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# Low Peripheral Nerve Conduction Velocities and Amplitudes Are Strongly Related to Diabetic Microvascular Complications in Type 1 Diabetes

## The EURODIAB Prospective Complications Study

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**OBJECTIVE** — Slow nerve conduction velocity and reduction in response amplitude are objective hallmarks of diabetic sensorimotor polyneuropathy. Because subjective or clinical indicators of neuropathy do not always match well with the presence of abnormal nerve physiology tests, we evaluated associations to nerve conduction in patients with type 1 diabetes.

**RESEARCH DESIGN AND METHODS** — Nerve conduction studies were performed in the distal sural and ulnar sensory nerves and the peroneal motor nerve in 456 individuals with type 1 diabetes who participated in the follow-up visit of the EURODIAB Prospective Complications Study (EPCS). We used multivariate regression models to describe associations to decreased nerve conduction measures.

**RESULTS** — In addition to an effect of duration of diabetes and A1C, which were both associated with low nerve conduction velocity and response amplitude, we found that the presence of nephropathy, retinopathy, or a clinical diagnosis of neuropathy was associated with low nerve conduction velocity and amplitude. In the case of nonproliferative retinopathy, the odds ratio (OR) for being in lowest tertile was 2.30 (95% CI 1.13–4.67) for nerve conduction velocity. A similar OR was found for each 2% difference in A1C (2.39 [1.68–3.41]).

**CONCLUSIONS** — We show that the presence of other microvascular diabetes complications, together with diabetes duration and A1C, are associated with low nerve conduction velocity and amplitude response and that cardiovascular disease or risk factors do not seem to be associated with these measures.

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Diabetic neuropathies are reported to affect up to 66% of individuals with type 1 diabetes, most frequently in the form of polyneuropathy (54% of the cohort), the remainder including focal, visceral autonomic, and other atypical varieties (1). However, prevalence estimates vary widely, most likely depending on differences in patient selection, neuropathy definition, and methods of assessment (2) The underlying pathophysiology of diabetic peripheral neuropathy is not well understood beyond the marked importance of chronic hyperglycemia as the key initiator of neurovascular damage (1,3,4). Diabetic neuropathy is generally assessed in clinical practice by a combination of objective and subjective measures. A consensus report from the American Academy of Neurology concluded that a combination of symptoms, signs, and electrophysiological test results provides the most accurate diagnosis of distal symmetric polyneuropathy (5). However, at the onset of neuropathy, clinical measures of dysfunction are often dissociated from the presence of abnormalities on nerve conduction studies (NCSs), which are considered by many to be the gold standard for nerve damage and the most consistent indicator of subclinical (largely asymptomatic) neuropathy (6).

Previous studies generally showed that age, male sex, height, diabetes duration, and glycemic control influence nerve conduction (7,8). We have previously highlighted the importance of conventional cardiovascular risk factors in the etiology of clinical neuropathy in individuals with type 1 diabetes (9), but their association to earlier abnormalities in nerve conduction is less certain. Further, the relation to the presence of other complications, such as nephropathy and retinopathy, remains unclear, largely because previous studies were underpowered and did not always have standardized measures of both risk factors and complications to enable simultaneous assessment.

We therefore set out to study the cross-sectional association among cardiovascular risk factors, anthropometric measures, the presence of complications, and ulnar, sural, and peroneal nerve conduction in individuals with type 1 diabetes who participated in the EURODIAB Prospective Complications Study (EPCS).

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## RESEARCH DESIGN AND METHODS

The EURODIAB Study recruited 3,250 patients with type 1 diabetes (1,668 men and 1,582 women; mean ± SD age 32.7 ± 10.2 years and duration of diabetes 14.7 ± 9.3 years). These participants were selected at random from age, diabetes duration, and sex strata from 31 diabetes clinics across Europe. Selection criteria and methods have been described previously (10). Twenty-seven centers participated in the follow up of the EURODIAB cohort (the EURODIAB Prospective Complications Study [EURODIAB PCS]). We present data collected in the 13 centers that participated in the Nerve Conduction substudy, conducted during the follow-up examinations (1997–1999). Patients were randomly selected by the EURODIAB Data Coordinating Center, and a list of selected patients was sent to the local main investigator. Selected patients were called for the nerve conduction study after they completed the main EURODIAB PCS follow-up examination.

A total of 1,894 patients completed the EURODIAB PCS follow-up examination. An NCS was performed in 634 patients. We excluded 44 patients because of incomplete data on cardiovascular risk factors; 130 patients were excluded because of incomplete nerve conduction data, 91 of these were only missing data from the sural nerve. Data from these 91 patients were initially included in analyses of the peroneal and ulnar nerves, but these results did not differ markedly from a complete data analysis (data not shown). Six patients were excluded because of extreme outlying values on nerve conduction tests, yielding a set of 456 patients with complete data. It is likely that some of these data were missing because the true value of nerve conduction was below the threshold of detection (i.e., the true nerve conduction value is not zero/missing, but rather too low to be measured); thus, we supplemented the complete-case analyses, on which this article is based, with analyses using multiple imputation techniques and single imputation (using the first percentile of nerve conduction values as imputed value) to explore the impact of missing values on our results. We report primary results based on complete-case analysis (456 patients) and provide results from the supplementary multiple and single imputation analysis for reference (supplementary methods, available in an online appendix at http://care.diabetesjournals.org/cgi/content/full/dc10-0456/DC1).

### Measurements

Blood samples were obtained ideally after an overnight fast. These were sent to a central laboratory and analyzed for A1C, total and HDL cholesterol, and triglycerides (11). LDL cholesterol was calculated. To compare the results with those of the Diabetes Control and Complications Trial (DCCT), measured A1C values were converted as reported previously (11) and used in all subsequent analyses.

The urinary albumin excretion rate was the average from two 24-h urine collections. A urinary albumin excretion rate of 20–200 μg/min was defined as microalbuminuria; a rate >200 μg/min was defined as macroalbuminuria.

The presence and severity of diabetic retinopathy were assessed from retinal photographs (two fields per eye) obtained with a wide-angle camera and scored centrally. Retinopathy for this analysis was dichotomized as nonproliferative or proliferative.

Cardiovascular disease (CVD) was defined as either a history of physician-diagnosed CVD (e.g., previous myocardial infarction, angina, coronary-artery bypass grafting, or stroke) or ischemic changes detected on a 12-lead electrocardiogram (classified by two observers according to the Minnesota code).

Clinical neuropathy was diagnosed in patients with two or more of the following four measures: the presence of one or more symptoms, the absence of two or more reflexes of the ankle or knee tendons, a vibration perception threshold that was abnormal for the patient's age, and abnormal autonomic function (loss of heart rate variability with a ratio of <1.04, postural hypotension with a fall in systolic blood pressure of ≥20 mmHg, or both). Descriptions of the specific tests have been published previously (12). The cutoff points and the definition of neuropathy were established before any examination of the outcome data.

The NCSs were performed with standard electrophysiological and electromyographic equipment provided by major manufacturers (e.g., Nicolet, Teca, and Disa). Digital skin thermometers accurate to 0.1°C and, when necessary, appropriate warming measures were used to ensure that skin temperatures were at least 32°C. Examinations were performed by trained electrophysiologists with extensive experience in recording and interpreting clinical data. Velocity was determined for the distal sural and ulnar sensory nerves and for the peroneal motor nerve (knee to ankle) unilaterally on the nondominant side. Response amplitude was measured overlying the dorsal surface of the foot for the sural nerve, at the fifth finger for the ulnar nerve and overlying the extensor digitorum brevis muscle for the peroneal nerve. All data were collected using standard surface techniques and specified anatomical landmarks for both stimulation and recording sites. Before testing of study participants, all participating electrophysiologists attended a standardization training meeting, and all centers were certified by submitting three satisfactory complete examinations using specific study procedures by the central reading site (J.C.A. at the Albert Einstein College of Medicine, New York, NY). Throughout the study, a sample of approximately one-third of the data from each center was reviewed by the central reading site to ensure overall quality and continued adherence to study procedures.

### Statistical analysis

We present cross-sectional analyses from the EPCS follow up visit. Statistical analyses were performed with Stata software (version 11; StataCorp, College Station, TX). Characteristics of patients who did and did not participate in the NCSs were compared with the use of the Student *t* test or Mann-Whitney *U* test where appropriate. In the case of unequal variances, means were compared by approximate inference based on the *t* distribution.

Multivariate linear regression models were used to describe the associations among cardiovascular risk factors, anthropometric measures, the presence/severity of complications, and ulnar, sural, and peroneal nerve conduction, which are reported as unstandardized β coefficients. Data were collected as crude data from each center; therefore, models for nerve conduction measures were adjusted for age, sex, height, diabetes duration, A1C, center, skin temperature, and distance between electrodes into the model. These covariates were prespecified as factors that may affect nerve conduction based on previously published evidence (13,14). Nerve conduction velocity (NCV) and nerve conduction amplitude (NCA) for the three nerves were standardized and summarized per individual in a total *z* score, which was used as an additional outcome in a separate

**Table 1—*Characteristics of all participants of the EURODIAB PCS and those who were included in the Nerve Conduction substudy analysis***

| | EURODIAB follow-up | Nerve conduction tests (complete case) |
|---|---|---|
| *n* | 1,886 | 456 |
| Male sex (%) | 52 | 50 |
| Caucasian (%) | 92 | 99 |
| Age (years) | 38.6 (26.2; 58.3) | 36.8 (26.5; 55.3) |
| Duration of diabetes (years) | 20.5 (9.7; 39.1) | 19.5 (9.4; 33.7) |
| A1C (% of hemoglobin) | 8.34 (6.4; 11.3) | 8.2 (6.4; 10.9) |
| Systolic blood pressure (mmHg) | 121.1 ± 18.6 | 117 ± 16.4 |
| Diastolic blood pressure (mmHg) | 74 ± 11.9 | 74 ± 10.7 |
| Weight (kg) | | |
| Men | 75.9 ± 10.7 | 74.5 ± 8.9 |
| Women | 64.7 ± 10.8 | 63.2 ± 10.3 |
| Height (cm) | | |
| Men | 174.8 ± 7.5 | 174 ± 7.4 |
| Women | 162.6 ± 7.1 | 162.8 ± 7.0 |
| Total cholesterol (mmol/l) | 5.33 ± 1.19 | 5.24 ± 1.1 |
| Triglycerides (mmol/l) | 0.99 (0.52; 2.66) | 0.915 (0.47; 2.21) |
| Smoking (ever/current) | 707 (38) | 145 (31) |
| Alcohol (>10 units/week) | 471 (28) | 99 (25) |
| CVD | 211 (11) | 35 (8) |
| Microalbuminuria (20–200 μg/min) | 306 (18) | 62 (15) |
| Macroalbuminuria (> 200 μg/min) | 216 (9) | 11 (3) |
| Nonproliferative retinopathy | 817 (53) | 205 (52) |
| Proliferative retinopathy | 305 (20) | 47 (12) |
| Neuropathy | 667 (35) | 107 (23) |

Data are means ± SD, skewed distribution: median (5th; 95th percentile), or *n* (%) unless otherwise indicated.

regression model. A slow/low nerve conduction measure was defined as being in the lowest tertile of ulnar, sural, and peroneal NCV or NCA, and odds ratios (ORs) for being in this group were calculated using a multivariate logistic regression model with adjustment for the sample variables as mentioned above. β coefficients and ORs are given with 95% CIs. Methods for the supplementary multiple imputation analyses are described in an online appendix.

**RESULTS** — Characteristics of the patients included in the current analyses compared with those of all the EURODIAB participants who completed the EPCS follow-up are shown in Table 1. Patients in the NCS analysis set were younger (36.8 years), had a shorter diabetes duration (19.5 years), and had more favorable levels of most cardiovascular risks factors and a lower prevalence of complications. We compared the patients excluded from our NCSs because of missing values and found that they were older (43.9 years), had longer diabetes duration (25.2 years), and had higher levels of all cardiovascular risk factors and complications. (The excluded patients had lower average nerve conduction measures.) Unadjusted mean NCV and NCA values for participants by complication status are presented in Table 2. The associations among cardiovascular risk factors, anthropometric measures, diabetes complications, and NCV/NCA are shown in supplementary Tables 1A and 2A (available in an online appendix). Comparison with results from the imputation analyses of velocity/amplitude *z* scores are shown in supplementary Tables 3A and 4A (available in an online appendix). β coefficients denote the difference in NCV/NCA per unit difference in each determinant; e.g., for a 1-year increment in age, ulnar NCV is 0.15 m/s lower.

We confirm that duration of diabetes and A1C were both negatively and statistically significantly associated with NCV and NCA in all three nerves. We also confirm that the presence of nephropathy or

**Table 2—*NCSs of ulnar and distal sural sensory nerves and the peroneal motor nerve (knee to ankle) unilaterally on the nondominant side in the EURODIAB PCS at follow-up***

| | Ulnar | | Sural | | Peroneal | |
|---|---|---|---|---|---|---|
| | Velocity (m/s) | Amplitude (mV) | Velocity (m/s) | Amplitude (mV) | Velocity (m/s) | Amplitude (mV) |
| CVD | | | | | | |
| None | 51.2 ± 6.3 | 18.6 ± 12.3 | 45.1 ± 7.0 | 10.3 ± 7.4 | 43.9 ± 4.5 | 5.4 ± 3.2 |
| Present | 48.3 ± 6.7 | 16.8 ± 10.9 | 44.7 ± 6.8 | 8.4 ± 6.7 | 43.0 ± 4.0 | 5.7 ± 4.5 |
| Neuropathy | | | | | | |
| None | 51.6 ± 5.7 | 19.7 ± 12.5 | 45.4 ± 7.2 | 11.0 ± 7.7 | 44.3 ± 4.5 | 5.7 ± 3.3 |
| Present | 48.7 ± 7.8 | 14.8 ± 10.3 | 44.1 ± 6.3 | 7.4 ± 5.5 | 42.6 ± 4.4 | 4.3 ± 3.1 |
| Albumin excretion | | | | | | |
| Normal | 51.3 ± 6.1 | 18.9 ± 12.2 | 45.8 ± 7.0 | 10.8 ± 7.8 | 44.3 ± 4.4 | 5.5 ± 3.1 |
| Microalbuminuria | 49.0 ± 7.0 | 15.6 ± 10.7 | 42.1 ± 7.0 | 7.7 ± 5.4 | 41.4 ± 4.6 | 4.1 ± 2.3 |
| Macroalbuminuria | 48.0 ± 8.7 | 11.5 ± 11.1 | 40.3 ± 4.6 | 5.1 ± 4.0 | 41.4 ± 3.6 | 4.0 ± 3.1 |
| Retinopathy | | | | | | |
| None | 52.1 ± 5.9 | 20.9 ± 13.2 | 47.6 ± 7.7 | 12.4 ± 9.1 | 46.0 ± 3.9 | 5.9 ± 4.0 |
| Nonproliferative | 51.4 ± 6.8 | 18.6 ± 11.8 | 45.0 ± 6.8 | 9.8 ± 6.2 | 43.6 ± 4.6 | 5.1 ± 2.8 |
| Proliferative | 47.5 ± 5.9 | 11.7 ± 8.6 | 41.2 ± 5.3 | 6.5 ± 4.7 | 40.9 ± 4.1 | 3.8 ± 2.7 |

Data are means ± SD and are unadjusted from the complete-case analysis.

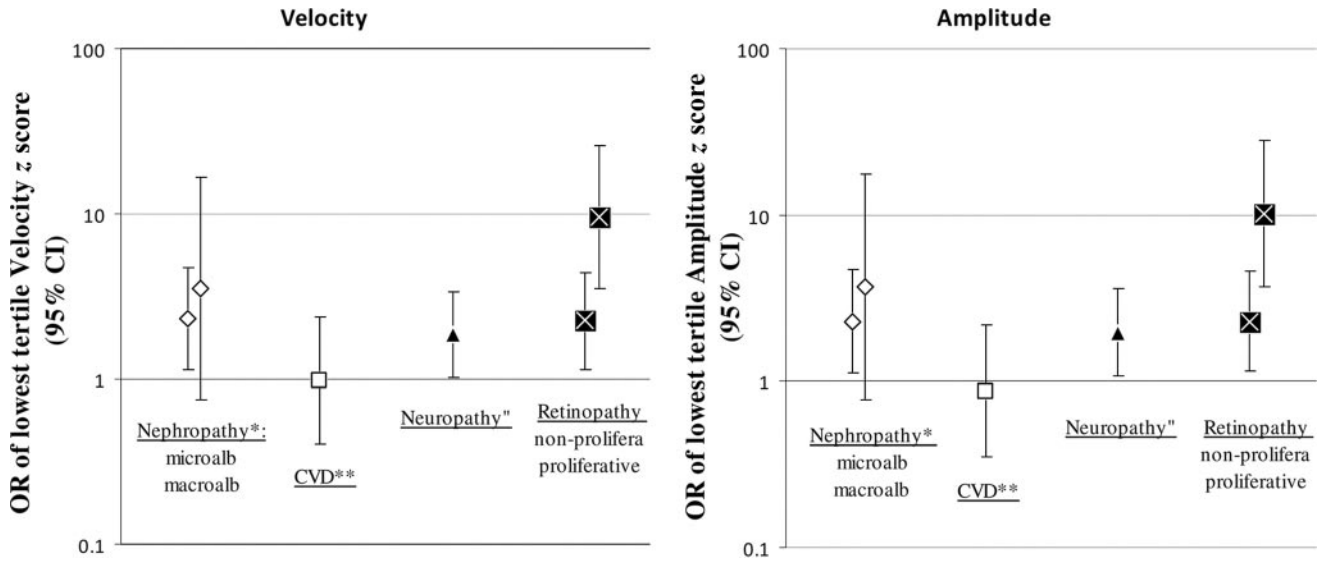


**Figure 1**—*OR of the lowest tertile of the velocity* (left) *and amplitude* z *score* (right)*, adjusted for age, sex, height, center, diabetes duration, A1C, and determinants of nerve conduction measures (skin temperature and distance between electrodes). z scores are calculated from a summed score of standardized NCV/NCA from ulnar and distal sural sensory nerves and the peroneal motor nerve (knee to ankle) unilaterally on the nondominant side. *Microalbuminuria (microalb): 20–200 μg/min; macroalbuminuria (macroalb) >200 μg/min. **Prevalence of CVD. "Composite score of symptoms, absent reflexes, abnormal vibration perception threshold, or autonomic dysfunction. non-prolifera, nonproliferative.*

retinopathy or a clinical diagnosis of neuropathy was associated with low NCV and NCA *z* scores. Age, sex, and height have major effects on nerve conduction in health. These effects were also seen in our population. Sex was not consistently significantly associated with the NCV and NCA of individual nerves. Weight was associated with a higher NCV *z* score, but this effect was not observed for NCA. The association between height and lower NCV or NCA was only present in the nerves of the lower extremity. ORs for having a *z* score in the lowest tertile of NCV/NCA by diabetes complication status are shown in Fig. 1. All diabetic microvascular complications were associated with lower nerve conduction measures. Microalbuminuria was associated with increased odds of low NCV or NCA (OR 2.25 [95% CI 1.15–4.40] and 2.29 [1.12–4.66], respectively). In the case of nonproliferative retinopathy, values were 2.30 [1.13–4.67] and 2.29 [1.15–4.58] for NCV and NCA, respectively. A similar increase in the odds of low NCV or NCA was found for each 2% difference in A1C (2.39 [1.68–3.41] and 2.47 [1.72–3.54], respectively) or a difference of 10 years of duration of diabetes (3.09 [2.09–4.57] and 3.01 [2.03–4.47], respectively). We repeated our analyses on a subset of the patients without clinical signs of neuropathy. This restriction did not materially affect our findings (data not shown).

Results from the subsidiary analyses using imputed datasets yielded results that were broadly similar to those for the complete-case analysis (supplementary Tables 1A and 2A).

**CONCLUSIONS** — We showed in one of the largest sets of patients with type 1 diabetes to date that, in addition to duration of diabetes and level of A1C, the presence of other microvascular diabetes complications is associated with low NCV and NCA. We did not find associations with blood pressure, lipid levels, BMI, waist-to-hip ratio, smoking, or alcohol consumption.

The EURODIAB PCS offers the possibility to study complications of type 1 diabetes, because it provides a large, multicenter, European cohort of patients attending a clinic at least once a year. In addition, all participating centers used similar standardized methods to obtain all measures. Therefore, compared with other studies, our study on nerve conduction has the strength of containing extensive information on these measures for 634 patients with type 1 diabetes, and we have the ability to take this information into account in our analyses.

Unfortunately, many patients had missing values on nerve conduction. Complete-case analysis could therefore be subject to a degree of selection bias because the term "missing" could reasonably be applied to one of three circumstances: *1*) the specific nerve was never tested (e.g., the patient did not permit testing of the ulnar nerve due to pain); *2*) data were collected, but judged to be technically unacceptable (e.g., the sensory response was distorted by a prolonged stimulus artifact); or *3*) correct procedures were followed, but the nerve response was below the detection thresholds using the applied surface recording procedures (i.e., patients with advanced neuropathy have an increased risk of obtaining a missing value). To explore the effect of missing values, we performed subsidiary analyses using single or multiple imputation methods. Multiple imputation is best applied when data are missing at random, a condition that is demonstrably not met in our data. Single imputation analysis, which assigns the lowest observed NCS values to those with a missing value, does not deal with the variance structure of the imputed values and may therefore lead to incorrectly narrow CIs. Because neither imputation method is satisfactory in our dataset, we focused on the complete-case analysis and provide the results of the subsidiary imputation analyses as reference. It is important to note that our main results and conclusions were not dependent on the chosen statistical method, indicating that the observed associations are unlikely to have been introduced by participant selection. It is known that age, sex, and height have major effects on nerve con-

duction in healthy individuals (13,14). These associations also exist in our population of type 1 diabetic patients, but we cannot investigate from our data whether the association goes beyond the effects in health.

Our study is based on a population of European Caucasian patients with type 1 diabetes, and one cannot readily generalize these findings to a broader diabetes population. It is possible that different associations or effect magnitudes are applicable among individuals with type 2 diabetes or in other populations. The patients included in our analysis were younger and had fewer potential risk factors than the rest of the EURODIAB population, but because the findings of imputation analysis confirm the findings from the complete-case analysis, we are confident that our conclusions are representative of the EURODIAB population and that the mechanisms of neuropathy development are likely to be similar for a majority of patients.

A direct comparison of different covariates on nerve conduction will increase the clinician's ability to identify those patients most likely to have neuropathic damage. Other studies have previously shown that duration of diabetes and glycemic control are related to nerve conduction measures. The DCCT showed the importance of glycemic control in the development of neuropathy and also showed that even in patients without diagnosable neuropathy there was a relation between glycemic control and nerve conduction (15). A cross-sectional analysis of 162 patients with type 1 diabetes and 267 patients with type 2 diabetes in the Early Diabetes Intervention Trial found that age, sex, and anthropometric factors were related to nerve conduction measures, with no difference by diabetes type (16). A smaller study of 25 patients with type 1 diabetes and 72 with type 2 diabetes found an association among glycemic control, male sex, diabetes duration, and height and lower NCV or NCA, but no impact of weight, systolic and diastolic blood pressure, neuropathy duration, and plasma cholesterol or triglyceride levels (17). Our study confirms the association with male sex, glycemic control, and diabetes duration on objective measures of nerve conduction.

Several of the smaller studies performed to date have examined the effect of cardiovascular risk factors on nerve conduction. Some found no impact of weight, systolic and diastolic blood pressure, neuropathy duration, and plasma cholesterol or triglyceride levels (17) but also suggested that vascular factors participate in the development of neuropathy (18), whereas others reported an independent association between pulse pressure and hypertension and diabetic peripheral neuropathy in patients with type 2 diabetes (19). A prospective study of 57 patients with type 2 diabetes did not confirm these findings (20). An association between elevated triglycerides and sural nerve myelinated fiber density has been reported (21). Because of their small size, these studies had a limited ability to adjust for potential confounding. Based on our findings, there does not seem to be a clear association of NCSs with cardiovascular risk factors, taking important covariates into account, and therefore the level of cardiovascular risk factors cannot help a clinician in selecting patients with neuropathic damages.

The strong association among retinopathy, nephropathy, and neuropathy has been noted by many others (1, 4, 9, 22, 23). A substudy from the Rochester Diabetic Neuropathy Study (RDNS) cohort, involving 238 patients with diabetes (80% type 2 diabetes), found that subclinical nerve dysfunction precedes the diagnosis of polyneuropathy and showed that a composite score of nerve conduction abnormality was unequivocally superior to clinical impairment, symptoms, or quantitative sensation testing in identifying patients with monotone worsening (6). The RDNS further showed that 24-h microalbuminuria was a significant risk factor for worsening of nerve conduction among patients with diabetes (6) and that microvessel disease, chronic hyperglycemic exposure, and type of diabetes were associated with the severity of diabetic polyneuropathy (24). Our findings confirm that there is a close relation between the presence of microvascular complications and reduced NCV/NCA, indicating that the deleterious microvascular effects of long-term exposure to hyperglycemia develop in parallel, even if the clinical presentation of symptoms may suggest a sequence.

In the EURODIAB population a strong association between neuropathy and a history of CVD has been reported previously. However, there was only a weaker association between the development of neuropathy and other markers of microvessel disease (9).

We considered several potential explanations for our finding of no association between cardiovascular disease and NCS results. Although the patients in our analysis may not be fully representative of the complete EURODIAB population, this selection is unlikely to affect the direction and magnitude of risk factor associations within the substudy. We performed a subanalysis excluding those with a positive neuropathy score at baseline and still found no association with CVD. It is conceivable that our assessment of CVD, which is based on physician-diagnosed CVD and verified ischemic changes on the electrocardiogram, lacks the precision needed to detect subtle associations with NCSs. However, we believe that our method may have a low specificity but has a good sensitivity to detect CVD. We found that 35 of 456 patients had CVD according to our definition, whereas 11 had macroalbuminuria and 47 had proliferative retinopathy. Any true association that we may have missed is therefore likely to be of small magnitude compared with those seen with the microvascular complications. Likewise, the results did not differ in the imputed datasets.

This finding supports the theory that there is a common pathophysiological pathway of microvessel disease, which has no direct relation to macrovascular disease. Because we did not find clear associations with other cardiovascular risk factors, the pathogenic effects of hyperglycemia appear to be the main etiological factor. However, this is a cross-sectional study, and thus we cannot infer any causal connection to risk factors. A prospective study with detailed assessment of microvascular pathophysiology and NCS progression from baseline would be necessary to answer this question.

It has been documented that neuropathy often is subclinical (15,25). Based on our finding of close associations among markers of microvessel disease, the finding of any indication of incipient microvessel disease should therefore alert the clinician toward thinking that the patient has an increased risk of having neuropathy. Therefore, if such a patient does not show signs of neuropathy on the clinical neurological assessment, referral for a NCS may be worth considering.

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M.C. researched data and wrote the manuscript. S.S.S.-M. collected data, contributed to discussion, and reviewed/edited the manuscript. S.T., J.H.F., and J.C.A. designed the study, collected data, contributed to discussion, and reviewed/edited the manuscript. N.C. designed the study, obtained the grant, checked and cleaned the main EURODIAB PCS dataset, contributed to discussion, and reviewed/edited the manuscript. D.R.W. collected data, researched data, and wrote the manuscript.

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