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Neuropathy Among the Diabetes Control and Complications Trial Cohort 8 Years After Trial Completion

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Abstract

OBJECTIVE—To evaluate the impact of prior intensive diabetes therapy on neuropathy among former Diabetes Control and Complications Trial (DCCT) participants.

RESEARCH DESIGN AND METHODS—At the conclusion of the DCCT, subjects in the intensive group were encouraged to maintain intensive therapy, and subjects in the conventional group were encouraged to begin intensive therapy. Thereafter, we annually assessed neuropathy as part of the Epidemiology of Diabetes Intervention and Complications (EDIC) study. Neuropathy was defined using the Michigan Neuropathy Screening Instrument (MNSI). We recorded potential adverse consequences of neuropathy.

RESULTS—At the first EDIC examination, 1,257 subjects participated in the neuropathy assessment. Consistent with DCCT results, the former intensive group showed a lower prevalence of neuropathy than the conventional group based on positive questionnaire (1.8 vs. 4.7%; $P = 0.003$) or examination (17.8 vs. 28.0%; $P < 0.0001$) results. Despite similar levels of glycemic control, symptoms and signs of neuropathy remained less prevalent among the former intensive group compared with the conventional group. At the beginning of the EDIC study, prior intensive therapy reduced the odds of having symptoms and signs of neuropathy using MNSI criteria by 64% ($P = 0.0044$) and 45% ($P < 0.0001$), respectively, with similar odds reductions observed for both neuropathic symptoms (51%, $P < 0.0001$) and neuropathic signs (43%, $P < 0.0001$) across 8 years of EDIC follow-up.

CONCLUSIONS—The benefits of 6.5 years of intensive therapy on neuropathy status extended for at least 8 years beyond the end of the DCCT, similar to the findings described for diabetic retinopathy and nephropathy.

The Diabetes Control and Complications Trial (DCCT) used a combination of self-reported symptoms, detailed neurological examinations, and nerve conduction studies to identify symptoms, signs, or electrophysiological evidence of distal symmetrical peripheral neuropathy (1,2). The primary neurological end point in the DCCT was the development of “confirmed clinical neuropathy” between baseline and completion of the DCCT, whereas “definite clinical

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A list of the people and institutions participating in the DCCT/EDIC Research Group appears in the APPENDIX.

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

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neuropathy" (symptoms and signs consistent with clinical neuropathy as determined by a board-certified neurologist) served as a secondary end point (1-3). Intensive therapy, designed to achieve glycemic levels as close as possible to the nondiabetic range, reduced the risk of developing confirmed clinical neuropathy by 60–69%, with similar reductions noted for definite clinical neuropathy (1-3).

The Epidemiology of Diabetes Intervention and Complications (EDIC) study is an epidemiologic follow-up of the DCCT cohort (4). The primary study goal is to examine the long-term effects of prior intensive compared with conventional therapy on the development and progression of diabetes complications and cardiovascular disease in type 1 diabetes. Surveillance of neuropathy in the EDIC study is performed annually by the EDIC nurse coordinator or diabetologist using the Michigan Neuropathy Screening Instrument (MNSI) (4,5), a 15-item self-administered patient questionnaire adapted from the Neuropathy Symptom Profile of Dyck et al. (6) and a structured foot examination. In the current analyses, we examined whether the difference in neuropathy status observed between intensive and conventional therapy groups during the DCCT persisted after completion of the DCCT, a time when both treatment groups achieved similar levels of glycemic control.

RESEARCH DESIGN AND METHODS

The DCCT design and eligibility criteria have been described elsewhere (1). Briefly, 1,441 subjects with a 1- to 15-year history of type 1 diabetes who were free of severe neuropathy (defined as neuropathy requiring medical intervention or treatment) and who had no or only minimal, 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) (7). Subjects were followed for 4–9 years (mean 6.5) (1). After completion of the DCCT, subjects in the intensive therapy group were encouraged to maintain intensive therapy and subjects in the conventional therapy group were instructed in and encouraged to adopt intensive therapy. All subjects were referred to their personal physicians for their diabetes and general health care needs. EDIC study annual examinations began in 1994, 1 year after completion of the DCCT. Approximately 95% of the surviving DCCT cohort participated in the follow-up evaluations (4). There were 1,398 EDIC subjects: 696 subjects from the intensive therapy group and 702 from the conventional therapy group, who had at least one MNSI assessment over the first 8 years of the study. EDIC nurse coordinators and diabetologists were trained in a central session and certified to perform the MNSI in the EDIC study. No systematic attempt was made to conceal the prior DCCT group assignment of individual subjects from the nurse coordinator or diabetologist performing the examination.

Outcome measures

Neuropathy status was ascertained annually by EDIC study personnel trained and certified to administer the MNSI, a validated instrument used to identify symptoms and signs of clinically evident neuropathy (4). The MNSI consists of a 15-item questionnaire and a structured examination. Neuropathic symptoms were assessed using the MNSI questionnaire, which inquires about positive (burning, tingling) and negative (numbness) sensory symptoms, cramps and muscle weakness, foots ulcers or cracks, and prior diagnoses of diabetic neuropathy by a physician. Neuropathic signs were assessed using the MNSI examination, a structured assessment of the feet to identify deformities, dry skin, calluses, infection, fissure, or ulcers, and evaluation of ankle reflexes and vibration sensation in the great toe. For this study, neuropathy was defined operationally as seven or more positive responses on the MNSI questionnaire or a score >2.0 on the MNSI examination, thresholds defined by prior validation studies (5,8). The criterion for a positive MNSI examination, the most objective component of

the MNSI, was established to achieve high specificity (95%) and sensitivity (80%), with a positive predictive value of 97% and a negative predictive value of 74% (5). These measures permit us to establish the presence or absence of neuropathy. The MNSI has not been validated as a measure of neuropathy severity. Clinically significant lower-extremity events commonly associated with neuropathy were recorded at each annual EDIC examination, including history or presence of lower-extremity ulcers requiring medical or surgical treatment by a health professional and surgical or traumatic amputations (4).

Glycemic control in the EDIC study

Evaluation of glycemic control was based on measurement of HbA_{1c} (A1C) using the same methods previously described for the DCCT (1). At DCCT completion, A1C was 7.4% in the intensive therapy group and 9.1% in the conventional therapy group ($P < 0.01$). At the first EDIC study examination, A1C separation between DCCT intensive and conventional therapy groups narrowed substantially to 7.9 vs. 8.3% ($P < 0.0001$) (1,9). By the 5th year of the EDIC study, the difference in A1C between groups was no longer significant (8.1 vs. 8.2%, $P = 0.10$) (10,11). By EDIC study year 8, the A1C levels were almost identical for the former intensive and conventional therapy groups (8.0 vs. 7.9%, $P = 0.82$) (11).

Statistical analysis

Analyses were performed according to original DCCT treatment group. Subjects were characterized as fulfilling MNSI questionnaire or MNSI examination criteria for neuropathy in each of the first 8 years of the EDIC study. We compared the frequency of definite clinical neuropathy (as determined by a board-certified neurologist) at the conclusion of the DCCT with neuropathy (as determined using the MNSI) at the first EDIC study evaluation. The effect of the prior DCCT treatment (intensive or conventional therapy) on MNSI neuropathy status and the frequency of lower-extremity events in EDIC study years 1–8 were assessed by contingency χ^2 analyses. The impact of glycemic control on neuropathy status was based on the cumulative mean A1C level (averaged from enrollment in the DCCT to the time of the EDIC neuropathy evaluation) and the concurrent A1C level (obtained at the time of the neuropathy assessment). The marginal odds of achieving a neuropathy-positive outcome (MNSI questionnaire or examination) was estimated using the generalized estimating equations method of Liang and Zeger (12), using a logit link and a Binomial distribution.

RESULTS

Neuropathy status at DCCT completion and EDIC onset

At completion of the DCCT, 19.1% of subjects fulfilled the DCCT criteria for definite clinical neuropathy (15.1% of the intensive therapy group and 23.0% of the conventional therapy group). At the beginning of the EDIC study, 3.3% met the MNSI questionnaire criteria for neuropathy (1.8% intensive therapy and 4.7% conventional therapy), and 22.9% of subjects met the MNSI examination criteria for neuropathy (17.8% intensive therapy and 28.0% conventional therapy) (Table 1). Prior intensive therapy reduced the odds of having symptoms of neuropathy (using the MNSI questionnaire) at the beginning of the EDIC study by 64% (95% CI 27–82%, $P = 0.0044$) and signs of neuropathy (using the MNSI examination) at the beginning of the EDIC study by 45% (27–58%, $P < 0.0001$). Nearly 20% of subjects without neuropathy at DCCT completion fulfilled MNSI examination criteria for neuropathy at the first EDIC study evaluation. At the first EDIC study evaluation, subjects classified with neuropathy at DCCT completion were five times more likely to have a positive MNSI questionnaire (9.7 vs. 1.8%, $P < 0.0001$) and nearly twice as likely to have a positive MNSI examination (37.1 vs. 19.7%, $P < 0.0001$) as subjects without neuropathy at DCCT completion.

Persistence of the DCCT treatment effect on neuropathy during the EDIC study

Despite narrowing of differences in glycemic control between DCCT intensive and conventional therapy groups after completion of the DCCT, prior intensive therapy had a durable effect on the MNSI definition of neuropathy based on the questionnaire and the examination among subjects without confirmed clinical neuropathy at the end of the DCCT (Figs. 1 and 2). Across all annual EDIC evaluations, fewer prior intensive therapy subjects had neuropathy by questionnaire ($P < 0.0001$) or by examination ($P < 0.0001$) compared with prior conventional therapy subjects. The likelihood of neuropathy based on the MNSI questionnaire and the MNSI examination was reduced 51% (95% CI 30–66%, $P < 0.0001$) and 43% (33–52%, $P < 0.0001$), respectively, among subjects with prior intensive therapy compared with conventional therapy across 8 years of EDIC follow-up. There was an unexplained decrease in the frequency of a positive MNSI examination observed over EDIC examination years 5 and 6 for both treatment groups relative to the preceding years, but the separation between former conventional and intensive therapy groups remained consistent across all 8 years of EDIC study follow-up.

Influence of cumulative and concurrent glycemic control on neuropathy

Neuropathy as defined by the MNSI questionnaire and examination was significantly associated with the cumulative mean A1C level. A 1% lower cumulative mean A1C reduced the odds of fulfilling MNSI questionnaire criteria for neuropathy by 38% (95% CI 28–47%, $P < 0.0001$) and MNSI examination criteria for neuropathy by 27% (22–32%, $P < 0.0001$). There was no significant association found between concurrent A1C and either positive MNSI questionnaire or positive MNSI examination.

Lower-extremity events associated with neuropathy

During the study, 15 subjects reported medical or surgical treatment for a total of 22 lower-extremity ulcers (20 foot ulcers and 2 leg ulcers). Fewer subjects in the DCCT intensive therapy group developed foot or leg ulcers than subjects in the conventional therapy group (4 vs. 11, $P = 0.01$). Seven subjects underwent lower-extremity amputations during the first 8 years of the EDIC study. Two were in the former intensive therapy group and five were in the conventional therapy group ($P = 0.45$).

CONCLUSIONS

Neuropathy was defined differently in the DCCT and the EDIC follow-up study. In the DCCT, the diagnosis of definite clinical neuropathy required the presence of symptoms and signs determined by a neurologist to be consistent with a distal symmetrical peripheral neuropathy of the type associated with diabetes. Confirmed clinical neuropathy required additional evidence of nerve conduction abnormalities consistent with diabetic neuropathy. Although it would have been ideal in the EDIC study to repeat the clinical and electrodi-agnostic measures, such detailed evaluations were not available in the EDIC study. The EDIC study evaluations used a validated screening instrument to define neuropathy. Despite general agreement between the results achieved using the two methods, we found a substantially higher prevalence of neuropathy at the start of the EDIC study than at the completion of the DCCT. The prevalence of definite clinical neuropathy we report at the DCCT end differs slightly from that described previously (1,3), which was based on examinations performed after ~5 years in the DCCT, not necessarily at DCCT completion. The neuropathy status at DCCT completion provides the most meaningful comparison to neuropathy status at the beginning of the EDIC study. The higher prevalence of neuropathy found at the beginning of the EDIC study relative to DCCT completion likely reflects the different methodologies and definitions used, rather than interval development of neuropathy. The DCCT definition of neuropathy was more specific than the definition based on the MNSI examination, because it required the clinician to make a clinical

judgment based on all available information about competing explanations for any identified signs.

Consistent with the results of the DCCT, we identified significant treatment group differences in the prevalence of neuropathy at the onset of the EDIC study, favoring former intensive therapy over conventional therapy. This group difference in the prevalence of neuropathy persisted over 8 years of EDIC follow-up, despite a narrowing and disappearance of prior glycemic separation. Neuropathy status in the EDIC study was associated with cumulative mean A1C levels from DCCT entry until the EDIC assessment. The finding of a durable effect of prior intensive therapy on the development of neuropathy is consistent with other reports of beneficial effects of metabolic control on neuropathy (13-15) and with the persistent risk reductions with intensive therapy reported for the development and progression of diabetic retinopathy and nephropathy in this cohort (9,11). Although limited by the small number of events, the disproportionate number of subjects developing leg or foot ulcers, favoring former intensive therapy over conventional therapy, is consistent with the conclusion that intensive therapy provided benefits that extended beyond the completion of the DCCT.

In summary, the beneficial effect of intensive therapy on neuropathy status persisted for at least 8 years after completion of the DCCT. The association between antecedent glycemic control and neuropathy status suggests that intensive therapy has a durable effect on clinically evident neuropathy, similar to the previously demonstrated effects on diabetic retinopathy and nephropathy (9,11). Repeat evaluations, including neurological examination and nerve conduction studies identical to those performed in the DCCT, and quantitative sensory testing to better characterize distal sensation are planned in the EDIC study cohort to confirm these preliminary findings and to assess the impact of changes in glycemic control on neuropathy.

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APPENDIX

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Abbreviations

DCCT, Diabetes Control and Complications Trial; EDIC, Epidemiology of Diabetes Intervention and Complications; MNSI, Michigan Neuropathy Screening Instrument.

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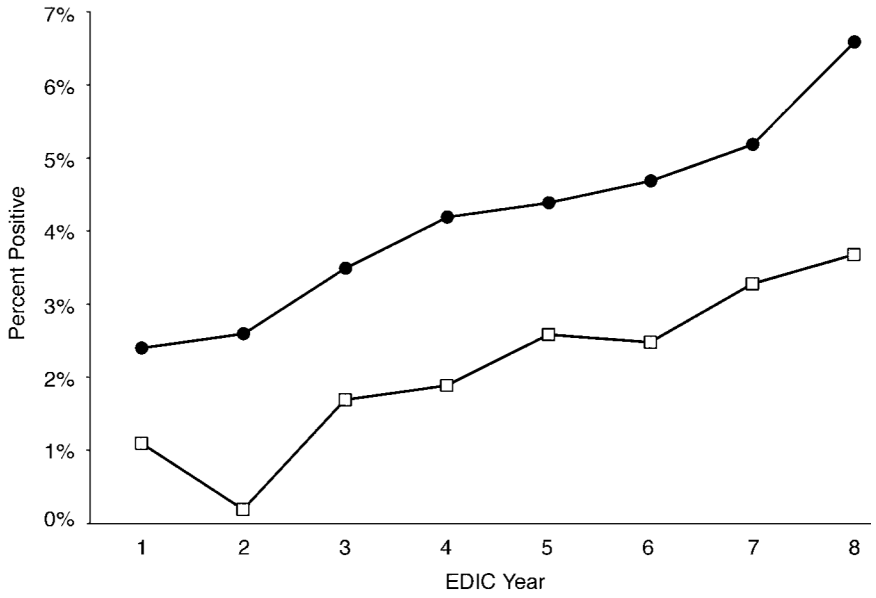

Figure 1.
Frequency of neuropathy-positive MNSI questionnaires across 8 years of the EDIC study among former DCCT conventional therapy (●) and intensive therapy (□) subjects without confirmed clinical neuropathy at the end of the DCCT. P < *0.0001 on average for all EDIC years combined.*

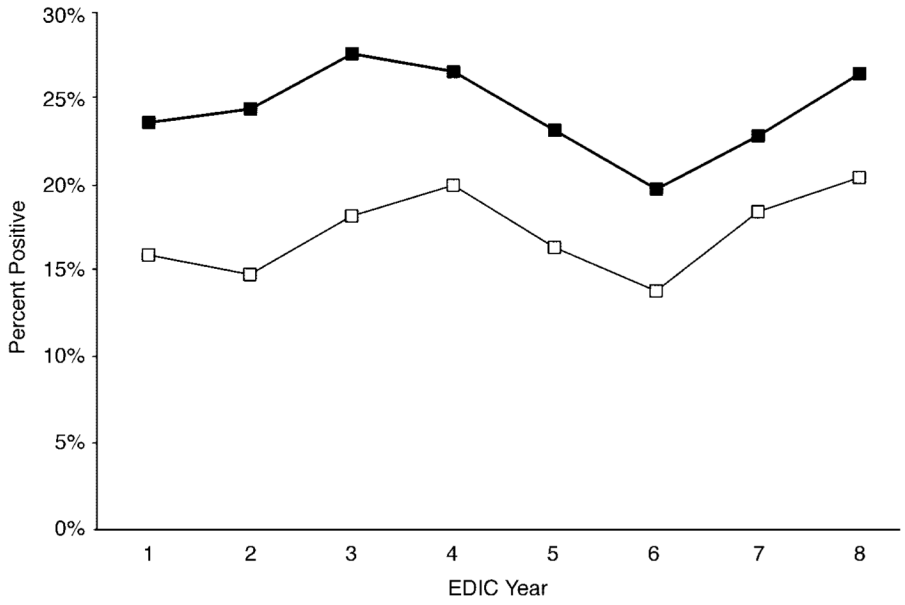

Figure 2.

Frequency of neuropathy-positive MNSI examinations across 8 years of the EDIC study among former DCCT conventional therapy (●) and intensive therapy (□) subjects without confirmed clinical neuropathy at the end of the DCCT. P < *0.0001 on average for all EDIC years combined*.

Table 1

Subjects satisfying MNSI criteria (questionnaire or examination) for neuropathy at the first annual EDIC study examination, separated by DCCT treatment group

	DCCT treatment group		
	Conventional	**Intensive**	***P***
n	633	624	
Neuropathy at EDIC study year 1			
Positive questionnaire	30 (4.7)	11 (1.8)	<0.0001
Positive examination	177 (28.0)	111 (17.8)	<0.0001

Data are *n* (%), unless otherwise indicated.