Subclinical Neuropathy Among Diabetes Control and Complications Trial Participants Without Diagnosable Neuropathy at Trial Completion

Possible predictors of incident neuropathy?

JAMES W. ALBERS, MD, PHD
WILLIAM H. HERMAN, MD, MPH
RODICA POP-BUSUI, MD, PHD
CATHERINE L. MARTIN, MS
PATRICIA CLEARY, MS
BARBARA WABERSKI, MS

FOR THE DIABETES CONTROL AND COMPLICATIONS TRIAL (DCCT)/EPIDEMIOLOGY OF DIABETES INTERVENTION AND COMPLICATIONS (EDIC) RESEARCH GROUP*

OBJECTIVE — We sought to evaluate the prevalence of subclinical neuropathy in intensive and conventional treatment groups at completion of the Diabetes Control and Complications Trial (DCCT).

RESEARCH DESIGN AND METHODS — We assessed neuropathy using nerve conduction results obtained at DCCT completion after stratifying the DCCT cohort to exclude subjects with progressively less severe degrees of diagnosable neuropathy. We began with those who had confirmed clinical neuropathy (the primary DCCT end point) and eventually excluded all subjects with any clinical or electrodiagnostic evidence of neuropathy.

RESULTS — After excluding subjects with confirmed clinical neuropathy at DCCT completion, 8 of 10 nerve conduction measures (including all lower-extremity measures) were significantly improved in the intensive treatment group (O'Brien rank-sum test across all nerve conduction measures, $P < 0.0001$). Conduction velocity group differences were substantial, and the peroneal conduction velocity averaged 3.1 m/s faster in the intensive compared with the conventional treatment group (45.1 vs. 42.0 m/s, $P < 0.0001$). Numerous significant differences in median and peroneal motor conduction velocities favoring the intensive treatment group persisted, regardless of the exclusion criteria applied.

CONCLUSIONS — Intensive and conventional treatment group subjects without diagnosable neuropathy at DCCT completion had significant differences in electrophysiologic measurements favoring the intensive treatment group. Differences in subsequent incident neuropathy between the original treatment groups may reflect, in part, their levels of subclinical neuropathy at DCCT completion, rather than persistent metabolic effects.

Diabetes Care 30:2613–2618, 2007

From the Diabetes Control and Complications Trial/Epidemiology of Diabetes Intervention and Complications Research Group, Bethesda, Maryland.

Address correspondence and reprint requests to James W. Albers, MD, PhD, DCCT/EDIC Research Group, Box DCCT/EDIC, Bethesda, MD 20892. E-mail: jwalbers@umich.edu.

Received for publication 2 May 2007 and accepted in revised form 13 July 2007.

Published ahead of print at http://care.diabetesjournals.org on 20 July 2007. DOI: 10.2337/dc07-0850. Clinical trial reg. no. NCT00360893, clinicaltrials.gov.

*A complete list of investigators and members of the Diabetes Control and Complications Trial (DCCT)/Epidemiology of Diabetes Intervention and Complications (EDIC) Research Group appears in refs. 1 and 15.

J.W.A. has received personal compensation from Eli Lilly for consulting and serving on a data monitoring committee, from Wyeth Research for serving on a safety monitoring committee, and from Prana Biotechnology for consulting and has received research funding from the National Institutes of Health.

Abbreviations: DCCT, Diabetes Control and Complications Trial; EDIC, Epidemiology of Diabetes Intervention and Complications.

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

The Diabetes Control and Complications Trial (DCCT) was a multicenter clinical trial conducted between 1983 and 1993. It enrolled 1,441 patients with type 1 diabetes and randomly assigned them to intensive or conventional diabetes treatment. The trial demonstrated that intensive diabetes treatment designed to achieve near-normal glycemia effectively delayed or prevented the development of retinopathy, nephropathy, and neuropathy during an average treatment period of 6.5 years (1). At DCCT completion, all subjects were encouraged to maintain or begin intensive therapy, and the Epidemiology of Diabetes Intervention and Complications (EDIC) study was established to study the long-term effects of prior treatment on micro- and macrovascular outcomes (2).

Longitudinal EDIC follow-up has shown that the former intensive treatment group continues to have a lower cumulative incidence of retinopathy and nephropathy, years after DCCT completion, even after adjusting for treatment group differences at DCCT completion and despite similar levels of glycemic control during EDIC (3–5). The persistent effect of past glucose control has been called "metabolic memory" (6). Preliminary results have suggested that the metabolic memory phenomenon also applies to new-onset (incident) neuropathy, as assessed during EDIC using the Michigan Neuropathy Screening Instrument (7). The observed prolonged beneficial effects of intensive therapy on future risk of diabetic neuropathy could also be explained, completely or in part, by an increased prevalence of subclinical neuropathy (defined here as the absence of symptoms, signs, or electrodiagnostic criteria for distal symmetrical polyneuropathy) at DCCT completion in the conventional treatment group compared with the intensive treatment group. Development of clinically evident diabetic neuropathy is a

Table 1—*Dichotomous clinical and nerve conduction measures used to identify distal symmetrical neuropathy at DCCT baseline and at DCCT completion*

	DCCT baseline	DCCT completion			
	All subjects	Subgroup 1	Subgroup 2	Subgroup 3	Subgroup 4*
Attribute/nerve (*n*)					
Intensive treatment group	711	647	607	470	361
Conventional treatment group	730	606	567	330	228
Clinical evidence of distal symmetrical neuropathy					
Symptoms					
Intensive treatment group	5.8	4.2	2.4†	2.7†	0.3
Conventional treatment group	6.6	7.5	5.5	7.1	1.4
Sensory signs					
Intensive treatment group	22.1	18.3	13.6	12.6	0.3
Conventional treatment group	20.8	21.6	16.2	14.9	1.0
Decreased reflexes					
Intensive treatment group	18.0	17.8‡	13.7‡	11.1	1.2
Conventional treatment group	15.7	25.9	21.7	15.2	3.4
Nerve conduction abnormality of selected nerve					
Abnormal median motor					
Intensive treatment group	20.9	11.4§	11.3§	4.2	3.8
Conventional treatment group	22.8	24.5	25.3	7.4	7.6
Abnormal median sensory					
Intensive treatment group	34.1	39.0	39.8	27.0	25.1
Conventional treatment group	32.0	42.9	44.3	24.0	23.3
Abnormal peroneal motor					
Intensive treatment group	35.4†	23.8§	24.4§	11.2‡	11.2
Conventional treatment group	42.3	46.1	47.9	19.9	17.1
Abnormal sural sensory					
Intensive treatment group	28.5	21.4§	22.2‡	7.4	6.5
Conventional treatment group	26.1	31.3	32.4	6.4	5.7

Data are percent, unless otherwise indicated. The dichotomous clinical and nerve conduction results for DCCT completion reflect analyses after sequentially excluding subjects with confirmed clinical neuropathy, the primary DCCT neuropathy end point (subgroup 1); definite clinical neuropathy (subgroup 2); definite clinical neuropathy or possible clinical neuropathy (subgroup 3); and definite clinical neuropathy, possible clinical neuropathy, or subclinical neuropathy (subgroup 4). Subgroup 4 represents subjects who did not meet any of the DCCT definitions of clinical or subclinical neuropathy. *The prevalence of symptoms and signs in this subgroup is not zero because the neurologist concluded that the potential abnormality consistent with distal symmetrical neuropathy had another explanation (e.g., 11 subjects had diffusely hypoactive or absent reflexes without symptoms or other signs of neuropathy). †$P < 0.01$; ‡$P < 0.001$; §$P < 0.0001$.

consequence of several factors, including age-related neuronal attrition and the cumulative consequences of diabetes. In the absence of other factors producing neuropathy, it is predictable that subjects with subclinical neuropathy would develop clinically evident neuropathy earlier than subjects without subclinical neuropathy. We base this conclusion on the known deterioration over time of all nerve conduction results among normal subjects (age-related neuronal attrition) and, to a greater extent, among diabetic subjects, as demonstrated in the DCCT (8). In this analysis, we evaluated whether significant group differences existed at DCCT completion in terms of symptoms, signs, or electrophysiologic features important to the future development of neuropathy among DCCT subjects who did not fulfill clinical or electrodiagnostic criteria for neuropathy at DCCT completion.

RESEARCH DESIGN AND METHODS

— The DCCT design and eligibility criteria have been described elsewhere (1). Briefly, 1,441 subjects with 1- to 15-year histories of type 1 diabetes who did not have neuropathy requiring medical intervention or treatment and who had only minimal or no microvascular complications were eligible to participate. Subjects were randomly assigned to intensive therapy (administering insulin three or more times daily by injection or by an external insulin pump) or conventional therapy (one to two injections of insulin daily) and followed for 4–9 years (mean 6.5) (1,9). At DCCT baseline, the two treatment groups were similar, with only minor exceptions noted below, in terms of their clinical and electrodiagnostic results. Among the seven categorical clinical or nerve conduction summary measures, only the peroneal nerve conduction was different between treatment groups at baseline (Table 1). That measure showed a lower prevalence of an abnormal result in the intensive compared with the conventional treatment group (35.4 vs. 42.3%, $P = 0.008$). None of the 10 continuous nerve conduction measures showed significant group differences (Table 2). After 5 years of treatment, numerous significant nerve conduction differences were observed between groups, all favoring better function (faster sensory and motor conduction velocities and shorter F-wave latencies) in the intensive treatment group (8).

DCCT assessment of neuropathy

Distal symmetrical polyneuropathy was defined in the DCCT using clinical and electrodiagnostic criteria. Board-certified neurologists who were masked to treatment group assignment performed the

Table 2—*Nerve conduction results at DCCT baseline and at DCCT completion*

	DCCT baseline	DCCT completion			
	All subjects	Subgroup 1	Subgroup 2	Subgroup 3	Subgroup 4
Attribute/nerve					
Intensive treatment group	711	647	608	470	361
Conventional treatment group	730	606	567	330	228
Median motor					
Amplitude (mV)					
Intensive treatment group	10.4 ± 4.1	10.4 ± 3.5	10.5 ± 3.6	10.7 ± 3.6	10.7 ± 3.7
Conventional treatment group	10.4 ± 4.0	10.4 ± 3.3	10.4 ± 3.4	10.7 ± 3.3	10.9 ± 3.4
CV (m/s)					
Intensive treatment group	54.0 ± 4.6	55.0 ± 4.1*	55.0 ± 4.1*	55.7 ± 3.5*	55.8 ± 3.5*
Conventional treatment group	53.8 ± 4.5	52.9 ± 4.6	52.9 ± 4.6	54.4 ± 3.7	54.4 ± 3.7
F-wave latency (ms)					
Intensive treatment group	28.2 ± 2.8	27.7 ± 2.6*	27.7 ± 2.6*	27.3 ± 2.4	27.3 ± 2.5
Conventional treatment group	28.2 ± 2.7	28.8 ± 2.9	28.8 ± 2.9	27.5 ± 2.2	27.4 ± 2.2
Median sensory					
Amplitude (μV)					
Intensive treatment group	21.3 ± 13.3	18.9 ± 13.7	18.8 ± 13.3	20.2 ± 13.4	20.4 ± 13.5
Conventional treatment group	22.3 ± 13.6	17.8 ± 12.4	17.6 ± 12.3	20.7 ± 12.6	21.4 ± 2.2
CV (m/s)					
Intensive treatment group	51.4 ± 7.5	51.5 ± 7.6†	51.4 ± 7.7†	53.0 ± 6.9	53.4 ± 6.6
Conventional treatment group	52.0 ± 7.5	50.1 ± 7.6	50.0 ± 7.7	52.3 ± 6.3	52.9 ± 6.3
Peroneal motor					
Amplitude (mV)					
Intensive treatment group	5.8 ± 2.6	6.0 ± 2.5*	6.0 ± 2.5*	6.3 ± 2.4	6.4 ± 2.4
Conventional treatment group	5.8 ± 2.7	5.4 ± 2.6	5.4 ± 2.6	6.0 ± 2.5	6.1 ± 2.5
CV (m/s)					
Intensive treatment group	43.6 ± 4.7	45.1 ± 4.2*	45.1 ± 4.2*	46.0 ± 3.7*	46.0 ± 3.7*
Conventional treatment group	43.4 ± 4.9	42.0 ± 4.8	41.9 ± 4.9	44.0 ± 3.5	44.4 ± 3.5
F-wave latency (ms)					
Intensive treatment group	50.6 ± 6.7	50.0 ± 5.6*	50.1 ± 5.6*	49.1 ± 4.9‡	49.2 ± 4.7
Conventional treatment group	50.8 ± 7.2	52.2 ± 6.5	52.4 ± 6.6	50.1 ± 5.2	50.0 ± 4.7
Sural sensory					
Amplitude (μV)					
Intensive treatment group	13.4 ± 8.5	12.9 ± 8.6*	12.9 ± 8.9*	14.1 ± 8.2	14.1 ± 7.2
Conventional treatment group	14.0 ± 8.7	11.3 ± 9.5	11.3 ± 9.7	13.5 ± 9.1	13.9 ± 9.1
CV (m/s)					
Intensive treatment group	44.4 ± 6.3	45.9 ± 6.1*	45.9 ± 6.2*	47.3 ± 5.6‡	47.4 ± 5.7
Conventional treatment group	44.9 ± 6.6	43.7 ± 5.9	43.7 ± 6.0	46.1 ± 5.2	46.2 ± 4.9

Data are means ± SD. Results for DCCT completion reflect analyses after sequentially excluding subjects with confirmed clinical neuropathy, the primary DCCT neuropathy end point (subgroup 1); definite clinical neuropathy (subgroup 2); possible clinical neuropathy or definite clinical neuropathy (subgroup 3); and possible clinical neuropathy, definite clinical neuropathy, or subclinical neuropathy (subgroup 4). Subgroup 4 represents subjects who did not meet any of the DCCT definitions of clinical or subclinical neuropathy. CV, conduction velocity. *$P < 0.0001$; †$P < 0.001$; ‡$P < 0.01$.

clinical neurological evaluations and identified causes of neuropathy other than diabetes (1). Nerve conduction studies evaluated the dominant median (motor and sensory), peroneal (motor), and sural nerves using standard techniques and specified anatomical landmarks or stimulation-to-recording electrode distances for each study. Absolute threshold levels for the individual attributes were defined as the median of the upper or lower limits provided by participating laboratories (8).

As shown in Fig. 1, the DCCT study end point of confirmed clinical neuropathy required the presence of both definite clinical neuropathy by the neurologist's examination (defined by at least two of the following: positive responses among symptoms, sensory signs, or absent or hypoactive reflexes consistent with a distal symmetrical polyneuropathy) and an abnormal nerve conduction study consistent with a distal symmetrical polyneuropathy (value above or below the absolute threshold of normal for amplitude, conduction velocity, distal latency, or F-wave latency in at least two anatomically distinct nerves) (1,8). (The original DCCT definition of confirmed clinical neuropathy permitted confirmation of neuropathy based on unequivocally abnormal autonomic test results. However, only 12 subjects fulfilled that criterion, and confirmation of distal symmetrical polyneuropathy in these analyses is based only on appropriate nerve conduction study abnormalities). Subjects with only one abnormal finding among symptoms,

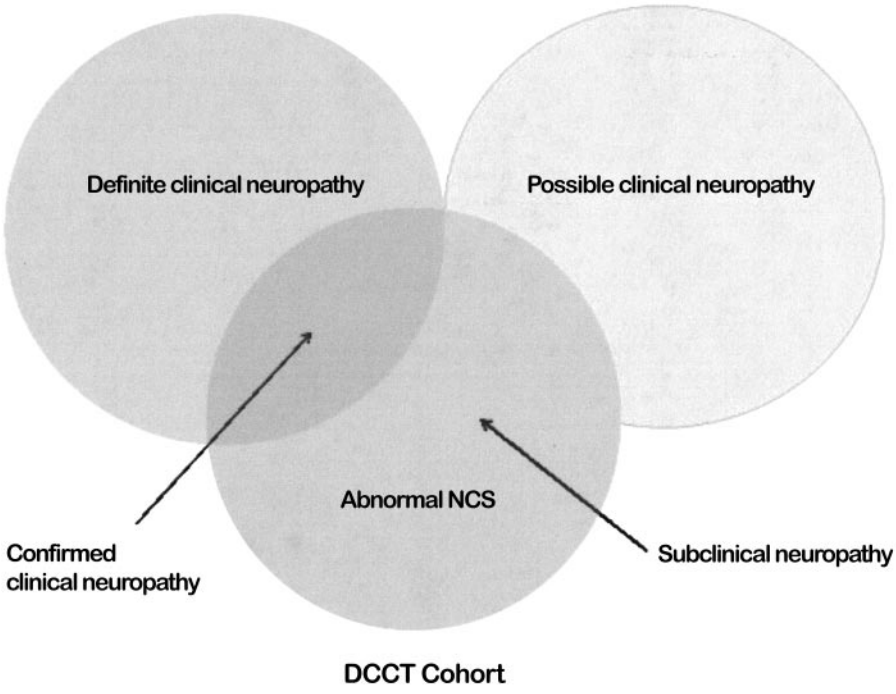

Figure 1—*Categories of distal symmetrical polyneuropathy among the entire population of DCCT subjects, including subjects with possible clinical neuropathy (one positive response among symptoms, sensory signs, or absent or hypoactive reflexes), definite clinical neuropathy (more than or equal to two positive responses among symptoms, sensory signs, or absent or hypoactive reflexes), confirmed neuropathy (definite clinical neuropathy and an abnormal nerve conduction study), and subclinical neuropathy (without definite clinical neuropathy but with an abnormal nerve conduction study). Proportions do not reflect the actual data.*

sensory signs, or absent or hypoactive reflexes, with or without abnormal nerve conduction studies, were classified as having possible clinical neuropathy. The term subclinical neuropathy was used to describe subjects who had an abnormal nerve conduction study suggestive of a distal symmetrical polyneuropathy but who did not fulfill criteria for definite clinical neuropathy.

Statistical analysis

For these analyses, we stratified the DCCT cohort at study completion by systematically excluding subjects with progressively less severe degrees of neuropathy. We first excluded those who fulfilled the primary DCCT end point of confirmed clinical neuropathy and sequentially excluded subjects with definite clinical neuropathy, possible clinical neuropathy, and subclinical neuropathy. In other words, we began by excluding subjects with the strongest evidence of neuropathy and eventually excluded all subjects with any clinical or electrodiagnostic evidence of neuropathy. Treatment groups comprised of the remaining subjects after exclusion of those fulfilling any of the definitions of neuropathy were compared in terms of the results of their neurologic and electrophysiologic evaluations. Treatment group differences were compared with the contingency χ^2 test for categorical (or qualitative) measures of neuropathy and Wilcoxon's rank-sum test for ordinal and numeric (or quantitative) nerve conduction measures. When the sample size was small, Fisher's exact test was used. A global evaluation of treatment groups across all nerve conduction measures was made for subgroup 1 using the O'Brien rank-sum test.

RESULTS — The comparisons of the neuropathy subgroups by treatment are shown in Table 1 (dichotomous clinical and nerve conduction measures) and Table 2 (continuous nerve conduction results). Analyses of subgroup 1, which excluded subjects who had a confirmed clinical neuropathy, showed numerous significant treatment group differences. All of the significant differences reflected better function among the intensive treatment group compared with the conventional treatment group in terms of the prevalence of sensory symptoms, decreased or absent reflexes, or the dichotomous nerve conduction abnormalities beyond the upper or lower limits of normal for the individual nerves. Similarly, the continuous nerve conduction study results were significantly better in the intensive treatment group than the conventional treatment group for 8 of the 10 measures, including all lower-extremity measures. The median motor and peroneal conduction velocities averaged >2 and 3 m/s faster, respectively, among intensive treatment subjects compared with conventional treatment subjects. Peroneal and sural amplitudes also showed significantly better performance (higher values), favoring the intensive treatment group.

Treatment group differences persisted, as additional subjects with progressively lesser degrees of neuropathy were eliminated from the comparisons, although the number of significant treatment group differences and the magnitude of the average group differences diminished. After eliminating subjects with definite clinical neuropathy (subgroup 2) and subjects with definite clinical neuropathy or possible clinical neuropathy (subgroup 3), numerous group differences remained, all of which favored the intensive treatment group. The final column (subgroup 4) in Tables 1 and 2 represents only those subjects who did not meet any of the DCCT definitions of clinical or subclinical neuropathy. That is, subgroup 4 includes subjects without any symptoms, signs, or electrodiagnostic abnormalities possibly attributable to a distal symmetrical polyneuropathy. As expected, none of the dichotomous indictors of neuropathy showed significant treatment group differences, but the continuous electrodiagnostic measures showed significant group differences in median and peroneal motor conduction velocities, reflecting faster conduction velocities in the intensive treatment group compared with the conventional treatment group (55.8 vs. 55.4 m/s, $P < 0.001$ and 46.0 vs. 44.4 m/s, $P < 0.001$, respectively).

CONCLUSIONS — Among subjects who did not meet any of the DCCT definitions of neuropathy at DCCT completion (subgroup 4 in Tables 1 and 2), those in the conventional treatment group had greater levels of subclinical neuropathy than subjects in the intensive treatment group. Subclinical neuropathy in this context, as opposed to the DCCT defini-

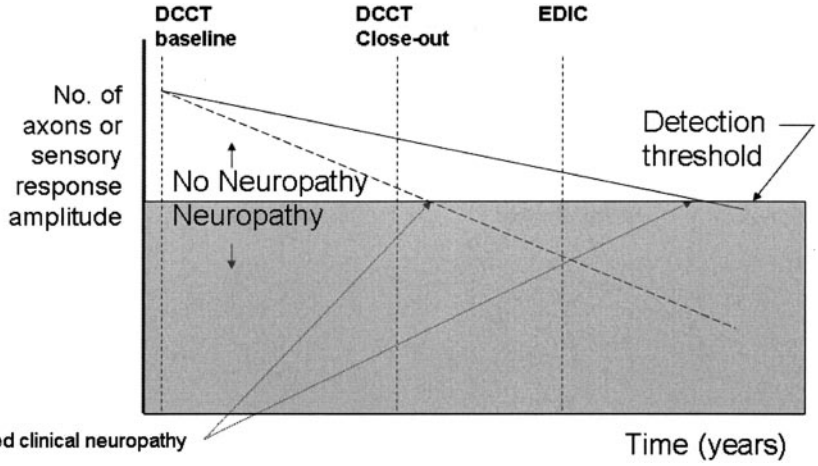

Figure 2—*Concept of a dichotomous (yes/no) definition of neuropathy defined using clinical or nerve electrophysiological criteria, shown in terms of any quantitative measure of neuropathy (such as number of axons or sensory response amplitude) versus time. The boundary between the shaded and unshaded area represents the detection threshold for neuropathy. The solid and dashed lines represent two patients, one of whom (dashed line) was deteriorating (in terms of developing neuropathy) more rapidly than the other (solid line). At DCCT baseline and completion, neither patient fulfilled criteria for neuropathy, yet one subject (dashed line) had a reduced margin of safety for developing neuropathy relative to the other.*

tion, represents a form of asymptomatic neuropathy that has not yet produced clinical signs or abnormal electrophysiology but that is inferred by inferior performance on sensitive nerve conduction studies that, nonetheless, remained within the range of normal. At DCCT completion, 8 of the 10 nerve conduction measures were significantly better in the intensive treatment group compared with the conventional treatment group after excluding subjects with confirmed clinical neuropathy, the primary DCCT end point (O'Brien rank-sum test across all nerve conduction measures, $P < 0.0001$). Because significant treatment group differences remained in the nerve conduction results regardless of the definitions of neuropathy used to exclude subjects from analysis, the two groups consisting of subjects without diagnosable neuropathy at the DCCT completion cannot be considered comparable for future studies of neuropathy.

Dichotomous classifications of neuropathy are well accepted but have limitations, and subjects receiving the same classification may differ substantially in important ways. Figure 2 depicts the temporal change in a hypothetical continuous attribute of neuropathy, such as the number of functioning axons per nerve, for two subjects who are initially identical but who deteriorate at different rates. In this figure, levels of axonal loss that remain above a critical threshold are insufficient to fulfill criteria for a diagnosis of neuropathy. Axonal loss from any cause, including age-related axonal attrition that remains above the threshold, nonetheless reduces the safety margin for developing neuropathy. In terms of the timing of DCCT/EDIC evaluations shown in Fig. 2, the two subjects differed substantially at DCCT completion in terms of the number of axons per nerve but neither fulfilled the dichotomous definition for "neuropathy." The subject deteriorating most rapidly fulfilled diagnostic criteria for neuropathy before the other subject who was deteriorating more slowly and would have done so even if their rates of deterioration had become similar after DCCT completion. Although the representation is hypothetical, it is potentially relevant to explaining the appearance of new-onset neuropathy among DCCT/EDIC subjects.

Few would argue with the concept of an asymptomatic or subclinical neuropathy. Patients without symptoms or signs of neuropathy are frequently found to have electrodiagnostic evidence of neuropathy during evaluation of an unrelated condition. Similarly, electrodiagnostic deterioration within the normal range may reflect a subclinical neuropathy. This concept has application in the context of chemotherapy-induced toxic neuropathy, one of the few situations in which asymptomatic, neurologically intact patients are evaluated sequentially as they develop neuropathy. In such trials, declining sensory amplitudes are used to monitor the onset and progression of neuropathy during chemotherapy. Among these patients, the existence of interval subclinical neuropathy that precedes the onset of symptoms and signs is only inferred. It is reasonable, however, to assume a continuum from normal nerve function to subclinical neuropathy to clinically evident neuropathy that is detectable on neurological examination, despite the predictably small window of severity that can be described as subclinical. For example, patients receiving cisplatin chemotherapy demonstrate a progressive decline in sensory response amplitudes within the normal range early in the course of cisplatin neuropathy, often before symptoms or objective evidence of sensory neuropathy develop (10,11). In studies involving thalidomide, an average decline of 40% from baseline in the sensory amplitude has been recommended as a physiological level associated with the onset of clinically detectable sensory neuropathy (12). This criterion does not depend on the cause of the neuropathy. Using this criterion, patients with baseline sensory amplitudes near or above the normal mean could experience a substantial amplitude decline with neither clinical nor electrodiagnostic evidence of neuropathy. It is these subjects with varying degrees of subclinical neuropathy who we found overrepresented in the conventional treatment group compared with the intensive treatment group and who contribute to the significant group differences we identified.

The DCCT used generic normal values to identify electrodiagnostic evidence of neuropathy. Use of normal values specific for age, sex, and anthropometric features would have likely identified additional subjects with confirmed clinical neuropathy or with subclinical neuropathy because what is normal for an elderly, heavy, tall male will not be normal for a young, slender, short female (13). Had additional subjects been classified with nerve conduction evidence of neuropathy, the pool of subjects without neuropathy may not have shown the same treatment group discrepancies we report.

The question remains whether the small group differences in nerve conduction results are important. In diabetic neuropathy, nerve conduction abnormalities reflect the severity of neuropathic symptoms and signs among patients with diabetic neuropathy (14). Nerve conduction changes associated with diabetic neu-

ropathy include declining response amplitude and conduction velocity, the latter finding differentiating diabetic neuropathy from axonal loss neuropathies. Nevertheless, small changes in conduction velocity could reflect a deleterious effect of relative hyperglycemia on the nerve membrane not associated with axonal degeneration. Clinically detectable and meaningful changes in the neurologic disability score correspond to a change in peroneal amplitude and conduction velocity of ~0.7 mV and 2.0 m/s, respectively (14). Meaningful changes in sensory amplitude (median and sural nerves) are ~3.9 μV. The treatment group differences we found after excluding subjects with confirmed clinical neuropathy for the peroneal nerve (0.6 mV and 3.1 m/s) were near or exceeded the values considered clinically significant for clinical trials. Although the median motor amplitude values did not differ between the treatment groups, the conduction velocity difference of 2.1 m/s did exceed the level considered clinically significant. The average change we observed in the median sensory and sural amplitude (1.3 μV) was less than that considered clinically detectable among diabetic subjects (3.9 μV) (14).

Our results suggest that different levels of subclinical neuropathy in the treatment groups at DCCT completion could contribute to the subsequent onset of neuropathy during EDIC (7). Namely, the timing of incident neuropathy could reflect, at least in part, previous subclinical diabetic-induced neuronal injury, as opposed to predetermined ongoing axonal damage or augmented neuronal apoptosis. In an ongoing EDIC study, the same measures performed in DCCT are being repeated on average 13 years after the completion of DCCT. In the planned analyses, we will adjust for the electrodiagnostic differences between treatment groups at DCCT completion and determine whether prior intensive therapy resulted in sustained improvements in neuropathy independent of treatment group differences at DCCT completion.

Acknowledgments— This work was supported by contracts with the Division of Diabetes, Endocrinology and Metabolic Diseases of the National Institutes of Diabetes and Digestive and Kidney Diseases and the General Clinical Research Centers Programs, National Center for Research Resources.

References

1. The Diabetes Control and Complications Trial Research Group: The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. *N Engl J Med* 329:977–986, 1993
2. Epidemiology of Diabetes Interventions and Complications (EDIC) Research Group: Epidemiology of Diabetes Interventions and Complications (EDIC) design, implementation, and preliminary results of a long-term follow-up of the Diabetes Control and Complications Trial cohort. *Diabetes Care* 22:99–111, 1999
3. The Diabetes Control and Complications Trial/Epidemiology of Diabetes and Complications Research Group: Retinopathy and nephropathy in patients with type 1 diabetes four years after a trial of intensive therapy: the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications Research Group. *N Engl J Med* 342:381–389, 2000
4. Writing Team for the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications Research Group: Effect of intensive therapy on the microvascular complications of type 1 diabetes mellitus. *JAMA* 287:2563–2569, 2002
5. Writing Team for the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications Research Group: Sustained effect of intensive treatment of type 1 diabetes mellitus on development and progression of diabetic nephropathy: the Epidemiology of Diabetes Interventions and Complications (EDIC) study. *JAMA* 290: 2159–2167, 2003
6. Nathan DM, Cleary PA, Backlund JY, Genuth SM, Lachin JM, Orchard TJ, Raskin P, Zinman B, Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) Study Research Group: Intensive diabetes treatment and cardiovascular disease in patients with type 1 diabetes. *N Engl J Med* 353:2643–2653, 2005
7. Martin CL, Albers J, Herman WH, Cleary P, Waberski B, Greene DA, Stevens MJ, Feldman EL, DCCT/EDIC Research Group: Neuropathy among the diabetes control and complications trial cohort 8 years after trial completion. *Diabetes Care* 29:340–344, 2006
8. The Diabetes Control and Complications Trial Research Group: Effect of intensive diabetes treatment on nerve conduction in the Diabetes Control and Complications Trial. *Ann Neurol* 38:869–880, 1995
9. Implementation of treatment protocols in the Diabetes Control and Complications Trial. *Diabetes Care* 18:361–376, 1995
10. Wald JJ, Albers JW, Simmons Z, Roberts JA, Capo B: Cisplatin neuropathy: clinical and nerve conduction correlation. *Muscle Nerve* 17:1116–1117, 1994
11. Albers JW, Berent S: Cisplatin. In *Neurobehavioral Toxicology: Neurological and Neuropsychological Perspectives*. London and New York, Taylor & Francis, 2005, p. 431–436
12. Molloy FM, Floeter MK, Syed NA, Sandbrink F, Culcea E, Steinberg SM, Dahut W, Pluda J, Kruger EA, Reed E, Figg WD: Thalidomide neuropathy in patients treated for metastatic prostate cancer. *Muscle Nerve* 24:1050–1057, 2001
13. Stetson DS, Albers JW, Silverstein BA, Wolfe RA: Effects of age, sex, and anthropometric factors on nerve conduction measures. *Muscle Nerve* 15:1095–1104, 1992
14. Dyck PJ, O'Brien PC: Meaningful degrees of prevention or improvement of nerve conduction in controlled clinical trials of diabetic neuropathy. *Diabetes Care* 12: 649–652, 1989
15. Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications Study Research Group, Jacobson AM, Ryan CM, Cleary P, Waberski B, Burwood A, Weinger K, Bayless M, Dahms W, Silvers N: Long-term effect of diabetes and its treatment on cognitive function. *N Engl J Med* 356:1842–1852, 2007