

The TODAY Study: An NIH Perspective on Its Implications for Research

Once referred to as adult-onset diabetes, type 2 diabetes (T2D) has emerged in youth as a consequence of the worldwide increase in obesity. The development of T2D among young individuals has significant public health consequences as these youth are likely to manifest the complications of diabetes, including retinopathy, nephropathy, neuropathy, and cardiovascular disease, at a time that should be the most active and productive of their lives.

In response to the emergence of T2D among youth in the mid-1990s, the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) of the National Institutes of Health sought to foster research to understand and address this public health threat. Since most of our knowledge about the epidemiology of T2D in the pediatric population was based on small clinic-based reports, NIDDK partnered with the Centers for Disease Control and Prevention (CDC) to establish the SEARCH for Diabetes in Youth Study to provide population-based statistics for diabetes in U.S. youth (1). SEARCH data from 2002–2003 indicated that approximately 3,700 youth were being diagnosed annually with T2D (2). T2D is rarely seen in children younger than 10 years. In non-Hispanic white youth 10–19 years of age, T2D represents 15% of the new cases of diabetes. However, T2D predominates in 10- to 19-year-old minority youth, representing 86% of the new cases among American Indians, 70% among Asian/Pacific Islanders, 58% in blacks, and 46% in Hispanics. SEARCH is continuing to ascertain diabetes incidence and is poised to provide critical information on trends in the incidence for both type 1 diabetes and T2D among U.S. youth. SEARCH has also described in great detail the characteristics of U.S. youth with T2D. Perhaps of greatest concern is that 27% of the youth with T2D enrolled in SEARCH had poor glycemic control (hemoglobin A_{1c} ≥9.5%), with the highest rates among those youth from racial/ethnic minority groups (3). These data highlight the need to more effectively treat T2D in youth.

To understand treatment strategies, NIDDK funded the TODAY study (Treatment Options for type 2 Diabetes in Adolescents and Youth) (4). Providers were unsure of how to approach treatment, especially since metformin is the only oral hypoglycemic agent approved for use in children. In addition, adolescence presents special challenges, which means that effective treatments in adults may not be easily transferable to youth. Finally, it was not known whether the pathophysiology and clinical course would be the same when T2D occurs at a young age.

The primary results of the TODAY study, reported last year, demonstrated that T2D may have a much more aggressive course in youth, with approximately half of patients unable to maintain glycemic control on metformin monotherapy despite good medication compliance (5). The data on insulin resistance and secretion derived from serial oral glucose tolerance tests in the TODAY study, published in this issue of *Diabetes Care* (6), suggest early and rapid deterioration of β -cell function in these youth compared with data published on adult individuals with newly diagnosed T2D. These data suggest the need to intervene aggressively and early in youth. Further analysis of the TODAY data may help identify those youth most likely to fail; research is also needed to determine whether high-risk youth could benefit from more intensive, early interventions to prevent the progression to diabetes. The extent to which it is possible to preserve β -cell function early in the course of T2D is not known. NIDDK has recently established the Restore Insulin Secretion (RISE) consortium to study approaches to maintain insulin secretion in adults and children with prediabetes or newly diagnosed T2D. Investigators will use hyperglycemic clamp studies to document the effects of various therapies, including pharmacologic treatments and bariatric surgery, on insulin sensitivity and secretion. Recent data (7) show that dedifferentiation, rather than cell death, may drive β -cell dysfunction in a mouse model of diabetes, suggesting that β -cells may not be irretrievably lost.

TODAY data also highlight the race/ethnic disparities seen in T2D. Both TODAY and SEARCH data have shown that, as in adults, T2D disproportionately affects youth from minority groups. The TODAY cohort (8) was predominately minority (32% African American, 41% Hispanic, 6% American Indian) and of low socioeconomic status (42% with household income <\$25,000); the majority of the TODAY participants came from single-parent households. The economic and psychosocial barriers faced by these families make aggressive glucose control a challenge. The TODAY study previously reported that almost 15% of the participants reported depressive symptoms at baseline (9). Data on poor risk factor control and emerging microvascular disease in this population, detailed in the articles published in this issue of *Diabetes Care* (10–12), are ominous—especially in the context of a rigorous clinical trial with extensive individual attention provided and a population selected for its ability to comply with protocol requirements—and may portend poor outcomes, including early cardiovascular disease. Further follow-up of the TODAY participants will provide valuable information about the development of complications in this population.

The challenges in effectively treating T2D in youth highlight the need for effective prevention of obesity and diabetes. The NIDDK-supported Diabetes Prevention Program (DPP) clearly established the effectiveness of weight loss or metformin in delaying the onset of T2D in individuals at high risk (13). The school-based HEALTHY study, funded by NIDDK with support from the American Diabetes Association, demonstrated that a population-based program could lower rates of obesity and hyperinsulinemia in middle school-aged children, although the combined rate of overweight and obesity fell in both the control and intervention schools (14). Despite these past successes, the TODAY lifestyle program did not lead to sustained weight loss, better body composition (15), or improved glycemic control. Further behavioral research is needed to develop approaches

that will lead to successful lifestyle changes in adolescents, especially those of low socioeconomic status who may face barriers to healthy eating and have limited opportunities for physical activity. The need is imperative to promote research to understand how to establish healthy habits at a young age rather than trying to correct “bad” habits later on.

To prevent obesity and T2D in youth requires tackling another critical issue—the role of metabolic imprinting in contributing to risk. Numerous studies have established that diabetes during pregnancy confers an increased risk of obesity and diabetes in offspring. The Hyperglycemia and Adverse Pregnancy Outcome (HAPO) study, funded by the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD) with support from NIDDK, demonstrated adverse perinatal outcomes at levels of hyperglycemia that are lower than established thresholds for gestational diabetes mellitus (16). NIDDK, with support from NICHD, recently launched a follow-up study of 7,000 mother-child HAPO dyads to examine whether hyperglycemia during pregnancy, less severe than diabetes, leads to adverse metabolic outcomes in the offspring at 8–12 years of age. The TODAY data reported in this issue highlight the need to tackle the effects of diabetes during pregnancy; during the TODAY study, there were 62 pregnancies occurring in 45 participants with six infants having congenital anomalies (17). Further research is needed to understand whether treatment during pregnancy can effectively break the vicious cycle of metabolic imprinting. To address this issue, NIDDK in collaboration with NICHD; the National Heart, Lung, and Blood Institute; the National Center for Complementary and Alternative Medicine; and the Office of Research on Women’s Health has recently launched the LIFE-Moms (Lifestyle Interventions for Expectant Moms) Study, which will test several lifestyle interventions to control weight gain during pregnancy in women who are overweight or obese. The investigators will also follow the women and their offspring up to 1 year after delivery to explore correlations between gestational weight gain and later metabolic status for both mother and baby.

T2D reduces quality of life in individuals with the disease and their families and imposes a huge economic burden on society. The results of the TODAY study lend urgency to the need to better understand the pathophysiology of T2D in youth so that better prevention and treatment strategies can be developed and effectively translated into practice. NIH is committed to building on the TODAY study findings through further research to understand the disease process and develop interventions that can modulate it.

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