertension in the cause or acceleration of diabetic microangiopathy (12–15). The pubescent or postpubescent state may be an important conditioning factor in the development of diabetic retinopathy (16). Moreover, the correlation between muscle capillary basement membrane thickening and the duration and degree of hyperglycemia is strongly influenced by puberty in IDDM (17). These observations have been interpreted to suggest that sex hormones or growth factors might modulate the adverse long-term effects of hyperglycemia on vascular disease (16).

Previous studies of the development of overt diabetic neuropathy have implicated only duration, degree of hyperglycemia, height (18–20), and possibly alcohol consumption (21) as risk factors. Neuropathy is apparently not related to HLA haplotype or acetylator status but is correlated with severity of hyperglycemia in age- and duration-matched neuropathic and nonneuropathic diabetic subjects (22). In this study, patients with severe, and presumably less reversible, peripheral nerve disease were excluded to enhance compliance with diabetes treatment protocols and to facilitate the demonstration of a treatment effect on neu-

ropathy in the prospective study. The 18 symptomatic DCCT subjects reflect carefully elicited histories rather than readily volunteered symptoms. The neurologists' experience in defining subtle asymptomatic sensory and motor deficits permitted the detection of early clinical somatic diabetic neuropathy in these generally asymptomatic DCCT subjects. The accuracy of their diagnoses was supported by the generalized slowing of nerve conduction in the 109 affected but predominantly asymptomatic subjects compared with those unaffected with clinical neuropathy. Many of the unaffected diabetic subjects had abnormal nerve conduction velocities compared with nondiabetic subjects.

DCCT subjects affected with peripheral neuropathy were older, taller, more likely to be male, more C-peptide deficient, more likely to have retinopathy, and had diabetes for longer duration than unaffected subjects. The relationship between clinical neuropathy and gender, duration of diabetes, and age is further supported by similar relationships noted with the neurophysiological results and the multivariate analysis. The association between age, gender, clinical peripheral neuropathy, and abnormal somatic and autonomic nerve function tests in this study persisted despite the removal of effects related to duration of diabetes, retinopathy status, height, and smoking history. It is unclear whether the relationship between age and clinical neuropathy primarily represents relative resistance to the development of neuropathy before puberty, as has been described for retinopathy (17), or a more continuous age-related acceleration of neuropathy, as has been suggested for uremic neuropathy (23). The persistence of age, but not pubertal status at diagnosis, as a risk factor in the partial correlations and multivariate analyses suggests that age itself is the more significant factor.

Only median motor nerve conduction velocity, sensory nerve conduction velocity, and F-wave latency showed age or gender effects in DCCT patients after removal of the effects of HbA_{1c} and height. In some (24) but not all (19) previous studies, diabetic males tended to have slower nerve conduction velocities than diabetic females. More striking effects of both gender and age on nerve conduction are observed in nondiabetic subjects (10,25–27). The gender-related differences in autonomic dysfunction demonstrated in this study have not been reported previously. Gender had no demonstrable effect on the Valsalva ratio in our nondiabetic reference population. Thus, the increased prevalence of clinical neuropathy and the greater abnormality in nerve conduction results and Valsalva ratio in DCCT men may represent a true gender effect on the development or expression of diabetic somatic and autonomic neuropathy.

The mechanisms by which age and gender might influence the development of diabetic neuropathy are unclear. Pickett (28) has suggested that the normally slower nerve conduction in men might render them more susceptible to various forms of neuropathy, although this contention remains purely speculative. The metabolic perturbations implicated in nerve conduction slowing in experimental diabetes, i.e., increased sorbitol production from glucose and decreased *myo*-inositol content (29), are also present in microvascular tissue and appear to be sex hormone dependent (30). This observation may take on added relevance in the light of recent studies by Low et al. (31) implicating microvascular abnormalities in experimental diabetic neuropathy in animals.

Other putative risk factors for the development of diabetic complications were not convincingly associated with clinical neuropathy in the DCCT analyses. Baseline HbA_{1c} values were not higher in subjects affected with clinical peripheral neuropathy. Although several published studies have linked clinically overt neuropathy to severity of hyperglycemia, these studies did not differentiate between IDDM and non-insulin-dependent diabetes mellitus (NIDDM) and probably contained a preponderance of patients with NIDDM (18,32–34). In the DCCT, baseline HbA_{1c} and duration of diabetes were negatively correlated ($-.242$, $P = .0112$), possibly masking a time-dependent effect of HbA_{1c} on the development of neuropathy. This issue will be resolved by prospective examination during the remainder of the DCCT, where it will constitute a major study question.

In contrast, higher HbA_{1c} and longer duration of diabetes had important negative influences on motor nerve but not sensory nerve conduction and on cardiovascular reflexes. A selective correlation of HbA_{1c} with motor nerve but not sensory nerve conduction has been reported in other studies (33,34). Hyperglycemia induces a number of biochemical abnormalities in peripheral nerves that may be relevant to the impairment of nerve conduction (29). These biochemical abnormalities, including altered sorbitol and *myo*-inositol content, glycosylation, and Na^+-K^+-ATPase activity, have been used to explain the direct relationship between motor conduction velocity and hyperglycemia that is usually seen in diabetic patients (32,33,35–37).

In summary, the careful assessment of clinical neuropathy and autonomic and peripheral nerve function in the relatively asymptomatic DCCT population reveals significant associations between male gender and age and the presence of diabetic neuropathy.

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