Type 2 Diabetes in Children and Adolescents

American Diabetes Association

Type 2 diabetes is a serious and costly disease affecting more than 15 million adult Americans. The chronic complications of diabetes include accelerated development of cardiovascular disease, end-stage renal disease, loss of visual acuity, and limb amputations. All of these complications contribute to the excess morbidity and mortality in individuals with diabetes. Moreover, the prevalence of type 2 diabetes in adults is increasing. Superimposed on this disturbing picture in adults are the recent reports of the emerging problem of type 2 diabetes in children and adolescents.

If the incidence and prevalence of type 2 diabetes in children are increasing and if this increase cannot be reversed, our society will face major challenges. That is, the burden of diabetes and its complications will affect many more individuals than currently anticipated, and the cost of diabetes to our society will cause us to consume enormous resources. Also, many more Americans will be taking potent medications, which have attendant risks, for most of their lives.

Despite the wealth of experience and knowledge concerning the epidemiology, pathophysiology, and medical management of type 2 diabetes in adults, we know little about the disease in children. To assess our present knowledge and understanding and to provide guidance to practitioners on medical management, the American Diabetes Association (ADA) convened a consensus development conference on type 2 diabetes in children and adolescents from 30 August 1999 to 1 September 1999.

An eight-member panel of experts in diabetes in children, complemented by representatives from the National Institute of Diabetes and Digestive and Kidney Diseases, the Division of Diabetes Translation at the Centers for Disease Control and Prevention, and the American Academy of Pediatrics, developed a consensus position on the following six questions:

1. What is the classification of diabetes in children and adolescents?
2. What is the epidemiology of type 2 diabetes in children and adolescents?
3. What is the pathophysiology of type 2 diabetes in children and adolescents?
4. Who should be tested for diabetes?
5. How should children and adolescents with type 2 diabetes be treated?
6. Can type 2 diabetes in children and adolescents be prevented?

QUESTION 1: What Is the Classification of Diabetes in Children and Adolescents?

The diagnostic criteria and etiologic classification (Table 1) of diabetes (Table 2) outlined by the ADA's Expert Committee report apply to children (1). In the pediatric population, the recent experience with nonimmune-mediated diabetes has highlighted the difficulty in distinguishing the etiology of diabetes in some children without sophisticated laboratory evaluation. This experience has created confusion over the criteria that should be used to classify diabetes in children.

Until recently, immune-mediated type 1 diabetes was the only type of diabetes considered prevalent among children, with only 1–2% of children considered to have type 2 diabetes or other rare forms of diabetes. Recent reports indicate that 8–45% of children with newly diagnosed diabetes have nonimmune-mediated diabetes. The variation in the percentages reported appears to depend on race/ethnicity and sampling strategy. The majority of these children have type 2 diabetes, but other types are being increasingly identified. For example, idiopathic or nonimmune-mediated type 1 diabetes has been reported, particularly in the African-American population.

Individuals with nonimmune-mediated diabetes may have clinical presentations indistinguishable from those of patients with immune-mediated type 1 diabetes. This is relevant because as the number of children with type 2 diabetes increases, it becomes increasingly important to classify their diabetes correctly so that appropriate therapy may be instituted.

The initial classification is usually based on the clinical picture at presentation. Typically, children with immune-mediated type 1 diabetes are not overweight and have recent weight loss, polyuria, and polydipsia. As the U.S. population becomes increas-

TABLE 1. Criteria for the Diagnosis of Diabetes

- Symptoms of diabetes plus casual plasma glucose concentration ≥200 mg/dl (11.1 mmol/l). Casual is defined as any time of day without regard to time since last meal. The classic symptoms of diabetes include polyuria, polydipsia, and unexplained weight loss.

  or
- FPG ≥126 mg/dl (7.0 mmol/l). Fasting is defined as no caloric intake for at least 8 h.

  or
- 2-h PG ≥200 mg/dl (11.1 mmol/l) during an OGTT. The test should be performed as described by the World Health Organization (20), using a glucose load containing the equivalent of 75-g anhydrous glucose dissolved in water.

In the absence of unequivocal hyperglycemia with acute metabolic decompensation, these criteria should be confirmed by repeat testing on a different day. The third measure (OGTT) is not recommended for routine clinical use. Adapted from the Report of the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus (1).

ingly overweight, however, the percentage of children with immune-mediated type 1 diabetes who are obese is increasing. As many as 24% may be overweight at the time of diagnosis. Children with immune-mediated diabetes usually have a short duration of symptoms and frequently have ketosis; 30–40% have ketoacidosis at presentation (2). After metabolic stabilization, they may have an initial period of diminished insulin requirement (i.e., honeymoon period), after which they require insulin for survival and are at continual risk for ketoacidosis. Of children with immune-mediated type 1 diabetes, 5% have a first- or second-degree relative with the same disease.

In contrast, most children with type 2 diabetes are overweight or obese at diagnosis and present with glycosuria without ketonuria, absent or mild polyuria and polydipsia, and little or no weight loss. But up to 33% have ketonuria at diagnosis, and 5–25% of patients who are subsequently classified as having type 2 diabetes have ketoacidosis at presentation. These patients may have ketoacidosis without any associated stress, other illness, or infection. Children with type 2 diabetes usually have a family history of type 2 diabetes, and those of non-European ancestry (Americans of African, Hispanic, Asian, and American Indian descent) are disproportionately represented.

While there is heterogeneity in the presentation of both type 1 and type 2 diabetes, there are certain clinical features that suggest type 2 diabetes. As noted above, obesity is a hallmark of type 2 diabetes, with up to 85% of affected children either overweight or obese at diagnosis. Occasionally, obesity may be masked by significant weight loss in the months or year before diagnosis. A family history of diabetes is usually present; 45–80% of patients have at least one parent with diabetes and may have a history of diabetes over several generations. Of the patients, 74–100% have a first- or second-degree relative with type 2 diabetes. Of note, diabetes in the parent or other relative may not be recognized until the child is diagnosed.

Acanthosis nigricans and polycystic ovarian syndrome (PCOS), disorders associated with insulin resistance and obesity, are common in youth with type 2 diabetes. Acanthosis is a cutaneous finding characterized by velvety hyperpigmented patches most prominent in intertriginous areas and is present in as many as 90% of children with type 2 diabetes (A. Fagot-Campagna, D. J. Pettitt, M. M. Engelgau, N. R. Burrows, L. S. Geiss, R. Valdez, G. Beckles, J. Saaddine, E. W. Gregg, D. E. Williamson, K. M. Venkat Narayan, *J Pediatrics.* In press). It is recognized more frequently in darker-skinned obese individuals. PCOS is a reproductive disorder characterized by hyperandrogenism and chronic anovulation not due to specific diseases of the ovaries, adrenals, and pituitary. Lipid disorders and hypertension also occur in children with type 2 diabetes.

Currently, children with type 2 diabetes are usually diagnosed over the age of 10 years and are in middle to late puberty. As the childhood population becomes increasingly overweight, type 2 diabetes may be expected to occur in younger prepubertal children.

Children with idiopathic type 1 diabetes may be difficult to distinguish from those with immune-mediated type 1 diabetes. The majority of those described with idiopathic type 1 diabetes have what has been termed atypical diabetes mellitus (ADM, type 1.5, or "Flatbush" diabetes) and are African-American (3,4). Their family history is positive for early-onset diabetes in many relatives in multiple generations. Insulin may not be required for survival after the resolution of the acute metabolic deterioration. Metabolic control, however, is poor without insulin therapy, and ketoacidosis may recur.

Maturity-onset diabetes of the young (MODY) is a rare form of diabetes in children that includes several disorders caused by monogenic defects in β-cell function inherited in an autosomal-dominant fashion (5). Recent studies suggest that the clinical spectrum of MODY is broad, ranging from asymptomatic hyperglycemia to a severe acute presentation. MODY has been reported in all races/ethnicities. These gene abnormalities are thought to be rare, and molecular

TABLE 2. Etiologic Classification of Diabetes

- Type 1 diabetes* (β-cell destruction, usually leading to absolute insulin deficiency)
  Immune-mediated
  Idiopathic
- Type 2 diabetes* (may range from predominantly insulin resistance with relative insulin deficiency to a predominantly secretory defect with insulin resistance)
- Other specific types
  Genetic defects of β-cell function (e.g., MODY)
  Genetic defects in insulin action (e.g., lipoatrophic diabetes)
  Diseases of the exocrine pancreas (e.g., cystic fibrosis)
  Endocrinopathies (e.g., Cushing's syndrome)
  Drug- or chemical-induced (e.g., glucocorticoids)
  Infections (e.g., congenital rubella)
  Uncommon forms of immune-mediated diabetes
  Other genetic syndromes sometimes associated with diabetes (e.g., Prader-Willi syndrome)
- Gestational diabetes mellitus (GDM)

* Patients with any form of diabetes may require insulin treatment at some stage of their disease. Use of insulin does not, of itself, classify the patient. Adapted from the Report of the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus (1).

diagnostic testing, currently only available in research laboratories, is required for specific classification. Until such testing becomes commonplace, children with MODY should be classified as having the type of diabetes that best fits their clinical picture.

In most patients, classification can be made reliably on the basis of clinical presentation and course. In the unusual circumstance that requires a specific classification to be made, other tests may be necessary, such as a fasting insulin or C-peptide determination, and occasionally, β-cell autoantibody measurements (Fig. 1). Individuals with type 2 diabetes do not generally have autoantibodies to β-cell proteins; fasting insulin and C-peptide levels are usually normal or elevated, although not as elevated as might be expected for the degree of hyperglycemia.

Specific autoantibodies to insulin, to GAD, or to the tyrosine phosphatases insulin antibody (IA)-2 and IA-2β are found at presentation in 85–98% of individuals with immune-mediated type 1 diabetes. To achieve a high degree of sensitivity, a combination of tests is required, which greatly increases the cost of classification. In the future, these tests may be standardized, more reliable, and less expensive. Immune-mediated type 1 diabetes also has a strong HLA association; however, HLA typing is not a useful diagnostic tool. Endogenous fasting insulin and C-peptide production in type 1 patients is low, with little or no increase after oral or intravenous glucose administration or after ingestion of a mixed meal. Specific laboratory evaluation to classify diabetes in children should only be used by diabetologists with pediatric expertise and only when a definitive classification is clinically required.

Patients with immune-mediated type 1 diabetes more frequently develop autoimmune disorders that may cause thyroid or adrenal disease, vitiligo, or pernicious anemia. Individuals with autoimmune diabetes are also more prone to celiac disease. The presence of other autoimmune disorders or celiac disease may suggest the need for further evaluation of a patient classified as having non-type 1 diabetes. Patients classified as having type 1 diabetes may also need to be reevaluated if their clinical course or family history is more consistent with type 2 diabetes.

QUESTION 2: What Is the Epidemiology of Type 2 Diabetes in Children and Adolescents?

The limited amount of information about the epidemiology of type 2 diabetes in children is in large part due to the relatively recent recognition of its emergence in this age-group. Table 3 summarizes the studies and reports that provide estimates of the frequency of type 2 diabetes in children (A. Fagot-Campagna, D. J. Pettitt, M. M. Engelgau, N. R. Burrows, L. S. Geiss, R. Valdez, G. Beckles, J. Saaddine, E. W. Gregg, D. F. Williamson, K. M. Venkat Narayan, *J Pediatrics*. In press). The Pima Indians in Arizona, known to have a high prevalence of type 2 diabetes, have been extensively studied. An analysis from 1992 to 1996 revealed a prevalence of type 2 diabetes of 22.3 per 1,000 in the 10- to 14-year-old age-group and 50.9 per 1,000 in the 15- to 19-year-old age-group. Affected individuals were identified in the course of clinical care or by having a 2-h blood glucose value ≥200 mg/dl during an oral glucose tolerance test (OGTT) (2-h plasma glucose [2-h PG]).

Fig 1. Research schema for classification of diabetes in children and youth. Americans of non-European descent are at greater risk for type 2 diabetes than those of European ancestry. In addition, 50–90% of youth with type 2 diabetes will have a BMI >27 kg/m² (or >85% for age). The preponderance of children with type 2 diabetes are over 10 years of age, are in middle or late puberty, and have a strong family history for diabetes. Until the full clinical spectrum of MODY is understood, it cannot be excluded in those not tested for β-cell autoantibodies or in autoantibody-negative individuals. The final diagnostic classification may require knowledge of the patient's clinical course during the initial 1–3 years after diagnosis. IM, immune-mediated.
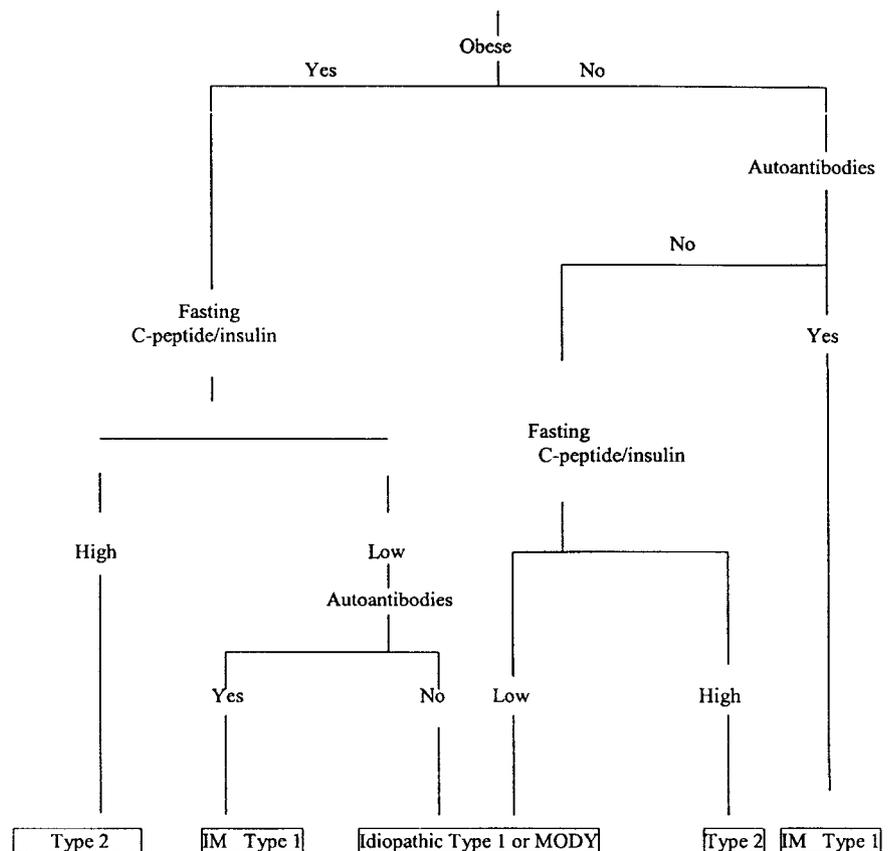
TABLE 3.   Estimates of the Magnitude of Type 2 Diabetes in North American Children

	Years	Race/Ethnicity	Age (Years)	Estimates
Study types				
Population-based studies				Prevalence per 1,000
Arizona	1992–1996	Pima Indians	10–14	22.3
			15–19	50.9
Manitoba	1996–1997	First Nations	10–19	36.0 in girls
NHANES III, all U.S.	1988–1994	Whites, African-Americans, Mexican Americans	12–19	4.1*
Clinic-based studies				
Indian Health Services (all U.S.)	1996	American Indians	0–14	1.3*
			15–19	4.5*
Manitoba	1998	First Nations	5–14	1.0
			15–19	2.3
Clinic-based studies				Incidence per 100,000/year
Cincinnati, OH	1994	Whites, African-Americans	10–19	7.2
Case series				Percentage of type 2 diabetes among new cases of diabetes
Cincinnati, OH	1994	Whites, African-Americans	0–19	16
			10–19	33
Charleston, SC	1997	Blacks	0–19	46†
San Diego, CA	1993–1994	Whites, African-Americans, Hispanics, Asian Americans	0–16	8
San Antonio, TX	1990–1997	Hispanics, Whites		18
Ventura, CA	1990–1994	Hispanics	0–17	45

* Estimates include type 1 and 2 diabetes; † percentage of type 2 diabetes among nonincident cases of diabetes. Adapted from A. Fagot-Campagna, D. J. Pettitt, M. M. Engelgau, N. R. Burrows, L. S. Geiss, R. Valdez, G. Beckles, J. Saaddine, E. W. Gregg, D. F. Williamson, K. M. Venkat Narayan, *J Pediatrics.* In press.

The Third National Health and Nutrition Examination Survey (NHANES III) constitutes a representative sample of the American population including 2,867 individuals aged 12–19 years who had blood glucose measurements between 1988 and 1994. Thirteen of those sampled had diabetes: nine based on insulin treatment, two based on treatment with oral agents, and two based on elevated blood glucose levels. These results projected a national prevalence estimate for all types of diabetes of 4.1 per 1,000 in this age-group, which can be compared with a prevalence of 0.3 per 1,000 for cystic fibrosis, one of the most common inherited disorders in U.S. children (6).

Additional information comes from reports of diagnosed cases in different areas of the U.S. For example, in Cincinnati, Ohio, the incidence of type 2 diabetes in 10- to 19-year-old patients increased from 0.7 per 100,000 in 1982 to 7.2 per 100,000 in 1994.

Evidence is accumulating suggesting that type 2 diabetes is increasing in children and adolescents in the U.S. The population-based data derived from the Pima Indians show a statistical increase in prevalence from 1967 to 1996 for those aged 10–14 and 15–19 years. Between 1988 and 1996, the Indian Health Service also documented a 54% increase in prevalence of reported diabetes in 15- to 19-year-old adolescents. Registry data from Allegheny County, Pennsylvania, and Chicago, further suggest an increase in type 2 diabetes. Finally, in other case series, type 2 diabetes constituted an increasing percentage of incident pediatric cases of diagnosed diabetes, with fewer than 4% reported before the 1990s and up to 45% in recent studies.

The emergence of type 2 diabetes in children is not limited to North America. The annual incidence of type 2 diabetes among junior high school children in Tokyo, detected by urine glucose screening and confirmed by glucose tolerance testing, increased from 7.3 per 100,000 in 1976–1980 to 12.1 per 100,000 in 1981–1985, and to 13.9 per 100,000 in 1991–1995. Data from Libya, Bangladesh, and aboriginal children in Australia and Canada indicate that childhood type 2 diabetes is occurring in these populations as well. One possible explanation for the emergence of type 2 diabetes in children is the increase of obesity and decreasing physical activity in children. Obesity is now reaching epidemic proportions in the U.S. and elsewhere.

Obesity is a very common finding in children with type 2 diabetes (A. Fagot-Campagna, D. J. Pettitt, M. M. Engelgau, N. R. Burrows, L. S. Geiss, R. Valdez, G. Beckles, J. Saaddine, E. W. Gregg, D. F. Williamson, K. M. Venkat Narayan, *J Pediatrics*. In press). In a young Pima Indian cohort with diabetes, 85% were obese. This association has been consistent in all reports, although the criteria for obesity and its severity have varied. The reported mean BMI ranges from 27 to 38 kg/m², and in most patients, the BMI was greater than the 85th percentile for age and sex. Although it has been well established in adults and in many populations that a "Westernized" lifestyle is associated with an increased frequency of type 2 diabetes, there are no well-controlled studies that have examined this issue in children. Decreased exercise and increased calorie and fat intake have been implicated as risk factors.

Family history of diabetes is strongly associated with type 2 diabetes in children. The frequency of a history of type 2 diabetes in a first- or second-degree relative has ranged from 74 to 100%. Among Pima Indians below the age of 25 years, diabetes has been reported exclusively in individuals with at least one diabetic parent. In the Pimas, offspring of mothers

who had diabetes during pregnancy had a markedly increased prevalence of diabetes compared with offspring of mothers without diabetes and those whose mothers developed diabetes after the child's birth. Low birth weight has also been associated with the development of type 2 diabetes in Pima Indian children. These findings have not been reported in other childhood populations.

Sex and puberty are also possible risk factors. In the U.S. adult population, the prevalence of diagnosed type 2 diabetes is slightly higher in women than in men. Most of the studies in children, including those that are population-based, indicate a higher frequency in females. Reported cases of type 2 diabetes in children showed a peak age of diagnosis during the usual pubertal age period, although there have been individuals described who were diagnosed prepubertally. The mean age of diagnosis was between 12 and 16 years. The youngest patient who has been described is a 4-year-old Pima Indian.

There are a number of factors that may influence the accuracy of much of the information discussed above. Although the population-based studies are carefully done and accurately reflect the North American populations examined, case study reports probably underestimate the true magnitude of the problem, since they only describe diagnosed cases. If pediatric type 2 diabetes mirrors the adult experience, there will be many affected individuals who are undiagnosed. There is also suspicion that with the relatively recent recognition of type 2 diabetes in this age-group, many children are still being misdiagnosed as having type 1 diabetes. Indeed, the Chicago Registry indicates that this misclassification occurred as frequently as in 25% of cases.

As this problem continues to be defined and described, there remain a number of research needs. It will be necessary to better define the magnitude of type 2 diabetes in children and confirm that there is a significant trend toward increasing incidence and prevalence. It will also be important to clearly define the characteristics of those affected and the risk factors for developing the disease. Finally, it will be important to describe the natural history of the disease in those affected at young ages.

QUESTION 3: What Is the Pathophysiology of Type 2 Diabetes in Children and Adolescents?

Type 2 diabetes is a complex metabolic disorder of heterogeneous etiology with social, behavioral, and environmental risk factors unmasking the effects of genetic susceptibility (7). There is a strong hereditary (likely multigenic) component to the disease, with the role of genetic determinants illustrated when differences in the prevalence of type 2 diabetes in various racial groups are considered. The recent increases observed in diabetes prevalence have occurred too quickly to be the result of increased gene frequency and altered genetic pool, emphasizing the importance of environmental factors.

Glucose homeostasis depends on the balance between insulin secretion by the pancreatic β-cells and insulin action. For hyperglycemia to develop, insulin resistance alone is not sufficient and inadequate β-cell insulin secretion is necessary. There has been considerable debate about whether insulin resistance or insulin hyposecretion is the primary defect in type 2 diabetes in adults. The constellation of clinical characteristics in children with type 2 diabetes suggests that the initial abnormality is impaired insulin action, compounded later with β-cell failure.

It is well recognized that resistance to insulin-stimulated glucose uptake is a characteristic finding in patients with type 2 diabetes and impaired glucose tolerance. Cross-sectional and longitudinal studies in populations at high risk for developing type 2 diabetes demonstrate that hyperinsulinemia and insulin resistance are present in the prediabetic normoglycemic state. The evolution from normal to impaired glucose tolerance is associated with a worsening of insulin resistance. In patients with type 2 diabetes, impaired insulin action and insulin secretory failure are both present. The failure of the β-cell to continue to hypersecrete insulin underlies the transition from insulin resistance (with compensatory hyperinsulinemia and normoglycemia) to clinical diabetes (with overt fasting hyperglycemia and increased hepatic glucose production).

It has been proposed that hyperglycemia may worsen both insulin resistance and insulin secretory abnormalities, thus enhancing the transition from impaired glucose tolerance to diabetes or aggravating the diabetes. This way, hyperglycemia may beget more hyperglycemia—a concept called glucose toxicity. Glucose toxicity-induced abnormalities of insulin secretion and action can be ameliorated by correction of hyperglycemia.

Puberty appears to play a major role in the development of type 2 diabetes in children. During puberty, there is increased resistance to the action of insulin, resulting in hyperinsulinemia (8). It has been known for many years that insulin responses during an OGTT increase significantly from the toddler ages to adolescence. After puberty, basal and stimulated insulin responses decline. Hyperinsulinemic-euglycemic clamp studies demonstrate that insulin-mediated glucose disposal is on average 30% lower in adolescents between Tanner stages II and IV compared with prepubertal children in Tanner stage I and compared with young adults. In the presence of normal pancreatic β-cell function, puberty-related insulin resistance is compensated by increased insulin secretion.

Both growth hormone and sex steroids have been considered as candidates for causing insulin resistance during puberty. The fact that sex steroids remain elevated after puberty while insulin resistance decreases makes sex steroids an unlikely cause of insulin resistance. Conversely, mean growth hormone levels increase transiently during puberty coincidental with the decrease in insulin action. In addition, administering growth hormone to nongrowth hormone-deficient adolescents is associated with deterioration in insulin action, while testosterone administration has no such effect. Thus, increased growth hormone secretion is most likely responsible for the insulin resistance during puberty,

and both growth hormone secretion and insulin resistance decline with completion of puberty.

Given this information, it is not surprising that the peak age at presentation of type 2 diabetes in children coincides with the usual age of mid-puberty. In an individual who has a genetic predisposition for insulin resistance, compounded with environmental risk exposure, the additional burden of insulin resistance during puberty may tip the balance from a state of compensated hyperinsulinemia with normal glucose tolerance to inadequate insulin secretion and glucose intolerance that continues beyond puberty.

The adverse effect of obesity on glucose metabolism is evident early in childhood. In healthy white children, total adiposity accounts for ~55% of the variance in insulin sensitivity. Obese children are hyperinsulinemic and have ~40% lower insulin-stimulated glucose metabolism compared with nonobese children. Moreover, the amount of visceral fat in obese adolescents is directly correlated with basal and glucose-stimulated hyperinsulinemia and inversely correlated with insulin sensitivity. In African-American children, as BMI increases, insulin-stimulated glucose metabolism decreases and fasting insulin levels increase. Furthermore, in these children, the inverse relationship between insulin sensitivity and abdominal fat is stronger for visceral than for subcutaneous fat. In a 7-year longitudinal study of African-American and white young adults 18 years and older, the strongest predictor for increases in both insulin and glucose concentrations was an increase in BMI.

Data about hyperandrogenism and type 2 diabetes are limited in the pediatric age-group. In adults, however, women with PCOS are at increased risk of type 2 diabetes because they have profound insulin resistance, independent of obesity, and they have abnormalities in β-cell function. In women with PCOS, 31% have impaired glucose tolerance and 7.5–16% have type 2 diabetes (9). Adolescents with PCOS have evidence of skeletal muscle insulin resistance with ~40% reduction in insulin-stimulated glucose disposal, compared with body composition-matched nonhyperandrogenic control subjects. Those adolescents with PCOS who have impaired glucose tolerance have ~50% decrement in first-phase insulin secretion.

Racial differences in insulin sensitivity are also evident in childhood. African-American 7- to 11-year-old children have significantly higher insulin levels than age-matched white children. The Bogalusa Heart Study evaluated plasma glucose and insulin levels during an OGTT in 377 children aged 5–17 years from a biracial community. After adjusting for weight, age, ponderal index, and pubertal stage, African-Americans showed higher insulin responses than their white counterparts, suggesting compensated insulin resistance. In other studies using clamp experiments, insulin sensitivity was 30% lower in African-American adolescents compared with white adolescents. These data suggest that minority children may have a genetic predisposition to insulin resistance, which, in the presence of environmental modulators, could increase their risk of type

2 diabetes and result in disease expression during physiologic (puberty) or pathologic (obesity) states of insulin resistance.

QUESTION 4: Who Should Be Tested for Diabetes?

Consistent with the recommendations of the ADA for screening in adults, only children at substantial risk for the presence or the development of type 2 diabetes should be tested. Case finding in an at-risk population requires that the condition tested for must be sufficiently common and serious to justify the cost and risks of testing. This criterion is met by the substantial risk for type 2 diabetes in obese children with a positive family history or signs of insulin resistance. Moreover, diabetes is associated with significant morbidity and premature mortality, and its complications are a major burden to individuals and to society.

The condition tested for should also have a prolonged latency period without symptoms during which abnormality can be detected. For example, case finding for type 1 diabetes in asymptomatic individuals is not considered appropriate because the latency period is relatively brief. As with type 2 diabetes in adults, a substantial number of children with type 2 diabetes can be detected in the asymptomatic state. Also, it is likely that, as with adults, there are many undiagnosed children with type 2 diabetes.

Further requirements for testing an asymptomatic group include the availability of a test that is sensitive (few false negatives) and accurate with acceptable specificity (minimal number of false positives). The fasting glucose test and 2-h OGTT have been applied to high-risk populations and are acceptably sensitive and specific. Lastly, there must be an intervention that is effective in the latency phase, and we do have interventions to reverse hyperglycemia, with the goal of preventing complications.

Testing Recommendations

Population selection.

Acknowledging that there are insufficient data to make definite recommendations, the Consensus Panel recommends that if an individual is overweight (defined as BMI >85th percentile for age and sex (10), weight for height >85th percentile, or weight >120% of ideal [50th percentile] for height) and has any two of the other risk factors listed below, testing should be done every 2 years starting at age 10 years or at onset of puberty if it occurs at a younger age. Testing may be considered in other high-risk patients who display any of the following characteristics:

- Have a family history of type 2 diabetes in first- and second-degree relatives;
- Belong to a certain race/ethnic group (American Indians, African-Americans, Hispanic Americans, Asians/South Pacific Islanders);
- Have signs of insulin resistance or conditions associated with insulin resistance (acanthosis nigricans, hypertension, dyslipidemia, PCOS).

Test methods.

As stated above, the fasting plasma glucose (FPG) and 2-h PG are both suitable. The FPG is preferred because of its lower cost and greater convenience. Fasting is defined as no consumption of food or beverage other than water for at least 8 h before testing. The recommended criteria for testing are given in Table 4.

The above recommendations are based on limited data. School- or community-based studies are needed. Such studies could establish the strength and risk level of various factors that might influence the development of type 2 diabetes (blood pressure, obesity, fat distribution, acanthosis nigricans, family history, race/ethnicity, and socioeconomic status). They would also provide useful information about the value of individual tests, including the FPG, 2-h PG, random glucose, and HbA_{1c}. These studies should be carried out in populations with sufficient numbers of children who are at high risk. In addition, longitudinal studies are needed to define the natural history and risk factors of the disease.

QUESTION 5: How Should Children and Adolescents with Type 2 Diabetes Be Treated?

The ideal goal of treatment is normalization of blood glucose values and HbA_{1c} (11). Successful control of the associated comorbidities, such as hypertension and hyperlipidemia, is also important. The ultimate goal of treatment is to decrease the risk of the acute and chronic complications associated with diabetes. There is strong evidence from the U.K. Prospective Diabetes Study that normalization of blood glucose substantially decreases the frequency of microvascular complications of type 2 diabetes in adults (12). Macrovascular outcomes were not significantly decreased; however, a substudy investigating the effectiveness of tight control of blood pressure did show a decrease in cardiovascular events that was statistically significant. The early age of onset of type 2 diabetes in children may particularly increase the risk of microvascular complications, which are known to be directly related to duration of diabetes and hyperglycemia.

The initial treatment of type 2 diabetes will vary depending on the clinical presentation. The spectrum of disease at diagnosis ranges from asymptomatic hyperglycemia to diabetic ketoacidosis (DKA) and hyperglycemic hyperosmolar nonketotic (HHNK) states. Both DKA and HHNK crisis are associated with high morbidity and mortality in children. Cerebral edema can occur in either circumstance. Early consultation and referral to pediatric and adolescent diabetologists/endocrinologists with experience in the management of DKA and HHNK should be considered.

Patients who are not ill at diagnosis can be managed initially with medical nutrition therapy and exercise, but most will eventually require drug therapy. Although insulin is the only drug approved by the Food and Drug Administration (FDA) for the treatment of diabetes in children, most pediatric diabetologists use oral agents for children with type 2 diabetes. Advantages of oral agents include potentially greater compliance and convenience for the patient and family. There is little evidence that insulin is superior to oral agents for initial treatment of type 2 diabetes in children.

Clinical features suggesting initial treatment with insulin include dehydration, presence of ketosis, and acidosis. In the less ill child with type 2 diabetes, initial treatment with diet, exercise, and an oral agent may be appropriate. In all patients, identification and treatment of comorbid conditions are important. With time and treatment, metabolic control may change, necessitating reevaluation of treatment, such as tapering of insulin and introduction of an oral agent in the patient whose glycemic control improves after insulin therapy.

Lifestyle Changes

All children with type 2 diabetes should receive comprehensive self-management education. The National Standards for Diabetes Self-Management Education is a useful framework for providing this invaluable component of treatment (13). Self-management education should include teaching self-monitoring of blood glucose (SMBG). SMBG should be performed as needed and during periods of acute illness or when symptoms of hyper- or hypoglycemia occur. Patients on insulin or sulfonylureas should also monitor periodically for asymptomatic hypoglycemia. Routine blood glucose monitoring should be tailored to individual needs but should probably include a combination of fasting and postprandial glucose measurements. HbA_{1c} should be assayed to monitor glycemic control and the results and their significance shared with the patient and family.

Referral to a dietitian with knowledge and experience in nutritional management of children with diabetes is necessary. Dietary recommendations should be culturally appropriate, sensitive to family resources, and provided to all caregivers. Encouraging healthy eating habits by the entire family is important. Behavior modification strategies for changing lifestyle and decreasing high-caloric high-fat food choices should be discussed (14).

Increasing caloric expenditure by increasing daily physical activity is an important component of ther-

TABLE 4. Testing for Type 2 Diabetes in Children

- Criteria*
  Overweight (BMI >85th percentile for age and sex, weight for height >85th percentile, or weight >120% of ideal for height)
  Plus
  Any two of the following risk factors:
  Family history of type 2 diabetes in first- or second-degree relative
  Race/ethnicity (American Indian, African-American, Hispanic, Asian/Pacific Islander)
  Signs of insulin resistance or conditions associated with insulin resistance (acanthosis nigricans, hypertension, dyslipidemia, PCOS)
- Age of initiation: age 10 years or at onset of puberty if puberty occurs at a younger age
- Frequency: every 2 years
- Test: FPG preferred

* Clinical judgment should be used to test for diabetes in high-risk patients who do not meet these criteria.

apy. Exercise can decrease insulin resistance and is an important component of weight management. Decreasing sedentary activity, such as television viewing and computer use, has been shown to be an effective way to increase daily physical activity in children. Involvement of family members can provide positive reinforcement and make overall family health a higher priority.

Successful treatment with diet and exercise is defined as cessation of excessive weight gain with normal linear growth, near-normal fasting blood glucose values (<126 mg/dl), and near-normal HbA$_{1c}$ (less than ~7% in most laboratories). Follow-up should include periodic reevaluation and reinforcement of treatment modalities as well as appropriate SMBG and contact with the health care team when treatment goals are not met.

Successful diabetes management without oral medication or insulin occurs in fewer than 10% of adult patients with diabetes over time. In addition, data from adults suggest that type 2 diabetes is a progressive disorder, and over time, worsening glycemic control will result in the need for one or more oral agents and ultimately insulin alone or in combination with oral agents, even with good adherence to dietary and lifestyle changes.

Pharmaceutical Therapy

Currently, there are five types of glucose-lowering oral agents available in the U.S. for the treatment of type 2 diabetes (15). Because the pathophysiology of type 2 diabetes in children and adolescents appears to be similar to that of type 2 diabetes in adults, it is reasonable to assume that such agents will be effective in children. Of note is the fact that efficacy and safety data are not available for children nor are any of the oral drugs FDA approved for use in children.

The available pharmaceutical agents and their mechanisms of action are as follows:

- Biguanides: decrease hepatic glucose output and enhance primarily hepatic and also muscle insulin sensitivity without a direct effect on β-cell function: metformin
- Sulfonylureas: promote insulin secretion: acetohexamide, chlorpropamide, gliclazide, glimepiride, glipizide, glyburide, tolazamide, and tolbutamide
- Meglitinide: short-term promotion of glucose-stimulated insulin secretion: repaglinide
- Glucosidase inhibitors: slow hydrolysis of complex carbohydrates and slow carbohydrate absorption: acarbose and miglitol
- Thiazolidinediones: improve peripheral insulin sensitivity: troglitazone, rosiglitazone, and pioglitazone.

Troglitazone has been associated with fatal hepatic failure; therefore, its use in children is not recommended. Until additional safety information about the other drugs in this class are available, their routine use in children cannot be recommended.

If treatment goals with nutrition education and exercise are not met, pharmacologic therapy is indicated. The first oral agent used should be metformin.

Metformin has the advantage over sulfonyl-ureas of a similar reduction in HbA$_{1c}$ and in overall glucose levels without the risk of hypoglycemia. In addition, weight is either decreased or remains stable, and LDL cholesterol and triglyceride levels decrease.

Treatment with metformin also may normalize ovulatory abnormalities in girls with PCOS and increase the risk of unplanned pregnancy. Therefore, preconception and pregnancy counseling should be part of the treatment regimen, as for all girls and women of childbearing age with type 2 diabetes. No oral agent should be used during pregnancy, highlighting the importance of counseling adolescents with type 2 diabetes about sexuality and pregnancy.

Because of concerns about lactic acidosis, metformin is contraindicated in patients with impaired renal function and should be discontinued with the administration of radiocontrast material. Metformin should not be used in patients with known hepatic disease, hypoxemic conditions, severe infections, or alcohol abuse. Metformin should be temporarily discontinued with any acute illness associated with dehydration or hypoxemia. Insulin should be used if glycemic control deteriorates acutely. The most common side effects of metformin are gastrointestinal disturbances. Because proper dosing in children has not been evaluated and because most patients are near or at adult weight, it is reasonable to use the doses recommended for adults.

If monotherapy with metformin is not successful over a reasonable period of time (i.e., 3–6 months), several alternatives can be considered. Some clinicians would add a sulfonylurea, whereas others might add insulin. Other insulin secretogogues are acceptable (e.g., meglitinide) as well as a glucosidase inhibitor, but these have been less frequently used in children. In the adolescent with an irregular eating schedule, meglitinide may have special advantages.

With greatly elevated blood glucose levels or in very symptomatic patients, starting treatment with insulin (bedtime insulin alone, twice-a-day insulin or multidose insulin regimens) may most effectively bring hyperglycemia and symptoms under control. When glucose control is established, adding metformin while decreasing insulin is a therapeutic option. Monitoring for urine ketones during this period may be helpful to identify those patients who have been misdiagnosed and actually have type 1 diabetes.

Monitoring for Complications

Dilated eye examinations should be performed in adolescents with type 2 diabetes according to the ADA's standards of medical care (11). Screening for microalbuminuria should also be performed yearly. It is unclear whether foot examinations are important in this age-group; however, these examinations are painless, inexpensive, and provide an opportunity for education about foot care.

Other than testing for and treating elevated blood pressure and lipid abnormalities, studies to detect macrovascular disease are probably not indicated, although there are no data in this age-group.

Hypertension Treatment

Careful control of hypertension in children is critical. ACE inhibitors are the agents of choice in children with microalbuminuria; because of the beneficial effects of ACE inhibitors on preventing diabetic nephropathy, many diabetologists consider ACE inhibitors the first line of therapy. The Joint National Committee VI report (16) also recommends α-blockers, calcium antagonists (long-acting), and low-dose diuretics. Although there has long been concern that use of β-blockers may worsen hypoglycemia and mask hypoglycemic symptoms, their benefits may outweigh their risks in selected patients. If normotension (for age and sex) is not achieved, combination therapy may be needed.

Hyperlipidemia Treatment

Children with type 2 diabetes may be hyperlipidemic. Weight loss, increased activity, and improvement in glycemic control often results in improvement in lipid levels. Changing food choices and their preparation may also be helpful. If these actions fail, medications should be used (17). Dyslipidemia far outweighs all other risk factors for cardiovascular disease in adults with type 2 diabetes, and this may also be true for children with type 2 diabetes. HMG CoA reductase inhibitors ("statins") are absolutely contraindicated in pregnancy and should not be used in females of childbearing potential unless highly effective contraception is in use and the patient has been extensively counseled.

QUESTION 6: Can Type 2 Diabetes in Children and Adolescents Be Prevented?

Attempts to prevent type 2 diabetes in children should follow the same general paradigm as those to prevent type 2 diabetes in adults. Primary prevention efforts can be directed to high-risk individuals or to the overall population of children. Prevention of type 2 diabetes in high-risk children requires the ability to accurately identify those at an increased risk and provide them with the service they need. Prevention of type 2 diabetes should be considered at two stages in its natural history. Intervention can take place at an early stage when blood glucose levels are still normal or at the stage of impaired glucose tolerance (IGT)/impaired fasting glucose (IFG) when glucose levels are elevated but not yet diagnostic of diabetes. To whatever degree hyperinsulinemia and insulin resistance contribute to long-term cardiovascular morbidity and mortality, early lifestyle intervention may have long-term beneficial effects.

Primary care providers have an obligation to encourage lifestyle modifications that might delay or prevent the onset of type 2 diabetes in children at high risk. Lifestyle interventions focusing on weight management and increasing physical activity should be promoted in all children at high risk for the development of type 2 diabetes. For those who have progressed to IGT/IFG, these lifestyle interventions should be more aggressively implemented, along with regular assessment and follow-up.

In the adult population at risk for type 2 diabetes, intervention strategies that have been considered include lifestyle changes in diet and physical activity and pharmacologic interventions. Results of prevention trials using drugs are not likely to become available for several years. Until the results of current trials with oral hypoglycemic agents in children are available, intervention using glucose-lowering drugs for prevention of diabetes in children is not recommended.

In obese adults, weight reduction is known to reduce insulin resistance and circulating insulin levels. This reduction is beneficial in the treatment of the obese type 2 diabetic subject. It is also possible that weight reduction will slow the progression of IGT/IFG to type 2 diabetes. In adults, reduction of calorie and fat intake and increased consumption of fruits and vegetables have been associated with weight loss and a reduced risk of progression to type 2 diabetes. However, sustained weight reduction in adults is unusual. Dietary intervention data in pediatric populations are limited, but nutritional surveys have demonstrated that children eat more fat and fewer servings of fruits and vegetables than is recommended in dietary guidelines.

Nutritional interventions in children should be guided by a health care provider with knowledge and expertise in growth and development in children. The most effective dietary approach has been appropriate reduction of energy intake along with exercise to increase energy expenditure. Specific recommendations need to be individualized, and continued evaluation is crucial for long-term success. Individualized plans need to be based on assessment of food preferences, timing and location of meals and snacks, food preparation, and willingness to change behaviors. Drug therapy to reduce weight (i.e., anti-obesity agents) is not recommended in children until more safety and efficacy data are available. Use of very-low-calorie or high-protein diets as well as other fad diets is also not recommended. Quick-fix weight loss programs are unsafe for children and rarely result in long-term weight control. In addition, they do not promote long-term healthy eating behavior. Weight loss programs with the best results have been those combining exercise and dietary components, along with behavior modification. In the 6-year Da Qing IGT and Diabetes Study (18), 126 Chinese men with IGT who were randomized to a program including both dietary and exercise intervention developed type 2 diabetes 32% less frequently than 133 men in a control group. Although results of other randomized controlled clinical trials of lifestyle interventions to reduce or delay the onset of type 2 diabetes in adults are not yet available, successful programs to promote improved nutrition and increased physical activity are likely to reduce the risk of type 2 diabetes.

Lack of physical activity is strongly associated with the development of obesity, type 2 diabetes, and cardiovascular morbidity and mortality. Despite information on the importance of exercise, only 25% of high school students participate in daily physical education classes, according to a 1995 survey con-

ducted by the Centers for Disease Control and Prevention's Division of Adolescent and School Health (19). Recommendations for increasing physical activity should include encouraging patients to do at least 30 min of physical activity daily, limit sedentary activity, and participate in sports. Specific recommendations need to be individualized to the family and social situation and include safety considerations. Continued follow-up is critical for long-term success.

Primary prevention of type 2 diabetes in children should ideally include a public health approach that targets the general population. Health professionals need to be involved in developing and implementing school- and community-based programs to promote improved dietary and physical activity behaviors for all children and their families. Programs that provide children and their families with the knowledge, attitudes, behavioral skills, and encouragement to consume a healthy diet and engage in regular physical activity may be effective in attenuating the expanding problem of obesity. At the community level, schools, religious organizations, youth and family organizations, and government agencies should assume some responsibility for promoting a healthy lifestyle. School programs should promote healthy food choices and increased physical activity. Planning of effective preventive efforts for populations at risk needs to involve members of the community.

APPENDIX

Consensus Panel Members

Arlan Rosenbloom, MD, Chair; Silva Arslanian, MD; Stuart Brink, MD; Katie Conschafter, RD, CDE, LD, MS; Kenneth Lee Jones, MD; Georgeanna Klingensmith, MD; Naomi Neufeld, MD; and Neil White, MD, CDE.

Organizational Representatives

Anne Fagot-Campagna, MD, PhD, Division of Diabetes Translation, Centers for Disease Control and Prevention; Sheila Gahagan, MD, American Academy of Pediatrics, Committee on Native American Child Health; and Barbara Linder, MD, PhD, National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health.

References

1. The Expert Committee on the Diagnosis and Classification of Diabetes Mellitus: Report of the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. *Diabetes Care* 22 (Suppl. 1):S5–S19, 1999
2. American Diabetes Association: *Medical Management of Type 1 Diabetes.* 3rd ed. 1998, p. 246
3. Winter WE, Maclaren NK, Riley WJ, Clarke DW, Kappy MS, Spillar RP: Maturity-onset diabetes of youth in black Americans. *N Engl J Med* 316:285–291, 1987
4. Banerji MA, Chaiken RL, Huey H, Tuomi T, Norin AJ, Mackay IR, Rowley MJ, Zimmet PZ, Lebovitz HE: GAD antibody negative NIDDM in adult black subjects with diabetic ketoacidosis and increased frequency of human leukocyte antigen DR3 and DR4: Flatbush diabetes. *Diabetes* 43:741–745, 1994
5. Velho G, Froguel P: Genetic metabolic and clinical characteristics of maturity onset diabetes of the young. *Eur J Endocrinol* 138:233–239, 1998
6. Libman I, Songer T, LaPorte R: How many people in the U.S. have IDDM? *Diabetes Care* 16:841–842, 1993
7. Kahn CR: Banting Lecture: Insulin action, diabetogenes, and the cause of type II diabetes. *Diabetes* 43:1066–1084, 1994
8. Arslanian SA, Kalhan SC: Correlations between fatty acid and glucose metabolism: potential explanation of insulin resistance of puberty. *Diabetes* 43:908–914, 1994
9. Legro RS, Kunselman AR, Dodson WC, Dunaif A: Prevalence and predictors of risk for type 2 diabetes mellitus and impaired glucose tolerance in polycystic ovary syndrome: a prospective, controlled study in 254 affected women. *J Clin Endocrinol Metab* 84:165–169, 1999
10. Hammer LD, Kraemer HC, Wilson DM, Ritter PL: Standardized percentile curves of body-mass index for children and adolescents. *AJDC* 145:259–263, 1991
11. American Diabetes Association: Standards of medical care for patients with diabetes mellitus (Position Statement). *Diabetes Care* 22 (Suppl. 1):S32–S41, 1999
12. UKPDS Group: Intensive blood glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). *Lancet* 352:837–853, 1998
13. American Diabetes Association: Clinical Practice Recommendations 1999. *Diabetes Care* 22 (Suppl. 1):S1–S114, 1999
14. Willet WC, Dietz WH, Coldtiz GA: Guidelines for healthy weight. *N Engl J Med* 341:427–434, 1999
15. DeFronzo RA: Pharmacologic therapy for type 2 diabetes mellitus. *Ann Intern Med* 131:281–303, 1999
16. National Institutes of Health, National Heart, Lung and Blood Institute: *The Sixth Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure.* Bethesda, MD, National Institutes of Health, National Heart, Lung and Blood Institute, 1997 (NIH publ. no. 98-4080)
17. Expert Panel on Blood Cholesterol Levels in Children and Adolescents: Treatment recommendations of the National Cholesterol Education Program report of the Expert Panel on Blood Cholesterol Levels in Children and Adolescents. *Pediatrics* 89 (Suppl.):525–584, 1992
18. Pan X-R, Li G-W, Hu Y-H, Wang J-X, Yang W-Y, An Z-X, Hu ZX, Lin J, Xiao J-Z, Cao H-B, Liu P-A, Jiang X-G, Jiang Y-Y, Wang J-P, Zheng H, Zhang H, Bennett PH, Howard BV: Effects of diet and exercise in preventing NIDDM in people with impaired glucose tolerance: the Da Qing IGT and Diabetes Study. *Diabetes Care* 20:537–544, 1997
19. U.S. Department of Health and Human Services: Physical activity and health. In *A Report of the Surgeon General.* Atlanta, GA, U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion, 1996, p. 186–207
20. World Health Organization: *Diabetes Mellitus: Report of a WHO Study Group.* Geneva, World Health Org., 1985 (Tech. Rep. Ser., no. 727)

Type 2 Diabetes in Children and Adolescents
American Diabetes Association

Updated Information & Services	including high resolution figures, can be found at: http://pediatrics.aappublications.org/content/105/3/671
Subspecialty Collections	This article, along with others on similar topics, appears in the following collection(s): **Pediatrician Wellness** http://www.aappublications.org/cgi/collection/pediatrician_wellness **Endocrinology** http://www.aappublications.org/cgi/collection/endocrinology_sub
Permissions & Licensing	Information about reproducing this article in parts (figures, tables) or in its entirety can be found online at: http://www.aappublications.org/site/misc/Permissions.xhtml
Reprints	Information about ordering reprints can be found online: http://www.aappublications.org/site/misc/reprints.xhtml

American Academy of Pediatrics
DEDICATED TO THE HEALTH OF ALL CHILDREN™

PEDIATRICS®

Type 2 Diabetes in Children and Adolescents
American Diabetes Association

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://pediatrics.aappublications.org/content/105/3/671

American Academy of Pediatrics
DEDICATED TO THE HEALTH OF ALL CHILDREN™