As rates of childhood obesity climb, type 2 diabetes mellitus has increasingly been diagnosed in children and adolescents, with the highest incidence occurring among youth from racial and ethnic minority backgrounds. The serious complications associated with type 2 diabetes mellitus make it essential for physicians to be aware of risk factors and screening guidelines, allowing for earlier patient diagnosis and treatment. It is also important for physicians to be aware of the treatment options available, including weight control through diet and exercise as well as common pharmacotherapeutic options.

Complications of obesity previously seen only in adults—atherosclerosis, dyslipidemia, and type 2 diabetes mellitus—are now being observed in children with increasing frequency. Type 2 diabetes mellitus, a condition that has typically affected individuals older than 40 years, is increasingly common among children in the United States. Studies indicate that, of all US children recently diagnosed as having diabetes, up to 45% have type 2 diabetes mellitus.

In an analysis of an Ohio-based diabetes clinic’s medical records, Pinhas-Hamiel et al found that type 2 diabetes accounted for 33% of all new diagnoses in individuals aged between 10 and 19 years. In fact, the number of patients from birth to age 19 who received this diagnosis increased from 4% in 1982 to 16% in 1994.

Pediatric onset of type 2 diabetes mellitus increases the risk of micro- and macrovascular complications arising later in life, imparting new urgency to early diagnosis and treatment.

Epidemiology
In the United States, the overall incidence of type 2 diabetes is higher among racial and ethnic minority populations than non-Hispanic whites (Figure 1). The same is true regarding individuals younger than 20 years.

According to the SEARCH for Diabetes in Youth Study Group, incidence rates among American Indians aged 15 to 19 years is 49.4%, compared to 5.6% in non-Hispanic whites of the same age group. Among youth in the United States, Pima Indian adolescents have the highest reported prevalence of type 2 diabetes mellitus. For Pima Indian children aged 5 to 9 years, the incidence rate is less than 0.5%; for children and adolescents aged 10 to 14 years, 1.5% to 3%; and for adolescents and young adults aged 15 to 19 years, 4% to 5%.

Pathophysiology
The etiologic process in type 2 diabetes mellitus begins with obesity and insulin resistance, which in turn leads to inflammation and destruction of the pancreas’ β cells by various chemical mediators. An evolutionary theory regarding the genetics of this process was first proposed by Neel in the early 1960s.

Neel postulated that, when humans were hunter-gatherers and did not know when the next meal was expected, some individuals developed “thrifty genes.” These genes caused the body to become insulin resistant by interfering with mechanisms that allowed blood glucose to be transported into cells where it would be phosphorylated and used for energy. Consequently, the pancreas had to make more insulin. The excess insulin allowed cells to store fat for use during times of relative famine, leading to a much higher survival rate. These genes may include uncoupling proteins, PPAR-γ and PPAR-α, CAL-PAIN 10, and adrenergic receptor polymorphisms.

When agrarian societies began to develop, thrifty genes began to cause weight gain because food was more plentiful. Gradually, the combination of thrifty genes, less physical labor, and multiple daily meals led to obesity and its complications.

<table>
<thead>
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<th>Race and/or Ethnicity</th>
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Figure 1. Incidence of type 2 diabetes mellitus among adolescents and young adults aged 15 to 19 years by race and/or ethnicity.
Atherosclerosis and hypertension have begun to appear in childhood as a direct result of obesity and hyperinsulinemia. Insulin resistance in addition to the inability of the pancreas to maintain adequate compensatory hyperinsulinemia leads to chronic hyperglycemia. Along with decreased muscle activity, this combination forms a vicious cycle that can lead to type 2 diabetes mellitus. Tissue necrosis factor, free triglycerides, and glucosamine have been implicated in the inflammation and destruction of the β cells that precede insulinopenia and the more difficult-to-treat type 2 diabetes mellitus.

**Risk Factors**

Type 2 diabetes mellitus risk factors include: family history (eg, insulin-resistant medical conditions), obesity, and physical inactivity, as well as race and ethnicity.

**Family History**

Genetics influence the development of type 2 diabetes mellitus, making family history of this condition a risk factor for patients. The lifetime risk for a first-degree relative of a patient with type 2 diabetes mellitus is five to ten times higher than that of an age- and weight-matched subject without this family history.

In one study, 39% of participants with type 2 diabetes mellitus had at least one parent with the disease. Another study of adult twins found a 50% type 2 diabetes mellitus concordance rate in monozygotic twins and a 37% concordance rate in dizygotic twins.

**Insulin-Resistant Conditions**

Polycystic ovarian syndrome (PCOS) and acanthosis nigricans are associated with insulin resistance. Polycystic ovarian syndrome is characterized by hyperandrogenism and amenorrhea or oligomenorrhea associated with chronic anovulation. Insulin resistance and hyperinsulinemia are major components of PCOS.

In one study, participating girls and young women with PCOS aged 14 to 19 years had a 13% rate of glucose intolerance. About 30% to 32% of all participants affected by PCOS had impaired glucose tolerance. Girls and young women with PCOS are at a significantly increased risk for glucose intolerance and type 2 diabetes mellitus at all weights and younger ages.

Acanthosis nigricans is a skin disorder that affects intertriginous areas of the body (eg, base of neck, axilla, antecubital areas), and causes increased roughness and thickness of the skin as well as hyperpigmentation. This condition is caused by excess insulin resulting from insulin resistance and is present in up to 90% of children who have type 2 diabetes mellitus.

**Obesity and Physical Inactivity**

About 85% of patients who have type 2 diabetes mellitus are also obese. According to the Centers for Disease Control and Prevention, a body mass index (BMI) between the 85th and 95th percentiles indicates risk for overweight; a BMI above the 95th percentile is considered overweight. In the United States, rates of overweight for individuals younger than age 20 are as follows:

- 10.4% of children aged 2 to 5 years
- 15.3% of children aged 6 to 11 years
- 15.5% of adolescents and young adults aged 12 to 19 years

By 1998, the percentage of children who are overweight as indicated by BMI reached 35% in Hispanic and African American populations and more than 20% in non-Hispanic whites.

Overweight individuals with impaired glucose tolerance have peripheral insulin resistance without compensatory insulin secretion and higher visceral and intramuscular fat deposition. Independent of measures of total body fat and ethnicity, abdominal fat deposition has been considered a risk factor for insulin resistance. The increasing prevalence of obesity in childhood and adolescence—accompanied by insulin resistance—may explain the increasing incidence of type 2 diabetes mellitus in adolescents, particularly in minority populations.

**Race and Ethnicity**

As previously noted, in the United States, type 2 diabetes mellitus is two to six times more prevalent in minority populations than in non-Hispanic whites. Data from throughout the world show that obesity, associated insulin resistance, and type 2 diabetes have dramatically increased in locations where lifestyles have recently been “westernized.”

In these studies, the term “westernization” indicates an energy-dense diet and reduced physical activity. Genetic markers for diabetes have been established for the following groups: North American non-Hispanic whites, Mexican Americans, Pima Indians, and Bosnian-Finnish.

**Screening Guidelines**

The American Diabetes Association (ADA) (Alexandria, Va) recommends that children receive screening for diabetes mellitus when they have a BMI in the 85th percentile or higher as well as any two additional risk factors:

- family history of type 2 diabetes mellitus (ie, first- or second-degree relative)
- racial or ethnic minority background (ie, African American, American Indian, Asian or Pacific Islander, and Hispanic)
- signs of insulin resistance or conditions associated with insulin resistance (eg, acanthosis nigricans, dyslipidemia, hypertension, or PCOS)

Follow-up screening should occur “every 2 years starting at the age of 10 or at the onset of puberty if it occurs at a younger age.”

Schwartz and Chadha • Review Article
Clinical Presentation

The mean age of diagnosis for type 2 diabetes mellitus among children is midpubertal, from 12 to 16 years of age. During puberty, resistance to the action of insulin increases, resulting in hyperinsulinemia. In children who have a genetic predisposition and environmental risk exposures (eg, poor diet and lack of exercise), the additional burden of insulin resistance at puberty may lead to uncompensated hyperinsulinemia and glucose intolerance.

Such patients usually present to physicians’ offices with glycosuria without ketonuria, absent or mild polyuria and polydipsia, and little or no weight loss. However, up to 33% of these children have ketonuria at diagnosis, and 5% to 25% of patients who are subsequently classified as having type 2 diabetes mellitus have ketoacidosis at initial presentation.

Laboratory Studies

All laboratory studies should be individualized to the clinical situation. The test of fasting plasma glucose (FPG) and/or the oral glucose tolerance test (OGTT) are generally used to diagnose diabetes mellitus. In 1997, the ADA determined that the OGTT should not be used for routine diagnosis, which led to much debate. In 2003, the ADA concluded that inadequate evidence exists to determine which test is superior for diagnostic purposes. While the OGTT is more sensitive, results from the FPG test are more reliable, convenient, and inexpensive.

Diabetes mellitus may be diagnosed (Figure 2) using the results of one of three tests:

- FPG level ≥126 mg/dL
- results from OGTT (2 hours postload) with glucose concentration levels ≥200 mg/dL
- hyperglycemic symptoms and casual plasma glucose concentration levels ≥200 mg/dL

The first two methods must be repeated at least once at a different time of day to confirm diagnosis. For the third method, “casual” is defined as occurring at any time of the day—regardless of meal times. After obese children receive a 2-hour postload OGTT, their insulin levels should also be measured for insulin resistance, glucose intolerance, and diabetes mellitus. Insulin levels are especially relevant when fasting glucose and insulin levels do not show insulin resistance.

Differential Diagnosis

In addition, the differential diagnosis for type 2 diabetes mellitus may include gestational diabetes, maturity-onset diabetes of youth, prediabetes, and type 1 diabetes mellitus.

Gestational diabetes is a form of diabetes that is defined as any degree of glucose intolerance beginning or first recognized during pregnancy. Based on ADA recommendations, an OGTT must be used to diagnose gestational diabetes mellitus.

Maturity-onset diabetes of youth (MODY) is a genetically inherited form of the disease that is the result of defects in β cell function. This condition most commonly arises before age 25 years.

Although at least six types of MODY exist, types 1, 2, and 3 involve deficient insulin secretion with normal insulin sensitivity. African Americans affected by MODY have low insulin concentrations, do not have associated obesity, and exhibit mitochondrial defects. In addition, patients with MODY may be distinguished from patients with type 2 diabetes mellitus with fasting insulin, C-peptide, or β cell autoantibody measurements.

Prediabetes, which is often a precursor to type 2 diabetes mellitus, is denoted by an FPG level between 100 mg/dL and 125 mg/dL (impaired fasting glucose). If an OGTT is used, a 2-hour postload glucose concentration level between 140 mg/dL and 199 mg/dL (impaired glucose tolerance) is suggestive of this clinical condition. Patients with prediabetes have an increased risk for type 2 diabetes mellitus as well as macrovascular disease.

Type 1 diabetes mellitus, a form of diabetes resulting from β cell destruction, may be difficult to distinguish from type 2 diabetes mellitus. A fasting C-peptide level greater than 1 ng/dL in a patient who has had diabetes mellitus for more than 1 year is suggestive of type 2 diabetes mellitus (ie, residual β cell function). Islet-cell autoantibodies are present in the early type 1 form of the disease, but not in type 2 diabetes mellitus.

Measurement of these autoantibodies within 6 months of diagnosis can help clinicians differentiate between type 1 and type 2 diabetes mellitus because titers usually decrease after 6 months. Antigliutamate decarboxylase antibodies may be present at the diagnosis of type 1 diabetes mellitus and in the future. If the diagnosis is unclear, insulin therapy should be implemented until the type can be determined.

Complications

In addition to hyperglycemia and hypoglycemia, diabetes mellitus can cause micro- and macrovascular complications,
including retinopathy, nephropathy, neuropathy, and cardiovascular disease. As a result of these associated complications in individuals aged 20 to 74 years, diabetes mellitus is the leading cause of new cases of blindness, nontraumatic lower-extremity amputation, and kidney disease. Diabetes mellitus can also lead to dental disease. In children, micro- and macrovascular complications must be considered and treated appropriately.

Urinary microalbumin excretion, fasting lipid levels, and dilated retinal examination by an ophthalmologist should be obtained at the time of diagnosis and annually thereafter to detect complications. Patients showing any signs of hypertension or renal disease should be placed on an angiotensin-converting enzyme inhibitor or angiotensin II–receptor blockers, respectively. These medications may also reduce risk of coronary artery disease independent of its effects on blood pressure. Statins may be administered for hyperlipidemia.

Chronic hyperglycemia is associated with an increased risk of microvascular complications, as shown in the Diabetes Control and Complications Trial (DCCT) for type 1 diabetes mellitus and the United Kingdom Prospective Diabetes Study (UKPDS) for type 2 diabetes mellitus.

In the 7-year DCCT, intensive therapy to maintain normal blood glucose levels greatly reduced the onset and progression of retinopathy, microalbuminuria, proteinuria, and neuropathy. Intensive therapy was not associated with a significant difference in either mortality or in incidence rates for major macrovascular events. Intensive therapy also did not decrease patient quality of life—though it did increase the likelihood of severe hypoglycemic episodes.

In the 15-year UKPDS, more than 5000 patients with type 2 diabetes mellitus were observed. Subjects in the intensive therapy group had a significantly lower rate of progressive microvascular complications than those receiving standard care. Rates of macrovascular disease were not altered except in the metformin monotherapy arm of the study, in which the risk of myocardial infarction was significantly decreased. Moreover, severe hypoglycemia occurred less often than it did for patients with type 1 diabetes mellitus in the DCCT. Immunologic, reproductive, and teratogenic complications were common for patients with type 2 diabetes mellitus in the UKPDS.

Therapeutic Options

Therapeutic options can be grouped into three categories: (1) weight control through diet and exercise, (2) hypoglycemic agents, and (3) insulin therapy.

Weight Control Through Diet and Exercise

Treatment of type 2 diabetes mellitus necessitates a multidisciplinary approach that includes the physician, diabetes nurse educator, dietitian, exercise physiologist or personal trainer, social worker, and psychologist. Family involvement is essential to initiate and maintain the lifestyle changes required for managing type 2 diabetes mellitus, especially in pediatric patients.

Skeletal muscle training leads to altered expression of insulin-signaling elements, in particular glucose transporters with increased glucose uptake and glycogen synthesis. Exercise leads to release of bradykinin locally, which has been shown to have stimulatory effects on glucose uptake. Evidence exists that insulin resistance of the liver can be improved as well. In addition, a reduction of hepatic glucose production occurs after endurance training. Likewise, insulin responsiveness toward glucose uptake can be enhanced in adipocytes after exercise.

Hypoglycemic Agents

Pharmacotherapy can be used to decrease blood glucose by increasing insulin secretion, increasing insulin action, decreasing hepatic glucose output, decreasing nutrient absorption, or sensitizing tissue to insulin. Of the hypoglycemic agents that are used to treat patients with diabetes mellitus, only metformin, a biguanide, has been approved for use in children by the US Food and Drug Administration (FDA). In adolescents, other medications are used, sometimes off-label, and often in combination therapy for patients whose conditions are difficult to control.

Oral hypoglycemic agents consist of biguanides, thiazolidinediones, sulfonylureas, meglitinides, and alpha-glucosidase inhibitors (AGIs). Hypoglycemic agents, such as incretin mimetics, dipeptidyl peptidase-4 inhibitors, and amylin analogues are also useful in adults and may soon be tested in children.

Biguanides, such as phenformin and metformin, increase peripheral sensitivity to insulin and decrease hepatic glucose output. They also stimulate weight loss and improve lipid profile. Phenformin has been associated with lactic acidosis. Metformin, the only FDA-approved oral medication for children aged 10 years and older with type 2 diabetes mellitus, very rarely causes lactic acidosis (0.03 cases per 1000 patient-years).

Adverse effects of metformin can include hypoglycemia as well as gastrointestinal upset. Malabsorption of vitamin B₁₂ and anemia are less common adverse effects.

Thiazolidinediones, such as pioglitazone and rosiglitazone, are agents that increase peripheral insulin sensitivity by increasing transcription of peroxisome proliferator-activated receptor-γ that helps increase uptake of glucose, probably with effects on free fatty acid levels. Their major effects are to stimulate glucose uptake in skeletal muscle and adipose tissue and to lower plasma insulin levels. Two or 3 months of treatment are needed to achieve maximal antihyperglycemic effect.

Thiazolidinediones can be used as monotherapy or in combination with other hypoglycemic agents. Drug-induced hypoglycemia may occur when thiazolidinediones are combined with sulfonylureas. Particular care should be taken with patients who have a history of anemia, cardiac failure, edema,
or liver dysfunction. Adverse effects of these medications include risk of fracture and may also include fluid retention and peripheral edema as well as upper respiratory tract infection, sinusitis, and muscle or tooth pain.

Sulfonylureas can increase insulin secretion by enhancing pancreatic β cell responsiveness to glycemic stimuli. They attach to β cell surface receptors (ATP-dependent potassium channels), causing depolarization, calcium influx, and stimulation of insulin release.

Drug-induced hypoglycemia is a potential effect of first- (chlorpropamide) and second-generation sulfonylureas (glyburide, glipizide, glimepiride) A high mortality rate has been shown when glyburide is used in combination with metformin. Adverse effects may include skin sensitivity, yellowing of skin or eyes, light-colored stools, dark urine, unusual bleeding or bruising, fever, sore throat, jaundice, hematologic complications, hyponatremia and fluid retention.

Meglitinide agents, such as repaglinide and nateglinide, are short-acting prandial insulin secretagogues. They also act on the ATP-dependent potassium channels in pancreatic β cells, allowing calcium channels to open and increasing insulin release. Repaglinide and nateglinide may cause hypoglycemia as well as headache, nasal congestion, joint aches, back pain, constipation, and diarrhea. Nateglinide also may cause runny nose and cough.

Alpha-glucosidase inhibitors, such as acarbose, are complex oligosaccharides that delay the digestion of ingested carbohydrates. Their major effect is to lower postprandial glucose levels. They are used as monotherapy or in combination with other hypoglycemic agents. Alone, AGIs do not cause hypoglycemia. Adverse gastrointestinal effects can be minimized by taking AGIs with a diet that is high in complex carbohydrates.

The goal of oral hypoglycemic therapy is to lower blood glucose levels to near-normal preprandial levels (ie, between 80 mg/dL and 140 mg/dL), to reduce glycosylated hemoglobin levels to less than 7%, and to maintain these levels for the patient’s lifetime. The goal of combination therapy using oral agents is to lower the fasting glucose level to 100 mg/dL.

Other Agents
Incretin mimetics, like exenatide, improve glycemic control for patients with type 2 diabetes mellitus by enhancing glucose-dependent insulin secretion by pancreatic β cells, suppressing inappropriately elevated glucagon secretion, and slowing gastric emptying. Adverse effects of exenatide may include hypoglycemia; stomach pain; nausea, vomiting, and diarrhea; hives, rash, and itching; difficulty breathing or swallowing; swelling of the face, throat, tongue, lips, eyes, hands, feet, ankles, or lower legs; hoarseness; or decreased urination.

Dipeptidyl peptidase-4 inhibitors, like sitagliptin, lower blood glucose through different pathways by increasing insulin biosynthesis and release, inhibiting the liver’s glucose production and delaying gastric emptying. The manufacturer of sitagliptin will be testing this product in children in the near future. Adverse effects of sitagliptin may include stuffy or runny nose, sore throat, headache, stomach pain, and diarrhea.

Amylin analogs, like pramlintide, delay gastric emptying, decrease postprandial glucagon release, and regulate food intake. Amylin is a hypoglycemic hormone co-secreted with insulin by the β cells, but it is degraded too quickly to have clinical applications. Amylin analogs may be used to treat type 1 or type 2 diabetes mellitus in combination with insulin. Adverse effects of pramlintide include gastrointestinal upset; excessive tiredness or dizziness; coughing or sore throat; joint pain; and redness, swelling, bruising, or itching at the injection site.

These agents have not been tested in large-scale studies with children. Additional research is needed to determine efficacy for this patient population.

Insulin Therapy
If acceptable target glucose levels are not achieved with these medications, once-daily long-acting insulin, such as glargine or detemir, should be instituted. If a regimen combining oral agents and long-acting insulin fails to bring glucose levels into normal range, patients should be switched to a daily multiple-injection schedule with premeal very rapid—acting insulin and longer acting basal insulin. In some cases, patients should be treated with a subcutaneous continuous insulin infusion pump.

Prevention
Efforts to reduce childhood obesity could play an important role in preventing the spread of type 2 diabetes mellitus in the pediatric population. Government entities and communities should take care to cultivate environments where children are encouraged to make healthy lifestyle choices.

In-school intervention efforts may range from eliminating candy and soda in cafeterias and vending machines to mandating 30 to 45 minutes of vigorous physical activity two or three times per week.

Children should be educated on appropriate diet and exercise habits from preschool through high school. Education on appropriate dietary habits should include information on how to shop for and prepare healthy, well-balanced meals.

Serious long-term approaches for primary prevention are needed to address this growing problem. We are obligated to protect young people from the grim outcomes of this disease constellation.

References


(continued)


Editor's Note: Interested readers may also wish to review two supplements to JAOA—The Journal of the American Osteopathic Association published earlier this year:


As rates of childhood obesity climb, type 2 diabetes mellitus has increasingly been diagnosed in children and adolescents, with the highest incidence occurring among youth from racial and ethnic minority backgrounds. The serious complications associated with type 2 diabetes mellitus make it essential for physicians to be aware of risk factors and screening guidelines, allowing for earlier patient diagnosis and treatment. It is also important for physicians to be aware of the treatment options available, including weight control through diet and exercise as well as common pharmacotherapeutic op