Type 2 Diabetes Mellitus in Childhood and Adolescence

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EDUCATION AND PRACTICE GAPS

The incidence and prevalence of type 2 diabetes mellitus (T2D) are increasing in children and adolescents as a result of the worldwide pediatric obesity epidemic. It is important to distinguish type 1 diabetes mellitus, which is more common in children, from T2D because clinical phenotypes may overlap at presentation, but clinical course and treatment options differ considerably. Thus, it is crucial to diagnose this disease early and to choose appropriate treatment. In addition, prevention of T2D by directly addressing and preventing or ameliorating excess weight gain in young people is of great importance in primary care.

OBJECTIVES *After completing this article, readers should be able to:*

1. Describe the pathophysiology and risk factors for type 2 diabetes mellitus (T2D) in children and adolescents.
2. Explain that there may be an overlap in the presentation between type 1 diabetes mellitus (T1D) and T2D: children with T1D may be overweight or obese, and children with T2D may present with ketosis or ketoacidosis.
3. Screen appropriate childhood populations for T2D.
4. Recognize that individuals with youth-onset T2D are at higher risk for diabetes-related complications than those with T1D and adults with T2D and, therefore, require careful longitudinal follow-up and treatment.

INTRODUCTION

The pediatric obesity pandemic of the past few decades has been accompanied by an increase in the incidence and prevalence of type 2 diabetes mellitus (T2D) in childhood, with a disproportionate disease burden in children of minority ethnic groups and low socioeconomic status (SES). (1) Childhood-onset T2D is associated with greater risk of microvascular and macrovascular complications than childhood-onset type 1 diabetes mellitus (T1D). (2) Thus, it is incumbent on pediatricians to diagnose children early in the disease course and refer for multidisciplinary intervention and intensive management. This review highlights the latest understanding and insights into this growing epidemic. Specific action points for the primary care pediatrician are highlighted in the text.

AUTHOR DISCLOSURE Dr Levitsky is a consultant to the Eli Lilly Co on a drug treatment trial for type 2 diabetes mellitus in youth. She is a site co-investigator on the TODAY trial. Dr Koren has no financial relationships relevant to this article. This commentary does contain a discussion of an unapproved/investigative use of a commercial product/device.

ABBREVIATIONS

ADA	American Diabetes Association
DKA	diabetic ketoacidosis
FDA	Food and Drug Administration
FPG	fasting plasma glucose
HbA1c	glycohemoglobin
IR	insulin resistance
LGA	large for gestational age
MODY	maturity-onset diabetes of youth
NAFLD	nonalcoholic fatty liver disease
RISE	Restoring Insulin Secretion
SES	socioeconomic status
SGA	small for gestational age
T1D	type 1 diabetes mellitus
T2D	type 2 diabetes mellitus
TODAY	Treatment Options for Type 2 Diabetes in Adolescents and Youth

T2D DEFINITION, DIAGNOSIS, AND SCREENING RECOMMENDATIONS

Definition and Diagnosis

The American Diabetes Association (ADA) classifies T2D as a disorder related "to a progressive loss of beta-cell insulin secretion, frequently on the background of insulin resistance [IR]," in the setting of metabolic stressors, inflammation, and genetic risk. This entity is distinct from T1D, where autoimmune β-cell destruction usually leads to "absolute insulin deficiency," and from other causes of diabetes mellitus in children, such as monogenic diabetes. (3) The diagnostic criteria for diabetes are 2 abnormal test results on the same test sample or on 2 different samples (4): 1) fasting plasma glucose (FPG) level ≥126 mg/dL (≥7.0 mmol/L), 2) plasma glucose level 2 hours after glucose challenge (oral glucose tolerance test of 75 g of glucose given fasting) of ≥200 mg/dL (≥11.1 mmol/L), 3) glycohemoglobin (HbA1c) level of ≥6.5%, and 4) random plasma glucose level of ≥200 mg/dL (≥11.1 mmol/L) with classic symptoms of hyperglycemia and/or hyperglycemic crisis.

Hyperglycemia is a spectrum; individuals whose glucose levels are elevated above the normal range but below these thresholds are considered to have prediabetes and are at increased risk for diabetes and cardiovascular disease.

The diagnostic criteria for prediabetes include the following (4): 1) impaired fasting glucose, defined by the ADA and the International Society of Pediatric and Adolescent Diabetes as an FPG level of 100 to 125 mg/dL (5.5 to <7.0 mmol/L) (5) and by the World Health Organization as an FPG of 110 to 125 mg/dL (6.6–6.9 mmol/L) (6); 2) impaired glucose tolerance, defined by both the ADA and the World Health Organization as a 2-hour postchallenge glucose level of 140 to 199 mg/dL (7.8–11.0 mmol/L) (7); and/or 3) an HbA1c value between 5.7% and 6.4%.

Children diagnosed as having diabetes or prediabetes based on blood glucose or HbA1c criteria then require further clinical or laboratory evaluation to determine whether they have or could develop T2D. HbA1c values may not accurately reflect glycemia in the presence of hemoglobinopathy, anemia, or other altered red blood cell turnover. The correlation between mean blood glucose and HbA1c levels is statistically significant in most people but is not clinically precise.

Recommendations for Screening in Childhood

General screening of all overweight/obese youth is unlikely to be cost-effective because T2D remains relatively rare in children. However, high-risk asymptomatic children and adolescents should be screened, and this screening will often be the province of the primary care pediatrician. The ADA and the International Society of Pediatric and Adolescent Diabetes recommend testing any youth who is overweight (defined as a BMI ≥85th percentile for age and sex) or obese (BMI ≥95th percentile for age and sex) beginning at age 10 years and/or puberty onset, whichever is earlier, and who has 1 or more of the following additional risk factors (8)(9): 1) history of maternal gestational or preexisting diabetes mellitus during the pregnancy, 2) history of being small for gestational age (SGA), 3) member of a high-risk racial or ethnic group (Asian, Native American, Pacific Islander, Hispanic, or African ancestry), 4) family history of T2D in a first- or second-degree relative, 5) signs of IR (usually acanthosis nigricans), and 6) previously diagnosed as having a condition associated with IR (including central adiposity, polycystic ovary syndrome, dyslipidemia, or hypertension).

In addition to these criteria, testing for abnormalities of glucose homeostasis in children and adolescents should be performed in any children with symptoms of hyperglycemia, including polyuria, polydipsia, nocturia or nocturnal enuresis, polyphagia, and/or unexplained weight loss.

Laboratory studies to screen for T2D in the young, as in adults, include measuring a fasting plasma glucose or HbA1c level or performing a 2-hour oral glucose tolerance test. Because hyperglycemia is a continuum, and various factors can influence measurement of HbA1c, these 3 tests do not provide identical results. (4)(9) A single abnormal laboratory test result does not make a diagnosis unless associated with symptoms or laboratory signs of hyperglycemic decompensation (see the Definition and Diagnosis subsection). In addition, if screening results are abnormal, testing should be confirmed on a separate day. (9) If test results are negative, it is recommended that testing be repeated at 3-year intervals or sooner if BMI continues to increase. (8)(9)

Differentiation of T1D, T2D, and Monogenic Diabetes

When a child presents with hyperglycemia, it is important to delineate the etiology, as treatment options, typical clinical course, and associated risks of sequelae may vary. The phenotypes of T1D and T2D may overlap at presentation; children with incident T2D may be asymptomatic or have classic hyperglycemic features, up to 33% may present with ketosis, 5% to 25% may present in diabetic ketoacidosis (DKA), and, rarely, a hyperglycemic hyperosmolar state (with or without DKA) can be seen at presentation. (10) Obesity is also not sufficient to differentiate T1D versus T2D. In the multicenter Treatment Options for Type 2 Diabetes in Adolescents and Youth (TODAY) study cohort, 9.8% of those initially thought to have T2D had at least 1 positive autoantibody associated with T1D, with a higher frequency of autoantibodies seen in non-Hispanic white children. (11) Family history of T2D may or may not be a helpful guide because many children with T1D may also have a family history of T2D. Thus, measurement of diabetes autoantibodies is usually important in the differential diagnosis.

Finally, screening for monogenic diabetes should always be considered. Monogenic diabetes, also known as maturity-onset diabetes of youth (MODY), is the result of a single-gene mutation and is frequently misdiagnosed as T1D or T2D. The SEARCH for Diabetes in Youth Study, a multicenter population-based study of individuals in the United States diagnosed as having diabetes mellitus younger than 20 years, found a 1.2% prevalence of MODY in the pediatric diabetes population. (12) Four and one-half percent of children enrolled in the TODAY trial as having T2D were determined to have monogenic diabetes. (13) The possibility of MODY should be suspected if there is a history of neonatal diabetes (diagnosed within the first 6 months after birth), a multigenerational family history of diabetes mellitus with an affected parent, mild fasting hyperglycemia (especially if young or familial and nonprogressing), and/or diabetes associated with extrapancreatic features such as renal disease or exocrine pancreatic insufficiency. It is important to diagnose MODY because this diagnosis can predict the clinical course, give a unifying diagnosis that may explain other associated signs and symptoms, allow for genetic counseling for the individual and family members, and guide appropriate treatment. Some causes of monogenic diabetes may require no drug treatment or may be treatable with oral sulfonylurea medications alone. The diagnosis of monogenic diabetes involves targeted testing for mutations in the suspected genes. Depending on the practice environment, differentiation among these causes of diabetes may be the province of the primary care pediatrician or a specialist.

EPIDEMIOLOGY OF T2D

Prevalence

The prevalence of youth-onset T2D is rising in the United States and worldwide. The SEARCH for Diabetes in Youth study found a 30.5% increase in T2D prevalence among US youth between 2001 and 2009, from 0.34 to 0.46 per 1,000, and an increased adjusted annual incidence of 4.8%, from 9 to 12.5 cases per 100,000 youths. (1)(14) The incidence and prevalence of T2D differed substantially among individuals of different racial or ethnic groups, being lowest in non-Hispanic white youth and highest in youth of Asian or Pacific Islander descent. (1) The relative frequency of T2D as opposed to T1D in youth, therefore, varies widely in different populations; for example, in Southeast Asia, most new-onset diabetes in youth is T2D rather than T1D, whereas in Europe, the opposite is true. (15)(16)(17)

Clinical Characteristics

Obesity is a significant risk factor in many groups—more than 80% of children and adolescents diagnosed as having T2D in the United States are overweight or obese. (18) By contrast, nearly half of individuals with pediatric T2D residing in urban areas in Southeast Asia are of a normal weight, possibly relating to differences in body composition. (19)(20)

Onset of childhood T2D is generally during puberty; overt T2D is rarely seen in prepubertal children. (8) Of the 20,262 individuals younger than 20 years with T2D in the SEARCH for Diabetes in Youth cohort, less than 2.5% were younger than 10 years (none were <5 years) and 75% were 15 to 19 years of age at diagnosis. (21) The midpubertal peak of T2D diagnosis may relate to insufficiently increased β-cell insulin secretion during the physiologic pubertal increase in IR, leading to hyperglycemia. (22)

Sex also modulates T2D risk. Youth-onset T2D is significantly more prevalent in females than in males in most populations, whereas age-standardized T2D prevalence is higher in adult men than women. (1)(9)(14)(23) The etiology of this difference may include higher muscle mass and lower fat mass in adolescent boys, as well as greater physical activity and greater insulin sensitivity in boys compared with girls. (24)(25)(26)

Maternal Influence

Offspring of women who were overweight or obese but normoglycemic during pregnancy are at higher risk for being large for gestational age (LGA) and having childhood obesity, IR, impaired glucose tolerance, metabolic syndrome, and T2D. (27)(28)(29) In the SEARCH for Diabetes in Youth cohort, maternal obesity increased the risk of youth-onset T2D 2.8-fold. (30) Maternal hyperglycemia increases this risk. The SEARCH for diabetes in the youth study found that children born to a mother with any form of diabetes mellitus were at 5.7-fold higher risk for T2D compared with children of mothers without diabetes. (30) The link between maternal obesity and offspring metabolic risk is likely multifactorial, incorporating genetic predisposition, environmental elements (eg, family dietary and activity patterns), SES, epigenetic modifications in the expression of genes involved in energy homeostasis, intestinal microbiome changes, and other factors. (27)(31)(32) The metabolic risk contribution of maternal hyperglycemia, in addition to all of the factors mentioned previously herein, is likely attributable in part to the resulting compensatory fetal hyperinsulinemia, additive risk of childhood obesity, and decrements in offspring β-cell secretory response to glucose. (33)

Correlates of Birthweight

The risk of youth-onset obesity and T2D is increased in young people born either LGA or SGA. (34)(35) The association between fetal macrosomia and an adverse metabolic phenotype, including greater risk of youth T2D, is partly due to maternal obesity and diabetes, which are associated with increased fetal weight gain. In addition, LGA fetuses are at increased risk for cesarean delivery, associated with 1.6-fold greater odds of

childhood obesity. (36) Fetal SGA is also a well-recognized risk factor for rapid postnatal weight gain, childhood adiposity, and T2D. (37) Explanations include fetal metabolic reprogramming, which predisposes to excess fat accumulation, IR, and T2D in conditions of adequate or overnutrition, (38) and the fetal salvage model positing that an undernourished fetus develops peripheral IR in the context of normal insulin secretion, permitting redistribution of nutrients to the brain. (39) Differential methylation and expression pattern of genes involved in lipid metabolism and glucose homeostasis in SGA infants may offer a molecular explanation for these findings. (40)

CLINICAL FINDINGS AND PATHOPHYSIOLOGY OF T2D

Acanthosis nigricans is a dermatologic marker of hyperinsulinism often seen in children with excess insulin release because of IR. It is not an independent risk factor for T2D in children. Velvety hypertrophic pigmentation is found on the back of the neck, around the umbilicus, under the arms, and in other intertriginous regions. It is often quite hyperpigmented, and the hyperpigmentation is more noticeable in children with somewhat darker skin. (41) Obesity is one of the causes of IR and may often be associated with the finding of acanthosis nigricans. However, acanthosis nigricans does not confirm a diagnosis of diabetes. It only confirms that the child is releasing large quantities of insulin or occasionally other hormones, which directly stimulate the insulinlike growth factor receptors in the skin. All studies of early T2D have determined that it is eventual failure of sufficient insulin release rather than IR that determines onset of T2D.

Causes of IR

IR can be genetic and related to absent or mutated insulin receptors. (42) However, in general, it is acquired and associated with inactivity, obesity, and acute and chronic inflammatory illness. Circulating immunoinflammatory mediators and local changes at the level of the tissue can induce the IR. Adipose tissue is a complex organ, which may induce IR by secretion of hormones and inflammatory cytokines from adipose organ cells, including adipocytes and macrophages. (43)(44) IR can be generalized or specifically located to liver, muscle, and fat or other tissues. (45) Young people with T2D have been demonstrated to have hepatic, adipose, and peripheral IR. (46) Postulated mechanisms include abnormal partitioning of fat in muscle cells, ectopic lipid accumulation in tissues other than adipocytes, elevated free fatty acid levels, and possible mitochondrial dysfunction. (45)(47) Epigenetic imprinting as a result of adverse nutrient exposure can alter metabolic function in both the exposed individual and future offspring. (48) In the most severe kind of genetic IR, children are born with absent or mutated insulin receptors. Babies with complete absence of functional insulin receptors are said to have leprechaunism or Donahue syndrome. They have severe resistance to insulin, which may give them fasting hypoglycemia and postprandial hyperglycemia; are born with marked intrauterine growth restriction; and have other characteristic physical findings. These children usually do not survive more than a year or so. Older children with poorly functioning insulin receptors are said to have Rabson-Mendenhall syndrome. They can have hyperglycemia, severe diabetes, and varying degrees of growth retardation and intellectual impairment. Severe acanthosis nigricans may accompany both types. (42) Many other genetic disorders have been associated with IR because of specific effects on insulin receptor pathways or distribution of lipid stores. Examples include myotonic dystrophy and lipodystrophies. (49)(50) Children with obesity-associated genetic disorders will often be insulin resistant because IR is induced by obesity and inactivity.

Causes of Failure of Insulin Release

Failure of insulin release in individuals with IR has been ascribed to both glucose toxicity and lipotoxicity. (51)(52)(53) Inhibition of mitochondrial metabolism leads to failure of the insulin secretion pathway and eventual metabolic burnout of β cells of the pancreatic islets. (54) However, underlying this burnout are both genetic and epigenetic effects on insulin secretory pathways. For instance, a variety of T2D genetic risk variants have been found to directly affect insulin secretory capacity, (55) and there are direct epigenetic effects on pancreatic islets exposed to hyperglycemia and high levels of fatty acids. (56) By age 4 years, SGA infants have been shown to have diminished insulin secretion as well as IR. (57) LGA neonates seem to mostly have IR at birth but later are at risk for diabetes as a result of diminished insulin secretion. (58) This likely correlates with widespread differential DNA methylation associated with birthweight, indicating epigenetic modification in utero, as well as inherited genetic polymorphisms associated with obesity and T2D. (59)(60) Thus, epigenetically modified patterns of IR and insulin release can become the "gift that keeps on giving" to future generations. The primary care pediatrician can help break this cycle for the next generation by counseling and support regarding maintenance of normal patterns of weight gain during childhood and adolescence.

COMPLICATIONS OF T2D

Acute Complications

Hyperglycemia, DKA, and a nonketotic hyperglycemic hyperosmolar state are the most common acute

complications of T2D. Primary care providers should have a high index of suspicion for such metabolic decompensation, which will usually require hospitalization. Hyperglycemia causes the classic symptoms of thirst, polyuria as a result of glycosuria, and hyperphagia because the brain poorly recognizes the hyperglycemia in the absence of insulin action. Weight loss may occur as a result of poor utilization of energy substrates because of failure of insulin action. Glycosuria may lead to candida infections of the genitalia in males and females. Chronically ineffective insulin action can eventually lead to DKA because relative insulin deficiency leads to breakdown of fat and muscle as well as failure to appropriately metabolize fat and its byproducts, including free fatty acids and ketone bodies. This leads to elevated circulating levels of ketoacids, coupled with dehydration as a result of hyperglycemia and glycosuria. (10) In T2D, there is also greater risk of development of a nonketotic hyperosmolar state because chronic dehydration and the development of hyperosmolarity and hyperglycemia may be more likely when insulin deficiency is relative rather than complete. Nonketotic hyperosmolar hyperglycemia is diagnosed when the blood glucose level is greater than 600 mg/dL (>33 mmol/L), effective plasma osmolality is greater than 320 mOsm/kg (>320 mmol/kg), and ketosis is not significant. It can lead to severe metabolic decompensation and coma and must be treated differently from DKA because it is associated with greater dehydration and greater electrolyte loss with minimal ketosis. Rehydration and electrolyte replacement should be well under way and hyperglycemia should begin to clear with rehydration before insulin therapy is considered. (10)(61)

Long-term Complications

Obesity itself is associated with an increased risk of metabolic syndrome with attendant hypertension, hyperlipidemia, myocardial and vascular remodeling and stiffness, nonalcoholic fatty liver disease (NAFLD), and, in young women, polycystic ovary syndrome. Obesity leads to a shortened life span because of vascular complications and a greatly increased risk of a variety of common solid malignancies. (62) In addition, obesity is a risk factor for increased severity of coronavirus disease 2019 infection in children and adults. (63)(64)

Long-term exposure to hyperglycemia and hyperlipidemia associated with the relative insulin deficiency of T2D increases the risk of hypertension, disorders of dyslipidemia, NAFLD, and chronic complications of diabetes, including microvascular and macrovascular disease, neuropathy, diabetic renal disease, and retinopathy. Large studies comparing the risk of these complications in T1D with those in T2D suggest that T2D is more likely to be associated with severe early complications related to renal disease, hypertension, cardiovascular disease, and perhaps retinopathy. (65)(66)(67) Young people with T2D may develop these complications in an accelerated manner compared with adults with T2D because control of T2D in young people has been so difficult. (68)(69) Therefore, young people diagnosed as having T2D require attentive follow-up and treatment of hyperglycemia as measured by HbA1c level, hypertension, NAFLD as measured initially by liver function studies, hyperlipidemia, polycystic ovary syndrome in young women, microalbuminuria or other evidence of renal disease, neuropathy by symptoms and signs, as well as ophthalmologic follow-up for retinopathy. In general, follow-up will be in the hands of a subspecialist, but primary care providers have important roles to play in maintaining follow-up and treatment and continuity of care so that their knowledge of the different management issues is most important. Most young people with diabetes should be seen at 3-month intervals to obtain HbA1c levels and for clinical assessment of care, with other laboratory studies obtained at least yearly.

PREVENTION OF OBESITY AND T2D

Obesity

Because obesity is a strong risk factor for incident T2D in childhood, public health interventions to reduce excess weight gain are crucial. A detailed discussion of these strategies is beyond the scope of this review, but we review some published approaches and note that determination of bias in studies of obesity is very important. Studies funded by food and beverage companies may be more likely to show bias favoring the company's product, (70) downplay the obesogenic nature of their product, and promote the role of exercise. (71) Thus, it is important to consider possible source bias when evaluating the efficacy of intervention strategies.

Socioeconomic Approaches

Childhood obesity prevalence is considerably higher in individuals of lower SES than in children of families with greater economic means. (72) The etiology of this disparity is multifactorial and includes availability of healthier food at homes and schools, expense of healthy foods versus processed foods, ease of access to purchase healthy foods, marketing of calorie-dense foods and drinks to specific populations, and availability of safe spaces for physical activity. (73)

State ordinances and national laws regarding food labeling and school food programs have attempted to enhance

public education and mandate healthier food. Given the socioeconomic disparities in childhood obesity, it is crucial that studies examining interventions to reduce pediatric obesity focus on the impact of low SES. (74)

Outcome Trials

There have been numerous obesity prevention outcomes trials, aimed at different stages of childhood obesity. Intervention strategies, including those that are parental/home-based, school-based, technology-based, and community-based, have been studied. Home-based interventions have provided resources to parents to encourage familial lifestyle changes, including less calorie-dense foods, more physical activity, and less screen time. School-based strategies have offered healthier meal/snack options and incorporation of greater physical activity during the school day. Technology-based interventions have included online lifestyle counseling. Community-based interventions have used parent groups, community centers, and other resources. The success of these interventions has been modest at best, and many studies report mixed or no results. Few studies showed substantial changes in BMI trends. (75)(76)(77)(78) Collectively, these studies illustrate the challenge of achieving substantial change in BMI trends in youth. Given the prevailing obesogenic environment, this challenge is neither a simple nor a straightforward task. Perhaps new trials targeting multilevel interventions will offer useful future approaches. (79) Nonetheless, on an individual level, targeting families in a pediatric practice with consistent, frequent, and helpful lifestyle management advice and support will prevent and ameliorate obesity in some children and families. (62)

Type 2 Diabetes Mellitus

A variety of studies have examined prevention of T2D in adults. The Diabetes Prevention Program multicenter clinical trial found that intensive lifestyle intervention in high-risk adults reduced T2D incidence by 58% and that metformin therapy reduced T2D by 31% compared with placebo; those effects persisted over 10-year follow-up. (80) Unfortunately, the Diabetes Prevention Program study results have not been replicated in community-based studies because sustained weight loss was generally not achieved and diabetes incidence risk was not reduced. (81) More recently, the Restoring Insulin Secretion (RISE) Consortium conducted a multicenter randomized clinical trial examining the impact of different interventions on preserving or improving β-cell function in adults and adolescents with prediabetes or very early T2D. Pharmacologic interventions in adults included metformin alone, insulin glargine for 3 months to achieve a target fasting glucose level, followed by 9 months of metformin, 12 months of liraglutide and metformin, or 12 months of placebo. β-Cell function after 12 months using an insulin clamp technique was improved in the 3 treatment groups compared with the placebo group. However, when treatment was stopped, 3 months later improvements in β-cell function were not sustained. (82) Therefore, there was an effect on insulin secretion during drug therapy only. In contrast, the same group of investigators also looked at a surgical protocol that randomized participants to adjustable gastric banding or metformin for a total of 24 months of observation. Body weight declined more rapidly in the gastric banding group and stayed lower than baseline and significantly lower than the metformin group at 24 months (10.7 kg vs 1.7 kg). By 24 months, the HbA1c level was significantly lower than at baseline after gastric banding but not after metformin therapy. Finally, there was no evidence of improvement in β-cell function in either group by 24 months. Thus, although β-cell function was not restored, bariatric surgery reduced hyperglycemia more than metformin alone. (83) Bariatric surgery, therefore, seemed to decrease IR in this population with very early changes of T2D.

The outcomes for adolescents with prediabetes or T2D diagnosed within the 6 months before enrollment were different from those for adults. At the time of the study, only metformin and insulin were approved drug options for these young people. Children and adolescents were randomized to receive 12 months of metformin alone versus 3 months of insulin glargine (target fasting glucose level of 79–90 mg/dL [4.4–5.0 mmol/L]) followed by 9 months of metformin therapy; both then had 3 months off treatment. The study found no significant difference between the metformin alone versus the early glargine and metformin treatment arms in HbA1c level, other glycemic markers, or β-cell function, which declined significantly at 12 and 15 months compared with baseline in both groups. (84) Therefore, these Food and Drug Administration (FDA)–approved interventions for the treatment of pediatric T2D failed to preserve β-cell function in youth with newly diagnosed T2D during treatment. This is a much poorer outcome than noted in adults, who are less insulin resistant. This study points to the tremendous need for other therapies.

TREATMENT OF OBESITY AND T2D

Drug Treatment of Obesity

The response to lifestyle modification therapy is limited in obese children and adolescents. Less than 15% of adolescents are reported to have durable weight loss that is clinically significant. (85) A variety of drugs are presently approved for

Table 1. Drug Therapy of Obesity (62)(85)(86)(87)(88)(89)

DRUG CATEGORY	TRADE NAME	EFFICACY (WEIGHT LOSS COMPARED WITH PLACEBO)	ADVERSE EFFECTS	COMMENTS
CNS stimulant/ sympathomimetic[a]				
Benzphetamine	Didrex	Short-term anorexic effect	Addiction, amphetamine effects	Infrequent use
Diethylpropion	Tenuate Tenuate Dospan	Short-term anorexic effect	Addiction, amphetamine effects	Infrequent use
Lisdextroamphetamine	Vyvanse	Mean weight loss of 4.8 lb (2.2 kg) in 4 wk	Anorexia, anxiety, hypertension, cardiovascular reactions	Approved for ADHD in children, not obesity
Phendimetrazine	Bontril Prelu-2	Short-term anorexic effect	Anorexia, anxiety, hypertension, cardiovascular reactions	Infrequent use
Phentermine	Adipex-P Fastin Suprenza Lomaira	BMI decrease 4.1% at 6 mo in adolescents	Anorexia, anxiety, hypertension, cardiovascular reactions	Most commonly used FDA approved for age >16 y
CNS neurotransmitter actions (other)				
Lorcaserin[b]	Belviq Belviq XR	3%–3.6% weight loss at 1 y	Headache, fatigue, dry mouth, depression, nightmares	No data in youth 5-hydroxy-tryptamine receptor agonist
Gut actions				
Liraglutide 3 mg[c]	Saxenda	4%–5.4%	Abdominal pain, nausea, diarrhea, pancreatitis, renal impairment	GLP-1 inhibitor formulation
Metformin (dimethylbiguanide)[d]	Fortamet Glucophage Glucophage XR Glumetza Riomet	BMI *Z* score decrease of 0.1 in 6 mo—less effective in youth	Nausea, gastrointestinal distress, vomiting, B_{12} deficiency; stop with illness, surgery, or intravenous contrast because of small risk of lactic acidosis	Decreases hepatic insulin resistance + direct gut effects on appetite
Orlistat[c]	Xenical Alli	3% weight loss at 1 y	Diarrhea, oily stools, stool leakage, flatulence	Inhibits pancreatic/gut lipase, causing malabsorption
Combination drugs				
Phentermine/topiramate[e]	Qsymia	8.6%–9.3% weight loss at 1 y	Dizziness, insomnia, paresthesia, constipation, dry mouth, anxiety, depression, teratogenic	Topiramate is teratogenic
Naltrexone/buproprion SR	Contrave	3.3%–4.8% weight loss at 1 y	Nausea, constipation, increased suicidal ideation	No data in youth; blocks opioid receptors and selective reuptake inhibitor

ADHD=attention-deficit/hyperactivity disorder; CNS=central nervous system; FDA=Food and Drug Administration; GLP-1=glucagonlike peptide-1; SR=sustained release.

[a]Of the drugs in the CNS stimulant/sympathomimetic class, only phentermine is commonly used long-term; the others are mostly of historic interest. There are no published controlled trials using lisdextroamphetamine for weight loss. It is approved for use in adults for binge eating disorder.

[b]Lorcaserin has been withdrawn by the manufacturer at the request of the FDA because of increased risk of malignancy.

[c]Approved for use in children older than 12 years.

[d]Approved for use in children but off-label use.

[e]Phentermine is approved for short-term use in children older than 16 years. Topiramate is approved for use in children older than 2 years for seizures and older than 12 years for migraines.

the treatment of obesity in adults. Outcomes of these drug therapies remain disappointing, although there may be individuals who have more pronounced responses to treatment, and, therefore, trials of these drugs should be considered.

Present FDA guidelines for approval of a weight-loss drug requires demonstration of 5% weight loss compared with placebo over 1 year. Weight loss of 3% to 9% in the first year of treatment has been reported in adults using

Table 2. Drug Therapy of Type 2 Diabetes (91)(92)(93)

DRUG CATEGORY	TRADE NAME	EFFICACY	ADVERSE EFFECTS	COMMENTS
Metformin[a] (dimethylbiguanide)	Fortamet Glucophage Glucophage XR Glumetza Riomet	Metformin with or without lifestyle modification maintained glycemic control in slightly less than half of TODAY trial youth, T2D participants after 4 y	Nausea, GI distress, vomiting, B_{12} deficiency; stop with illness, surgery, or intravenous contrast because of small risk of lactic acidosis	Decreases hepatic insulin resistance + direct gut effects on appetite
Long-acting insulin analogs[a]		Given SC	Hypoglycemia, weight gain	Long-acting insulin with short-acting insulin before meals is recommended if metformin is not sufficient. Titrate to morning euglycemia without hypoglycemia. Except as noted all insulins are 100 U/mL.
Insulin glargine	Lantus Toujeo Basaglar	Very effective given daily or twice daily		Toujeo is 300 U/mL compared with 100 U/mL for other glargine insulins
Detemir	Levemir	Very effective—often requires twice daily dosing		
Degludec	Tresiba	Very effective—has a long half-life of ≥3 d		Available as 100 or 200 U/mL
Short-acting insulin analogs[a]		Most act within 15 minutes given SC	Hypoglycemia, weight gain	All parenteral short-acting insulins except Fiasp are approved for children; use before meals if basal insulin is not sufficient
Lispro	Humalog			Available as 100 or 200 U/mL
Glusiline	Apidra			
Aspart	Novolog Fiasp			Fiasp is designed to be even more rapid-acting than Novolog Aspart
Inhaled powdered insulin	Afrezza		Decreases pulmonary function by 10%	Not approved for children
Glucagonlike peptide-1 (GLP-1) receptor agonists		Given SC	Diarrhea, nausea, vomiting, (increase in thyroid C-cell tumors in animals)	Slow gastric emptying, inhibit pancreatic glucagon secretion, increase insulin release
Dulaglutide	Trulicity	Given once weekly		
Exenatide	Byetta Bydureon	Given before breakfast and dinner Given once weekly		
Liraglutide[a]	Victoza Saxenda	Given once daily	May worsen renal impairment	Victoza approved for use in T2D >10 y Approved for weight loss only
Lixisenatide	Adlyxin	Given once daily		Also available combined with insulin glargine (Soliqua)

Continued

Table 2. (Continued)

DRUG CATEGORY	TRADE NAME	EFFICACY	ADVERSE EFFECTS	COMMENTS
Sodium glucose co-transporter (SGLT)-2 inhibitors		Oral medications given daily or twice daily	Dehydration, increased urination, genital moniliasis, urinary tract infections, severe genital infections, ketoacidosis without hyperglycemia	Work by increasing renal glucose excretion May decrease cardiovascular risk in high-risk populations
Canagliflozin	Invokana		Decreased bone density	
Dapagliflozin	Farxiga			
Empaglifozin	Jardiance			
Ertuglifozin	Steglatro			
Dipeptidyl peptidase-4 inhibitors		Oral agents usually taken once daily	Nausea, diarrhea, stomach pain, headache, rhinorrhea, skin reactions Joint pain, heart failure	Raises endogenous GLP-1 levels May have increased risk of pancreatitis, pancreatic cancer
Sitagliptin	Januvia			
Saxagliptin	Onglyza			Metabolized in liver
Linagliptin	Tradjenta			
Amylin analogues				
Pramlinitide	Symlin	SC injection before meals separate from short-acting insulin	Nausea, vomiting, headache	Slows gastric emptying suppresses glucagon Relatively low efficacy
Alpha-glucosidase inhibitors		Oral with meals	GI distress	Decrease breakdown of sucrose, fructose, other complex carbohydrates, slowing glucose absorption
Acarbose	Precose			
Miglitol	Glyset			
Sulfonylureas[a]		Second-generation drugs oral once daily	Hypoglycemia, GI distress	Stimulate insulin release—may increase risk of hypoglycemia, cardiovascular disease, may lead to β-cell "burn-out" with need for insulin, other drugs—not used with insulin
Glybenclamide	Glyburide			
Glimepiride	Amaryl			
Glipizide	Glucotrol			
Thiazolidinediones			Weight gain, fluid retention, heart failure worsening, decreased bone density	Insulin sensitizers
Pioglitazone	Actos	Oral once daily	Headache, cough, edema	
Rosiglitazone	Avandia	Oral once or twice daily	Headache, cough, edema	Used in TODAY drug trial but not approved for youth

GI=gastrointestinal; SC=subcutaneous; T2D=type 2 diabetes mellitus; TODAY=Treatment Options for Type 2 Diabetes in Adolescents and Youth; XR=extended release.

[a]FDA approved for use in children.

[b]First-generation drugs such as tolbutamide and chlorpropamide are rarely used; the most common second-generation drugs are listed.

various approved agents, with continued maintained weight loss while receiving medication after 2 to 4 years of only 2% to 4% of baseline weight compared with placebo. This means that on average a 200-lb (91-kg) individual would be expected to weigh 192 to 196 lb (87–89 kg) several years after starting one of these drugs. FDA approval of these treatments has not been dependent on a decrease in serious comorbidities of obesity, although some of the drug treatments have had positive effects on hyperlipidemia and hypertension.

Currently approved drugs for adults and their actions and adverse effects are listed in Table 1. (62)(86)(87)(88)(89) Those that are approved for weight loss or other uses in children are noted. Medications must be continued to maintain weight loss. Both orlistat and liraglutide are now FDA approved in children older than 12 years for such use. (89) Metformin is approved in children for the treatment of T2D and may have a small effect on weight loss and weight maintenance, less in young people than in adults. (90) It is hoped that these drug classes and others in development (eg, agonists of melanocortin receptor 4), which serve to suppress or enhance various components of the central appetite control system, will lead, in combination perhaps, to effective pharmacologic treatments for obesity. In any case, drugs that pharmacologically point to the mechanism for weight loss or modify the homeostatic mechanisms that lead to weight maintenance may point toward future treatment paradigms. (86)

Drug Treatment of T2D in Childhood and Adolescence

Although lifestyle modification including nutritional counseling and increasing exercise and activity are the cornerstones of management of T2D, drug therapy is required for most adolescents with this disorder. (8)(9) Until very recently, the only FDA-approved drugs for the treatment of T2D in young people have been insulin and metformin. Metformin decreases hepatic IR and may lead to slight weight loss, but insulin often enhances weight gain. Liraglutide, which is a glucagonlike peptide-1 receptor agonist, is now approved for treatment and has greatly extended the armamentarium in the treatment of youth younger than 18 years with T2D. (91) We anticipate that many of the other classes of drugs presently available to treat adults with T2D will become available to the younger age group, who are so poorly served by insulin and metformin alone. Nonetheless, we recognize that many pediatricians care for young people older than 18 years and wish to better understand presently available drug treatment paradigms. Drugs for the treatment of T2D are briefly described in Table 2. A comprehensive management algorithm describing the use of the many classes of drugs available to lower blood glucose levels in individuals older than 18 years is a useful reference. (92)

The newest ADA Standards of Medical Care for Children and Adolescents suggest that in obese youth with T2D, insulin should be used initially to control severe metabolic decompensation, or in youth with HbA1c levels greater than 8.5% during metformin titration. However, in youth who present without severe symptoms and in whom T2D has been confirmed by absence of T1D antibodies, liraglutide should be considered if metformin and lifestyle change are not sufficient to lower blood glucose levels into an acceptable range. Initiation of insulin therapy is an alternative recommendation. (93) Based on adult data and this guideline, we suggest that liraglutide is the drug of choice in most young people with confirmed T2D if metformin and lifestyle change are not sufficient. Insulin therapy should be reserved for youth who present with metabolic decompensation (DKA or hyperosmolar hyperglycemic state), or HbA1c level greater than 8.5%, and it can often be discontinued after recovery and the addition of lifestyle changes, metformin, and liraglutide to the regimen. Insulin should also be used for young people who do not have excellent control of blood glucose (HbA1c level ≤7%) after the addition of liraglutide to management.

Hyperglycemia is not the only factor in the development of long-term complications of T2D. It is also important to treat and prevent the comorbidities and complications of T2D, including hypertension, hyperlipidemia, retinopathy, and renal disease. Angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers should be first-line drugs in all individuals with hypertension or microalbuminuria. Pregnancy is a known contraindication. These agents can lead to fetal malformations because of decreased fetal urine output, so adolescent girls must be warned and receive adequate contraception. Hyperlipidemia should be treated using statin drugs if diet modification is insufficient. Because of the serious fetal developmental neurotoxicity of these agents, adolescent girls should receive adequate contraceptive advice and be warned about this worrisome adverse effect. Smoking is another major risk factor for vascular complications and retinopathy. It should be discouraged, and effective smoking cessation programs should be used if necessary. (8)(9) Because nicotine is the likely risk factor in animal studies, "smokeless" devices for the delivery of nicotine should not be considered protective. (94)(95) The primary health-care provider can play a most important role in initiating and reinforcing these associated management approaches.

Bariatric Surgery for Treatment of Both Obesity and T2D

Surgical procedures to decrease nutrient intake have included approaches to restrict food intake by limiting the size of the gastric pouch, facilitate malabsorption, or a

combination of the two. A Roux-en-Y gastric bypass procedure both creates a small stomach pouch and leads to malabsorption because the small created gastric pouch is joined to a segment of jejunum, bypassing the rest of the stomach and the duodenum. A vertical sleeve gastrectomy, used often in adolescents, reduces the size of the stomach but does not lead to malabsorption. Laparoscopic gastric banding, which restricts stomach size, is rarely used at the present time because of a high rate of ongoing complications and need for reoperation. (62) Bariatric surgery can treat both obesity and T2D. The multicenter Teen-LABS (Longitudinal Assessment of Bariatric Surgery) is a prospective observational cohort study examining outcomes in adolescents undergoing bariatric surgery (sleeve gastrectomy or Roux-en-Y gastric bypass). (96) Similar to adult studies, 3-year follow-up data found 27% weight loss, 95% remission of T2D, and 76% remission of prediabetes after surgery. (97) Five-year outcome data in adolescents versus adults who underwent bariatric surgery in the Teen-LABS and the related adult LABS cohort studies found that adolescents sustained a similar degree of weight loss compared with adults that was maintained at 5 years (26% vs 29%) but were significantly more likely than adults to have sustained remission of T2D (86% vs 53%) and hypertension (68% vs 41%). Mortality rates were similar between the 2 groups, although more adolescents than adults had low ferritin levels (48% vs 29%) and required repeated surgeries (19 vs 10 repeated operations per 500 person-years). (98) These results contrast with the relatively dismal data regarding progression of T2D with available medical therapy and suggest that bariatric surgery should be considered as an intervention for more of the pediatric T2D population. On the other hand, individuals who have had these procedures must maintain careful medical follow-up and adhere to a drug regimen that includes multivitamin, iron, calcium, and vitamin D supplementation. This may be difficult for many adolescents. In addition, some investigators have found a higher incidence of adverse neuropsychiatric behaviors after surgery, including depression, other addictive behaviors, and additional abnormal binge eating behaviors. These are particularly seen in individuals with presurgical addictive behaviors and depression. (99) All postbariatric surgical patients deserve psychological support and follow-up. (62)(100)

Summary

Based on strong epidemiological evidence:

- Obesity is common in children and adolescents today whereas type 2 diabetes mellitus (T2D) is less common even in high-risk groups, but the incidence is increasing. (1)(17)
- T2D is most common in high-risk obese adolescents of Asian, Native American, Pacific Islander, Hispanic, and African ancestry. (1)(15)(16)(17)
- Risk of T2D is increased in youth born small or large for gestational age and to obese mothers or mothers with diabetes. (30)(31)(34)(35)

Based on research evidence as well as consensus:

- T2D should be distinguished from type 1 diabetes mellitus and monogenic diabetes. (10)(11)(12)(13)
- T2D and its associated disorders in young people are associated with very poor outcomes, which could be ameliorated by prevention, identification, and initiation of early effective treatment. (8)(9)(10)(62)(63)(64)(65)(66)(67)

References for this article can be found at http://pedsinreview.aappublications.org/content/42/No. 4/167.

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1. An obese Vietnamese 9-year-old girl is brought to your office by her parents as a new patient. The family just moved to the area. Her medical history is normal, and she takes no medications. The family history is notable for type 2 diabetes mellitus (T2D) in her father. On physical examination her BMI is 28. Her Sexual Maturity Rating is stage 3 for pubic hair and stage 2 for breast tissue. No acanthosis nigricans is seen on examination. In discussing with the parents the testing criteria for this patient, based on the American Diabetes Association– and International Society of Pediatric and Adolescent Diabetes–recommended criteria, which of the following is the most appropriate plan for testing this patient for T2D?

   A. Defer testing until she is older than 10 years.
   B. Defer testing until she reaches Sexual Maturity Rating stage 4.
   C. Initiate testing if she develops acanthosis nigricans.
   D. Initiate testing if she develops hypertension.
   E. Initiate testing today.

2. A 14-year-old white girl, with a long-standing history of obesity (BMI, 32), is brought to the clinic because of constantly feeling thirsty at night and frequent urination. She is found to have 3+ glycosuria. A random blood glucose level is 290 mg/dL (16.1 mmol/L). Her father is obese and has diabetes for which he takes insulin, as do both grandmothers, one of whom has been taking insulin since she was 30 years old. Laboratory studies are ordered. You explain to the parents that she could have T1D or T2D. Which of the following tests ordered is most helpful to differentiate between the two and confirm a diagnosis in this patient?

   A. 2-Hour oral glucose tolerance test.
   B. Fasting blood glucose level.
   C. Hemoglobin A1c level.
   D. Testing for autoantibodies.
   E. Testing for targeted genes.

3. A 15-year-old girl with a BMI of 27 has prominent acanthosis nigricans on the back of the neck, under the arms, and around the umbilicus. She reached menarche at age 12 years but has had only approximately 2 periods a year since that time. She is bothered by her acne and the presence of hair on her abdomen. A hemoglobin A1c level determined today is 5.2% (reference range, 4.5% to <5.7%). You suspect polycystic ovary syndrome. Which of the following best explains the cause of her skin findings?

   A. Genetic mutation in the insulin receptor.
   B. Impaired glucose tolerance.
   C. Insulin deficiency.
   D. Insulin excess.
   E. Presence of pancreatic autoantibodies.

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4. An obese 16-year-old boy is brought to the emergency department with a 5-day history of polyuria, polydipsia, and some weight loss. His family history is remarkable for T2D in his mother and his paternal grandfather. On physical examination he is somnolent but arousable. His blood pressure is 150/60 mm Hg, and his pulse is 110 beats/min. He is noted to have doughy skin. Laboratory studies reveal trace urine ketones and a blood glucose level of 1,100 mg/dL (61 mmol/L). Serum electrolyte levels are as follows: sodium, 136 mEq/L (136 mmol/L); potassium, 4.5 mEq/L (4.5 mmol/L); chloride, 98 mEq/L (98 mmol/L); and bicarbonate, 18 mEq/L (18 mmol/L). Compared with the treatment of a patient with diabetic ketoacidosis, this patient will require which of the following treatment strategies?

   A. Earlier insulin replacement.
   B. Fluid restriction.
   C. Intravenous hydrocortisone.
   D. Less potassium replacement.
   E. More intravenous fluid.

5. A 15-year-old boy is brought to the clinic by his parents because of increasing concern about his obesity and a recent diagnosis of T2D. He is taking metformin and a long-acting insulin but his hemoglobin A1c level is 8.0% and his BMI has increased from 33 to 35 in the past year since diagnosis of T2D. His parents ask if bariatric surgery is a viable option for the treatment of his obesity and T2D at his age versus waiting till he is an adult. Compared with adults, teenagers who undergo bariatric surgery are more likely to have which of the following outcomes at 5 years?

   A. Higher mortality rates.
   B. Higher sustained remission of T2D.
   C. Less degree of weight loss.
   D. Less need for revision surgery.
   E. Worse T2D outcomes than with metformin and insulin combination therapy.