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Further Insight on the Limits of Success of Glycemic Control in Type 1 Diabetes

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The successful extraction, purification, and use of insulin in the early 1900s led to greater survival in persons with type 1 diabetes as well as to a better understanding of the impact of diabetes on visual impairment and blindness (1). However, it was not until the completion of the Diabetes Control and Complications Trial (DCCT) that we fully understood the impact of the level of glycemia on the development of complications of diabetes, especially retinopathy (2). The DCCT was designed to assess the relationship between glycemic control and the development, progression, or amelioration of early vascular complications, such as retinopathy, in persons with type 1 diabetes. The trial recruited two groups of persons with type 1 diabetes: those with no complications of diabetes (the primary prevention group) and those with generally longer duration of diabetes and who had mild to moderate diabetic retinopathy and limited albumin excretion in the urine. The persons in these groups were randomly assigned to intensive or conventional diabetes therapy. The trial cohort was followed for a mean duration of 6.5 years. Development and progression of the severity of retinopathy were the primary end points. The trial was well designed and the outcome clearly demonstrated the beneficial effect of intensive glycemic control on the progression of diabetic retinopathy (2).

This landmark trial informed and subsequently transformed the care of persons with type 1 diabetes. Patients in the general population were urged to self-monitor their levels of glycemia and to adjust their insulin doses accordingly (3,4). The functional impact seems to be reflected in the decreased prevalence of visual impairment in persons with type 1 diabetes (3). In fact, projections of the prevalence of severe retinopathy in persons with type 1 diabetes for the U.S. should likely be revised downward based on observed temporal trends (5,6).

After the DCCT ended, the cohort continued to be followed by the Epidemiology of Diabetes Interventions and Complications (EDIC) study. The EDIC study found evidence of the sustained impact of intensive glycemic control on further progression of retinopathy within 4 years of termination of the DCCT; progression was slower in the former intensive treatment group compared with the conventional treatment group despite similar levels of glycemia between the groups (7). This phenomenon was dubbed "metabolic memory," a term sometimes suggested to imply an alteration in the process leading to microvascular disease that might endure. The slower progression of diabetic retinopathy to severe stages, such as proliferative diabetic retinopathy, was noted again 10 years after the conclusion of the DCCT (8) when there was no significant difference in the glycosylated hemoglobin (HbA_{1c}) levels between the original treatment groups, but those in the intensively treated group had a reduced incidence of progression of retinopathy compared with the conventional group. However, the relative reduction in the hazard ratio for progression was diminished compared with those observed 4 years after the DCCT.

In this issue of *Diabetes*, the DCCT/EDIC investigators have reported on the continued follow-up of the study cohort. The 18-year post-DCCT data (9) provide further insights into long-term effects of the level of glycemia on retinopathy and other complications. Those formerly in the DCCT intensive treatment group continue to have a lower cumulative incidence of retinopathy compared with the conventional treatment group, but the yearly incidence of the outcomes is now similar, a further continuation of the trend observed at the 10-year follow-up. The reduction in risk of

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See accompanying article, p. 631.

COMMENTARY

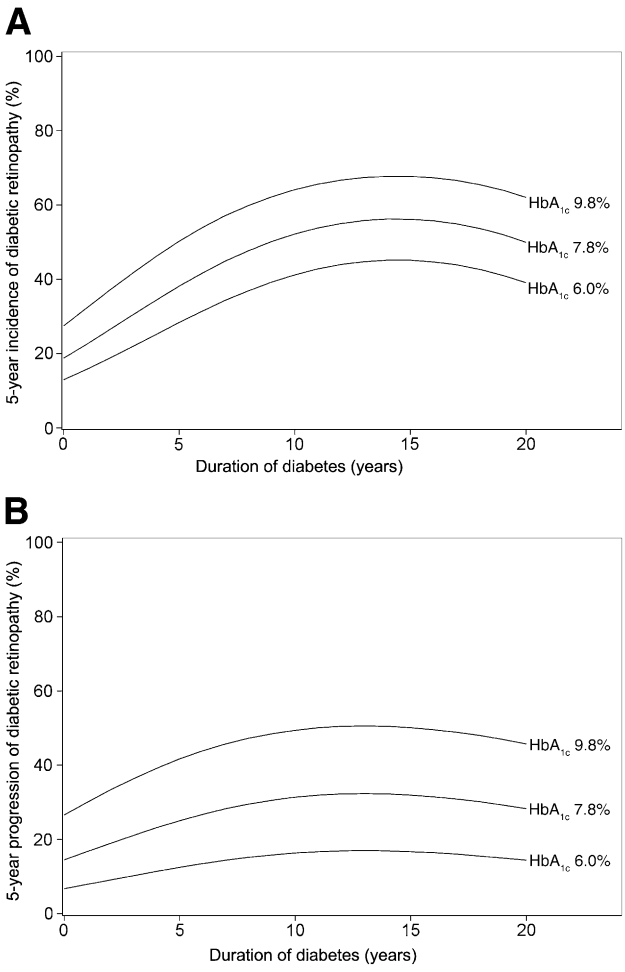

Figure 1—The estimated 5-year incidence (*A*) and progression (*B*) of diabetic retinopathy by level of HbA_{1c} and duration of diabetes. Derived from data from the first three study visits of the Wisconsin Epidemiologic Study of Diabetic Retinopathy. In a general population, individuals with type 1 diabetes and HbA_{1c} of 7.8% (approximately the same HbA_{1c} level of the intensive and conventional groups after the DCCT) were likely to develop retinopathy or have their retinopathy progress within a 5-year interval. Even individuals with HbA_{1c} levels of 6.0% (a level that most patients do not achieve or sustain) and a short duration of diabetes were likely to have incident or progressive retinopathy within 5 years. The risk of incidence and progression rose for individuals with higher levels of HbA_{1c}.

progression of retinopathy appears to be attributable to the protective effects of improved glycemic control. Thus, these carefully collected data corroborate effects seen in population-based studies; namely, the important public health implication that all persons with diabetes appear to benefit by receiving more intensive treatment of glycemia than was received in the past (as recently as 30 years ago). The DCCT/EDIC data also suggest that risk reduction may essentially be due to a cumulative dose effect; that is, the "dose" of HbA_{1c} was lower for an average of 6.5 years in the intensive compared with the conventional treatment group, but when the intensive treatment was no longer imposed, the yearly rate of retinopathy end points became nearly parallel. There may be no "metabolic memory" aside from that of a higher cumulative dose of HbA_{1c} in the conventional group. This was implied in the current article (9) but not directly stated.

The DCCT/EDIC study (9) has further highlighted the most important issue in the care of persons with diabetes—that current treatment regimens are imperfect, with 15.5% of persons in the DCCT intensive treatment group and 31.2% in the conventional group having developed severe nonproliferative retinopathy and with both groups having developed other complications of diabetes. Persons in the intensive treatment group were not willing or able to sustain the regimen imposed on them during the trial, while those in the conventional treatment group were willing and able to tolerate more intervention than they had experienced before or during the trial but not to the extent that the intensive group had. This most recent report from the DCCT/EDIC study shows that years of hyperglycemia and its long-term effects in the retina are still very serious problems for persons with diabetes and the effects are likely corroborated in persons with type 1 diabetes in a general population (Fig. 1). The figure strongly suggests that higher levels of glycemia put an individual at greater risk of incidence (Fig. 1*A*) or progression (Fig. 1*B*) of retinopathy regardless of duration of diabetes and that current methods of glycemic control do not protect patients from retinopathy. Diabetic retinopathy and other microvascular complications appear to be on a continuum of severities; once clinical evidence of complications is observed, it is rare that the progression can be stopped, although progression can be altered by current modes of glycemic control. New methods of glycemic control (and possibly new understanding of other pathological processes that contribute to retinopathy) in type 1 diabetes are needed. Stopping or severely retarding the progress of this disease must be an important research priority with novel approaches toward both the prevention of diabetes and the prevention of development and progression of its complications.

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