CME

Screening for Metabolic and Reproductive Complications in Obese Children and Adolescents

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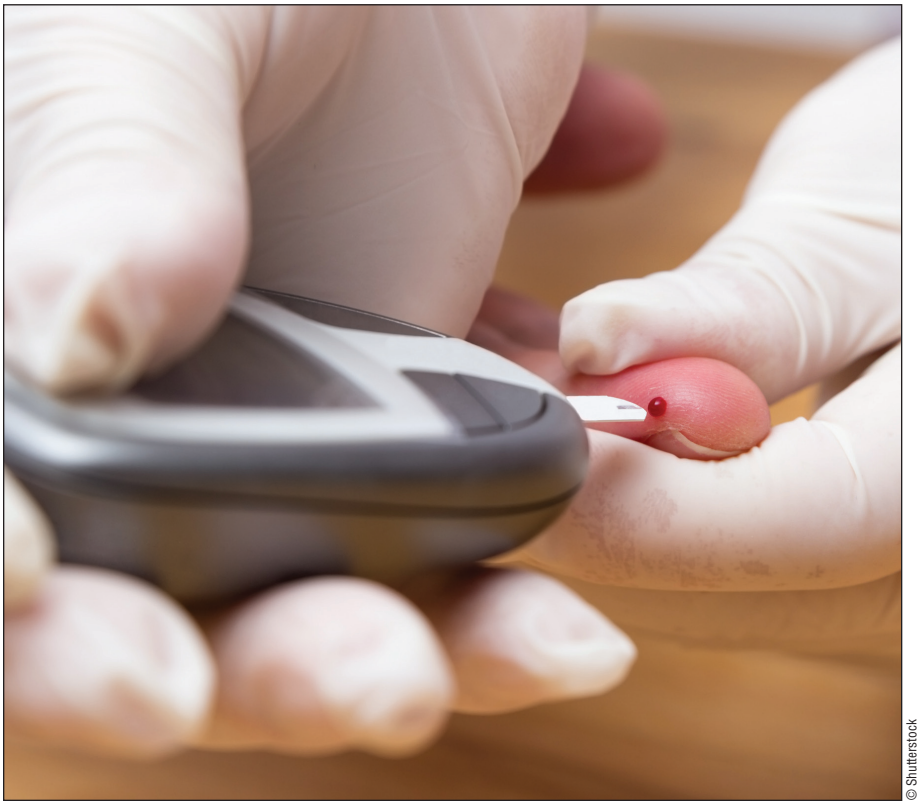
Abstract

Childhood obesity is associated with a number of metabolic comorbidities. These include glucose intolerance and type 2 diabetes mellitus, hyperlipidemia, fatty liver disease, and reproductive complications, such as polycystic ovary syndrome. The occurrence of these complications in a child or adolescent may result in progressive health decline at an early age. We, therefore, advocate screening and early diagnosis. This purpose of this review is to outline a rational, evidence-based approach to screening obese children and adolescents for metabolic and reproductive complications. In each section, the aim is to provide the primary care provider with a review of the literature supporting current screening practices. As such, this review is designed to assist the primary care provider in the selection and interpretation of screening tests and to make recommendations regarding the referral of patients for subspecialty care. **[*Pediatr Ann*. 2014;43(9):e210-e217.]**



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The rising prevalence of obesity in childhood and adolescence is linked to comorbidities associated with insulin resistance, including type 2 diabetes mellitus, dyslipidemia, hypertension, fatty liver disease, and ovarian hyperandrogenism. When these comorbidities are undiagnosed or treated inadequately, they can have serious clinical consequences, such as pancreatitis, progressive liver and renal disease, reproductive dysfunction, and cardiovascular disease.

SCREENING FOR GLUCOSE INTOLERANCE

Obesity is the major risk factor for type 2 diabetes mellitus (T2D)[1] and a critical determinant of cardiovascular disease.[2] It is crucial that obese patients be screened for glucose intolerance to slow and possibly prevent the progression to T2D.

The progression to glucose intolerance and T2D generally begins with visceral as well as generalized adiposity. Accumulation of visceral and abdominal fat is associated with selective defects in insulin action (insulin resistance) in liver, adipose tissue, skeletal muscle, brain, and peripheral vasculature. In response to insulin resistance, the pancreatic beta cells produce more insulin. Initially this compensatory hyperinsulinemia maintains glucose tolerance; however, progressive loss of beta cell mass and function reduces insulin secretion. In the setting of insulin resistance, a relative or absolute lack of insulin secretion causes postprandial hyperglycemia (impaired glucose tolerance [IGT]) and fasting hyperglycemia (impaired fasting glucose [IFG]).[3] Indeed, failure to upregulate insulin in the face of insulin resistance is a critical feature in the progression from obesity to IFG, IGT, and overt T2D (**Figure 1**).[3]

The American Diabetes Association (ADA) has defined diagnostic criteria for pre-diabetes, a term used to signify IFG and/or IGT (**Table 1**).

Screening for glucose intolerance should be considered when children are overweight and have two or more risk factors for diabetes mellitus. The ADA recommends that screening be initiated at age 10 years or at the onset of puberty, with repeat screening every 3 years (**Table 2**).[4]

Fasting and Postprandial Insulin and Glucose Levels

During fasting, the liver initially maintains glucose homeostasis through glycogenolysis. After glycogen stores are depleted, the liver and kidney sustain blood glucose through gluconeogenesis. Thus, fasting blood glucose is a measure of hepatorenal glucose production. Both glycogenolysis and gluconeogenesis are inhibited by insulin and are increased when insulin production is inadequate or insulin action is impaired.

Skeletal muscle is a primary site of postprandial glucose uptake.[3] Insulin stimulates glucose uptake into muscle and white adipose tissue through translocation of glucose transporter 4 (GLUT4) from the cytosol to the plasma membrane. Insulin resistance is associated with impaired glucose uptake in skeletal muscle and adipose tissue. Therefore, postprandial glucose is one measure of the efficiency of insulin-dependent glucose uptake into peripheral tissues.

Insulin levels are often measured in obese children but may be difficult to interpret. Fasting insulin levels are often high in children with insulin resistance. This makes fasting insulin useful for assessing insulin sensitivity and for monitoring patient responses to lifestyle intervention or treatment with insulin sensitizers such as metformin. However, blood glucose levels may be normal despite elevated insulin levels. Conversely, insulin levels may be inappropriately normal or low in obese patients with glucose intolerance (**Figure 1**). Thus, fasting or postprandial insulin levels alone cannot be used to identify obese children with pre-diabetes or T2D because insulin is not a direct measure of glucose tolerance.

Fasting and postprandial glucose levels are often used as screening tests for pre-diabetes and T2D. However, glucose levels may also be hard to interpret in obese and pre-diabetic children. For example, one study found that 73% of patients with postprandial glucose levels in the pre-diabetic range had normal fasting blood glucose levels.[5] Conversely, some children with IFG have normal post-prandial glucose levels. Moreover, abnormalities in fasting or postprandial glucose levels may not persist in all patients over time: Kleber et al[6] noted that two-thirds of children with IGT, as defined by oral glucose tolerance tests (OGTT), reverted to normal glucose tolerance after 1 year in the absence of lifestyle interventions or medication. For these reasons, fasting glucose and/or postprandial glucose may not be entirely reliable for screening obese children for glucose intolerance when used independently of other measures, including hemoglobin A1c (HbA1c).

HbA1c

The OGTT has been considered the gold standard for diabetes mellitus screening in adults. However, it requires fasting, lacks reproducibility, and is time consuming and expensive, making it impractical in the general pediatric clinic.[4,7] Therefore, many clinicians prefer to measure HbA1c for screening since its use was adopted by the ADA in 2010.[4]

HbA1c estimates the average blood glucose level for the previous 3 months.[8] The measure of HbA1c is based on the premise that hemoglobin becomes irreversibly glycosylated by ambient glucose during the 120-day lifespan of the red blood cell. HbA1c can be measured on a small volume of blood by point of care in the clinic and does not require fasting. In general, HbA1c below 5.7% makes overt T2D unlikely, whereas

TABLE 1.

Diagnostic Criteria for IGT, IFG, and Diabetes Mellitus in Children

Diagnosis	Fasting Glucose, mg/dL	Postprandial, Random, or Post-OGTT Glucose, mg/dL	HbA1c, %
Normal	70-99	<140	≤5.6
Pre-diabetes	100-125	140-199	5.7-6.4
Diabetes mellitus	≥126	≥200	≥6.5

HbA1c = hemoglobin A1c; IFG = impaired fasting glucose; IGT = impaired glucose tolerance; OGTT = oral glucose tolerance test.
(Adapted from American Diabetes Association.[4])

TABLE 2.

Screening for Pre-Diabetes and Type 2 Diabetes Mellitus in Children

Overweight	Plus TWO of the Following Risk Factors
BMI >85th percentile for age and sex; Weight for height >85th percentile; and/or Weight >120% of ideal for height	Family history of type 2 diabetes mellitus in 1st- or 2nd-degree relative
	High-risk racial group (Native American, African American, Latino, Asian American, Pacific Islander)
	Signs or conditions associated with insulin resistance (acanthosis nigricans, hypertension, dyslipidemia, and/or polycystic ovary syndrome)
	Maternal history of diabetes mellitus or gestational diabetes

BMI=body mass index.
(Adapted from American Diabetes Association.[4])

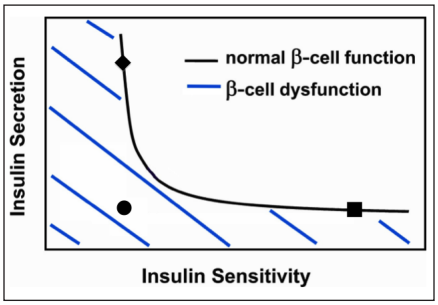

Figure 1. Insulin secretion relative to insulin sensitivity. The black square indicates low insulin levels are adequate for maintenance of glucose tolerance if the insulin sensitivity is high. The black diamond indicates appropriately high insulin secretion maintains glucose tolerance even when insulin sensitivity is low (insulin resistance). The black circle indicates inappropriately low insulin secretion in the presence of low insulin sensitivity (insulin resistance) leads to glucose intolerance.

HbA1C of 6.5% or more is nearly always associated with IGT or T2D.[8]

Despite these obvious advantages, the use of HbA1c as a screening tool in the pediatric population remains controversial for four reasons.

First, HbA1c levels in children are lower than those in adults, and the recommended cutoff levels for glucose intolerance in children (more than 5.6%) differ from those in adults (more than 5.9%). Normal HbA1c levels average 4.9% in prepubertal children and should fall below 5.7% in normal-weight children and adolescents.[9]

Second, the relationship between HbA1c and glucose levels is variable and somewhat inconsistent. A study by Shah et al[1] found that HbA1c of 6% or more had high sensitivity and specificity for predicting T2D in obese adolescents; others consider that HbA1c values ranging from 5.5% to 6.4% constitute evidence for glucose intolerance or pre-diabetes.[5,7,8] However, as many as one-fourth of high-risk obese adolescents with HbA1c below than 5.7% had pre-diabetes according to OGTT, and approximately half of adolescents with HbA1c between 5.7% and 6.4% had normal OGTT.[8]

Third, some investigators find that Blacks, Hispanics, American Indians, and Asians have higher HbA1c levels than Whites for a given blood glucose.[5] These findings suggest that there may be racial or ethnic differences in hemoglobin glycation or red blood cell survival.[5] It is not known whether these differences in HbA1c result in differences in rates of microvascular or macrovascular complications.[10]

Fourth, HbA1c levels reflect ambient glucose concentrations less faithfully in patients with disorders of red blood cell (RBC) survival, such as hemolytic anemias and cystic fibrosis.

Nevertheless, the current authors consider HbA1c a valuable screening tool when combined with measures of fasting and postprandial glucose. They recommend that fasting and postprandial glucose levels be obtained in any child with HbA1c exceeding 5.6%; the level of concern rises in proportion to the level of HbA1c, the magnitude of weight excess, and the presence of additional risk factors for T2D.

Fructosamine

As noted previously, conditions that increase RBC turnover and decrease RBC lifespan will reduce HbA1c. These include, but are not limited to, states of decreased oxygenation (chronic lung disease or cystic fibrosis), increased RBC destruction (hemoglobinopathies), and chronic transfusions. In these cases, fructosamine can be used to estimate blood glucose levels over the preceding 2 weeks.[11]

The fructosamine assay measures serum protein glycosylation.[11] Similar to HbA1c, higher blood glucose concentrations will result in higher fructosamine levels. However, fructosamine can be falsely low if total body protein or albumin levels are low, as in children with malnutrition, inflammatory bowel disease (Crohn's disease or ulcerative colitis), and severe liver disease. Few studies have examined the use of fructosamine as a screening tool for glucose intolerance in obese children.

Summary of the Authors' Screening Recommendations

The ADA recommends screening high-risk children for glucose intolerance beginning at age 10 years or at the onset of puberty (Table 2). Although the guidelines capture a majority of cases, there are obese prepubertal children who develop IGT or T2D before the age of 10. Therefore, the authors recommend that some form of screening be considered in any prepubertal child with a body mass index (BMI) in the 97th percentile or above for age and sex. Screening should also be considered at any age in overweight and obese patients treated chronically with glucocorticoids or other drugs that reduce insulin sensitivity.

Although OGTT may identify patients with IFG and IGT, the test is time consuming and often impractical in the clinical setting. When OGTT is not feasible, the authors recommend initial screening of patients with HbA1c and random blood glucose. In the appropriate setting, this can be accomplished with a single finger-stick blood sample. HbA1c should be measured by an assay that is certified by the National Glycohemoglobin Standardization Program.[12]

Children with random glucose levels in the pre-diabetic or diabetic range should be referred to a pediatric endocrinologist for evaluation and ongoing management. Management of those with normal random glucose levels will depend on the level of HbA1c (**Figure 2**). If the HbA1c is below 5.7% and random sugar is normal, the health care provider should initiate or intensify diet and exercise counseling and monitor progress over time. If the HbA1c ranges from 5.7% to 6.4%, the provider may consider an oral glucose tolerance test or provide a prescription for a glucometer; this enables the family to obtain fasting and 2-hour postprandial glucose levels on several consecutive days. A referral to a pediatric endocrinologist is warranted if the child has glucose levels in the pre-diabetic or diabetic range and/or a strong family history of T2D. An HbA1c value of 6.5% or more warrants an immediate consultation with a pediatric endocrinologist to exclude type 1 diabetes mellitus and to consider treatment with oral hypoglycemic agents and/or insulin. Dietary management and training in daily home blood glucose monitoring are obligatory.

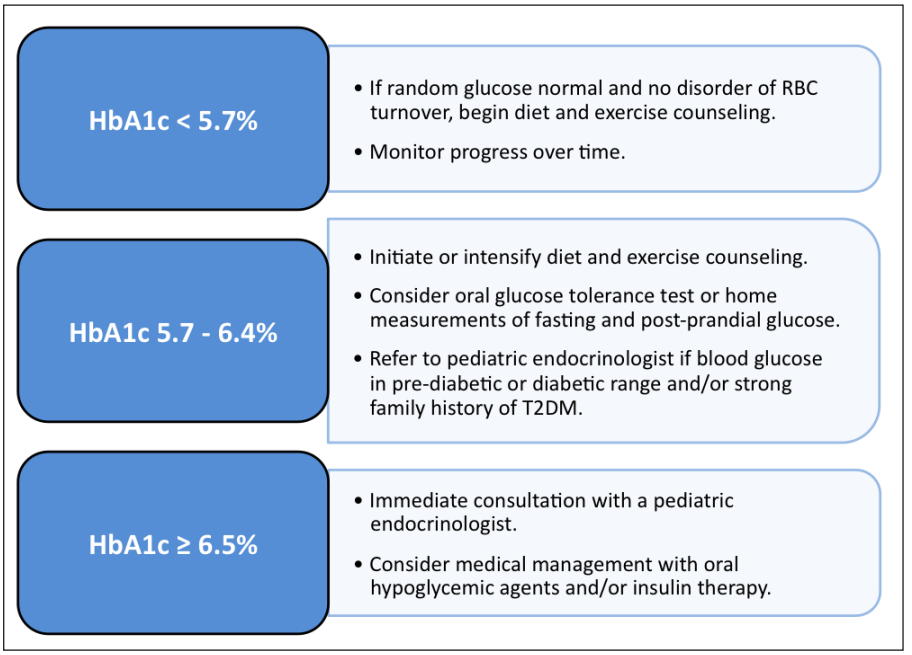

Figure 2. Suggested diabetes mellitus screening algorithm. HbA1c = hemoglobin A1c; RBC = red blood cell; T2DM = type 2 diabetes mellitus.

SCREENING FOR HYPERLIPIDEMIA

Background

Cardiovascular disease is the most common cause of death in the United States.[2] Several major studies have shown that early atherosclerotic lesions in children and adolescents are associated with hypercholesterolemia, hypertriglyceridemia, low levels of high-density lipoprotein (HDL) cholesterol, and other cardiovascular risk factors.[13] Dyslipidemia can be caused by primary genetic disorders, including familial hypercholesterolemia and familial mixed hyperlipidemia, or secondary causes, including obesity with insulin resistance, diabetes mellitus, nephrotic syndrome, obstructive liver disease, and hypothyroidism. The classic dyslipidemia associated with obesity includes hypertriglyceridemia; decreased HDL cholesterol; and increased small, dense low-density lipoprotein (LDL) cholesterol.[14]

The Pathobiological Determinants of Atherosclerosis in Youth (PDAY) study[15] and the Bogalusa Heart study[16] evaluated the risks and prevalence of postmortem atherosclerotic lesions in children, adolescents, and young adults. The PDAY study assessed the relationship between modifiable cardiovascular risk factors (cholesterol, smoking, blood

TABLE 3.

Physical Stigmata of Hyperlipemic States

State	Appearance	Lipid Abnormality
Eruptive xanthomas	Small, yellow, domed lesions with erythematous base	Hypertriglyceridemia
Tuberous xanthomas	Larger, domed lesions, often confluent and found on extensor surfaces	Hypercholesterolemia
Xanthelasma	Pale yellowish-white plaques along the eyelids	Hypercholesterolemia
Corneal arcus	White or gray ring surrounding the cornea	Hypercholesterolemia

TABLE 4.

Conditions That Warrant Early or Additional Lipid Screening in Children

Family history of hyperlipidemia, stroke, and/or early cardiovascular disease (women, ≤65 years old; men, ≤ 55 years old)
Obesity
History of smoking
Physical stigmata of hyperlipidemia (xanthoma, xanthelasma)
Underlying disease that causes hyperlipidemia (primary genetic hyperlipidemias, type 1 diabetes mellitus, type 2 diabetes mellitus, other states associated with insulin resistance, nephrotic syndrome, obstructive liver disease, hypothyroidism)
Chronic use of medication(s) that causes hyperlipidemia (estrogens, androgens, progestins, glucocorticoids, protease inhibitors, isoretinoin, atypical antipsychotics, anti-epileptics)
History of acute illness caused by hyperlipidemia (pancreatitis [hypertriglyceridemia], stroke and deep venous thrombosis [increased lipoprotein(a)], myocardial infarction)
Other disorders associated with high intrinsic risks of cardiovascular disease (diabetes mellitus, hypertension, Kawasaki disease, systemic lupus erythematous, end-stage renal disease, HIV, cardiac trauma, cardiac transplant)

pressure, obesity, and hyperglycemia) and measurements of atherosclerotic streaks and plaques in the coronary arteries. For every 30 mg/dL increase in non-HDL cholesterol (calculated as total minus HDL cholesterol), there was an incremental increase in the extent and severity of atherosclerosis.[17] The Bogalusa Heart study measured the extent of fatty streaks and fibrous plaques in the aorta and coronary arteries in individuals ranging from 2 to 39 years. The development and progression of atherosclerosis was related to the number and severity of cardiovascular risk factors beginning in childhood, with obesity as a strongly tracked risk factor.[16] Subsequent investigations showed that obesity in childhood and adolescence is associated with an increased risk of myocardial infarction in adulthood.[16,18,19]

Clinical consequences of hyperlipidemia may include pancreatitis (from hypertriglyceridemia), deep venous thrombosis (DVT), stroke, and myocardial infarction. Physical stigmata are rare in pediatrics unless there is marked hyperlipidemia (**Table 3**).

Causes of secondary dyslipidemia should be considered in all hyperlipidemic patients. These include endocrine and metabolic disorders (hypothyroidism, type 1 and 2 diabetes mellitus, lipodystrophy, and other conditions associated with insulin resistance), renal diseases (nephrotic syndrome or chronic renal disease), obstructive liver disease, cholestasis, alcohol, and a variety of medications (**Table 4**). Primary genetic causes, including familial mixed hyperlipidemia and familial hypercholesterolemia, should be considered in young children with strong family histories of early cardiovascular disease.

Evaluation

The 2011 Expert Panel of Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents recommended screening for hyperlipidemia at an early age, with the rationale that atherosclerosis and its risk factors begin in childhood and can be managed with lifestyle interventions and in some cases pharmacotherapy (**Table 4**).[20] Fasting lipids should be measured as early as age 2 years if there is a strong family history of early cardiovascular disease (**Table 4**).[20] Otherwise, routine universal screening of fasting lipid profile begins before the onset of puberty at age 9 to 11 years. Puberty in boys causes 10% to 20% reductions in total cholesterol and LDL cholesterol[19]; therefore, repeat screening in otherwise healthy children is recommended at ages 17 to 20 years. Conditions that warrant early or additional screening in children are shown in **Table 4**.

Interpretation and Referral

Acceptable levels of total and LDL cholesterol in children are less than 170 mg/dL and less than 110 mg/dL, respectively.[20] Fasting HDL cholesterol levels in normal children exceed 45 mg/dL. Normal triglyceride levels are less than 75 mg/dL before age 9 years and

less than 90 mg/dL after age 9 years. Treatment decisions for children with higher lipid levels should be based on the severity of dyslipidemia and the presence or absence of associated risk factors. The first aim in all cases should be modification of diet, lifestyle, and physical activity. The 2010 Dietary Guidelines for Americans provide age-appropriate dietary recommendations based on the Cardiovascular Health Integrated Lifestyle Diet (CHILD-1).[21] Pharmacotherapy may be indicated in children with severe or persistent hyperlipidemia, particularly those with one or more of the risk factors listed in **Table 4**.

The authors recommend referral to a lipid specialist for patients at highest risk, including (a) children younger than 10 years with LDL cholesterol higher than 200 mg/dL and/or triglycerides of 400 mg/dL or higher); (b) children aged 10 years or older with LDL cholesterol of 190 mg/dL or higher and/or triglycerides of 400 mg/dL or higher[20]; and (c) other hyperlipidemic children with genetic lipid disorders, a family history of early cardiovascular disease, or other conditions that increase the risk of cardiovascular disease (**Table 4**).

SCREENING FOR NONALCOHOLIC FATTY LIVER DISEASE

Background

Nonalcoholic fatty liver disease (NAFLD) represents a spectrum ranging from isolated accumulation of triglycerides within hepatocytes (steatosis) to steatohepatitis and cirrhosis. In addition to constituting a major cause of liver-related morbidity and mortality in children, NAFLD is an independent risk factor for insulin resistance, T2D, and cardiovascular disease.[22] Early detection of NAFLD may identify children with fibrosis/cirrhosis who are at risk for severe acute and chronic complications, including portal hypertension and hepatic failure.

TABLE 5.

Screening for Fatty Liver Disease

Age, y	BMI	Risk Factors	Screening
≥10	85th-94th percentile	With risk factors (hyperglycemia, hyperlipidemia)	ALT and AST every 2 y*
≥10	≥95th percentile	Without risk factors	ALT and AST every 2 y*

ALT = alanine aminotransferase; AST = aspartate aminotransferase; BMI=body mass index.
**Referral to a pediatric gastroenterologist is recommended when AST or ALT exceed 60 U/L on two separate occasions. It should be noted that levels of serum transaminases in nonobese children and adolescents are normally lower than 25 U/L in boys and 22 U/L in girls.[23,28] Additional evaluation should include screening for dyslipidemia, hypertension, impaired glucose tolerance, and diabetes mellitus.*

NAFLD is now the most common cause of chronic liver disease in children, with obesity as the leading risk factor.[23] The overall prevalence of NAFLD in American children aged 2 to 19 years ranges from 5% to 10%; far higher rates are recorded in obese Hispanic, Asian, and White children than in obese Black children.[24]

Screening, Interpretation, and Referral

Part of the challenge in screening for NAFLD is the absence of physical signs and symptoms, particularly early in the disease course. When present, symptoms and signs may include abdominal pain, fatigue, and hepatomegaly. Jaundice is not observed. Given the absence of symptoms, screening for NAFLD relies on levels of serum transaminases. Other causes of hepatitis must be excluded in those with high alanine aminotransferase and/or aspartate aminotransferase , including, but not limited to, viral hepatitis, autoimmune hepatitis, Wilson's disease, alpha-1-antitrypsin deficiency, inborn errors of metabolism, and medication toxicity. The diagnosis of NAFLD may be confirmed with a liver biopsy showing 5% or more of hepatocytes with macrovesicular steatosis.[23]

The American Gastroenterological Association, American Association for the Study of Liver Diseases, and American College of Gastroenterology have recently published clinical practice guidelines outlining current recommendations for NAFLD screening in children (**Table 5**).[25-27] Based on their recommendations, children aged 10 years or older with a BMI higher than the 85th percentile should be screened if there are risk factors. Once the BMI percentile exceeds 95%, screening should begin even in the absence of risk factors.

The first line of therapy for NAFLD is intensive lifestyle modification, with reductions in sugary drinks and other sources of fructose. In one study, Italian children who lost more than 20% of their body weight with lifestyle modification had improved serum ALT and steatosis on ultrasound.[28] Limited evidence suggests that antioxidants and possibly metformin may be useful when lifestyle changes fail.[28] More recent studies show promise in modulating hepatocyte response to oxidative stress using dietary long-chain polyunsaturated fatty acids such as docosahexaenoic acid, which is found in fish oil.[29] Patients who fail to respond to lifestyle intervention are at risk for progression to hepatic cirrhosis and end-stage liver disease[25-27] and should be followed by a pediatric gastroenterologist.

SCREENING FOR OVARIAN HYPERANDROGENISM

Background

Polycystic ovarian syndrome (PCOS) is a common condition in adolescent

TABLE 6.

2003 Rotterdam PCOS Consensus

1. Oligo or anovulation
2. Clinical and/or biochemical signs of hyperandrogenism
3. Polycystic ovaries and exclusion of other etiologies*

PCOS = polycystic ovary syndrome.
**Polycystic ovary morphology may be evident in normal adolescence.*
(Adapted from Rotterdam ESHRE/ASRM-Sponsored PCOS Consensus Workshop Group.[33])

girls, affecting more than 5% of reproductive-age women.[30] Clinical suspicion should arise in any adolescent girl with hirsutism, acne, and menstrual irregularities (oligo/amenorrhea); approximately 60% of patients with PCOS are overweight or obese. Neonatal risk factors predisposing to PCOS include fetal macrosomia, maternal gestational obesity, and congenital virilizing disorders.[31] Conditions associated with development of PCOS in adolescence include premature pubarche, atypical central precocious puberty, insulin resistance, metabolic syndrome, and a family history of the condition.[31]

The hyperandrogenism of PCOS is accompanied by anovulation, relative enlargement of the ovaries, increased numbers of small ovarian follicles, and lack of a dominant follicle. Free testosterone levels are high, and sex hormone–binding globulin levels (SHBG) are low. Fasting hyperinsulinemia and glucose intolerance are more common in obese patients than in thin patients.[30] The etiology of the condition is likely multifactorial and heterogeneous, with insulin resistance playing a contributory or causative role. Insulin in excess stimulates androgen production by ovarian theca cells and reduces SHBG production by the liver; in combination, these effects increase pituitary luteinizing hormone secretion and the levels of free testosterone in the circulation.[32] Diagnostic criteria for PCOS remain controversial; the 2003 Rotterdam criteria, accepted by many (but not all) clinicians, are shown in **Table 6**.[33] The 2013 Endocrine Society Guidelines recommend use of the Rotterdam criteria for the diagnosis of PCOS but note that polycystic ovary morphology may be evident in normal adolescents during sexual maturation.[34]

In adolescent girls with presumed PCOS, the physician should exclude other causes of hyperandrogenism, such as nonclassical congenital adrenal hyperplasia, Cushing's syndrome, androgen-secreting tumors, and hyperprolactinemia.

Screening and Referral

Menstrual irregularity is common in obese adolescents, yet the combination of hyperandrogenism (hirsutism, acne, increases in muscle mass, hairline recession, and/or deepening of the voice) and irregular menses should prompt an evaluation for PCOS and other virilizing conditions.[35] Biochemical evidence of PCOS includes elevated free testosterone and decreased SHBG; prolactin levels may be mildly elevated (15 to 25 ng/mL). A pelvic ultrasound may reveal polycystic ovaries, defined as the presence of 12 or more follicles in each ovary measuring 2 to 9 mm in diameter and/or increased ovarian volume (more than 10 mL).[33] There may be normal or mild isolated elevations of dehydroepiandrosterone sulfate (DHEAS) and androstenedione;[35] however, these are not consistenly reliable measures of hyperandrogenism in PCOS.[33] Marked elevations of DHEAS and androstenedione raise concern for adrenal tumor or congenital adrenal hyperplasia. An androgen-secreting tumor should be considered if clinical presentation includes rapid progression of hyperandrogenism (hirsutism, severe acne, growth spurt). Cushing's syndrome should be considered if clinical features include broad, hemorrhagic, or atrophic striae; central adiposity; hypertension; stunted height velocity; and/or hyperglycemia. Nonclassical congenital adrenal hyperplasia due to 21-hydroxylase deficiency is accompanied by elevations in 17-hydroxyprogesterone. Finally, severe hyperprolactinemia can be associated with mild hyperandrogenism in addition to galactorrhea and oligo/amenorrhea.

Comorbidities in PCOS include obesity, insulin resistance, dyslipidemia, and glucose intolerance. Management of PCOS in adolescents is aimed at the control of hyperandrogenism and treatment of comorbidities. This is usually accomplished with lifestyle intervention and oral contraceptive therapy because exogenous estrogen suppresses luteinizing hormone and increases hepatic SHBG production, thereby decreasing free testosterone levels.[31] This in turn reduces acne and hirsutism and improves menstrual regularity. Patients with more severe acne or hirsutism can benefit from the addition of an anti-androgen such as spironolactone. Weight loss can increase insulin sensitivity and reduce comorbidities in obese patients.[31] Metformin, an insulin sensitizer, may also limit weight gain and prevent progression of insulin resistance, thereby blunting the androgenic effects of hyperinsulinemia.

When PCOS is suspected, the authors recommend screening for glucose intolerance with HbA1c and random glucose. Fasting and postprandial glucose levels should be obtained in those with HbA1c exceeding 5.6%. The authors recommend referral to a pediatric endocrinologist if the patient has glucose intolerance, dyslipidemia, and/or striking virilization or fails to respond to conventional therapy.

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