

Diagnosis and management of type 2 diabetes in children

Sarah Garvick, MS, MPAS, PA-C; Lilli Altenburg, MMS, PA-C; Bailey Dunlap, MMS, PA-C; Abby Fisher, MMS, PA-C; Amanda Watson, MMS, PA-C; Tanya Gregory, PhD

ABSTRACT

The incidence of type 2 diabetes in children has risen 4.8% over the past decade, correlating with steadily rising obesity rates in children. Updated guidelines from the American Academy of Pediatrics and the American Diabetes Association encourage early identification and pharmacologic intervention for children with type 2 diabetes. Because of the aggressive disease course in children, comprehensive treatment must include prevention of complications such as diabetic nephropathy and neuropathy as well as management of comorbidities such as cardiovascular disease and dyslipidemia. Because the highest incidence of type 2 diabetes is reported in patients from racial or ethnic minority groups and those of low socioeconomic status, clinicians must work with patients and families to identify socioeconomic disparities that could affect adherence to diabetes management plans and to connect patients with community resources.

Keywords: diabetes, pediatric, type 2, rural healthcare, minority, children

Learning objectives

- Recognize signs and symptoms of type 2 diabetes in children.
- Know the ADA criteria for screening and diagnosis of type 2 diabetes in children.
- Understand pharmacologic and non-pharmacologic treatments for type 2 diabetes in children.
- Identify barriers to care and how to overcome them.

The prevalence of type 2 diabetes in children has risen 4.8% over the past decade, correlating with the also steadily rising obesity rate in children.¹⁻³ Cases of type 2 diabetes in children ages 10 to 18 years have increased worldwide; however, in the United States alone, diabetes affects more than 190,000 youth (defined as age under

Sarah Garvick is associate program director of the PA program at Wake Forest School of Medicine and practices with the Appalachian District Health Department, both in Boone, N.C. At the time this article was written, **Lilli Altenburg**, **Bailey Dunlap**, **Abby Fisher**, and **Amanda Watson** were students in the PA program at Wake Forest School of Medicine. **Tanya Gregory** is an assistant professor and



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20 years).² Studies have shown that one in three cases of childhood diabetes is type 2, with an even higher ratio occurring in racial and ethnic minorities.^{3,4} Further research shows that 64.8% of children with type 2 diabetes were female and 80.9% were minorities; non-Hispanic Whites, Blacks, and Hispanic children with type 2 diabetes had four times the prevalence of obesity as those without diabetes.³ A study by Copeland and colleagues found that a significant percentage of children with type 2 diabetes are from families with low socioeconomic status.⁴

Recognizing the disproportionate effect of type 2 diabetes on minority patients is not sufficient by itself. Clinicians also must recognize their own knowledge gaps in addressing the complex psychosocial and cultural environments that may discourage patients from adhering to clinical recommendations. In addition, a detrimental disconnect exists between research developments and increasing disease prevalence of type 2 diabetes. Studies have shown that type 2 diabetes in children is pathologically different from type 1 diabetes and also different from type 2 diabetes in adults.^{5,6} Despite the increasing number of children with type 2 diabetes, there is insufficient research about the best

director of student services in the Department of PA Studies at Wake Forest School of Medicine in Winston-Salem, N.C. The authors have disclosed no potential conflicts of interest, financial or otherwise.

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Key points

- Cases of type 2 diabetes in children have been steadily increasing in the United States and worldwide.
- A body mass index (BMI) at the 85th percentile or higher is a strong predictor of eventual progression to type 2 diabetes.
- Pharmacologic and nonpharmacologic therapy should be initiated at the time of diagnosis.
- Frequent reevaluation, therapy escalation, and specialist referrals are essential for preventing disease progression.

way to manage this specific patient population.^{5,7} One study showed that most youth receiving treatment for an average of 7 years still were not at the A1C goal recommended by the American Diabetes Association (ADA).⁸ A large proportion of children with youth-onset diabetes are not being treated to goal, and increased risk of early vascular complications is a significant concern.⁸ As the prevalence of type 2 diabetes in children outpaces the developments in disease management, clinicians must continually adapt their approaches to diagnosis and care in a way that reflects ongoing research, while also tailoring treatment to their patients' unique circumstances.

PATHOPHYSIOLOGY

Type 2 diabetes results from an imbalance between insulin secretion from beta-cells in the pancreas and insulin sensitivity.⁶ Insulin sensitivity declines as the body becomes overwhelmed with larger intakes of glucose than normal.⁶ As sensitivity decreases, beta-cells must increase insulin secretion to prevent hyperglycemia.^{6,9} However, in patients with type 2 diabetes, abnormally high glucose levels overwhelm beta-cells in the pancreas.^{6,9} When beta-cells are unable to maintain adequate insulin secretion, glucose levels continue to rise.^{6,9} Chronically elevated serum glucose levels will lead to manifestations of prediabetes, and then to diabetes, unless the patient receives appropriate treatment.^{6,9}

In children with type 2 diabetes, beta-cells decline in function and lead to complications more rapidly than in adults with type 2 diabetes.^{6,9} This rapid decline in beta-cell function is attributed to hormonal changes in puberty that induce insulin resistance.⁶ In addition, children with type 2 diabetes have been found to have a decreased incretin effect.⁶ Incretins are hormones that regulate the amount of insulin secreted in response to the amount of glucose in food.⁶ A decreased incretin effect causes undersecretion of insulin, further contributing to increased glucose levels after eating.⁶

RELATIONSHIP WITH OBESITY

Increase in body mass is a large contributor to insulin resistance.⁹ Research on the relationship between obesity and type 2 diabetes is ongoing. A leading theory about this

relationship involves the *HSD11B1* gene, which is expressed in the liver and adipose tissue and converts cortisone to its active form.¹⁰ Overexpression of the gene has been shown to be associated with the development of central body fat, insulin resistance, and diabetes.¹⁰

Another theory involves vaspin, an adipocytokine (bioactive molecule) that is secreted from visceral adipose tissue.¹¹ Vaspin is thought to be associated with hyperinsulinemia, inflammation, and metabolic syndrome.¹² Studies show that patients with obesity and those with metabolic syndrome have a higher serum vaspin level than those with a healthful body weight.¹¹ Specifically, serum vaspin levels are higher in people with type 2 diabetes than in those without the disease.¹¹ Further, vaspin levels were correlated with triglycerides and systemic markers of inflammation such as C-reactive protein (CRP).¹² A dysregulation of adipokines, such as vaspin, has been associated with obesity, type 2 diabetes, hypertension, inflammation, and cardiovascular disease.¹²

SCREENING AND CLINICAL EVALUATION

At the primary care level, do not wait until a child is symptomatic to begin a workup for type 2 diabetes, because many children are asymptomatic at presentation. Because of this, identifying the appropriate at-risk population is a crucial step in determining which patients need to be screened. Consider risk-based screening for prediabetes and/or type 2 diabetes for children after the onset of puberty, or for children age 10 years or older who are overweight (BMI at or above the 85th percentile) and have one or more additional risk factors for diabetes.^{13,14} The ADA lists these risk factors:

- Maternal history of diabetes or gestational diabetes during the child's gestation
- Family history of type 2 diabetes in a first- or second-degree relative
- Native American, Black, Latino, Asian American, Pacific Islander
- Signs of insulin resistance or conditions associated with insulin resistance (acanthosis nigricans, hypertension, dyslipidemia, polycystic ovary syndrome, or small for gestational age birth weight).¹⁴

HISTORY AND PHYSICAL EXAMINATION

The history and physical examination are crucial elements for children suspected of having type 2 diabetes.^{5,13,14} Screening components include family history, social history, review of systems, and a thorough physical examination.

Family history Assess for nonmodifiable risk factors that are predictors of the development of type 2 diabetes in children.⁷ These risk factors include minority race and ethnicity, history of type 2 diabetes in first- or second-degree relatives, and exposure to gestational diabetes.^{5,14}

Social history Address specific lifestyle habits while obtaining a social history, including excessive caloric intake,

low physical activity, and increased sedentary behaviors.⁵ Explore modifiable risk factors such as chronic stress, depression, and inadequate amounts of sleep because of their connection to obesity and type 2 diabetes.⁵ Other social factors that are linked to type 2 diabetes in children are single-parent households, parents with no education beyond high school, and annual household income below \$25,000.³

Review of systems Children with type 2 diabetes do not always present with symptoms, so a broad review of systems can uncover findings that could identify underlying comorbidities and quantify disease severity.^{5,14} Screen for polyuria, polydipsia, and polyphagia, which are common symptoms of diabetes.^{15,16}

Physical examination As with the review of systems, the physical examination of a child suspected of having type 2 diabetes should be comprehensive in order to avoid missing any underlying illnesses or comorbidities. If found, the following specific examination findings should warrant a further diagnostic workup for type 2 diabetes:

A BMI at the 85th percentile or higher is a predictor of hyperglycemia and eventual progression to type 2 diabetes.⁴ However, patients with a BMI lower than the 85th percentile should not be excluded from a workup if they are symptomatic.¹⁶

Elevated BP can develop before or after type 2 diabetes.¹⁴⁻¹⁶ According to the American Academy of Pediatrics (AAP), 32% of adolescents with type 2 diabetes have a concomitant diagnosis of hypertension.¹⁶

Additionally, the presence of *acanthosis nigricans* should raise suspicion for type 2 diabetes.¹⁵ Examine the nape of the neck, axilla, groin, and flexor surfaces for any thickened, darkened, or velvety skin.¹⁵

DIFFERENTIAL DIAGNOSIS

A variety of conditions can mimic the signs and symptoms of type 2 diabetes in children. The most important to consider are type 1 diabetes and metabolic syndrome.^{13,17}

Distinguishing pediatric type 1 diabetes from type 2 diabetes can be difficult because the two diseases manifest similarly. Given the obesity epidemic, obesity is a common finding in children with either type of diabetes.¹³ About one-third of children with type 1 diabetes present with diabetic ketoacidosis, but most present with complaints of polyuria or polydipsia, which further causes blurring between the diagnosis of type 1 or type 2.¹³ Children suspected of having type 2 diabetes should be screened with a panel of islet autoantibodies to rule out type 1 diabetes as the cause of their symptoms.^{13,14}

Metabolic syndrome in children can manifest similarly to type 2 diabetes because the biggest identifier is obesity and waist circumference.¹⁷ The criteria for a diagnosis of metabolic syndrome is having three or more abnormalities in the following components: waist circumference at 90th percentile or higher, BP at 90th percentile or higher for the

child's age, triglycerides 110 mg/dL or higher, high-density lipoprotein (HDL) 40 mg/dL or lower, fasting serum glucose 100 mg/dL or higher, or known type 2 diabetes.¹⁷

DIAGNOSTICS

Appropriate diagnostic tools to test for type 2 diabetes in children include any of the following: fasting plasma glucose (FPG), 2-hour plasma glucose during a 75-g oral glucose tolerance test (OGTT), or hemoglobin A1C.¹⁴ Using clinical judgment based on specific patient presentation is an acceptable approach for clinicians to decide which screening method to use. OGTTs and A1C are equally effective methods of identifying type 2 diabetes in children.⁵ Although these tests identify pediatric type 2 diabetes at a similar rate, evidence has shown that screening with A1C increases clinician adherence to screening recommendations compared with OGTT.¹⁴ Conversely, the ADA does not recommend screening with A1C in children with cystic fibrosis or symptoms suggestive of type 1 diabetes.¹⁴

Confirmation of type 2 diabetes can be achieved by obtaining two abnormal test results from the same sample or in two separate test samples.¹⁴ If clinical suspicion for type 2 diabetes is high but the diagnostic results are within normal limits, repeat testing at a minimum of 3-year intervals or more frequently if the patient's BMI is increasing.¹⁴

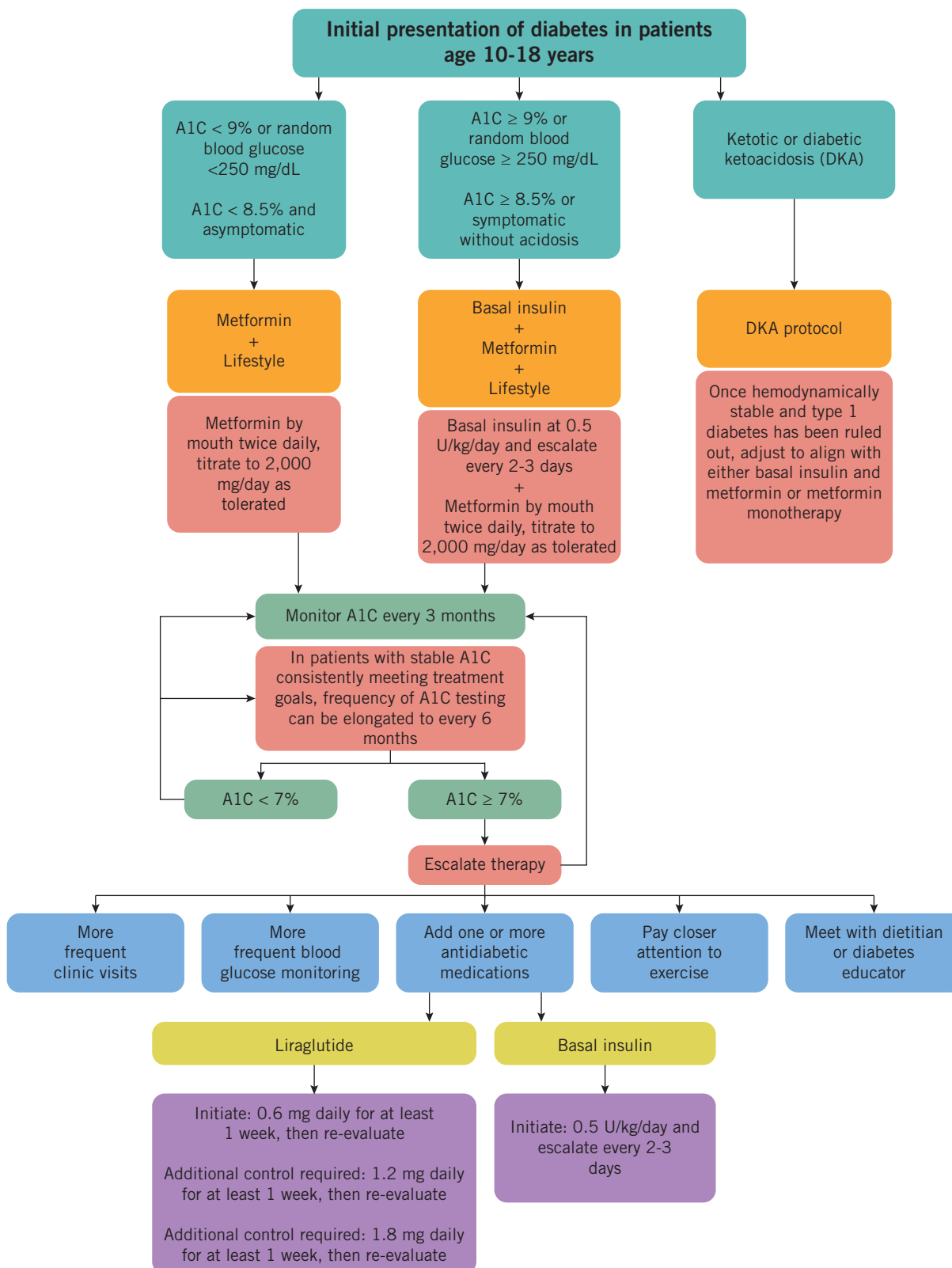
TREATMENT

Start treatment of type 2 diabetes in children at the time of diagnosis and include pharmacologic and lifestyle therapy.^{7,13}

Pharmacologic management Three drugs are available for managing type 2 diabetes in children: metformin, insulin, and liraglutide.¹⁸⁻²¹ Initial treatment is guided by the patient's clinical presentation and laboratory values at the time of presentation (**Figure 1**).

- Patients who are asymptomatic, are older than age 10 years, and have an initial A1C of less than 8.5% should be started on metformin monotherapy.^{7,13,18} Metformin should be taken twice daily and titrated to 2,000 mg/day as tolerated.^{13,18} Do not use metformin in patients with severe renal impairment or diabetic ketoacidosis.¹⁸
- Patients who are symptomatic, have an initial A1C of 8.5% or greater, or have a random venous or plasma blood glucose greater than 250 mg/dL should be started on combination therapy with basal insulin (glargine for patients age 6 years and older; or detemir for patients age 2 years and older) and metformin.^{13,19,20} Start insulin therapy at 0.5 units/kg/day and increase it every 2 to 3 days.¹³ Prescribe metformin as above.
- Although not included in the initial management strategy, liraglutide, a glucagon-like peptide-1 (GLP-1) receptor agonist, is an option for the escalation of type 2 diabetes therapy in children older than age 10 years (more on this below).^{13,21} Liraglutide is contraindicated in patients with a personal or family history of medullary thyroid

FIGURE 1. Management of type 2 diabetes in children^{7,13,18-21}



carcinoma and in patients with multiple endocrine neoplasia syndrome type 2.²¹

Treatment goals and monitoring Most children with type 2 diabetes have a fasting blood glucose target of 70 to 130 mg/dL and an A1C goal of less than 7%.^{7,13} In patients at an increased risk of hypoglycemia, an A1C goal of less than 7.5% is acceptable.^{7,13}

All patients with a new diagnosis of type 2 diabetes should perform fingerstick blood glucose testing before each meal and at bedtime.¹³ Once fasting blood glucose concentrations are consistently at target, the frequency of fingerstick monitoring may be modified through shared goal setting between the clinician and patient.⁷ De-escalation of fingerstick monitoring should take into consideration the medication being used, the intensity of the regimen, and the patient's risk of hypoglycemia and hyperglycemia.⁷ Encourage children to self-manage their diabetes to the extent appropriate for their age, although the burden of monitoring may initially fall on the caregiver.

Patients with a new diagnosis of type 2 diabetes should have their A1C concentration measured every 3 months.⁷ When the A1C concentrations are consistently at goal, the frequency of A1C testing can be reduced to every 6 months.⁷

Treatment escalation If patient-specific A1C goals are not being met, intensify therapy without delay.¹³ Strategies include more-frequent blood glucose monitoring and clinic visits, and having the patient and their family meet with a registered dietitian and a diabetes educator, paying closer attention to the patient's diet and exercise, and adding one or more antidiabetic medications (**Figure 1**).⁷ Clinicians should be comfortable with the indications and strategies for therapy escalation given the likelihood that adequate glycemic control may not be maintained with initial treatment.

In patients over age 10 years who do not achieve an A1C less than 7% on initial treatment, consider adding liraglutide at 0.6 mg daily; this medication can be titrated up to a dose of 2.8 mg daily.^{21,22}

Nonpharmacologic management Along with pharmacologic management, nonpharmacologic interventions remain essential to the management of type 2 diabetes in children.^{7,13} At the time pharmacologic therapy is initiated, offer patients and families counseling on diet, physical activity, and nutrition, along with developmentally and culturally appropriate comprehensive lifestyle programs.^{7,13} Research shows that engaging family members not only improves medication adherence but that lifestyle changes are more successful when the patient's entire family is involved.²³ Because type 2 diabetes disproportionately affects minorities, ensure that family-centered education is culturally appropriate.

Behaviors proven to significantly affect A1C include increased exercise, decreased saturated fat intake, and increased fiber intake. Because significant benefits to cardiometabolic status have been observed in overweight

patients with a greater than 7% weight loss, all children, including those with controlled or uncontrolled type 2 diabetes, should engage in moderate-to-vigorous exercise for at least 60 minutes daily.¹³ Further, nonacademic screen time should be limited to less than 2 hours per day, and nutritional counseling for children with type 2 diabetes should be part of ongoing management, not presented at the time of diagnosis only.⁷

The involvement of a nutrition specialist and the use of family-based, multicomponent interventions that are at least 26 hours in duration have been identified as most effective in achieving the 7% weight loss.²³ Do not assume that patients have access to and ability to adhere to these interventions, and make every lifestyle recommendation during an open and honest conversation aimed at identifying barriers to care.

COMPLICATIONS AND COMORBIDITIES

Long-term exposure to hyperglycemia, along with additional associated risk factors including insulin resistance, dyslipidemia, obesity, hypertension, and chronic inflammation, are thought to be associated with increased morbidity and mortality risk in younger patients with type 2 diabetes.⁵ For these reasons, childhood-onset type 2 diabetes is associated with a significant vascular risk burden and a concomitant increase in cardiovascular morbidity and mortality.⁵ This significant risk emphasizes the importance of the prevention and management of diabetic complications and comorbidities in children.

Some of the most common complications associated with type 2 diabetes in children are nephropathy, neuropathy, and retinopathy.¹³ The ADA and other governing bodies such as the American Academy of Ophthalmology (AAO) recommend BP screenings at every visit, urine albumin-to-creatinine ratio measured at diagnosis and annually thereafter, annual foot examinations, and annual dilated funduscopy or retinal photography screenings.^{5,13,24}

Comorbidities, including nonalcoholic fatty liver disease (NAFLD), obstructive sleep apnea, polycystic ovary syndrome, cardiovascular disease, and dyslipidemia, are likely to be present at the time of diagnosis of type 2 diabetes in children.^{5,13,25} The ADA also recommends measuring aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels, and screening for symptoms of sleep apnea, such as snoring, at every visit. Perform lipid testing when initial glycemic control has been achieved and annually thereafter.^{5,13}

REFERRAL TO SPECIALISTS

Pediatricians and primary care providers should feel comfortable managing pediatric type 2 diabetes, diabetic complications, and comorbidities in their scope of practice. However, referral to a specialist is warranted in some cases.

- The Pediatric Endocrine Society (PES) recommends that all children with a new diagnosis of diabetes be immediately

TABLE 1. Overcoming barriers to care^{26,29-32,34-36}

Barrier	Resources
Access to healthcare	
<ul style="list-style-type: none"> • Inadequate health insurance coverage • Cost 	<ul style="list-style-type: none"> • Targeted diabetes screening events at community centers, churches, and local health fairs • Medicaid-supported well-child checks • State health department preventive care services
Lack of transportation	<ul style="list-style-type: none"> • Local public transportation • Closer-to-home community resources (such as a health fair) • Clergy volunteer drivers • Medicaid-provided transportation • Telehealth visits
Food insecurity	
Access to healthful and affordable foods	<ul style="list-style-type: none"> • Supplemental Nutrition Assistance Program (SNAP) • National School Lunch Program • YMCA-provided after school/summer meal programs
Adherence to dietary recommendations	<ul style="list-style-type: none"> • CDC-led Diabetes Prevention Program

referred to a pediatric diabetes center or a pediatric endocrinologist to establish and initiate a care plan.²⁵

- An ill-appearing child with ketones in urine should be referred directly to the ED for management and possible admission.²⁵
- The ADA recommends referral to nephrology if pediatric type 2 diabetes manifests with kidney pathology of unknown cause, a steadily increasing urine albumin-to-creatinine ratio, or a reduced estimated glomerular filtration rate.^{5,13}
- The AAO recommends referral to an ophthalmologist if a child's diabetic retinopathy is of moderate severity or higher. Their definition of moderate severity includes the presence of microaneurysms and other signs, such as "dot and blot hemorrhages," hard exudates, or cotton-wool spots, without evidence of proliferation.²⁴
- The ADA recommends referral to gastroenterology for evaluation for NAFLD upon the discovery of persistently elevated and/or worsening transaminases.^{5,13}
- The ADA recommends referral to a pediatric sleep specialist for evaluation and assessment, if indicated.¹³

OVERCOMING BARRIERS TO CARE

Poverty and ethnicity are major contributors to healthcare disparities in the United States. Evidence supports the association of socioeconomic status, neighborhood and physical environment, food environment, healthcare, and social context with diabetes-related outcomes due to lack of health insurance coverage, transportation, safety, and cost.^{26,27} These barriers to care can prevent at-risk children from timely screening, diagnosis, and management of type 2 diabetes. Understanding and mitigating the effect of social determinants of health are priorities for reducing disease prevalence, economic costs, and disproportionate population burden. Clinicians should use targeted social determinants of health screenings, such as intake surveys,

that apply to children when considering how to best tailor their care.²⁸

Use of free targeted diabetes screening events at community centers, churches, and local health fairs could help circumvent cost barriers, aid in diagnosing diabetes earlier, and provide prompt intervention in at-risk patients.²⁹ Services such as those provided by the United Way can help connect patients with community-based programs, including transportation, medical care, and nutrition options.³⁰ Additionally, many programs run by the Food and Nutrition Service in the US Department of Agriculture are pivotal for the health of communities, as they work to increase food security by providing access to healthful food and nutrition education to low-income families.³¹ Maintaining a healthful diet is a crucial component in reducing the risk for pediatric obesity, and clinicians should be familiar with such programs in their community.^{23,32} Overall, using community resources to overcome these barriers to care is an effective way to improve outcomes in the underserved population (Table 1).

CONCLUSION

Cases of type 2 diabetes in children have been steadily increasing in the United States and worldwide over the past 2 decades, disproportionately affecting racial and ethnic minorities and children of low socioeconomic status.^{2,3} Most youth treated with metformin and/or insulin still are not at the glycemic goal recommended by the ADA and AAP clinical practice guidelines.^{7,33} When at-risk patients are identified, an extensive workup is indicated to provide a definitive diagnosis of type 2 diabetes.¹⁴ Pharmacologic therapy should be initiated at the time of diagnosis, and nonpharmacologic interventions should be incorporated into a comprehensive management plan.¹³ Frequent reevaluation, subsequent escalation of therapy,

and appropriate specialist referrals are essential for preventing the progression of disease and development of complications.^{5,13,24,25} In formulating comprehensive management plans, primary care providers must evaluate and address barriers to care if they are to meet the challenge of pediatric type 2 diabetes with competence. **JAAPA**

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