

# Youth-Onset Type 2 Diabetes Mellitus: Lessons Learned From the TODAY Study

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## Abstract

Type 2 diabetes mellitus is increasingly diagnosed in obese children and adolescents. Evidence suggests that this disease commonly progresses more rapidly in youth compared with adults and is associated with high rates of early microalbuminuria, hypertension, and dyslipidemia. The Treatment Options for Type 2 Diabetes in Adolescents and Youth (TODAY) study was the first multiethnic, multicenter randomized trial in the United States to compare 3 treatment approaches in obese youth with new-onset type 2 diabetes (n=699; ages 10-17 years): monotherapy with metformin, metformin with rosiglitazone, and metformin with an intensive lifestyle intervention. The primary outcome was glycemic control. Diabetes-related complications and cardiovascular risk factors were also examined. Approximately half of the participants could not maintain glycemic control by using metformin alone. Combination therapy with metformin and rosiglitazone resulted in better durability of glycemic control, and metformin plus intensive lifestyle intervention was intermediate but not superior to metformin alone. Deterioration in glycemic control was associated with rapid loss of beta cell function, not worsened insulin sensitivity, and could not be explained by differences in adherence or body mass index. After 3.9 years, 236 (33.8%) of participants had hypertension and 116 participants (16.6%) had microalbuminuria. Only 55.9% of participants had a low-density lipoprotein cholesterol level less than 100 mg/dL (to convert to mmol/L, multiply by 0.0259) after 3 years, and 71 of 517 participants (13.7%) had retinopathy. The significance of the findings from this important trial for the management of youth and young adults with youth-onset type 2 diabetes and its complications is discussed. An aggressive multifaceted approach is needed to prevent or forestall premature microvascular and macrovascular complications in youth-onset type 2 diabetes.

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The incidence of type 2 diabetes mellitus in children and adolescents is increasing as the rates of childhood obesity have increased. The natural history of youth-onset type 2 diabetes and its complications, and ways in which it differs from that of adult-onset diabetes, are described in this review. Early development of hypertension, microalbuminuria, and dyslipidemia has important implications for monitoring and treatment. The Treatment Options for Type 2 Diabetes in Adolescents and Youth (TODAY) study is the first multiethnic, multicenter randomized trial of youth-onset type 2 diabetes to compare 3 therapeutic approaches to maintaining glycemic control and to examine diabetes-related complications and cardiovascular risk factors over time. This review summarizes the problem of type 2 diabetes in youth and the results of the TODAY study. The significance of the findings from this important trial for the management of type 2

diabetes and its complications in the pediatric population as well as the implications for providers for the care of these individuals as they enter adulthood are discussed (Table 1).

## SCOPE OF THE PROBLEM

Obesity is the most important risk factor for the development of type 2 diabetes in adolescents. Body mass index (BMI) between the 85th and 95th percentile classifies children as overweight, and BMI at or above the 95th percentile for age classifies children as obese.<sup>5</sup> The prevalence of BMI higher than the 95th percentile in children has significantly increased from 1999 to 2004: from 14% to 16% in female adolescents and from 14% to 18% in males.<sup>6</sup> There is a disproportionate increase in the prevalence of overweight and obesity among children from minority groups, approaching 23% in non-Hispanic black and Mexican American adolescents compared with 13% in non-Hispanic white adolescents.<sup>6</sup>



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## ARTICLE HIGHLIGHTS

- Risk factors for the development of type 2 diabetes mellitus in youth are being overweight, having a family history of diabetes, race/ethnicity (black, Hispanic, American Indian, and Asian/Pacific Islander), having signs of insulin resistance (acanthosis nigricans, hypertension, dyslipidemia, polycystic ovarian disease, and having been small for gestational age), and having a maternal history of diabetes or gestational diabetes during the child's gestation
- Metformin therapy is less effective in youth-onset diabetes compared with the adult onset, with poor durability of glycemic control observed in half of the youth in the Treatment Options for Type 2 Diabetes in Adolescents and Youth (TODAY) study
- Deterioration in glycemic control in the TODAY study was associated with rapid loss of pancreatic beta cell function
- The addition of an intensive lifestyle change program to standard diabetes education and metformin therapy did not result in meaningful sustained weight loss and did not significantly improve glycemic control in youth in the TODAY study
- Hypertension, microalbuminuria, and dyslipidemia are common in youth-onset type 2 diabetes

Unfortunately, overweight and obesity in childhood predispose to obesity in adulthood.<sup>7</sup> There is a strong relationship between early-onset obesity and increased risk of diabetes in adults.<sup>8</sup>

Type 2 diabetes, previously diagnosed only in adults, is now increasingly diagnosed in children.<sup>9-13</sup> Recent US data indicate that the rate of new cases of type 2 diabetes among those younger than 20 years is 8.5 per 100,000<sup>14</sup>; approximately 20,000 children in the United States are affected by type 2 diabetes.<sup>15</sup> For Asian/Pacific Islander and American Indian youth aged 10 to 19 years, the rate of new cases of type 2 diabetes is now higher than for type 1 diabetes.<sup>2,14</sup> Risk factors in children include being overweight, having a family history of diabetes, race/ethnicity (black, Hispanic, American Indian, Asian/Pacific Islander), having signs or conditions associated with insulin resistance (including acanthosis nigricans, hypertension, dyslipidemia, polycystic ovarian disease, and having been small for gestational age), and having a maternal history of diabetes or gestational diabetes during the child's gestation.<sup>16,17</sup>

## THE TODAY STUDY: RATIONALE AND DESIGN

As type 2 diabetes emerged in the pediatric population, it was recognized that an understanding of biological differences between youth and adults with type 2 diabetes and their development of diabetes complications is essential for optimal treatment. There was a lack of knowledge concerning the safety and efficacy of oral glycemic control medications used in adults for the management of type 2 diabetes in youth. Only metformin and insulin were approved for use in the pediatric population. Hormonal changes in adolescence coupled with varying physical and emotional factors, including family interactions, peer influences, and poor socioeconomic conditions typically seen in youth-onset type 2 diabetes and obesity,<sup>18</sup> pose unique challenges, especially when promoting lifestyle change. The hypothesis tested in the multisite TODAY trial was that the use of combination treatment in new-onset type 2 diabetes in youth is more effective in maintaining glycemic control than metformin monotherapy.

The TODAY trial evaluated the effectiveness of 3 treatment approaches on glycemic control and studied diabetes-related complications, cardiovascular risk factors, and psychosocial factors in new-onset type 2 diabetes in obese youth (Figure 1).<sup>19</sup> Eligibility criteria included age of 10 to 17 years, recent onset of type 2 diabetes (<2 years), BMI greater than or equal to the 85th percentile for age and sex, availability of a "family support person" (an adult caregiver willing to participate and support the youth participant), negative antibodies to glutamic acid decarboxylase and insulinoma-associated protein 2, and a fasting C-peptide level greater than 0.6 ng/mL (to convert to nmol/L, multiply by 0.331). After a run-in period, in which patients were treated with metformin alone, received diabetes education, demonstrated adherence to medications and attendance at visits, and maintained hemoglobin A<sub>1c</sub> (HbA<sub>1c</sub>) levels at less than 8% (to convert to proportion of total hemoglobin, multiply by 0.01), participants were randomized to receive metformin alone (1000 mg twice daily; 500 mg twice daily if higher doses were not tolerated), metformin with rosiglitazone (4 mg twice daily), or metformin with an intensive lifestyle intervention program.<sup>19</sup> The intensive lifestyle

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