



# Diabetes Control: Thanks for the Memories

## Can Good Glycemic Control for a Short Time, Reduce Diabetes Complications Long Term?

Evan D. Rosen, M.D., Ph.D.  
Assistant Professor of Medicine, Harvard Medical School

A little more than a decade ago, a major debate in diabetes was put to rest. The question centered on whether the complications of diabetes, such as kidney, eye, nerve, and cardiovascular disease, were the direct result of high glucose levels. Opponents of this so-called "glucose hypothesis" posited that these complications resulted from other diabetes-related abnormalities (like elevated lipid levels) or from a common inherited predisposition to both diabetes and to complications.

The publication of the Diabetes Control and Complications Trial (DCCT) in 1993 answered this question definitively, at least with respect to type 1 diabetes. In that landmark study, more than 1,400 people with type 1 diabetes were split into two groups. The first group was given "conventional" insulin treatment, which led to them having hemoglobin A1c values of around 9%. The second group received "intensive" insulin therapy, which brought their A1c down to 7.4%. After an average of 6.5 years, a significant reduction in complications was noted in the intensive treatment group. The benefit was clear in terms of eye, kidney, and nerve disease. There were fewer heart attacks and strokes in the intensive group as well, but the overall number of these events was so low that it was difficult to draw meaningful conclusions about cardiovascular disease and diabetes control.

The results of the DCCT study ushered in a sea change in the way we approach diabetes control. We now recommend that patients with diabetes attempt to control their glucose levels with a target hemoglobin A1c of <7% (lower even than the levels achieved with intensive therapy in the DCCT). These recommendations are the same for patients with type 2 diabetes, as later studies in Japan and the United Kingdom indicated the validity of the glucose hypothesis for this population as well.

When a clinical trial is over, the participants are told the results and encouraged to manage their condition in the best possible way given the results of the study. This is exactly what happened to the people in the DCCT, with one exception. After the DCCT ended, the participants continued to be monitored for progression of complications in what was termed the Epidemiology of Diabetes Interventions and Complications (EDIC) Study. The goal of the EDIC study was to see what would happen to these patients after they were taken out of the two original study groups.

First of all, there were big changes in hemoglobin A1c in both groups. The patients in the conventional group saw a reduction in their mean hemoglobin A1c levels down to 8.2% (averaged over the 8 years of the EDIC study); not terrific to be sure, but much better than the 9.1% they had carried through the DCCT years. The intensive group had the opposite trend—liberated from the rigorous control imposed by the DCCT and its enforcement by study nurses and doctors, this group let their glucose control slip a bit, and they settled out at a mean A1c of 8.0%. The net result was that both groups ended up at about the same A1c level within the first year after the DCCT, and stayed there for the remaining 7 years of EDIC.

This "leveling" of glucose control allowed the EDIC researchers to ascertain whether the rate of complications would also even out over time. In fact, this is NOT what happened. What happened was that the complication rate remained significantly lower in the patients that used to be in the intensive group. In a paper published last year, it was noted that the intensively treated folks had

fewer cases of retinopathy. Now, a new paper by the same authors points out that the people who had been treated intensively have a 60% reduced likelihood of developing small amounts of protein in the urine (an early sign of diabetic kidney disease) and an 80% reduced likelihood of developing more serious amounts of urine protein. Although not enough patients had such severe progression of their kidney disease that they required dialysis or transplantation, it was interesting to note that there were fewer cases like this in the people who had been treated intensively in the DCCT. Finally, and perhaps most intriguingly, there was a significantly reduced risk of high blood pressure in the intensive group. And all of this benefit accrued to the intensive group despite the fact that their control was no better than the conventional group over the most recent eight years.

The results of EDIC indicate that there may be a "metabolic memory," where the benefits of a period of good glucose control continue even after A1c levels have slipped. This memory may work in the opposite direction as well. One of the findings of the original DCCT was that it took several years for the intensively treated group to experience reduced complications relative to the conventional group, as if their bodies needed time to get over the preceding years of poor control. One would predict then that over the next several years, the complication rates of the two groups in EDIC will begin to look more and more alike, as the body's "memory" resets to a hemoglobin A1c around 8%.

For patients, it almost certainly doesn't mean that they can strive for a period of good control and then let go, secure in the knowledge that they will always enjoy the benefits of their metabolic memory. But it would be fascinating to learn the cellular and molecular basis of the memory phenomenon. It would then be theoretically possible to identify medications that would trick the body into believing that sugar levels were near normal levels all the time, thus reducing complications without the risks associated with tight glucose control, such as hypoglycemia and weight gain. Until that time, however, there is no substitute for good control, and patients should strive to have the lowest hemoglobin A1c levels possible with an acceptable rate of adverse events.

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#### **References:**

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