

Glycemic Control Is Related to the Electrophysiologic Severity of Diabetic Peripheral Sensorimotor Polyneuropathy

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OBJECTIVE — The aim of the present study was to examine risk factors for the electrophysiologic severity of diabetic peripheral sensorimotor polyneuropathy (DSP).

RESEARCH DESIGN AND METHODS — A total of 97 patients with type 1 diabetes (25 patients) or type 2 diabetes (72 patients) were included in this cross-sectional study. Nerve conduction studies (NCS) were performed on median motor and sensory nerves, peroneal motor nerve, and both sural nerves. The severity of DSP was expressed as the sum of nerve conduction velocities (SNCV) and the score of distal amplitudes (SAMP) of the above-mentioned nerves. General linear models were used to assess the relationship between overall severity of DSP, as well as the severity of lower extremity, upper extremity, motor nerve, or sensory nerve involvement and various risk factors.

RESULTS — GHb was significantly related to both SNCV and SAMP in univariate and multivariate regression analyses. This relationship was present in models where GHb was handled either as a continuous variable or as a categorical variable with highest significance level, with a GHb cutoff level of 9%. The difference in NCV for individual nerves in patients with good-to-moderate glycemic control (GHb \leq 9%) and those with poor glycemic control (GHb \geq 9%) ranged from 1.8 to 3.6 m/s. SAMP was also significantly lower in patients with poor control. SNCV was also significantly related in multivariate analysis to duration of diabetes and height, while SAMP was related to duration of diabetes, age, and male sex.

CONCLUSIONS — The severity of DSP expressed by electrophysiologic criteria was significantly related to glycemic control in a study including patients with type 1 or type 2 diabetes. Based on the results of the present study, it might be predicted that better diabetic control would decrease the severity of DSP.

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Diabetic peripheral sensorimotor polyneuropathy (DSP) is one of the most frequent complications of type 1 and type 2 diabetes. Both cross-sectional and prospective epidemiologic studies have identified a number of risk factors for this complication. Among them the most important is poor diabetic control as reflected by increased GHb level, diabetes duration, and demographic parameters

such as age, height, and male sex (1–5). Some of these studies have shown that risk factors for atherosclerosis, such as hypertension, smoking, and increased triglyceride and decreased HDL cholesterol levels, might also be risk factors for DSP (1–3).

The majority of the above-mentioned studies have focused on identification of risk factors for the presence of DSP but not for the severity of DSP. Severity of DSP can

be defined by different clinical and/or neurophysiologic scoring systems (6–8). Nerve conduction studies (NCS), primarily nerve conduction velocities (NCV), are considered one of the most sensitive indices of the severity of DSP. Although nerve amplitudes have a higher variance than NCV, they better indicate the severity of DSP, as they reflect the degree of nerve fiber loss (7,9). The purpose of this cross-sectional study was to identify which risk factors are independently related to the severity of DSP in patients with type 1 or type 2 diabetes and mild diabetic neuropathy.

RESEARCH DESIGN AND METHODS — A total of 97 patients (70 men and 27 women) with diabetic peripheral polyneuropathy were included in the cross-sectional study. These patients were enrolled in a double-blind placebo-controlled randomized study of the effects of an aldose reductase inhibitor in patients with diabetic polyneuropathy. These patients are not representative of all patients with diabetes in Toronto, but are representative of patients with mild diabetic polyneuropathy. All data were collected before randomization and initiation of treatment with the active drug or placebo. The study was approved by The Toronto Hospital Committee for Research in Human Subjects.

Criteria for selection included patients with type 1 diabetes (25 patients) or type 2 diabetes (72 patients), GHb \geq 6.7% by affinity chromatography at screening, neuropathy diagnosed on the basis of abnormalities in two of four major categories (symptoms, signs, NCS, and quantitative sensory testing), the presence of sural potentials (bilaterally) and peroneal motor potential, and vibratory threshold at the toe \leq 10.0 vibration units. Patients with peripheral neuropathy principally from causes other than diabetes, such as alcohol abuse, liver or renal disease, toxic exposure, endocrine, metabolic, or nutritional disorders, inflammatory diseases or monoclonal gammopathy, were excluded. The mean age (\pm SD) of patients was 52.7 \pm 4.8 years, the mean diabetes duration was 12.5 \pm 9.5 years, and the mean duration of symptoms of neuropathy was 3.2 \pm 2.0 years.

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Abbreviations: DCCT, Diabetes Control and Complications Trial; DSP, diabetic peripheral sensorimotor polyneuropathy; LE, lower extremity; NCS, nerve conduction study; NCV, nerve conduction velocity; SAMP, score of distal amplitude; SNCV, sum of nerve conduction velocity; UE, upper extremity.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

Table 1—Pearson's correlation coefficients between the severity of DSP and the investigated risk factors

	SNCV	SAMP
GHb	−0.39 (0.0001)	−0.36 (0.0004)
Diabetes duration	−0.26 (0.011)	−0.25 (0.015)
Height	−0.41 (<0.0001)	−0.25 (0.014)
Age	−0.17 (0.10)	−0.32 (0.001)

Data are *r* (*P*). Severity of neuropathy is expressed as SNCV and SAMP from five examined nerves (median motor and sensory, peroneal, right and left sural).

NCS were performed using Counterpoint (Dantec, Copenhagen). Recordings were performed with temperature control (32–34°C), careful distance measurements, and recording of well-defined and artifact-free responses. We used surface, silver-silver chloride discs with a standardized size of 4 × 7 mm to record all nerve responses. The study was limited to patients with mild neuropathy; patients were excluded if they had unobtainable sural or peroneal nerve responses or severely elevated vibration perception thresholds at the initial visit. Three NCS were done within two to three weeks. The median values of NCV and distal amplitudes from the following nerves were used: median motor and median sensory nerves on the nondominant side, peroneal motor nerve on the dominant side, and both right and left sural nerves. Composite variables were created using the measured conduction velocities and amplitudes. The overall severity of DSP was expressed as the sum of NCV (SNCV) and the score of distal amplitudes (SAMP [motor amplitudes in millivolts, sensory amplitudes in microvolts]) of all five examined nerves. The potential sizes were scored as the values relative to reference values are similar for motor and sensory potentials, and the degree of abnormality of each, not the absolute values, was pertinent in these analyses.

GHb, cholesterol, and triglycerides were measured using routine biochemical tests.

Statistical analysis

Statistical evaluation was done with SuperANOVA 1.11 and Statview 4.5 (Abacus Concepts, Berkeley, CA, 1989 and 1992) software for Macintosh. In univariate analyses, Pearson's coefficients of correlation between both SNCV and SAMP with independent variables were calculated. Student's *t* test was used for comparison of two groups. General linear regression modeling using analysis of covariance (ANCOVA) was used in multivariate analyses to evalu-

ate the effect of more independent variables on NCV and amplitudes and to adjust means for confounding variables. Post hoc analyses in these models were done by Duncan's test.

RESULTS — The relationship between the severity of DSP and the examined risk factors was first investigated by univariate correlation analysis. SNCV and SAMP from all examined nerves were used to express the overall severity and extent of DSP. The results of correlation analysis are shown in Table 1. SNCV significantly inversely correlated with GHb, diabetes duration, and height. There was no significant correlation with age, weight, systolic and diastolic blood pressure, neuropathy duration, and plasma cholesterol or triglyceride levels. Among binary variables, sex had a highly significant effect on SNCV, with lower mean SNCV (i.e., lower conduction velocities) in men than in women (207.8 ± 20.4 vs. 226.9 ± 21.0 m/s, *P* = 0.0001). There were no significant differences in mean SNCV between patients with type 1 and type 2 diabetes, as well as between current smokers and non-smokers. Similarly, SAMP correlated significantly with GHb, diabetes duration, and height, as well as with age. Mean SAMP was

significantly lower in men than women (34.8 ± 14.5 vs. 45.1 ± 14.5, *P* = 0.002).

In multivariate analysis, the variables significantly related to the severity of DSP in univariate analysis were studied: GHb, diabetes duration, sex, height, and age. Statistical significance of the individual risk factors related to NCV in general linear models is displayed in Table 2. Five different models were examined, with dependent variables used to express the severity of DSP based on NCV: SNCV for the overall severity; lower extremity (LE) and upper extremity (UE) NCV for the severity of LE involvement and UE involvement, respectively; and sensory and motor NCV for involvement of the sensory and motor nerves, respectively. These variables are described in Table 2. GHb, an index of long-term diabetes control, was included in all five models with the high level of statistical significance, while diabetes duration was included significantly in all models, with the exception of the model predicting the severity of UE neuropathy. There were some differences in inclusion of confounding factors in different models. Height significantly predicted the overall DSP severity and the severity of both LE and sensory neuropathy. Sex was significantly included in the models predicting the severity of both LE and motor neuropathy. Finally, age significantly contributed to the prediction of both UE and motor neuropathy. These models accounted for 32% (UE NCV) to 41% (LE NCV) of the NCV variance. Adding the type of diabetes to the models did not increase significantly their predictive value, and the type of diabetes was not significantly included in any model. When modeling was done separately for the 72 patients with type 2 diabetes, the results were very similar to those of the entire

Table 2—Multiple linear regression models with NCVs as dependent variables and risk factors for severity of DSP

	HbA _{1c}	Diabetes duration	Age	Sex (male)	Height	<i>r</i> ²
SNCV (ms ⁻¹)	0.0005	0.009	0.051	0.056	0.024	0.40
LE NCV (ms ⁻¹)	0.0050	0.001	NS	0.038	0.013	0.41
UE NCV (ms ⁻¹)	0.0002	NS	0.023	0.095	NS	0.32
Sensory NCV (ms ⁻¹)	0.0016	0.008	0.055	0.079	0.041	0.37
Motor NCV (ms ⁻¹)	0.0014	0.021	0.037	0.030	NS	0.34

n = 97. All relationships with continuous variables are inverse. SNCV is the sum of the conduction velocities of the median motor and median sensory nerves, peroneal, and both right and left sural nerves. LE NCV is the sum of peroneal and right and left sural NCV. UE NCV is the sum of median motor and median sensory NCV. Sensory NCV is the sum of median sensory and right and left sural NCV. Motor NCV is the sum of median motor and peroneal NCV. NS, *P* > 0.1.

Table 3—Multiple linear regression models with nerve amplitudes (AMP) as dependent variables and risk factors for severity of diabetic sensorimotor neuropathy

	GHb	Diabetes duration	Age	Sex (male)	Height	r ²
SAMP	0.0007	0.008	0.0001	0.040	NS	0.37
LE AMP	0.0043	0.035	0.0006	NS	NS	0.25
UE AMP	0.0039	0.017	0.0011	0.0003	NS	0.38
Sensory AMP	0.0002	0.021	0.0001	0.065	NS	0.37
Motor AMP	NS	0.017	0.053	NS	NS	0.14

n = 97. All relationships with continuous variables are inverse. SAMP is the sum of the distal amplitudes of the median motor and median sensory nerves, peroneal, and both right and left sural nerves. LE AMP is the sum of the distal amplitudes of the peroneal and right and left sural nerves. UE AMP is the sum of the distal amplitudes of the median motor and median sensory nerves. Sensory AMP is the sum of the distal amplitudes of the median sensory and right and left sural nerves. Motor AMP is the sum of the distal amplitudes of the median motor and peroneal nerves. The amplitudes of the motor nerves are in millivolts and of the sensory nerves in microvolts. NS, *P* > 0.1.

group with the exception of sex, which was not significantly included in any model.

Models showing factors predicting SAMP and other combined amplitude scores are displayed in Table 3. GHb significantly contributed to the prediction of SAMP and the other amplitude scores with the exception of motor amplitudes. Diabetes duration was significantly included in all models. Age significantly predicted amplitude scores in all models except the model predicting motor amplitudes. In general, the relationship between amplitudes and age was much stronger than the relationship between NCV and age. In contrast to NCV, whose relationship with sex disappeared in multivariate analysis, SAMP and UE amplitudes were related to male sex in multivariate analysis.

In all the above-mentioned models, GHb was handled as a continuous variable. To identify which cutoff level of GHb would best differentiate between the less severe and more severe forms of DSP, GHb was investigated in different models for predicting SNCV as a categorical variable (low vs. high) with cutoff values of 8.0, 8.5, 9.0, 9.5, and 10.0%. Using the cutoff point of 9.0%, GHb as a categorical variable in a general linear model gave the highest level of statistical significance (*P* = 0.002). Further, we investigated the effect of diabetic control on NCV of different nerves. The study group was divided into two groups according to the 9.0% cutoff value: good-to-moderate control (GHb ≤ 9.0%) and poor control (GHb > 9.0%). The results of this analysis are shown in Table 4. The differences between means of NCV for different nerves ranged from 1.8 m/s for the peroneal nerve to 3.6 m/s for the right sural nerve. In summary, the mean SNCV was

6.3% lower in patients with poor diabetic control as compared with those with good-to-moderate control. When the effect of diabetes control on nerve amplitudes was evaluated, patients with good-to-moderate control had significantly higher SAMP than did patients with poor control (45.0 ± 13.5 vs. 36.8 ± 15.5, *P* = 0.009).

CONCLUSIONS — The present study shows that diabetes control characterized by GHb level is related not only to the presence of DSP but also to the severity of DSP. This relationship was shown in two ways: in univariate correlation analysis and in multivariate analysis using general linear modeling. The overall severity of DSP, as well as the severity of LE or UE involvement and motor or sensory nerve involvement, was expressed by using the SNCV and the SAMP of five peripheral nerves. In addition to GHb, diabetes duration and demographic variables such as age, sex, and height were included in the different models.

Table 4—NCVs of individual nerves in subjects with good-to-moderate (GHb ≤ 9%) and poor (GHb > 9%) glycemic control

	GHb ≤ 9%	GHb > 9%	<i>P</i>
<i>n</i>	29	68	—
MMCV (ms ⁻¹)	51.0 ± 4.8	48.6 ± 5.4	0.026
MSCV (ms ⁻¹)	54.8 ± 4.5	51.2 ± 5.2	0.001
PCV (ms ⁻¹)	40.1 ± 4.6	38.3 ± 5.2	0.089
RSCV (ms ⁻¹)	39.6 ± 5.3	36.6 ± 6.0	0.014
LSCV (ms ⁻¹)	38.6 ± 4.7	36.1 ± 5.3	0.016
SNCV (ms ⁻¹)	224.8 ± 19.1	210.7 ± 21.8	0.002

Data are means ± SD. The means are adjusted for age, sex, height, and the duration of diabetes. MMCV, median motor conduction velocity; MSCV, median sensory conduction velocity; PCV, peroneal conduction velocity; RSCV, right sural conduction velocity; LSCV, left sural conduction velocity.

GHb as an index of long-term diabetic control has been shown to be related to the incidence and the prevalence of DSP in both cross-sectional and prospective epidemiologic studies. These studies have mainly included patients with type 1 diabetes, such as the Pittsburgh Epidemiology of Diabetes Complications Study (1,3), the EURODIAB Type I Complications Study (2), and the Diabetes Control and Complication Trial (DCCT) (10). A study that included patients with both types of diabetes (the Seattle Prospective Diabetic Foot Study) produced similar results (4). This is in accordance with the finding that in subclinical diabetic neuropathy, there are considerable similarities between the electrophysiologic results in patients with type 1 and type 2 diabetes (11). In the present study, the results in the subgroup of type 2 patients, who accounted for approximately three-quarters of our study subjects, were similar to the results in the entire study group; the subgroup of patients with type 1 diabetes could not be evaluated separately because of the lower number of subjects.

Some studies have shown a relationship between diabetic control and NCV of separate nerves both in type 1 diabetes (12,13) and type 2 diabetes (14,15), as well as a relationship between GHb and nerve amplitudes in type 1 diabetes (13). The present study extends this knowledge by showing that, in multivariate analysis taking into account various confounding factors, the overall severity of DSP, as well as the severity of involvement in different nerve groups (lower extremities, upper extremities, motor nerves, sensory nerves), is consistently related to diabetic control. When GHb as a continuous variable was substituted in general linear models for a categorical variable (i.e., high or low), a cutoff point of 9% was

found to have the highest predictive value in these models. On the other hand, when this cutoff value was used for different nerves, the difference in NCV between patients with GHb $\leq 9\%$ and those with GHb $> 9\%$ ranged from 1.8 to 3.6 m/s after adjustment for age, sex, height, and diabetes duration. This finding corresponds with an assumed clinically meaningful degree of prevention or improvement of nerve conduction (16), as well as with the degree of prevention observed in DCCT, so far the only effective intervention study regarding diabetic neuropathy (17). Many metabolic and vascular mechanisms by which increased blood glucose level might lead to the development of diabetic neuropathy have been hypothesized, and they have been recently reviewed (17).

The duration of diabetes, which has been reported to be a risk factor for the presence of DSP (1,2,5), was shown in the present study to be related to the severity of DSP in all models except the model predicting NCV in the upper extremities. In this model, the patient's age was the only other factor significantly included in the model. Height was represented in some models predicting NCV, but in none of the models predicting amplitudes. Sex of subjects (with slower NCV and lower amplitudes in men) was represented in some models, and this finding is in accordance with results reported in both normal and diabetic subjects (19–21). This finding suggests that more severe disease occurs in diabetic men. Although some studies observed relationships between the presence of DSP and hypertension, smoking, or triglyceride level (2,3), we did not find any relationship between these factors and the severity of DSP.

In summary, the present study shows that poor diabetic control is the most important factor related to the severity of DSP in patients with either type of diabetes. Other factors such as diabetes duration, male sex, height, and age are also related to the severity of DSP; however, none of them are amenable to intervention. Effective control of diabetes has been shown to have beneficial effects on NCV in patients with type 1 diabetes (22). Because the majority of subjects in the present study had type 2 diabetes, it might be assumed that, similar to patients with type 1 diabetes, strict metabolic control might prevent further neuropathic deterioration in patients with type 2 diabetes. However, similar interventional studies in such patients are needed.

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