Recognizing and Managing Type 2 Diabetes Mellitus in Children

An Algorithm for Primary Care Providers

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During the last two decades, type 2 diabetes mellitus increasingly has been seen in children. Although still not as common as type 1 diabetes among children, it has become the leading form of diabetes among adolescents of certain ethnicities. It is imperative that primary care providers recognize the risk factors, perform appropriate screening tests, and initiate therapy for children who have type 2 diabetes or prediabetes. This article discusses the epidemiology and pathogenesis of the disease, complications, and treatments, and includes a concise, easy-to-follow algorithm to assist providers in diagnosing and treating young patients.

Type 2 diabetes and features of the metabolic syndrome (obesity, insulin resistance, dyslipidemia, and hypertension) almost exclusively have been observed in adults. However, over the past two decades, the prevalence of pediatric type 2 diabetes mellitus has been increasing steadily in the United States, particularly among children of certain ethnic backgrounds.[1,2] Although the absolute number of new pediatric cases remains relatively small, type 2 diabetes mellitus accounts for the majority (or near majority) of diabetes cases among Native American, Asian/Pacific Islander, African-American, and Latino adolescents in the United States. A dramatic rise in the rate of pediatric obesity among children has undoubtedly been a factor in the increase in cases of pediatric type 2 diabetes, as obesity is a well-established primary risk factor for developing the disease.[3-5]

The rise in the pediatric obesity and type 2 diabetes rates affects not only health outcomes but also resource planning. Since obese children are also more likely to become obese adults,[6,7] a generation of young adults facing obesity-derived metabolic complications and a shorter life expectancy is likely to emerge. Moreover, the same complications occurring alongside or independent of type 2 diabetes in adults are now being seen in the pediatric population,[8] placing this generation of obese children at greater risk for early cardiovascular disease and related health problems. Children with type 2 diabetes mellitus are also at an increased risk for early development and accelerated progression of microvascular complications such as nephropathy.[9]

Estimated costs related to diabetes in the United States in 2007 were $174 billion,[10] a figure that is likely to increase in the years ahead as rates of diabetes continue to rise.[11] Those trends have mandated the need for developing effective screening and treatment plans to prevent, diagnose, and manage pediatric patients with type 2 diabetes.

In this article, we briefly review current epidemiologic data regarding pediatric type 2 diabetes mellitus in the United States and population-based estimates in Minnesota, the pathophysiologic mechanisms of the disease, and basic therapeutic approaches. We also

provide an algorithm written by members of the Minnesota Department of Health's Diabetes Steering Committee that offers primary care providers a simplified strategy for identifying, testing, and intervening with peripubertal youths who have or are at risk for type 2 diabetes.

Epidemiology

In the past, type 2 diabetes mellitus comprised a very small percentage of all childhood diabetes cases; however, recent data indicate that that percentage is growing.[12] The SEARCH study, an ongoing, observational, population-based study analyzing rates of diabetes in different geographic areas of the United States including Washington, Colorado, California, Hawaii, Ohio, South Carolina, and American Indian reservations, has provided valuable information about the trends in pediatric diabetes, especially type 2 diabetes.[1]

Not surprising, age is a highly influential factor in determining rates and type of disease. Cases of type 2 diabetes among 5- to 9-year-olds are exceedingly rare, with an incidence rate of only 0.8 per 100,000 person-years. However, rates increase sharply during adolescence to an incidence of 8.1 per 100,000 person-years in 10- to 14-year-olds and 11.8 per 100,000 person-years in 15- to 19-year-olds.

Incidence rates are also strongly influenced by ethnic background. The incidence of type 2 diabetes mellitus is highest among older American Indian adolescents (49.4 per 100,000), followed by Asian/Pacific Islander (22.7 per 100,000), African-American (19.4 per 100,000), Hispanic (17 per 100,000) and finally non-Hispanic white youths (5.6 per 100,000).[1]

Overall, the prevalence estimate for type 2 diabetes in the United States ranges from about 1 in 5,000 white children to close to 1 in 500 American Indian children. This is equivalent to approximately 3,700 new cases of type 2 diabetes in children in the United States each year.[13] Nearly 90% of children diagnosed with type 2 diabetes are obese or overweight,[5] magnifying the positive relationship between obesity and type 2 diabetes. In addition, females are 1.7 times as likely as males to develop the disease, regardless of race.[14] This difference is most dramatic among American Indian children, where a ratio of 4 to 6:1 females to males with type 2 diabetes has been reported.[14]

Pediatric Type 2 Diabetes in Minnesota

Based on 2009 state census data, more than 705,000 children ages 10 to 19 years of age reside in Minnesota.[15] According to the 2010 Minnesota Student Survey, approximately 20% of children in grades 6 through 12 are of African-American, Latino, American Indian, or Asian heritage.[16] Based on current national incidence rates among people with these racial and ethnic backgrounds, it can therefore be reasonably deduced that approximately 35 to 45 new cases of type 2 diabetes will occur among this group each year in addition to 15 to 25 new cases among Caucasian adolescents. Perhaps much more alarming, an estimated 92,000 adolescents between the ages of 12 and 19 years may have prediabetes[17] and be at risk for progression to full-blown disease.

Because of the slow-but-steady increase in cases of pediatric type 2 diabetes and its associated comorbidities and complications, it is imperative that effective strategies be used to prevent, identify, and treat type 2 diabetes among youths. Given the declining supply of pediatric endocrinologists in the country,[18] especially in rural areas, this task will increasingly fall to primary care providers. To aid them, a subcommittee from the Minnesota Department of Health's Diabetes Steering Committee created a diagnostic and therapeutic algorithm (Figure) to increase awareness of pediatric type 2 diabetes among providers; guide clinicians in regard to diagnostic evaluations and therapeutic interventions; and provide practitioners with a concise tool that can be easily referenced in clinic.

Pathogenesis of Type 2 Diabetes in Children

Insulin resistance refers to a decrease in hepatic and peripheral cellular glucose uptake.[19] It is the core metabolic derangement that predisposes to type 2 diabetes. However, for diabetes to occur, it must be accompanied by a decline or defect in pancreatic beta cell function. A continuum of insulin resistance leading to variable beta cell failure exists, accounting for the progression from insulin resistance to prediabetes and eventually to type 2 diabetes. Obesity, particularly central or visceral adiposity, is strongly associated with the development of insulin resistance in both children and adults.[20] Increased visceral adiposity promotes a cascade of metabolic derangements and inflammation that negatively affect insulin signaling and increase the strain on the already-stressed beta cells to overcome inherent insulin resistance in order to maintain euglycemia. When an individual's beta cells can no longer compensate, glycemic decompensation occurs, leading to frank type 2 diabetes mellitus. Because puberty is a period of physiologic increased insulin resistance,[21,14] most cases of type 2 diabetes in children present around this time.

Although few specific genes have been linked to pediatric type 2 diabetes, strong familial tendencies and increased prevalence among children of certain ethnic backgrounds point to the importance of genetic variation on disease risk. As an example, a case control study in Germany demonstrated that polymorphisms in TCF7L2 are associated with an increased risk of impaired glucose tolerance in obese youths,[22] similar to the association observed in adults. Several other loci have been identified as imparting risk for development of type 2 diabetes in the adult population (although not always consistently), but additional pediatric associations have not yet been identified. Nevertheless, a family history of type 2 diabetes is extremely common among pediatric patients who have prediabetes or type 2 diabetes mellitus.[23] Indeed, compared with those who are overweight and have no family history of type 2 diabetes, an overweight child with a sibling who has type 2 diabetes, carries a four-fold increased risk of having impaired glucose tolerance.[24]

Intrauterine and perinatal factors have also emerged as important risk factors for

the development of type 2 diabetes. Maternal gestational diabetes is a risk factor for a child becoming insulin resistant and obese later in life.[25] Alternatively, infants who are born small for their gestational age or who have a history of intrauterine growth retardation and rapid weight gain during the first few months of life have also been found to be at increased risk for later development of the disease.[26] "Malprogramming" of the hypothalamic center, which is responsible for controlling metabolism, food intake, and subsequent weight gain, has been proposed as a possible mechanism for this phenomenon.[25]

Comorbidities and Complications

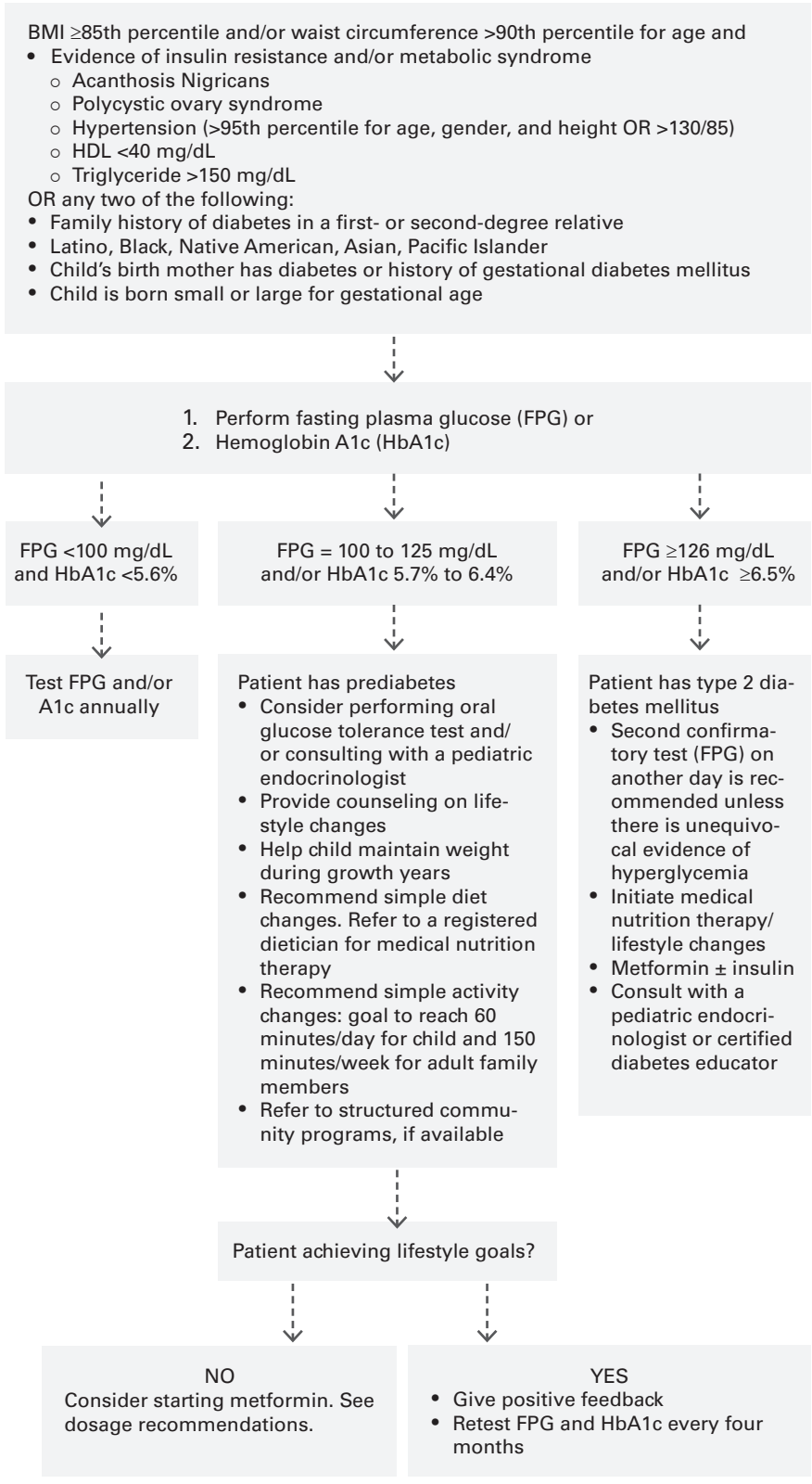
The micro- and macrovascular complications associated with poorly controlled diabetes in adults are well-documented. For example, individuals with diabetes are two to four times as likely to experience cardiovascular disease as others; in addition, diabetes mellitus is now the leading cause of blindness, lower leg amputation, and chronic kidney disease among adults in the United States.[27] Children with type 2 diabetes may have their own set of comorbid metabolic abnormalities. For example, those presenting in diabetic ketoacidosis have a more rapid decline in their beta-cell function compared with adults.[28] Microvascular disease in the form of microalbuminuria is often present at the time of diagnosis.[29] Dyslipidemia is more common among youths with type 2 diabetes compared with those with type 1 diabetes.[30] Hypertension is present in 14% to 32% of cases of pediatric type 2 diabetes at the time of diagnosis.[29] Twenty-five percent to 40% of children with the disease will present in a state of diabetic ketoacidosis, and the hyperglycemic hyperosmolar state may also occur, carrying with it a very high mortality rate.[31]

Recognizing and Treating Children with Prediabetes and Type 2 Diabetes

Children identified as having prediabetes (impaired fasting glucose or impaired glucose tolerance on an oral glucose toler-

Figure

Algorithm for Prediabetes and Type 2 Diabetes Mellitus Identification and Intervention for Youths (Ages 10 to 17 Years or Peripubertal)



METFORMIN: Start dosage at 500 mg QD with food. Increase dose every one to two weeks to achieve clinically effective dose of 1,000-2,000 mg/day, based on tolerability. Consider use of extended-release formulation if patient is experiencing significant side effects. Follow-up: Every one to three months. Do not use in patients with underlying kidney disease. *Metformin use in overweight adolescents not meeting criteria for type 2 diabetes mellitus is off-label and based on limited published data and consensus of Minnesota Diabetes Steering Committee.*

Prediabetes and Diabetes: Screening and Diagnosis

The current recommended diagnostic test to identify children with prediabetes in order to begin lifestyle interventions is either HbA1c or FPG. HbA1c is a measure of long-term blood glucose control and is used to monitor the effectiveness of therapy and risk for complications in persons with diagnosed diabetes. However, an HbA1c of ≥5.7% may help identify an additional group of at-risk children. An HbA1c ≥6.5% performed in a laboratory using standardized methods is now considered a criterion for a diagnosis of diabetes. An oral glucose tolerance test may define impaired glucose tolerance or diabetes and should be considered in children with impaired fasting glucose or an HbA1c in the prediabetes range. To calculate BMI and blood pressure, refer to:

- www.cdc.gov/growthcharts/ (BMI)
- www.nhlbi.nih.gov/guidelines/hypertension/child_tbl.htm (blood pressure)

Prediabetes and Diabetes: Recommended Lifestyle Changes for Entire Family

Simple Dietary Changes

- Become a label reader and limit portion sizes; observe serving size and calories per serving
- Limit snacks to one serving size; try fresh fruits and vegetables for snacks two to three days per week
- Eat fewer processed and high-fat foods; limit fast-food and restaurant meals to fewer than one to two per month
- Switch to 1% or skim milk
- Encourage water consumption; eliminate carbohydrate-containing beverages (pop, sweetened tea, energy drinks, juice)
- Eat breakfast and try not to skip meals

Simple Activity Changes

- Be active together as a family; eat meals together whenever possible
- Walk and take the stairs; park in distant spots and walk farther when shopping
- Try new sports or activities that increase physical activity
- Limit screen time (TV, computer, video games) to two hours per day
- Participate in community programs (eg, YMCA, YWCA, park and recreation centers)

Resources

- NDEP - Tips for Teens: Lower Your Risk for Type 2 Diabetes at http://ndep.nih.gov/teens/index.aspx and http://ndep.nih.gov/media/kids-tips-lower-risk.pdf
- DHHS - Small Step Kids: www.smallstep.gov/ (also in Spanish)
- ADA - Nutrition Tips: www.eatright.org (for additional help with label reading)
- AAP - Pediatric Obesity Management: www.aap.org/obesity/practice_management_resources.html

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Common ICD-9 Codes for Diabetes Screening

V77.1	Diabetes screening
790.21	Impaired fasting glucose
790.22	Impaired glucose tolerance test (oral)
790.29	Prediabetes NOS/abnormal glucose value

Codes Describing Risk Factors

277.7	Dysmetabolic syndrome
278.00	Obesity
278.02	Overweight
701.2	Acanthosis nigricans
V18.0	Family history diabetes

ance test, or an intermediate hemoglobin A1c [HbA1c] in the 5.7% to 6.4% range) should be counseled about lifestyle modifications (improving diet and increasing physical activity) that can lead to weight stabilization or loss. Instituting an exercise program has been shown to improve insulin sensitivity.[32] Use of metformin to prevent type 2 diabetes in such children remains controversial. However, there is growing evidence, including results of a recent randomized controlled trial,[33] that metformin may be a useful adjunct to stabilize weight in obese youth with evidence of insulin resistance or prediabetes who are at risk for progression to type 2 diabetes.

Treatment strategies for those who have type 2 diabetes should be aimed at reducing insulin resistance and enhancing insulin secretion. Goals of therapy need to include not only achieving glycemic control but also management of associated metabolic comorbidities (eg, dyslipidemia, hypertension, and nonalcoholic fatty liver disease).[34,35] The core therapeutic approach is to maintain a healthy weight and limit weight gain.

Addressing lifestyle issues is central to any diabetes-management plan. Eating healthful foods can be challenging for both practical and financial reasons: Unhealthy food is cheaper, easier to obtain, and can be more appealing to children than healthful food. Successfully overcoming such challenges requires the entire family to make a commitment to eating more healthfully.[35,36] Making simple changes is the first step in this process. These should include eliminating high-calorie beverages such as juices, soft drinks, and energy drinks, focusing on portion control, and eating smaller meals more often rather than one large meal per day. Physicians can advise limiting screen time to no more than two hours a day. In addition, young people should be encouraged to increase the amount of physical activity they engage in. They should be encouraged to explore different forms of exercise in order to find ones they enjoy.[37,38]

Although an essential part of managing patients with type 2 diabetes, lifestyle modifications are often not sufficient

to achieve adequate glycemic control.[39] Pharmaceutical agents may be required to maximize control of the disease. Several oral hypoglycemic agents that have different mechanisms of action are approved for use in adults. In the pediatric population, however, the only oral hypoglycemic agent approved for use for treating type 2 diabetes is metformin.[40] Metformin reduces hepatic gluconeogenesis while promoting insulin uptake by muscle and fat.[41] In addition to its effect on glycemic control, several studies have demonstrated a modest neutral or negative effect on weight.[40]

Insulin is also approved for use in treatment of pediatric patients with type 2 diabetes. Insulin should be considered if significant beta-cell failure, diabetic ketoacidosis, or nonketotic hyperosmolar state are present at diagnosis. Gradual transition to monotherapy with metformin along with continued lifestyle modifications may be possible once a patient achieves adequate glycemic control. With such patients, it is important to check for diabetes autoantibodies that may impose a more rapid deterioration of beta-cell function and require long-term insulin therapy.[42]

There are several other classes of oral hypoglycemic pharmaceuticals including sulfonylureas, maglitinides, glucosidase inhibitors, thiazolidinediones, and incretin-based therapies. At this point, none of those agents are approved for use in the pediatric population. The TODAY (Treatment Options for Type 2 Diabetes in Youth) study should provide important data on the relative effectiveness and safety of thiazolidenediones compared with metformin and/or lifestyle modifications.[43]

Conclusion

Type 2 diabetes mellitus is slowly becoming more prominent and troublesome among adolescents. We have new knowledge about risk factors for the disease and the proposed pathophysiologic mechanisms that lead to it. Thus, we are now aware of risk factors that need to be considered in children. Although there are few therapies for children and adolescents with type 2 diabetes,[39] strategies such as making lifestyle changes should be encouraged in this population. Reliable screening tools for type 2 diabetes in children and adolescents are needed, given the importance of early identification and intervention. The algorithm presented represents a step toward assisting primary care providers in diagnosing and treating pediatric patients. **MM**

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