Milestone 13

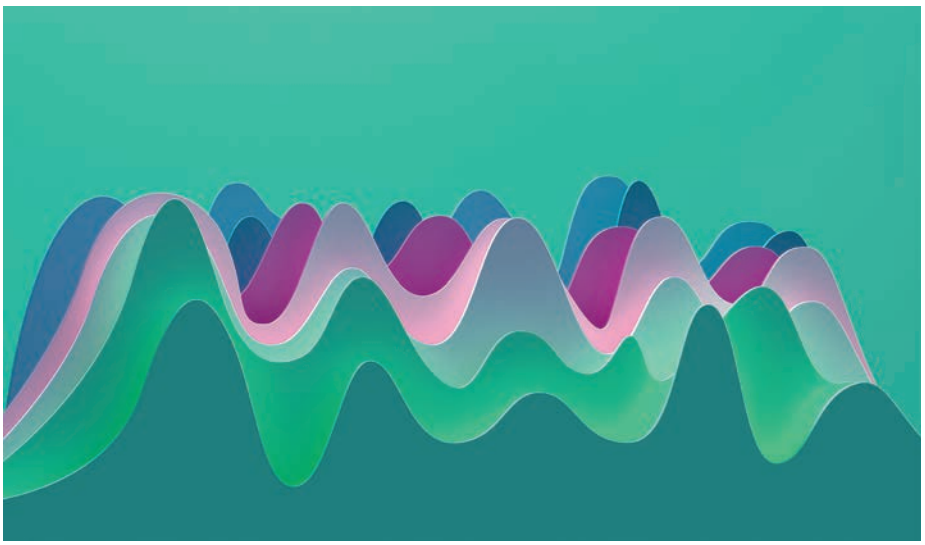
Findings from DCCT — glycaemic control prevents diabetes complications

The complications from type 1, 'insulin-dependent', diabetes include microvascular, neurological and macrovascular sequelae that cause substantial morbidity and mortality (Milestone 5). In 1983, the Diabetes Control and Complications Trial (DCCT) started recruiting patients to examine whether intensive treatment — in which insulin is administered with an external pump or by three or more daily injections of insulin with the goal of achieving glucose control as close to the non-diabetic range as safely possible — could improve outcomes for patients with type 1 diabetes. Compared with standard treatment at the time (one or two daily injections), intensive treatment reduced the occurrence of retinopathy, neuropathy and nephropathy by a range of 35% to >70%. The publication of these results in 1993 marked a new era in diabetes management.

The DCCT was a multicentre, randomized trial that examined patients with type 1 diabetes from two categories: those with no clinical evidence of retinopathy (the 726-patient primary prevention cohort) and those with early retinopathy (the 715-patient secondary intervention cohort). Patients aged 13–39 years were randomly assigned to receive either intensive or standard therapy. The choice of insulin doses in the intensive therapy arm was guided by frequent self-monitoring of blood glucose levels. Patients were followed up for a median of 6.5 years, and the primary outcome was retinopathy.

In the primary prevention cohort, the cumulative incidence of retinopathy was approximately 50% lower in the intensive therapy group than in the standard therapy group. In the secondary intervention cohort, there was an increase in retinopathy in the first year in patients who received intensive therapy. However, from 36 months onwards, patients who received intensive therapy had a 54% lower risk of progression of existing retinopathy than those who received standard therapy. Other end points, including nephropathy and neuropathy, were substantially lower in the intensive therapy group than in the standard therapy group in both cohorts.

The most common adverse event was severe hypoglycaemia, including instances of coma or seizure, which was approximately three times higher in the intensive therapy group than in the standard therapy group. The benefits, however, substantially outweighed the risks, and the study authors recommended intensive therapy for most patients with type 1 diabetes.



"intensive treatment reduced the occurrence of retinopathy, neuropathy and nephropathy by a range of 35% to >70%"

At the conclusion of the DCCT, patients in the standard therapy group were offered intensive therapy and most were enrolled in the Epidemiology of Diabetes Interventions and Complications (EDIC) study, a long-term observational study.

During the EDIC study, the original intensive therapy group continued to have decreased incidence and slower progression of existing retinopathy, nephropathy and neuropathy. More severe microvascular outcomes, cardiovascular disease and mortality were also less common in this group than in the original standard therapy group, which switched to intensive therapy in the EDIC study. The continued separation in outcomes occurred despite the convergence of glycaemic levels between the two original treatment groups. These results suggest that intensive therapy is most effective when started early and that benefits persist throughout therapy. The likelihood of worsening complications, including developing the first signs of complications, strongly correlated with levels of HbA_{1c}, a marker of chronic blood glucose levels.

This seminal work, begun in the DCCT and continued in the EDIC study, established that maintaining blood glucose levels at near-normal values is key to avoiding the complications of diabetes.

Megan Cully Senior Editor,
Nature Reviews Drug Discovery

Milestone study

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)

Further reading

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