Long-term Outcomes in Youths with Diabetes Mellitus

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KEYWORDS

• Diabetes mellitus • Retinopathy • Microalbuminuria • Diabetic neuropathy
• CVD risk factors • Neurocognition • Neuroimaging

KEY POINTS

- Clinically significant diabetes-related complications are uncommon in children and adolescents, but patients with youth-onset diabetes do develop life-altering complications during their young adult years.
- Retinopathy, nephropathy (microalbuminuria), and neuropathy are associated with glycemic control; current levels of glycemic control seem inadequate to completely prevent these complications.
- Cardiovascular disease (CVD) associated with diabetes starts during adolescence, and vigorous attention to CVD risk factors (dyslipidemia and hypertension) is an important component of caring for children and adolescents with diabetes.
- Type 2 diabetes with its onset in youth is likely associated with more and earlier diabetes-related microvascular and macrovascular complications than type 1 diabetes.
- Recent and emerging data show that hyperglycemia as well as hypoglycemia may have lasting effects on brain function and structure, especially in young children.
- Taken together, these considerations support the need for continuing research into new approaches and technology to improve the long-term overall glycemic control of those with diabetes of all ages, including young children.

The Diabetes Control and Complications Trial (DCCT) and its ongoing longitudinal observational follow-up study, the Epidemiology of Diabetes Interventions and Complications (EDIC) study, represent a major turning point in our understanding of the long-term outcomes of type 1 diabetes (T1D). The DCCT clearly demonstrated that intensive therapy for diabetes that lowered hemoglobin A1c (HbA1c) levels by about 2% (9.0%–7.1%) reduced the incidence of onset and progression of diabetic retinopathy (DR), diabetic nephropathy, and diabetic neuropathy by 47% to 54%, 39%, and

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60%, respectively, in both young adults (18–39 years old)[1] and adolescents (13–18 years old)[2] with a diabetes duration of 1 to 15 years at the time of enrollment. During the EDIC follow-up study, the benefits on cardiovascular disease (CVD) outcomes also became apparent with a 42% reduction in CVD events after 17 years.[3] The ongoing EDIC study subsequently showed that these benefits not only persisted but indeed widened at 4[4,5] and 10[6,7] years after the end of the DCCT during a time of equivalent glycemic control between the original conventional and intensive groups in the DCCT; this has been called *metabolic memory*. The between-group differences in complication rates in DCCT and EDIC and the metabolic memory phenomenon were almost entirely a result of the differences in HbA1c between the groups during the DCCT.[4–7] Other factors contributed little if any to these differences.

Intensive therapy, as implemented in the DCCT and along with many subsequent pharmacologic and technologic advances, has now become the standard of care for T1D. With this changing standard of care for T1D during the last 2 decades since the release of the DCCT results, the morbidity and mortality associated with the microvascular and macrovascular complication of T1D has been reduced or delayed but not eliminated.[8] Comparing complication rates from about 20 years earlier to those in the DCCT/EDIC cohort after 20 years of follow-up, the cumulative incidence of proliferative DR (PDR) and nephropathy decreased from 50% and 35%, respectively, to 30% and 12%, respectively; the rates of end-stage renal disease (ESRD) requiring dialysis or transplantation have also declined (**Fig. 1**). The rates of other clinically severe complications also decreased dramatically. There remains no cure or prevention of T1D, and indeed the incidence of T1D and the overall impact of its complications seem to be increasing.

Simultaneous with the changing climate surrounding T1D, and along with the increasing prevalence of childhood obesity not only in the United States but also around much of the developed world, the incidence of type 2 diabetes (T2D) is

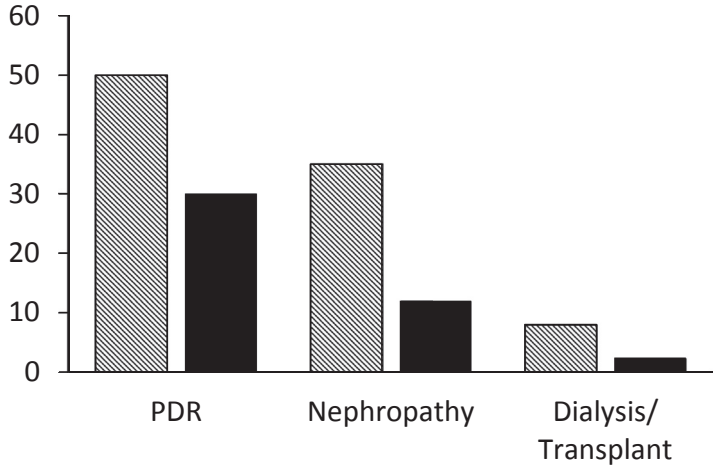

Fig. 1. Cumulative incidence of PDR, nephropathy (≥300 mg/d albumin, serum creatinine ≥2.0 mg/dL, or dialysis/transplantation), and ESRD requiring dialysis or renal transplantation during the pre-DCCT era (*hatched bars*) and the post-DCCT era (*solid bars*). (*Adapted from* Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications [DCCT/EDIC] Research Group. Modern-day clinical course of type 1 diabetes mellitus after 30 years' duration. Arch Intern Med 2009;169(14):1306–16.)