## THERAPEUTICS

# Intensive glycaemic control prevented or delayed diabetic neuropathy

*The Diabetes Control and Complications Trial Research Group.* ***The effect of intensive diabetes therapy on the development and progression of neuropathy.*** *Ann Intern Med. 1995;Apr 15: 122:561-8.*


### Objective
To determine whether intensive therapy designed to normalise glucose levels prevents or slows the progression of neuropathy in insulin-dependent diabetes mellitus (IDDM).

### Design
Randomised, single-blind, controlled trial with a mean 6.5-year follow-up.

### Setting
29 North American clinical centres.

### Patients
726 patients (52% men) with no retinopathy or microalbuminuria and IDDM for 1 to 5 years formed the primary prevention cohort (PPC). 715 patients (54% men) with mild to moderate nonproliferative retinopathy, an albumin excretion of < 200 mg/24 h, and IDDM for 1 to 15 years formed the secondary intervention cohort (SIC). Mean age was 27 years. Follow-up was 99%.

### Intervention
730 patients (378 PPC and 352 SIC) were assigned to usual care: 1 or 2 insulin injections/d to prevent glycaemic symptoms. 711 patients (348 PPC and 363 SIC) were assigned to intensive therapy: insulin pump or ≥ 3 insulin injections/d with adjustments based on glucose self-monitoring.

### Main Outcome Measures
Confirmed clinical neuropathy (abnormal physical examination confirmed by abnormal nerve conduction or autonomic nervous system dysfunction), clinical neuropathy (abnormal history and physical examination), and subclinical neuropathy (abnormal nerve conduction or autonomic dysfunction).

### Main Results
49 patients switched transiently to usual care; 106 patients switched to intensive therapy (95 because of pregnancy), usually for brief periods. Patients receiving intensive therapy had lower haemoglobin $A_1$ concentrations (7.2% vs. 9.1%; $P < 0.001$). After 5 years, fewer patients receiving intensive therapy than patients receiving usual care had confirmed neuropathy in the PPC (2.8% vs. 9.6% {95% CI for the 6.8% absolute risk reduction [ARR], 2.7% to 11.1%; $P = 0.001$; relative risk reduction [RRR], 71%; number needed to treat [NNT], 15; CI, 9 to 35}*), the SIC (6.7% vs. 16.9% {CI for the 10.2% ARR, 5.3% to 15.5%; $P < 0.001$; RRR, 60%; NNT, 10; CI, 6 to 19}*), and the total cohort (5.0% vs. 13.4% {CI for the 8.4% ARR, 5.2% to 11.8%; $P < 0.001$; RRR, 63%; NNT, 12; CI, 8 to 19}*). Similar benefits were obtained for unconfirmed clinical neuropathy for the PPC (6.8% vs. 15.1% {CI for the 8.3% ARR, 3.2% to 13.6%; $P = 0.003$}*), the SIC (11.7% vs. 21.2% {CI for the 9.5% ARR, 3.6% to 15.3%; $P = 0.002$}*), and the total cohort (9.6% vs. 18.2% {CI for the 8.6% ARR, 4.7% to 12.6%; $P < 0.001$}*).

### Conclusion
Intensive therapy designed to normalise glucose levels prevented or slowed the progression of neuropathy in IDDM.



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* Numbers calculated from data in article.

## Commentary

Neuropathy is one of the most distressing long-term manifestations of diabetes mellitus. Its role in the development of foot lesions is well described (1). Neuropathy comprises a heterogeneous group of disorders that are not easily defined. The study by the Diabetes Control and Complications Trial (DCCT) Research Group brings together the methods of the randomised trial and acceptable definitions of neuropathy.

The value of tight metabolic control in the prevention of diabetic neuropathy has been actively debated for some years. The association of neuropathy with previous poor control (as mentioned in this report) and the improvement of conduction velocities after improvements in glycaemic control (2) have persuaded most clinicians to strive for tight control. The results presented here mean that no doubt now exists, at least for IDDM, that this is the case. The importance of these findings for clinical practice cannot be overemphasised.

As reported in the first DCCT publication (3), a price is paid for this tight control. As would be expected, the frequency of hypoglycaemic episodes was higher in the intensive therapy group. Also, the generalisability of this approach outside the highly motivated group of patients studied by the DCCT Research Group to health care systems with less well-motivated patients and severe resource constraints needs to be carefully thought through. Nevertheless, this and other articles by the DCCT Group are milestones in the development of our understanding of diabetes therapy.


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