

"TODAY" Reflects on the Changing "Faces" of Type 2 Diabetes

The diabetes landscape has seen unprecedented changes over the recent past. On the one hand, there have been consistent and impressive advancements in clinical care, which include new therapeutic agents, novel dietary approaches, technical advances in glycemic monitoring and closed-loop technology, and a heightened awareness of individuals at risk. The tools required to treat and halt the progression of diabetes complications and the clinical evidence in support of effective management strategies have been established. On the other hand, the need for these developments has never been greater given the global burden of the diabetes epidemic. A particularly disturbing observation is that the "faces" of those who develop type 2 diabetes are becoming younger by the year as evidenced by the reports demonstrating the increased frequency of both type 1 and type 2 diabetes in youth (1–3). Until recent data were made available, it was really not known how adolescents would respond to therapies normally reserved for the adult population. We also had no evidence regarding the rate and severity of the complications in this age-group or the prevalence and progression of other risk factors. In this regard, the TODAY (Treatment Options for type 2 Diabetes in Adolescents and Youth) study has succeeded in filling a major gap in knowledge (4–10). Thus, given the importance of the problem of type 2 diabetes in youth and the need to effectively disseminate the information, our editorial team has elected to feature the TODAY study in this issue of *Diabetes Care*. Specifically, articles from the TODAY study researchers featured in this issue provide new data on the efficacy and safety of clinical treatment and longitudinal observations of specific risk factors and complications for the new "faces" of the type 2 diabetes epidemic—namely, adolescents!

As I reflect on the problem of type 2 diabetes in adolescents, it is now hard to believe it was not that long ago that published reports viewed this condition as rare. For example, in a review reported in 1997, Glaser states, "Most subtypes of NIDDM that occur in childhood are

uncommon, but some, such as early onset of 'classic' NIDDM, seem to be increasing in prevalence" (11). It is also remarkable that only 11 years ago, Drake et al. (12) reported on only four cases of type 2 diabetes in obese, white children in the U.K., at that time a rare observation. In the opening sentence of their article, they state, "Type 2 diabetes is still rare in childhood, but recent reports indicate an increasing prevalence in minority populations around the world. This is particularly the case in the USA, but has also been reported in Japan, Libya, Bangladesh, Australia, and Canada" (12). In their conclusion, Drake et al. state, "As far as we are aware, these are the first cases of type 2 diabetes described in white children in the UK; however, this phenomenon is likely to become increasingly common." Again, I remind you that this report was only 11 years ago, and if a manuscript that described only four cases of type 2 diabetes in youth was submitted today, we would have a hard time justifying publication just based on novelty. However, the early reports did have one thing in common as they all seemed to portend much worse things to come, and that prediction appears to have come to fruition. The increasing frequency of type 2 diabetes in youth, in my opinion, is the most disturbing and worrisome aspect of the current diabetes epidemic.

Before we can even consider management strategies, a key first step would be to ascertain the characteristics of type 2 diabetes in youth, to obtain reliable data on how many children have type 2 diabetes, and to assess changes over time. As outlined in an accompanying commentary from the National Institutes of Health (NIH) (13), which also appears in this issue, these goals were essentially addressed in the SEARCH for Diabetes in Youth Study, a multicenter, epidemiological study initiated in 2000 and funded by the Centers for Disease Control and Prevention (CDC) and the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK). As described, SEARCH evaluated the prevalence, incidence, and classification of diabetes mellitus in youth and was designed to characterize the

burden of both type 1 and type 2 diabetes, along with the associated complications, the levels of care, and the impact on the daily lives of children and youth in the U.S. From this study we now have the critical information about the prevalence and incidence of type 1 and type 2 diabetes and stratification based on age, sex, and race (1,2). Importantly, we now have information on the risk factors and acute and chronic complications of both types of diabetes for adolescents (14–19).

Whereas SEARCH identified and further characterized the problem, TODAY evaluated the treatment strategies. As understood, the only approved therapies for children with type 2 diabetes are either metformin or insulin. In the TODAY study, children and teens aged 10–17 years and within 2 years of a diagnosis of type 2 diabetes were randomly assigned to one of three treatment groups: metformin alone, metformin plus rosiglitazone, or metformin plus intensive lifestyle changes designed to reduce weight and increase physical activity (4). The efficacy of the treatments, reported in 2012 (4), suggested that type 2 diabetes presenting in youth may have a much more aggressive course. Specifically, monotherapy with metformin was associated with durable glycemic control in approximately half of the children and adolescents with type 2 diabetes. Importantly, we learn so much more about the disease in this issue of *Diabetes Care*. As discussed in this issue, we now have new data about insulin sensitivity and B-cell function as favorable effects on insulin action and pancreatic function achieved early in the course of treatment with combination metformin/rosiglitazone may be the major contributing factors explaining the increase in glycemic durability over treatment with metformin alone and metformin plus lifestyle (5). We also learn that initial β -cell reserve and HbA_{1c} observed at randomization appear to be independent predictors of glycemic durability. We now appreciate that the three treatment approaches were generally safe and well tolerated with the most common adverse events being gastrointestinal in nature. Interesting, this adverse event was lower

in the group randomized to metformin/rosiglitazone (6). It was reported that despite differential effects on measures of adiposity among the treatment groups, group differences generally were small and unrelated to treatment effects in sustaining glycemic control (7). Despite the observations on the metformin/rosiglitazone combination, one relevant question will be whether we can expect thiazolidinediones to be part of the routine treatment for children with type 2 diabetes given the concerns with adverse events with use of agents in this class. In this regard, I will refer you to an accompanying commentary on this very important topic appearing in this issue of *Diabetes Care* (20). Specifically, Tamborlane and Klingensmith comment on this very relevant question—and the topic of drug therapy in children in general—and provide a unique perspective for future clinical research in this area.

In addition to the data on glycemic durability and the most effective treatment options, the information from the TODAY study that reports on complications is of great interest. As designed, the TODAY study examined lipid profiles and inflammatory markers and compared changes across the treatment groups. The observations suggest that dyslipidemia and chronic inflammation were common in youth with type 2 diabetes and appeared to worsen over time (8). Despite some treatment group differences in lipid and inflammatory marker change over time, the TODAY study group reports that the specific diabetes treatment as outlined in the study was felt to be generally inadequate to control these specific risk factors (8). The prevalence of retinopathy and its association with HbA_{1c} and diabetes duration in the TODAY cohort was reported to be similar to that previously reported in youth with type 1 diabetes and in adults with type 2 diabetes of known duration (9). Interestingly, adolescents in the highest BMI tertile appeared to have had the lowest prevalence of retinopathy, and the precise mechanism of action underlying the reduced risk of retinopathy in these individuals is unknown. In addition, TODAY provided novel information regarding incidence and progression of hypertension and microalbuminuria. During the TODAY study, hypertension and microalbuminuria were analyzed for effect of treatment, glycemic control, sex, and race/ethnicity, and the prevalence of both increased over time regardless of diabetes treatment (10).

Male sex and higher BMI provided the greatest risk for hypertension, whereas the risk for microalbuminuria was more closely related to glycemic control (10).

It has been approximately 30 years since the initiation of the Diabetes Control and Complications Trial (DCCT), the landmark study evaluating glycemic control and complications in individuals with type 1 diabetes. As well appreciated, type 1 diabetes is considered the primary diabetes presentation in children. Who would have ever thought when the DCCT started that we would be at this stage that we would have to worry about the problem of type 2 diabetes in children? Again, the major concern is that type 2 diabetes has traditionally been a condition we associate with onset in adulthood and one that, when diagnosed in adulthood, is still associated with significant morbidity and mortality over time. And yet, in what seems like a “blink of an eye,” the presentation of the disease has taken on a completely different aspect. What can we expect 10, 20, or even 30 years from now? Indeed, only recently Imperatore et al. (3) estimated the future burden of diabetes in youth by type in the major race/ethnic groups in the U.S. using the most recent population-based estimates of diabetes incidence and prevalence and taking into account demographic changes over time. The authors projected that at the current incidence rates over the next 40 years, the number of youth with type 1 and type 2 diabetes may increase by 23 and 49%, respectively (3). However, from this article, a more dire prediction from the authors stated that “if the incidence of T1DM or T2DM increases, there may be more than a threefold increase in the number of youth with T1DM and about a fourfold increase in the number of youth with T2DM, especially among minority youth” (3).

We are not prepared as a medical community or as a global society at this time to effectively address the growing problem of type 2 diabetes in youth. We should heed the advice as outlined in an elegant editorial by Dr. Robert Ratner, Chief Scientific and Medical Officer at the American Diabetes Association, who stated, “Research and public policy changes are required to slow and ultimately reverse the deleterious impact diabetes has on our population, our health care system, and our economy. Effective strategies must be identified before we are able to move forward on the prevention of type 1 diabetes, but type 2 diabetes must

be addressed now” (21). Until such a coordinated attack on this problem is realized, we can expect to continue to see the increased morbidity and mortality associated with the disease.

If nothing else, with this issue of *Diabetes Care* featuring the TODAY study, it was my clear intent to sound the alarm of type 2 diabetes presenting in youth. As an editorial team, we desired to disseminate novel information on its treatment and to specifically focus on what I feel is one of the most significant medical problems facing our society. The statistics are sobering, and the problem is real! To state that we have a huge challenge ahead and no real solutions is an understatement. I applaud the NIH, the CDC, and the investigators of the TODAY and the SEARCH studies for their work, dedication, and support in providing us with a much better understanding of the problem of type 2 diabetes in youth and novel information on its treatment. These studies provide important first steps, but also provide for a major leap in knowledge that will guide the design of evolving strategies at multiple levels, e.g., health care policy, screening, medical and behavioral intervention, etc., which can begin to address the problem of type 2 diabetes in youth. The steps taken will ultimately help reduce disease burden for the changing and much younger “faces” of the type 2 diabetes epidemic.

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