TODAY Study Sounds Alarm Bell for Youth with Type 2 Diabetes
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Some youths with type 2 diabetes have a more aggressive form of the disease than is seen adults, with a high risk for complications such as early renal and cardiovascular disease, according to a number of new reports from the Treatment Options for Type 2 Diabetes in Adolescents and Youth (TODAY) study, which together form a special section of the June issue of Diabetes Care.

"What was really striking is that [type 2 diabetes]...appears a little more aggressive in children as opposed to adults," editorial author William T. Cefalu, MD, from the Pennington Biomedical Research Center, Baton Rouge, Louisiana, and editor in chief of Diabetes Care, told Medscape Medical News. "Knowing the complications of type 2 diabetes, one can imagine what these children will be faced with in 15 to 20 years down the road."

Dr. Cefalu adds that this "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 solution is an understatement," he writes in an editorial accompanying the studies.

Similarly, Phil Zeitler, MD, from the University of Colorado, Aurora, and TODAY study chair, commented that it is "alarming" that at least a subset of adolescents with type 2 diabetes have an aggressive form of the disease, so that "when they are entering their 20s and 30s [they] will be facing medical problems rather than [concerns] about education and jobs."

Treat Type 2 Diabetes Early and Aggressively in Young

Statistics showed that 3700 youths in the US were diagnosed with type 2 diabetes in 2002 – 2003, and among African American and Hispanic young, half of the new cases of diabetes were type 2, the researchers explain.

To investigate this further, TODAY enrolled 699 overweight or obese youth aged 10 to 17 who had had type 2 diabetes for less than 2 years between 2004 and 2009. The participants were racially diverse, and 64.7% were girls. They were randomized to metformin, metformin plus lifestyle counseling, or metformin plus rosiglitazone (Avandia, GlaxoSmithKline) and followed for an average of 3.9 years.

The primary outcome was treatment failure, defined as HbA1c of 8% or higher for 6 months or a need for insulin. As reported last year in the New England Journal of Medicine, half the children and adolescents were unable to maintain glycemic control with metformin alone and needed insulin (N Engl J Med 2012;366:2247–2256). Treatment with both metformin and rosiglitazone reduced the need for insulin therapy by 25%.

The new series of papers from TODAY examines outcomes for different comorbidities among the youths studied. They illustrate that an alarming number had cardiovascular risk factors, with a third having hypertension by the end of the study period. Similarly, early signs of renal disease almost tripled, and almost 14% of participants developed signs of retinopathy during the course of the trial.

The results also show that participants who had about 50% lower beta-cell function than their peers at randomization did not achieve sustained glycemic control, regardless of subsequent treatment.
Treatment with rosiglitazone, one of the few options available to this age group at the time, reduced the need to transition participants to insulin therapy and appeared to help preserve beta-cell function, which in turn aided glycemic control. Those who received rosiglitazone plus metformin had significantly improved insulin sensitivity in the first 6 months, which was sustained until 4 years, compared with their peers.

"The message here is that if you are going to treat youth with type 2 diabetes effectively, it must be done early and aggressively...to improve beta-cell function and insulin resistance," said lead author of this part of the study, Silva Arslanian, MD, from the University of Pittsburgh, Pennsylvania.

However, because of concerns about cardiovascular and other adverse effects, rosiglitazone is unlikely to be used now in young patients with type 2 diabetes.

Current treatment options are therefore confined to metformin and insulin, indicating a desperate need for new diabetes drugs to be approved for use in children and adolescents with type 2 diabetes, say all the researchers.

Better Ways to Control CVD Risk Factors Needed

Meanwhile, those reporting on cardiovascular-disease (CVD) risk factors concluded that better ways are also needed to control these comorbidities in the young with type 2 diabetes.

More than 1 in 10 of the adolescents in TODAY had hypertension at baseline, and by 3.9 years one third had hypertension, Jane Lynch, MD, from the University of Texas Health Science Center, San Antonio, and colleagues report. Male sex and greater body mass index (BMI) but not poor metabolic control or race/ethnicity were linked with risk for hypertension.

And a total of 6.3% of the TODAY participants had microalbuminuria at baseline, but by 3.9 years 16.6% had this early sign of kidney disease. The rates were similar for boys and girls, but participants who attained glycemic control were less likely to develop this complication.

"These outcomes show evidence of a more rapid progression of hypertension and renal disease risk than we expected to see, and that’s under the best-case scenario of being treated with ACE-inhibitor medications and counseling and very close monitoring," Dr. Lynch said.

Nor did any of the 3 diabetes treatment interventions prevent the worsening of lipids or inflammatory markers over time, Ruth Weinstock, MD, from SUNY Upstate Medical University, Syracuse, New York, and colleagues report in their paper.

Levels of LDL cholesterol, apolipoprotein B, triglycerides, and non-HDL rose over 12 months and stabilized over the next 24 months. The percentage of participants taking LDL-lowering medications or having LDL-cholesterol levels above 130 mg/dL rose from 4.5% to 10.7% over 36 months.

Only 55.9% percent of participants had LDL-cholesterol levels of less than 100 mg/dL over these 3 years, "a frightening number," according to Dr. Weinstock.
"The diabetes treatment was generally inadequate to control this worsening risk," she noted, adding, "We are going to have to find better ways to decrease cardiovascular risk in youth with type 2.

"These are youth we hope will have many decades of life ahead of them, and only half were at goal. I cannot tell you what the future looks like for these youth, but I can tell you I am concerned," she said in a statement.

Time to Intervene Is Before Diabetes Develops

With regard to retinopathy in TODAY, 13.7% of participants developed the nonproliferative form after an average duration of diabetes of 4.9 years, similar to the rate reported for adults with type 2 diabetes, according to Lynne Levitsky, MD, from Harvard Medical School, Boston, Massachusetts, and colleagues.

Adolescents in the highest BMI tertile appeared to have the lowest prevalence of retinopathy — an obesity paradox that has also been reported in adults.

But with regard to obesity per se, reductions in weight were less than hoped for following metformin plus intensive lifestyle interventions and were not sustained beyond 24 months, Kenneth C. Copeland, MD, from University of Oklahoma, Oklahoma City, and colleagues note in another paper.

Meantime, metformin plus rosiglitazone resulted in the best glycemic control but the largest accumulation of body fat.

"What it says is that reductions in body fat and BMI through lifestyle change are extremely hard to accomplish in this group of profoundly affected diabetic youth," Dr. Copeland notes. "The implications are that the time to intervene is before diabetes develops."

According to Barbara L Linder, MD, from the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), Bethesda, Maryland, and colleagues, writing in an accompanying commentary, "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."

In his editorial, Dr. Cefalu says: "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. These studies provide...a major leap in knowledge that will guide the design of evolving strategies."

Key to success will be findings new ways "to break up the logjam of unapproved drugs for adolescents with type 2 diabetes," he and his colleagues write.

William V. Tamborlane, MD, from the Yale School of Medicine, New Haven, Connecticut, and Georgeanna Klingensmith, MD, from the University of Colorado School of Medicine, Aurora, agree.

Due to the restrictions on rosiglitazone, "pediatric diabetes practitioners are left with just metformin and insulin for adolescents with type 2 diabetes," they lament in their commentary.

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