Type 2 Diabetes in Children and Adolescents: Risk Factors, Diagnosis, and Treatment

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As an unfortunate consequence of the current epidemic of obesity among children and adolescents, physicians can logically expect to encounter increasing numbers of young patients presenting initially with signs and symptoms associated with uncontrolled hyperglycemia and relatively advanced cases of diabetes. Understanding the wide array of risk factors for type 2 diabetes that frequently accompany obesity can facilitate diagnosis and proper classification of the condition, especially within these younger age groups for whom diagnoses of type 1 diabetes were once handed down practically by default.

While the decision to initiate insulin therapy can be made independently of diabetes classification in cases where hyperglycemia is severe, the type of diabetes will affect how much insulin is required for adequate treatment. The priority in such cases is to bring blood glucose levels under control as quickly as possible. Once under adequate control, various options for glycemic management can be implemented based on type of diabetes, patient lifestyle, motivation, family support, and other factors.

The following case and suggestions for therapeutic intervention are presented for purposes of educational discussion. Although based on an authentic case, the actual treatment course and outcome have not been disclosed. The case presentation has been condensed, and some details have been modified in order to both protect the patient's privacy and to facilitate discussion.

Presentation

E.J. is a 13-year-old Hispanic girl who presents to her primary care provider with a complaint of vaginal discharge for the previous 5 days. She is not sexually active. On questioning, she reports excessive fluid intake that her mother attributes to the summer heat. She is otherwise asymptomatic. A urine dipstick test reveals 4+ glucose and trace ketones. She is referred immediately for a pediatric endocrinology consultation.

On physical examination, E.J.'s weight is 257 lb and pubic hair and breasts are Tanner stage IV. Her vaginal discharge is consistent with a candida infection. She has marked acanthosis nigricans on her posterior neck and striae on her abdomen and breasts. Her respirations are not rapid or labored, and she is not dehydrated. A random blood glucose measurement of 287 mg/dl is obtained, and fingerstick hemoglobin A_{1c} (A1C) test result is 11.1%.

E.J.'s mother has type 2 diabetes,

IN BRIEF

Along with the epidemic of obesity among children and adolescents in the United States, additional risk factors for type 2 diabetes among these age groups are becoming increasingly apparent. This article discusses the case of a young adolescent with multiple risk factors for type 2 diabetes. Issues relevant to the diagnosis and classification of diabetes in many young patients are explored, along with the importance of initiating therapy that will allow rapid attainment of glycemic control.

which was initially diagnosed during her pregnancy with E.J. Her mother also has "foot trouble" resulting from diabetes, and she walks with a cane. She is unable to work because of her foot problems. E.J.'s paternal grandmother and grandfather both have type 2 diabetes. Her father, who works as an auto mechanic at a local car dealership, has a history of hypertension. Her 18-year-old brother is described as "big," but he has not seen a doctor recently, and his glycemic status is unknown.

Commentary

No longer considered to be a condition of primarily adult onset, type 2 diabetes has become increasingly common among children aged 6–11 years and adolescents aged 12–19 years. Although there has been no definitive large-scale reporting of incidence within these age groups, a recent epidemiological review has led to the suggestion that as many as 8–45% of new-onset pediatric diabetes cases in the United States may be type 2.[1-3] The Centers for Disease Control and Prevention reported ~ 206,000 cases of diabetes among those < 20 years of age in the United States, giving an estimated prevalence of 0.25%.[4] As in adults, it may be that many childhood cases also go unrecognized, resulting in the possibility of a substantial number of children and adolescents with undiagnosed type 2 diabetes.

The increase in type 2 diabetes among children and adolescents has emerged in parallel with an alarming rise in the number of young people who have become overweight or obese (Figure 1). Along with family history, obesity stands

out as a prominent risk factor for the development of type 2 diabetes. Over the past 20 years, the prevalence of childhood and adolescent obesity has doubled, and without increased measures for prevention, these numbers will likely continue to rise.[5] Although children and adolescents representing all racial, ethnic, and socioeconomic groups have been affected by this trend, Native Americans, Hispanics, and African Americans have become particularly susceptible to the epidemic of obesity[2,6] (Figure 2). Type 2 diabetes is especially on the rise within these groups, and the prevalence of hypertension among African-American and Hispanic children is also increasing, putting them at increased risk for developing cardiovascular disease.[7]

Insulin resistance is an almost inevitably associated comorbidity of obesity and often precedes the development of type 2 diabetes.[8] Abdominal obesity, and in particular increased visceral fat, has been implicated as contributory to insulin resistance. A study of 32 overweight or obese Hispanic children without diabetes but with a family history of type 2 diabetes indicated that increased visceral fat was independently related to both increased insulin resistance and decreased insulin secretion.[9] Although insulin resistance is characteristic of obesity in childhood, it typically increases markedly during normal puberty,[10–12] even in nonobese individuals. Irrespective of ethnicity, insulin sensitivity is reduced, while fasting glucose levels are increased in both nonobese and obese children during Tanner stages II–IV of pubertal development.[11–13] Insulin resistance as well as hyperinsulinemia generally are associated with obesity in childhood and may progress to impaired glucose tolerance (IGT) and type 2 diabetes.[14] Although no criteria for diagnosis of metabolic syndrome specific for children and adolescents have been universally accepted, it is apparent that insulin resistance and hyperinsulinemia are common characteristics among this complex array of
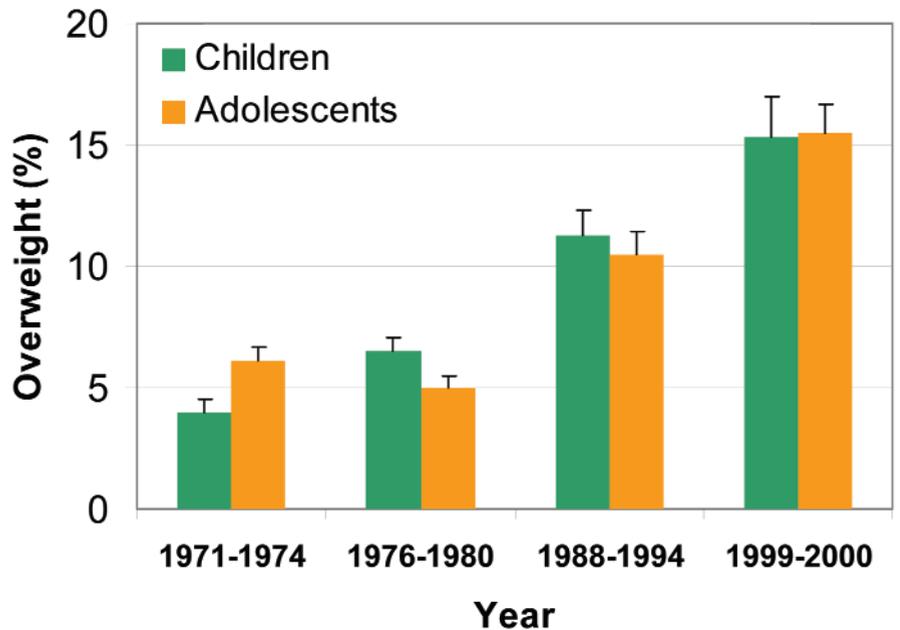

Figure 1. Overweight prevalence among U.S. children and adolescents. Children were aged 6–11 years, and adolescents were 12–19 years of age. Determined on the basis of BMI, overweight designation included those in the ≥ 95th percentile. Original data were from the National Health and Nutrition Examination Surveys I, II, III, and 1999–2000. Collected here from Ref. 6.
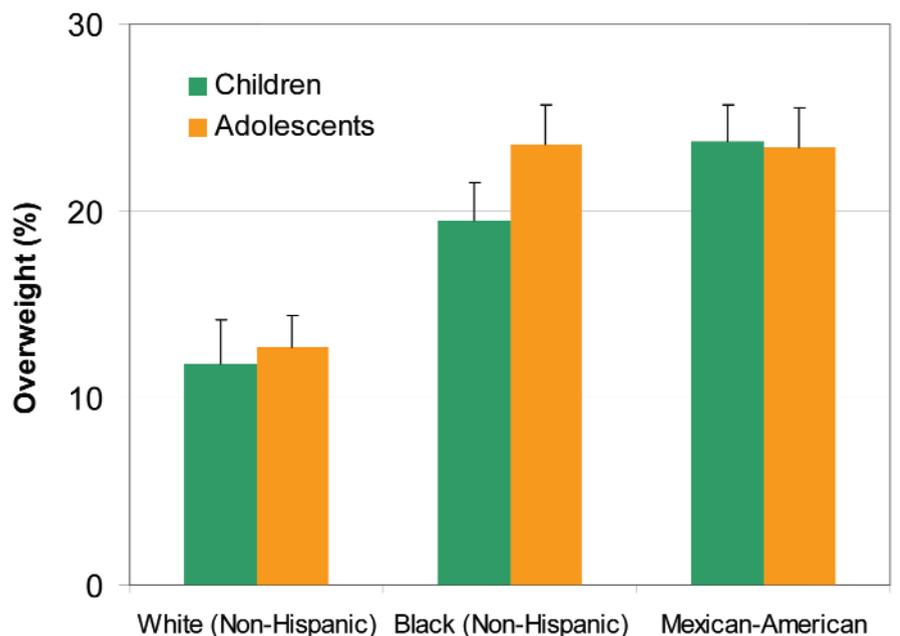

Figure 2. Differences in race and ethnicity affect overweight prevalence among U.S. children and adolescents. Children were aged 6–11 years, and adolescents were 12–19 years of age. Determined on the basis of BMI, overweight designation included those in the ≥ 95th percentile. Original data were from the National Health and Nutrition Examination Survey 1999–2000. Collected here from Ref. 6.

disorders.[15] Hyperinsulinemia is often sufficient to compensate for insulin resistance during childhood; however, the pancreatic β-cell may be unable to compensate adequately for the state of increased insulin resistance associated with puberty, and IGT or diabetes may ensue.[16] In a recent study of 491 obese children and adolescents at high risk for developing type 2 diabetes, there was a high prevalence (37%) of IGT with no differences observed related to ethnicity.[17] Metabolic syndrome in obese children and adolescents has been estimated to range from 28.7 to 49.7%.[18,19] In a recent study of 126 overweight Hispanic children aged 8–13 years with a family history of type 2 diabetes, prevalence of metabolic syndrome was found to be 30%.[20,21]

The American Diabetes Association (ADA) criteria for diagnosis of diabetes are the same for children, adolescents, and adults. According to these guidelines, E.J.'s diabetes could be diagnosed by the presence of polydipsia along with a random plasma glucose level > 200 mg/dl. Classification of the type of diabetes is generally more difficult than establishing a diagnosis of diabetes. In many cases, classification is based on observation of clinical features and course, or it may be accomplished with the aid of data from additional testing (e.g., C-peptide test, detection of autoantibodies, and determination of fasting insulin level).[2] Neither C-peptide nor fasting insulin levels has been standardized for distinguishing a diagnosis of type 2 from type 1 diabetes in children;[22] however, it is probable that there are many patients who have clinical and biochemical features of both type 1 and type 2 diabetes.[23,24]

The classification of diabetes could be assigned in E.J.'s case as highly likely to be type 2, based on the presence of only trace amounts of ketones in her urine (which if present usually indicate absolute or marked insulin deficiency), along with the presence of obesity, acanthosis nigricans, and a strong family history of typical type 2 diabetes. A more

relevant question is whether differentiating patients such as E.J. as having type 1 or type 2 diabetes will affect the course of therapy. In cases such as this, in which the chief complaint was vaginal discharge found to be associated with hyperglycemia, classification may not be immediately critical for initial treatment. Whether a patient has type 1 or type 2 diabetes is often of little consequence when the immediate goal is simply to bring the plasma glucose levels under manageable control as quickly as possible. Unfortunately, there are currently no data from clinical trials specific to children and adolescents that would guide the choice of therapy in this case.

There are many issues to consider when initiating a therapeutic regimen for a child or adolescent with type 2 diabetes, including illness severity and stage, anticipated adherence, developmental stage, and family socioeconomic status and level of support. Ideally, the therapeutic regimen chosen should be one that will be accepted and afforded and will be sufficiently efficacious to result in achievement of the glycemic targets without untoward side effects, including severe or frequent hypoglycemia. Lifestyle changes that involve the entire family, including detailed attention to diet and exercise, constitute the foundation of an effective treatment plan. Rarely, simple modification of diet and exercise habits alone are sufficient to provide optimal or even adequate glycemic control. In the case of E.J., a dietary and exercise regimen would be a necessary but most likely insufficient component of the therapeutic plan. Pharmacotherapy, in addition to behavioral modifications, would be required in this case to achieve optimal glycemic control within a reasonable period of time.

Choosing the best treatment for an individual patient requires balancing many factors, including efficacy, likely side effects, simplicity, and convenience of the treatment regimen. Ideally, a treatment regimen that the patient finds simple and convenient will foster adherence to therapy, which hopefully will lead to

rapid and sustained achievement of glycemic targets, although in many cases the progression of diabetes will require implementation of more aggressive regimens over time. This needs to be balanced with the need to attain glycemic control to reverse the insulin resistance associated with glucose toxicity,[25] which is likely to be significant with an A1C this high.

There are differences of opinion as to how to approach the therapeutic needs of these patients. Some would argue that a simplified regimen would be preferred because it would allow time for patients to adjust to their treatment, with anticipation that intensification of therapy might become more easily acceptable than if it were initiated immediately at diagnosis. Others feel that patients do better with rapid intensified correction of their metabolic status, which would then allow maintenance on a more simplified regimen if so desired. Examples of a simplified approach that might be useful in the case of E.J. include once-daily long-acting insulin analog with or without oral antidiabetic agents, the use of oral agents alone, or the twice-daily use of a premixed insulin analog. The counterargument to this sort of "phased intensification" approach is that a more aggressive initial approach actually might be more readily acceptable at the time of diagnosis, compared to several months or years later, after habits and routines are well established.

Long-acting insulin analogs, such as insulin glargine, may be administered once daily and can be used in conjunction with oral agent therapy. Glargine is provided to deliver the required daily basal insulin needs, independent of insulin needs related to food ingestion. In adults, supplemental rapid-acting insulin or oral agent therapy often is required to meet postprandial insulin needs. Oral agent therapy alone should also be considered in the case of E.J., at least shortly after diagnosis is made, because of its simplicity and the opportunity to avoid injections, although this is unlikely to be as effective as initial

treatment with insulin in achieving a timely normalization of glycemia. Most experts would agree that an insulin sensitizer is the oral agent of choice, and metformin is the most widely prescribed oral agent. Metformin has been shown to be safe and effective in pediatric use,[26] although as monotherapy in children and adolescents with type 2 diabetes, it may not provide adequate glycemic control over an extended period of time.[27] Combination therapy (using different classes of oral agents in combination) could also be attempted in order to increase efficacy. The dilemma is whether the use of insulin secretagogues may accelerate β-cell demise in this age group, especially if there is evidence of autoimmunity.

With an A1C > 11%, insulin as initial therapy likely will be helpful in achieving rapid glycemic control. The choice of a premixed insulin or a premixed insulin analog would be reasonable and sufficient to control fasting and postprandial plasma glucose in some cases. However, the use of a premixed formulation reduces flexibility in meal timing, pattern, and carbohydrate content. The choice between premixed insulin and premixed insulin analogs depends on the needs of the patient with respect to timing insulin administration and meals. If taken immediately before meals, premixed insulin analogs are preferable in attempts to deliver both basal and postprandial glycemic coverage in every dose. Twice-daily administration of a premixed insulin analog obviates the need for mixing in the syringe, as well as the need for an injection during school hours, thus reducing possible barriers to compliance. The convenience associated with disposable insulin delivery pen devices may promote adherence to therapy in select patients. As with any treatment regimen, and especially those using insulin, frequent monitoring of blood glucose levels and corresponding dose adjustments are essential.

Although adolescents with poor glycemic control often present special challenges in achieving glycemic control

and the requisite degree of adherence, many are successful in adopting and managing an intensive insulin regimen successfully. Openly discussing the therapeutic options, including the advantages and limitations of each option, with E.J. and her family would give the physician an opportunity to gauge her likelihood of success with whatever approach is chosen. Over the course of therapy, discussions regarding the eventual failures of more simplified regimens to continue providing her with adequate glycemic control should be clearly explained as characteristic of the disease rather than personal failing on E.J.'s part. Because type 2 diabetes is a progressive condition, more intensified treatment regimens such as multiple daily injection therapy or continuous subcutaneous insulin infusion (pump therapy) may eventually become necessary for E.J. to maintain adequate glycemic control into adulthood. Increasingly, these treatments rely on rapid-acting insulin analogs, either alone as in pump therapy, or in combination with a long-acting insulin analog in multiple daily injection therapy. Regardless of the treatment plan selected, sufficient and age-appropriate initial education, ongoing contact, and family support and supervision will increase the likelihood of long-term success.

Regardless of the initial treatment chosen for E.J., a critical factor in her management of diabetes is likely to be the support and involvement of her family. From the case description, it seems that E.J. lives in an intact, two-parent home, which implies that some parental support for managing her diabetes is likely. Although having other people in the home who have been diagnosed with diabetes might be an advantage in learning the components of diabetes management (e.g., diet, blood glucose testing, injection techniques), the fact that E.J.'s mother has developed chronic diabetic complications might indicate that her own glycemic management has been less than optimal for some time. Multiple risk factors clearly indicate that testing of E.J.'s father and brother

for diabetes would also be recommended, in accordance with ADA guidelines for screening.

Special consideration should be given to the treatment of any child or adolescent with type 2 diabetes, with particular attention to physical, developmental, and emotional maturity; social environment; and resources. Despite an often "adult" body size, children and adolescents must not be treated simply as younger adults. The use of adult-appropriate diabetes educational materials is often not helpful, and the use of type 1 diabetes educational materials for children or adolescents with type 2 diabetes is inappropriate and occasionally destructive. It is always ideal to attempt to match a younger patient's level of commitment with an appropriately designed therapy, considering any possibilities to increase the likelihood of adherence and compliance to therapy. Finally, although not always possible because of geographic distances and variable availability of resources, the involvement of a pediatric diabetes health care team (e.g., pediatric endocrinologists, certified diabetes educators, dietitians, nurses, and psychologists, with access to social workers and other physician specialists, including ophthalmologists and nephrologists) experienced in management of type 2 diabetes is ideal.

The emergence of type 2 diabetes in childhood and adolescence is alarming, especially when one considers the long-term public health and societal ramifications as these patients progress to chronic complications, potentially at a very young chronological age. Although prevention is preferable, the recent advances in diabetes technology, including newer and more powerful oral agents, insulin analogs that provide a more physiological delivery of insulin, insulin infusion devices, and accurate and less invasive methods of assessing glycemic control, offer great promise that improved, if not ideal, glycemic control and associated health-related benefits might be achieved, thus reducing or preventing the

long-term complications of diabetes in patients such as E.J.

REFERENCES

[1]Fagot-Campagna A, Petitt DJ, Engelgau MM, Burrows NR, Geiss LS, Valdez R, Beckles GLA, Saaddine J, Gregg W, Williamson DF, Narayan V: Type 2 diabetes among North American children and adolescents: an epidemiologic review and a public health perspective. *J Pediatr* 136:664–672, 2000

[2]American Diabetes Association: Type 2 diabetes in children and adolescents. *Diabetes Care* 23:381–389, 2000

[3]Dietz WH: Overweight and precursors of type 2 diabetes mellitus in children and adolescents. *J Pediatr* 138:453–454, 2001

[4]Centers for Disease Control and Prevention: *National Diabetes Fact Sheet: General Information and National Estimates on Diabetes in the United States, 2003*. Rev. ed. Atlanta, Ga., U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, 2004

[5]Krebs NF, Jacobson MS, for the American Academy of Pediatrics Committee on Nutrition: Prevention of pediatric overweight and obesity. *Pediatrics* 112:424–430, 2003

[6]Ogden CL, Flegal KM, Carroll MD, Johnson CL: Prevalence and trend in overweight among US children and adolescents, 1999–2000. *JAMA* 288:1728–1732, 2002

[7]Sorof JM, Lai D, Turner J, Poffenbarger T, Portman RJ: Overweight, ethnicity, and the prevalence of hypertension in school-aged children. *Pediatrics* 113:475–482, 2004

[8]Sinha R, Fisch G, Teague B, Tamborlane WV, Banyas B, Allen K, Savoye M, Rieger V, Taksali S, Barbetta G, Sherwin RS, Caprio S: Prevalence of impaired glucose tolerance among children and adolescents with marked obesity. *N Engl J Med* 346:802–810, 2004

[9]Cruz ML, Bergman RN, Goran MI: Unique effect of visceral fat on insulin sensitivity in obese Hispanic children with a family history of type 2 diabetes. *Diabetes Care* 2:1631–1636, 2002

[10]Amiel SA, Sherwin RS, Simonson DC, Lauritano AA, Tamborlane WV: Impaired insulin action in puberty. A contributing factor to poor glycemic control in adolescents with diabetes. *N Engl J Med* 315:215–219, 1986

[11]Bloch CA, Clemons P, Sperling MA: Puberty decreases insulin sensitivity. *J Pediatr* 110:481–487, 1987

[12]Goran MI, Gower BA: Longitudinal study on pubertal insulin resistance. *Diabetes* 50:2444–2450, 2001

[13]Goran MI, Ball DC, Cruz ML: Obesity and risk of type 2 diabetes and cardiovascular disease in children and adolescents. *J Clin Endocrinol Metab* 88:1417–1427, 2003

[14]Caprio S: Insulin resistance in childhood obesity. *J Pediatr Endocrinol Metab* 15 (Suppl. 1):487–492, 2002

[15]Molnár D: The prevalence of the metabolic syndrome and type 2 diabetes mellitus in children and adolescents. *Int J Obesity* 28:S70–S74, 2004

[16]Ten S, Maclaren N: Insulin resistance syndrome in children. *J Clin Endocrinol Metab* 89:2526–2539, 2004

[17]Wiegand S, Maikowski U, Blankenstein O, Biebermann H, Tarnow P, Grüters A: Type 2 diabetes and impaired glucose tolerance in European children and adolescents with obesity: a problem that is no longer restricted to minority groups. *Eur J Endocrinol* 151:199–206, 2004

[18]Cook S, Weitzman M, Auinger P, Nguyen M, Dietz WH: Prevalence of a metabolic syndrome phenotype in adolescents. *Arch Pediatr Adolesc Med* 157:821–827, 2003

[19]Weiss R, Dziura J, Burgert TS, Tamborlane WV, Taksali SE, Yeckel CW, Allen K, Lopes M, Savoye M, Morrison J, Sherwin RS, Caprio S: Obesity and the metabolic syndrome in children and adolescents. *N Engl J Med* 350:2362–2374, 2004

[20]Cruz ML, Goran MI: The metabolic syndrome in children and adolescents. *Curr Diabetes Rep* 4:53–62, 2004

[21]Cruz ML, Weigensberg MJ, Huang TT-K, Ball G, Shaibi GQ, Goran MI: The metabolic syndrome in overweight Hispanic youth and the role of insulin sensitivity. *J Clin Endocrinol Metab* 89:108–113, 2004

[22]Silverstein J, Klingensmith G, Copeland K, Plotnick L, Kaufman F, Laffel L, Deeb L, Grey M, Anderson B, Holzmeister LA, Clark N: Care of children and adolescents with type 1 diabetes: a statement of the American Diabetes Association. *Diabetes Care* 28:186–212, 2005

[23]Libman IM, Pietropaolo M, Arslanian SA, LaPorte RE, Becker, DJ: Evidence for heterogeneous pathogenesis of insulin-treated diabetes in black and white children. *Diabetes Care* 26:2876–2882, 2003

[24]Brooks-Worrell BM, Greenbaum CJ, Palmer JP, Pihoker C: Autoimmunity to islet proteins in children diagnosed with new-onset diabetes. *J Clin Endocr Metab* 89:2222–2227, 2004

[25]Yki-Järvinen H: Glucose toxicity. *Endocrine Rev* 13:415–431, 1992

[26]Jones KL, Arslanian S, Peterokova VA, Park J-S, Tomlinson MJ: Effect of metformin in pediatric patients with type 2 diabetes. *Diabetes Care* 25:89–94, 2002

[27]Zuhri-Yafi MI, Brosnan PG, Hardin DS: Treatment of type 2 diabetes in children and adolescents. *J Pediatr Endocrinol Metab* 15 (Suppl. 1):541–546, 2002

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