Type 2 Diabetes Mellitus in Children and Adolescents

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Objectives

After completing this article, readers should be able to:

1. Delineate the population in which type 2 diabetes mellitus is reaching epidemic proportions.
2. List the characteristics of type 2 diabetes mellitus.
3. Explain the increasing prevalence of type 2 diabetes mellitus among children.
4. Characterize the clinical and laboratory features as well as the course of the disease that will assist in classification of the patient who has diabetes mellitus.
5. Describe the treatments for type 2 diabetes mellitus.

Introduction

Type 2 diabetes mellitus (DM) is a common disease affecting more than 15 million Americans. Its prevalence among adults is increasing, but more worrisome is the recent recognition of type 2 DM among children and adolescents. Little is known about the etiology, management, and changing epidemiology of this disease in pediatric populations. Nonetheless, practitioners who care for children and adolescents must consider the diagnosis of type 2 DM in the child presenting with hyperglycemia.

Definition

The diagnostic criteria and etiologic classification of DM are listed in Tables 1 and 2. The diagnosis of DM is based on blood glucose measurements that may be obtained randomly, in the fasting state, or during an oral glucose tolerance test. The fasting blood glucose test is easy and inexpensive to perform and is recommended for screening by the American Diabetes Association (ADA). The criteria for making the diagnosis of DM were changed in 1997 by the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus to propose simple and sensitive screening tests for carbohydrate metabolism derangements.

DM represents a group of diseases characterized by hyperglycemia resulting from defects in insulin secretion, insulin action, or both. Type 1 DM is due to insulin deficiency usually caused by autoimmune destruction of the insulin-producing beta cells of the pancreas. Autoimmune type 1 DM is the most common form of DM among children. Type 2 DM is a more heterogeneous disease, and its etiology is less clearly understood. Insulin resistance, relative insulin deficiency, and a secretory beta-cell defect all contribute to the etiology of hyperglycemia in affected patients.

Diagnosis and classification are based on clinical presentation, laboratory evaluation, and the course of the disease. There is no "test" for type 2 DM, and accurate classification may be difficult. Until recent years, immune-mediated type 1 DM was the only type of DM that was believed to be prevalent among children. The recent recognition of nonimmune-mediated DM among children and adolescents highlights the difficulty sometimes encountered in evaluating a child who has new-onset DM.

Epidemiology

Because the recognition of type 2 DM among pediatric populations is relatively new, data on its incidence and prevalence are incomplete. Several reports illustrate an increase in the frequency of type 2 DM among children. Some of these increases are dramatic and considered epidemic among some populations.

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Table 1. Criteria for the Diagnosis of Diabetes Mellitus (DM)*

- Symptoms of DM plus a random blood glucose level of ≥11.1 mmol/L (≥200 mg/dL) OR
- FPG ≥7.0 mmol/L (≥126 mg/dL) OR
- 2-hr PG ≥11.1 mmol/L (≥200 mg/dL) during an OGTT

Classic symptoms of DM include polyuria, polydipsia, and weight loss.
FPG = fasting plasma glucose, PG = postprandial glucose.
The oral glucose tolerance test (OGTT) should be performed as described by the World Health Organization.
*Adapted from the Report of the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus.

Type 2 DM was an uncommon disease among children before the 1990s, comprising only 1% to 4% of all cases of DM in this age group. Recent reports suggest that type 2 DM now represents 8% to 46% of all DM cases among children. Many centers report increases in incidence of type 2 DM in children each year of the past decade. In some pediatric populations, the rates of type 2 DM now exceed those of type 1 DM.

The increase in type 2 DM among children appears to occur in populations that have high rates of disease among adults. This was noted initially among Pima Indians, a group having the highest rates of type 2 DM in the world. Pima Indian children have higher rates of type 2 DM than the general population, and the rates increase with age. Between the late 1980s and the mid-1990s, the rates of DM among adolescent Pima Indians increased 54%.

Table 2. Etiologic Classification of Diabetes Mellitus (DM)*

- Type 1 DM (beta-cell destruction, usually leading to absolute insulin deficiency)
  - —Type 1a—immune-mediated
  - —Type 1b—idiopathic
- Type 2 DM (may range from predominant insulin resistance with relative insulin deficiency to a predominantly secretory defect with insulin resistance)
- Other specific types
  - —Genetic defects of beta-cell function (eg, MODY)
  - —Genetic defects of insulin action (eg, lipoatrophic DM)
  - —Diseases of exocrine pancreas (eg, cystic fibrosis)
  - —Endocrinopathies (eg, Cushing syndrome)
  - —Drug-induced (eg, glucocorticoids, chemotherapeutics)
- Gestational DM

*Adapted from the Report of the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus.

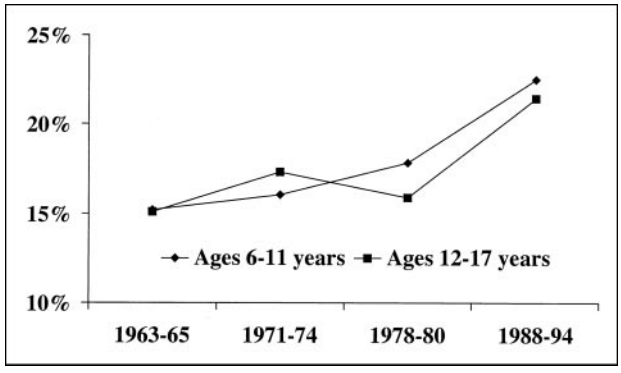

Figure 1. Trends of overweight (>85th percentile body mass index) for all children. Data from Troiano et al.

Similar increases have been described among Japanese, Asian-American, Mexican-American, and African-American children. In some clinics, as many as 21% of diabetic children of Mexican-American ethnicity have type 2 DM. Other clinics have reported that 69% of pediatric patients who had type 2 DM were African-American.

Trends in the prevalence of obesity and physical inactivity among children may help to explain the increasing rates of type 2 DM. Large population-based surveillance studies demonstrate increases in the rates of overweight and obesity among all age groups since the 1960s (Fig. 1). Rates of overweight and obesity among children are epidemic in parts of the United States. Although this observation does not explain the rise in type 2 DM completely, the weight trends parallel the trends of type 2 DM among children.

Additionally, children are less physically active in recent years than previously. Only 50% of United States young people ages 12 to 21 years regularly participate in vigorous physical activity; 25% report no physical activity. Participation in all types of physical activity declines as age and grade in school increase. From 1991 to 1995, overall daily attendance in school physical education classes decreased from 41.6% to 24.5%.

Pathogenesis

Type 2 DM can arise from a number of causes that result in the inability to maintain euglycemia. Normal carbohydrate metabolism involves the sensing of glucose concentration by pancreatic beta cells, the synthesis and release of insulin, the binding of insulin to receptors in muscle

and adipose tissues, and the peripheral uptake of glucose for metabolism and storage in these organs. Derangements in one or more of these aspects of normal carbohydrate metabolism may result in hyperglycemia.

Although the specific etiologies of type 2 DM are not known, autoimmune destruction of pancreatic beta cells does not occur. The abnormalities that result in type 2 DM are complex and include peripheral insulin resistance, impaired insulin secretion, and excessive hepatic production of glucose.

Insulin resistance is likely the underlying abnormality in patients who have type 2 DM and may be present for many years before DM becomes apparent. Insulin resistance results in a compensatory hyperinsulinism that may maintain euglycemia for some time. When the beta cells become unable to maintain this level of hyperinsulinemia, a relative insulin deficiency develops that is not adequate to maintain euglycemia. Hence, hyperglycemia and type 2 DM develop. Hyperinsulinism also is implicated in the etiologies of hypertension, irregular menses, polycystic ovary syndrome, dyslipidemias, and acanthosis nigricans, which are common among patients who have type 2 DM.

Insulin resistance seems to have a strong hereditary component, as illustrated by the clustering of type 2 DM among families and certain populations. However, it is unlikely that the gene pool has changed sufficiently in recent years to account for the increasing rates of disease. Environmental factors must be important in the expression of this genetic predisposition. Obesity and physical inactivity worsen insulin resistance, while weight loss and physical activity improve it. The genetic predisposition to insulin resistance coupled with environmental factors such as obesity and physical inactivity result in the phenotypic expression of type 2 DM.

Clinical Aspects

Patients who have type 2 DM may have presenting symptoms similar to those who have type 1 DM, which can make correct initial classification difficult. There are, however, features of each presentation and laboratory evaluation that will assist the clinician in this classification and in choosing appropriate treatments.

Classic symptoms of DM include polyuria, polyphagia, and polydipsia. The presentation of type 1 DM is usually more acute than that of type 2 DM. Patients who have type 1 DM often present with hyperglycemia, acidosis, and dehydration. Frequently, they also have experienced significant weight loss. After insulin and fluid therapy are initiated, the hyperglycemia and acidosis clear readily, and most regain the weight they had lost.

Type 2 DM usually has a more indolent presentation. Some patients are found to have glucosuria on routine urinalysis, which leads to the diagnosis. They may or may not have polyuria and polydipsia. Weight loss at diagnosis is not as common or impressive as for type 1 DM. Acute metabolic decompensation (eg, diabetic ketoacidosis) can occur, but is rare. However, approximately 25% of patients presenting with type 2 DM have ketonuria at diagnosis.

Clinical features of type 2 DM may assist in initial classification. Most affected patients are overweight; more than 85% are overweight or obese at diagnosis. A family history of type 2 DM is found in a majority of patients who have newly diagnosed type 2 DM. In addition, the presence of acanthosis nigricans on physical examination is common. This skin condition is characterized by hyperpigmentation and a velvety texture that often is found on the nape of the neck, in the antecubital areas, and along the inner thighs (Fig. 2). Acanthosis nigricans is a sign of long-standing hyperinsulinism. More than 85% of patients who have type 2 DM have acanthosis nigricans.

In addition to clinical signs and symptoms, laboratory evaluation and assessment of the clinical course are necessary to classify a patient accurately. Autoantibodies to islet cells, insulin, or glutamic acid decarboxylase are present in more than 85% of patients who have type 1 DM. Patients who have type 2 DM have no such serologic evidence of beta-cell destruction. Fasting insulin and C-peptide levels are usually normal or elevated for patients who have type 2 DM, but they might be low at the time of diagnosis because many patients present at a time of relative insulin deficiency. Insulin and C-peptide levels are more meaningful after a few weeks of treatment have improved glycemic control. Finally, the clinical course of the patient after diagnosis may provide clues to the correct classification. Patients who have type 2 DM may require insulin initially to correct hyperglycemia, but most will not need it after a period of improved glycemia. The majority will be maintained successfully on oral medications and lifestyle modifications, in contrast to patients who have type 1 DM and require insulin for survival.

Management

Management of diabetes involves daily self-care skills that may include taking oral medications or insulin injections, watching food intake, exercising regularly, and self-monitoring blood glucose levels. Adherence to a complicated treatment plan is often difficult for patients and their families. Therefore, a working relationship between

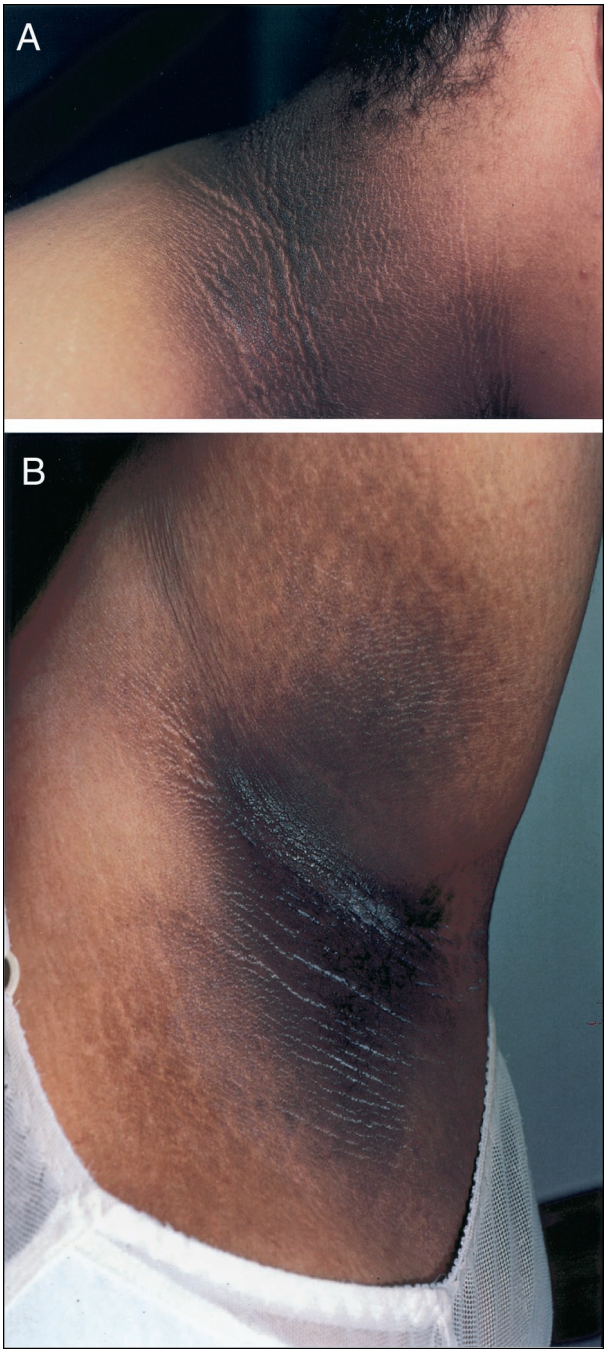

Figure 2. Acanthosis nigricans of the nape of the neck (A) and axilla (B) in an African-American adolescent who has type 2 DM.

the primary care practitioner and a diabetes care team experienced in the education and management of children who have DM is optimal. The primary care practitioner may offer regular contact with the patient or family and could coordinate medical specialty or psychosocial services as needed.

The goal of treatment is to achieve near-normal blood glucose and hemoglobin A1C values. The United Kingdom Prospective Diabetes Study illustrates that normalization of blood glucose levels in patients who have type 2 DM decreases the frequency of microvascular complications. This is particularly important in affected children because microvascular complications are due to long-term hyperglycemia.

Treatment options vary and range from diet and exercise modifications alone to many different types of medications, including oral agents and insulin. Patients who present with type 2 DM without acidosis or considerable ketosis may be prescribed diet and exercise therapy, although most require medication at some time. Insulin may be required at diagnosis for patients who present with acidosis, ketosis, or significant dehydration. After a period of improved glycemic control, many of these patients may discontinue insulin therapy and initiate or continue oral medications. The treatment course is dynamic and needs to be re-evaluated periodically. A patient may change back and forth from monotherapy to combination therapy throughout the course of the disease.

Lifestyle changes are important components of the patient's treatment but can be the most difficult to maintain. A dietitian who is knowledgeable in the management of children who have DM should make appropriate dietary recommendations. Healthy levels of physical activity are essential. Patients should monitor their blood glucose levels, as determined by the health-care team.

Although insulin is the only United States Food and Drug Administration (FDA)-approved medication for the treatment of DM in children, most physicians experienced in treating type 2 DM in children use oral medications in their management. Several classes of medications are available.

The sulfonylureas have been used for decades in the treatment of adults who have type 2 DM. Because these medications promote insulin secretion from the pancreas, hypoglycemia can occur, and the ability to detect and self-monitor for hypoglycemia is a prerequisite for their use. Sulfonylureas include chlorpropamide, glipizide, glyburide, and tolbutamide.

The biguanides also have been used for many years in adults. Metformin decreases hepatic glucose production and indirectly enhances insulin sensitivity without directly affecting beta-cell function. Therefore, hypoglycemia from metformin monotherapy is uncommon. Rarely,

lactic acidosis is a severe complication of metformin therapy, and the drug should be discontinued when dehydration might occur, such as during a gastroenteritis illness or diabetic ketoacidosis, or with the administration of radiocontrast material. It should not be used for patients who are known to have hepatic disease.

The thiazolidenediones (rosiglitazone and pioglitazone) are the only DM medications that directly improve peripheral insulin sensitivity. Because medications in this class are associated with hepatic toxicity, their use in children is not recommended.

The glucosidase inhibitors (acarbose and miglitol) might have a role in the treatment of children who have type 2 DM because they are not absorbed systemically. These drugs slow the hydrolysis of carbohydrates and their absorption from the gastrointestinal tract. This should be particularly helpful in preventing postprandial hyperglycemia. Although they are safe, the flatulence associated with their use may make them undesirable for some patients.

If blood glucose and hemoglobin A1C targets are not met by diet and exercise, the ADA recommends metformin as first-line oral medication. If additional medications are necessary to achieve near-normal glycemic control, careful consideration should be given to adding a sulfonylurea, a glucosidase inhibitor, or insulin.

Target values for hemoglobin A1C, fasting blood glucose, and postprandial blood glucose should be individualized. Measures of glycemia should be as close to normal as possible to ensure adequate growth and development without causing significant or frequent hypoglycemia. Practitioners differ in their opinions of these values, but a target hemoglobin A1C value of less than 8% is a reasonable starting point.

Screening

The ADA recommends screening only patients who are at substantial risk of developing type 2 DM (Table 3). Testing should start at age 10 years or at the initiation of puberty and should be repeated every 2 years. The easiest and most cost-effective test for screening is the fasting blood glucose.

Implications

Type 2 DM presenting in adults (in the fifth and sixth decades) carries tremendous public health implications, accounting for nearly $140 billion annually in healthcare costs. The public health implications of type 2 DM presenting in children decades earlier are unknown but concerning.

Table 3. Testing for Type 2 DM in Children and Adolescents*

Criteria†
• Overweight (body mass index >85th percentile for age and gender, weight for height >85th percentile, or weight >120th percentile of ideal for height)
PLUS
• Any two of the following risk factors:
—Family history of type 2 DM in first- or second-degree relative
—Race/ethnicity (American Indian, African-American, Hispanic, Asian/Pacific Islander)
—Signs of insulin resistance (acanthosis nigricans, polycystic ovary syndrome, hypertension, dyslipidemia)
Age of Initiation
Age 10 years or at onset of puberty if before age 10 years
Frequency
Every 2 years
Test
Fasting plasma glucose preferred

*From American Diabetes Association. *Pediatrics.* 2000;105:671–680.
†Use clinical judgment to test for diabetes in high-risk patients who do not meet these criteria.

Summary

Type 2 DM is becoming increasingly common among children and adolescents. Once considered a disease of adults, it is now almost as common as type 1 DM in some pediatric populations. Type 2 DM should be considered in any child who presents with hyperglycemia, but particularly in the child who is obese, has a family history of DM, has nonketotic hyperglycemia, or has signs of insulin resistance (eg, acanthosis nigricans). A thorough evaluation of the child's overall health, glycemic control, and social and family issues should guide treatment. Adherence to the individualized treatment is optimized by a cooperative relationship between the primary care practitioner and a diabetes care team.

Suggested Reading

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PIR Quiz

Quiz also available online at *www.pedsinreview.org.*

1. Increases in the frequency of type 2 diabetes mellitus (DM) in children parallels which of the following incidence trends?

   A. Decrease in diabetes in the adult population.
   B. Decrease in hypertension.
   C. Decrease in other endocrinopathies.
   D. Increase in obesity among children.
   E. Increase in physical activity among children.

2. The *most* likely underlying abnormality in patients who have type 2 DM is:

   A. Autoimmune destruction of pancreatic beta cells.
   B. Decreased hepatic production of glucose.
   C. Dyslipidemia.
   D. Insulin resistance.
   E. Insulin underproduction.

3. In contrast to type 1 DM, patients who have type 2 DM *most* commonly present with:

   A. Acanthosis nigricans.
   B. Hyperglycemia and dehydration.
   C. Ketoacidosis.
   D. Polyuria, polyphagia, and polydipsia.
   E. Weight loss.

4. Diet and exercise are the mainstays of therapy for type 2 DM. If long-term medication is required, which of the following therapies is recommended as first-line oral therapy?

   A. Biguanides (eg, metformin).
   B. Glucosidase inhibitors (eg, acarbose and miglitol).
   C. Insulin.
   D. Sulfonylureas (eg, chlorpropamide, glipizide).
   E. Thiazolidenediones (eg, rosiglitazone, pioglitazone).

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