Treatment Options for Type 2 Diabetes in Youth Remain Limited

Colette Meehan, MD, and Janet Silverstein, MD

The incidence and prevalence of type 2 diabetes (T2D) in youth are steadily increasing. The Centers for Disease Control and Prevention recently published the projected prevalence of T2D in youth using the SEARCH for Diabetes in Youth Study database from 2001 for prevalence and 2002 for incidence. Based on these data and assuming a 2.3% increase annually, it is predicted that the prevalence of T2D in youth could quadruple in 40 years.[1] As in adults with T2D, adolescents develop macrovascular and microvascular complications, including albuminuria, hypertension, and dyslipidemia. These complications occur earlier and appear to be more rapidly progressive in youths than in adults.[2] Thus, prevention and treatment of T2D is paramount.

Prevention begins with addressing known risk factors for developing T2D, the most important of which is obesity. Most youths with T2D have a body mass index (BMI) greater than the 85th percentile and are diagnosed between the ages of 10 and 16 years, around the time of puberty and the associated physiologic insulin resistance.[3] Occurrence is familial; 74%-100% of adolescents with T2D have an affected first or second degree relative.[4] Other risk factors for developing T2D are large for gestational age or small for gestational age birthweights and high risk ethnicities. American Indians are the most affected, followed in decreasing order by African Americans, Hispanics, Asian/Pacific Islanders, and non-Hispanic Whites.[3]

Understanding the pathophysiology of diabetes has led to the development of novel treatments. T2D is due to insulin resistance and a relative insulin deficiency due to beta cell dysfunction with eventual beta cell failure. The time to beta cell failure in youth is more rapid than in adulthood, with the rate of beta cell function declining by ~20% per year in 6 youths who underwent clamp studies.[5] Explanations for the beta cell failure include beta cell exhaustion because of increased insulin secretion to compensate for insulin resistance, desensitization of the beta cell because of hyperglycemia (glucotoxicity), lipotoxicity, and a reduction of beta cell mass from amyloid deposition.[6] At diagnosis, many youths have insulin resistance and glucose toxicity and require initial treatment with insulin. Once glucose control is established, most patients transition to oral medication alone or in conjunction with insulin. Lifestyle modification in an effort to achieve weight loss is the cornerstone of treatment, though infrequently sustainable. Overall weight loss and lifestyle changes have been shown to delay or slow the progression of T2D. Achieving a 5% weight loss in adults reduced or delayed the development of T2D and decreased the cardiovascular comorbidities associated with obesity in those with "prediabetes."[7] Multiple studies have shown that lifestyle modifications are more effective than treatment with metformin alone in slowing the progression of T2D in adults. A 43% reduction of progression to T2D at 20 years was found in the Da Qing study[8] and at 7 years in the Finnish Diabetes Prevention Study.[9] In the US Diabetes Prevention Program Outcomes Study, a 34% reduction of progression to T2D was seen at 10 years.[10]

Unfortunately, lasting lifestyle changes are difficult for youth and adults with T2D. The barriers to achieving optimal control include lack of understanding of the disease, poor adherence to medications, and lack of financial resources. A systematic review of 28 articles from 2000-2012 synthesized self-reported barriers to medication adherence by adolescents with chronic illness and reported the top 5 barriers to be forgetting, physical well-being (avoidance of side effects, undesirable changes in appearance, feeling well and believing they did not need their medication), conflicts with their parents, striving for normality, desire for peers' acceptance, and not wanting to feel different than their peers.[11] Many of these youth are from families of low socioeconomic status, which can impact adherence to their diabetes regimen. In the Treatment Options for Type 2 Diabetes in Adolescents and Youth Study cohort, 41.5% of the participants' families had an annual household income of less than $25 000, 26.3% of their parents received an education level less than a high school degree, and only 38.8% lived with both biological parents.[12] Youths and their families with limited financial resources face an undue economic burden. According to the 2014 National Diabetes Statistics Report, the estimated costs associated with the medical care of people with diabetes were 2.3 times higher than in those without diabetes.[13] In addition to lack of family resources, youths may also have difficulty interacting with their peers. Twenty-four

BMI	Body mass index
DPP-4	Dipeptidyl peptidase IV
FDA	Food and Drug Administration
GLP-1	Glucagon-like peptide 1
Hb	Hemoglobin
INGAP	Islet cell neogenesis-associated protein
RYGB	Roux-en-Y gastric bypass
T2D	Type 2 diabetes

From the Division of Endocrinology, Department of Pediatrics, University of Florida, Gainesville, FL

J.S. is conducting clinical trials for Daichi Sankyo and Boehringer Ingelheim; and serves as an Editorial Board member for *The Journal of Pediatrics*. C.M. declares no conflicts of interest.

http://dx.doi.org/10.1016/j.jpeds.2015.11.015

adolescents with T2D participating in a focus group stated that they experienced barriers related to social situations, including embarrassment, feeling different from their peers, and having difficulty seeking acceptance from their peers. They also had difficulty balancing diabetes care with their other social and school demands, resulting in decreased attention to their disease.[14]

Adults with T2D face similar barriers. A systematic review of 80 articles evaluating barriers to diabetes management in adults included poor adherence (failure to take medication, attend physician appointments, and reluctance to start insulin), lack of knowledge about T2D and poor understanding of health outcomes, culture (food and dietary preference, lifestyles, traditional and religious beliefs, and beliefs about health in general), financial strain, competing comorbidities, and lack of social support.[15] Thus, even when youths leave the care of their pediatricians and become adults, many barriers persist. Overall, the treatment of youths with T2D is not only limited by few treatment options, but also many developmental impediments as they navigate the journey from adolescence to adulthood.

This article will focus on the current approved treatments available to adolescents with T2D, discuss newer classes of medications (**Table**), review clinical trials being conducted in youth with T2D, and the role of bariatric surgery.

Methods

A literature search was conducted using PubMed with librarian assistance. We included systematic reviews[4,16-21] as well as retrospective and randomized prospective trials of medications and bariatric surgery that were limited to persons under the age of 18 years with T2D. Only research from the past 10 years was considered. We also reviewed ClinicalTrials.gov looking at active trials using the search terms "type 2 diabetes children" and "type 2 diabetes pediatrics."

Approved Therapies in Children

The only Food and Drug Administration (FDA)-approved medications for the treatment of T2D in youth are metformin and insulin, with lifestyle change considered to be a key component of management. Nonetheless, the ability to maintain lifestyle changes is usually transient in youth and, therefore, is rarely successful for treatment of T2D when used alone. Thus, the current recommendation is to initiate treatment with metformin or insulin in addition to lifestyle changes.[17]

Metformin. The FDA in December 2000 approved metformin for youths less than 18 years of age with T2D. No other oral medications have been approved for this age group. Traditionally, metformin was thought to mainly act to increase hepatic insulin sensitivity, with resultant decrease in the production of glucose in the liver, increased glucose utilization, and decreased lipogenesis.[22] Multiple mechanisms of action have been proposed with the most common explanation being the activation of 5′ adenosine monophosphate-protein kinase by metformin. Meng et al[23] have shown that low concentrations of metformin promote the formation of the heterotrimeric 5′ adenosine monophosphate-protein kinase ($\alpha\beta\gamma$) complex in primary hepatocytes, thus suppressing glucose production. Experiments in rats have shown that metformin results in increased conversion of lactate to pyruvate by inhibiting the mitochondrial isoform of glycerophosphate dehydrogenase, thus, limiting the availability of the gluconeogenic precursors glycerol and lactate.[24] Recently, a phase 2, 12-week, placebo-controlled trial of 240 subjects found that delayed-release metformin (formulated for lower bowel release) had a ~40% increase in potency compared with extended-release metformin, leading the authors to conclude that metformin may have a lower-bowel mechanism of action as well.[25] Benefits of treatment with metformin are lack of weight gain with reports of weight loss when used in conjunction with diet and exercise[26] and low risk of hypoglycemia. Some initial weight loss can be due to associated gastrointestinal symptoms, including diarrhea, abdominal cramping, and flatulence. Besides gastrointestinal side effects, metformin also increases the risk of vitamin B-12 deficiency. Lactic acidosis is a potential adverse event listed on the package insert, but no instances of lactic acidosis have been reported in children. This complication had contraindicated the use of metformin in patients with chronic kidney disease, though, recent studies have shown that metformin may be used in those with mild to moderate chronic kidney disease, with appropriate dosage reduction based on the estimated glomerular filtration rate.[27]

Because of the success of metformin, many studies have focused on comparing potential new T2D drugs with metformin either alone or in combination with metformin. In general, the addition of another medication to metformin lowers hemoglobin (Hb)A1c no more than 1%.[28]

The Treatment Options for Type 2 Diabetes in Adolescents and Youth Study, a multicenter randomized trial in the US, compared 3 treatment regimens for new onset T2D in 10- to 17-year-old youths: (1) monotherapy with metformin; (2) metformin with the thiazolidinedione, rosiglitazone; or (3) metformin with an intensive lifestyle intervention. Thiazolidinediones bind to the peroxisome proliferator-activated receptor, thus, increasing insulin sensitivity. There was an 8- to 24-week run in period and at least 2 years of follow-up in this study. One-half of the participants could not maintain glycemic control with metformin alone over 4 years. The most effective therapy was metformin and rosiglitazone. Metformin alone was inferior to metformin plus lifestyle changes. There was an associated increase in central adiposity in the metformin plus rosiglitazone group, a side effect, which must be considered when choosing a treatment plan.[29] Rosiglitazone is not approved for use in pediatric patients because of concerns about increased risk of heart attacks and strokes,[2] although recent data indicate rosiglitazone is not associated with increased cardiovascular risk.[30] At this point, no long-term studies evaluating the efficacy and safety of thiazolidenediones in youth have been completed.