

DIABETES

Early intensive insulin slows cardiovascular neuropathy

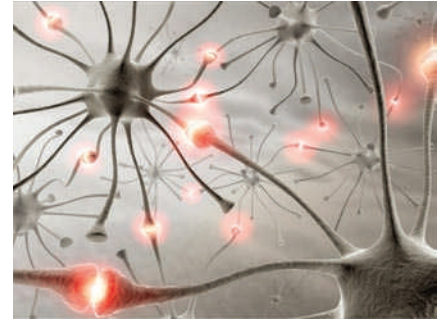
Intensive insulin therapy initiated soon after a diagnosis of type 1 diabetes mellitus has prolonged protective benefits on the cardiac autonomic nervous system, even if glucose levels are not well-controlled in the long term.

The EDIC (Epidemiology of Diabetes Interventions and Complications) study is an ongoing prospective, observational investigation of patients from the Diabetes Control and Complications Trial (DCCT), which was conducted between 1983 and 1993. The DCCT showed that onset and progression of diabetic retinopathy, nephropathy, and neuropathy is slowed by intensive insulin therapy. This finding was fundamental to changes in treatment recommendations for patients with type 1 diabetes. After the DCCT was completed, patients were invited to continue with follow-up evaluations; "...we still have more than 94% active participants in [the] EDIC [study] now, 15 years after [the] DCCT ended, which is remarkable," says Dr Rodica Pop-Busui. In the DCCT, patients were randomly assigned to intensive or standard insulin therapy. After the trial ended, all those who continued to participate were encouraged to follow the intensive insulin regimen.

The primary aim of the EDIC investigation is to determine the effects of diabetes—and the treatment of this

disease—on the autonomic nervous system, and the renal, retinal, peripheral and cardiac sequelae. Damage to the nerves of the heart (cardiovascular autonomic neuropathy; CAN) can manifest as cardiac arrhythmia, which increases the risk of ischemia and cardiac death. In the EDIC study, the presence of CAN was assessed by measuring R–R variability, the Valsalva ratio, and changes in diastolic blood pressure after standing.

These data from the 13th to 14th years of follow-up in the EDIC study showed that the prevalence of CAN had increased in both groups since the end of the DCCT, but was significantly lower among those who had been in the intensive-therapy group than in those who had received the standard regimen. Prior intensive insulin therapy reduced the risk of incident CAN at years 13–14 by 31%. After adjustment for covariates, R–R variability and low Valsalva ratios were more common in patients who initially received standard insulin therapy than among those who were allocated to intensive treatment. Notably, although individuals with prior intensive therapy had better glycemic control than those on the standard regimen when the DCCT closed, there is no longer a significant difference in glycosylated hemoglobin levels between the two groups. "...Although these subjects had a less than optimal control of



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blood glucose for the last 14 years ... the prevalence and incidence of heart nerve damage continued to be much lower in the group that was intensively treated for a mean of 6.5 years during [the] DCCT," concludes Dr Pop-Busui.

The EDIC study is now entering its 16th year and the investigators plan to continue with the follow-up of these individuals. Professor Richard Nesto of Harvard Medical School suggests that "it would be interesting to ascertain what percentage of the reduction of cardiovascular events observed in DCCT/EDIC could have been attributed entirely or in part to the abrogation of the natural history of CAN as a consequence of intensive glycemic control."

Alexandra King

Original article Pop-Busui, R. *et al.* Effects of prior intensive insulin therapy on cardiac autonomic nervous system function in type 1 diabetes mellitus. The Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications Study (DCCT/EDIC). *Circulation* 119, 2886–2893 (2009).