# Metabolic Syndrome

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Author Disclosure
Drs Lee and Arrington Sanders have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

## Educational Gap

**The metabolic complications associated with obesity, such as insulin resistance, hypertension, hyperlipidemia, and the potential for arteriosclerotic heart disease, are on the rise in the pediatric population. Definition of the metabolic syndrome and determination of its significance is a changing process in which resolution has not yet been achieved, and its constellation of signs may have clinical significance beyond that of the individual risk factors.**

## Objectives

**After completing this article, readers should be able to:**

1. **Understand metabolic syndrome and identify implications for pediatric populations.**
2. **Describe the pathophysiology and biochemical markers implicated in the metabolic syndrome and identify its risk factors and clinical associations.**
3. **Use treatment and management strategies for children at risk for metabolic syndrome.**
4. **Recognize future research directions in pediatric metabolic syndrome.**

## Introduction

With the burgeoning global epidemic of childhood obesity, there is growing concern that the metabolic complications associated with obesity, such as insulin resistance, hypertension, and hyperlipidemia, historically encountered primarily in adults, are now on the rise in the pediatric population also. The metabolic syndrome (MetS) is characterized by a constellation of metabolic risk factors and is associated with the development of atherosclerotic cardiovascular disease and type 2 diabetes mellitus (T2DM) in adults. Efforts to identify children and adolescents at risk of developing MetS to prevent or mitigate its associated outcomes have been active areas of research within this population. However, several questions remain with regard to establishing a consensus definition of pediatric MetS and its long-term clinical implications. Does the constellation of signs have clinical significance beyond that of the individual risk factors?

### Abbreviations

| | |
|---|---|
| AHA: | American Heart Association |
| ATPIII: | Adult Treatment Panel III |
| BP: | blood pressure |
| DM: | diabetes mellitus |
| HDL: | high-density lipoprotein |
| IDF: | International Diabetes Foundation |
| IGT: | impaired glucose tolerance |
| LDL: | low-density lipoprotein |
| MetS: | metabolic syndrome |
| NAFLD: | nonalcoholic fatty liver disease |
| NHLBI: | National Heart, Lung, and Blood Institute |
| PCOS: | polycystic ovary syndrome |
| TG: | triglyceride |
| T2DM: | type 2 diabetes mellitus |
| VLDL: | very-low-density lipoprotein |
| WC: | waist circumference |

## Definition

Although the term "metabolic syndrome" was first used by Hanefeld and Leonhardt in the early 1980s, (1)(2) the observation that certain metabolic disturbances appeared to cluster together has been noted since the beginning of the past century, when Swedish and Spanish physicians Kylin and Marañon independently described the frequent copresentation of diabetes mellitus (DM) and hypertension. (1)(3) The MetS has since been variously labeled as the *deadly quartet*, *Syndrome X*, and the *insulin resistance syndrome*, and its definition has evolved as more is known about the pathophysiology of the syndrome and its associated clinical features.

Gerald Reaven introduced the concept of insulin resistance as a common etiologic factor for the group of metabolic disturbances and disorders he collectively called Syndrome X. In addition to hypertension, Reaven's definition

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included impaired glucose tolerance (IGT), hyperinsulinemia, high levels of very-low-density lipoprotein (VLDL) triglycerides (TGs), and low levels of high-density lipoprotein (HDL) cholesterol. (4) Central adiposity was added subsequently as a clinical feature of MetS by Norman Kaplan, (5) and current definitions of MetS now include the following key characteristics: hyperinsulinemia or insulin resistance, dyslipidemia, hypertension, and obesity, with a particular emphasis on central adiposity.

Over the past 15 years, several organizations, including the World Health Organization, the International Diabetes Foundation (IDF), the American Heart Association (AHA), and the National Heart, Lung, and Blood Institute (NHLBI), have proposed diagnostic criteria to better define MetS in adults. (6) In 2009, representative members from the AHA, NHLBI, IDF, and several other major organizations released a joint interim statement proposing a unified set of common criteria for the clinical diagnosis of adult MetS in an effort to reconcile the different clinical definitions that existed. (7) As a result, each of the 5 clinical measures (body weight, TGs, HDL, blood pressure [BP], and glucose) was given a single set of categorical cut points; an exception was waist circumference (WC), which was defined by population and country-specific definitions.

### Diagnostic Criteria in the Pediatric Population

In light of the challenges of defining MetS in adults, defining clinical criteria for pediatric MetS is complicated further by the physiologic changes that occur during growth and development throughout childhood and puberty. For example, insulin resistance increases in early puberty, but stabilizes in mid-adolescence and may vary also between genders. (8) Lipid profiles also have been noted to vary across ages. (9)

Additionally, there are several other challenges to defining pediatric MetS and to understanding its clinical significance in children. These barriers include the frequently subtle abnormalities that manifest in most children who have suspected metabolic disturbances; the lack of definitive normal ranges of insulin levels throughout childhood and puberty; and the absence of WC parameters to define central obesity associated with morbidity related to MetS in the pediatric population. (10) As a result, there are currently no consensus guidelines providing specific diagnostic criteria for pediatric MetS. Instead, criteria frequently have been adapted from adult standards of the National Cholesterol Education Program Adult Treatment Panel III (ATPIII) criteria, or other definitions by using gender- and age-specific normal values appropriate for children and adolescents.

In 2007, the IDF published a proposed set of criteria specific to children and adolescents to provide guidance on establishing a unified definition for pediatric MetS. (11) Table 1 demonstrates the wide range of diagnostic parameters that have been used in research studies frequently cited in the literature along with the diagnostic criteria proposed by the IDF.

## Epidemiology

Given the varying definitions available for pediatric MetS, determining its prevalence in children and adolescents is problematic. An analysis of the NHANES 1999–2002 data by Cook et al (12) compared the prevalence of pediatric MetS by using four previously published definitions and found that the prevalence of pediatric MetS ranged from 2% to 9% in the general population and from 12% to 44% in obese children, depending on the definitions used. Goodman examined prevalence rates in a school-based study comparing the National Cholesterol Education Program/ATPIII and World Health Organization criteria and reported overall prevalence rates of 4% and 8%, respectively. In the same study, the prevalence of MetS in obese patients increased substantially to 20% and 39%, respectively. (13) By using modified ATPIII criteria, de Ferranti et al (14) found an overall prevalence of 9% in a sample of US adolescents from the NHANES 1988–2004 data and also showed racial and ethnic distributions similar to adults, with Mexican-Americans and non-Hispanic white individuals having greater prevalence than non-Hispanic black people.

There is concern, however, that existing criteria underestimate the MetS prevalence in certain high-risk populations, such as non-Hispanic black individuals. (15) Although prevalence may vary because of inconsistent criteria, the variations in prevalence across different populations suggest a need to define diagnostic parameters appropriate for these populations. Not surprisingly, these studies consistently demonstrate a significant increase in prevalence of pediatric MetS in obese children compared with the general population.

The clinical utility of diagnosing pediatric MetS is also complicated by the instability of the diagnosis throughout childhood and adolescence. In a convenience sample of children ages 6 to 12 years at risk for developing adult obesity, 46% of those diagnosed as having MetS at baseline did not meet the diagnostic criteria for MetS at long-term follow-up (mean 5.6 ± 1.9 years). (16) Goodman et al (17) reported both loss (49%–56% of participants depending on criteria used) and gain (4%–5%) of a MetS diagnosis at 3-year follow-up in a school-based study of 1,098 adolescents.

Table 1. **Examples of Diagnostic Criteria Used in Pediatric Research and Proposed IDF Criteria for Pediatric MetS**

| Study/Group | Diagnostic Parameters | Obesity | Blood Pressure | Triglycerides | HDL | Glucose Intolerance |
|---|---|---|---|---|---|---|
| IDF, 2007 (11) | Central obesity and 2 additional risk factors[a] | ≥10–16 y: WC ≥90th percentile or adult cutoff if lower | ≥10–16 y: Systolic BP ≥130 or diastolic BP ≥85 mm Hg | ≥ 10–16 y: ≥ 150 mg/dL | ≥10–16 y: <40 mg/dL | FPG ≥ 100 mg/dL or known T2DM |
| | | 16+ y: Adult criteria | 16+ y: Systolic BP ≥130 or diastolic BP ≥85 mm Hg or treatment for hypertension | 16+ y: ≥150 mg/dL or specific treatment for high TG | 16+ y: <40 mg/dL in males and <50 mg/dL in females or specific treatment for HDL | |
| de Ferranti et al, 2004 (14) | ≥3 risk factors | WC ≥75th percentile (age-, gender-specific, ATPIII) | ≥90th percentile (age-, gender-, and height-specific, NHBPEP) | ≥97 mg/dL (Lipid Research Clinics) | <50 mg/dL (Lipid Research Clinics) | FPG ≥110 mg/dL |
| Cruz et al, 2004 (103) | ≥3 risk factors | WC ≥90th percentile (age-, gender-, and race-specific, NHANES III) | >90th percentile (age-, gender-, and height-specific, NHBPEP) | ≥90th percentile (age- and gender-specific, NHANES III) | ≤10th percentile (age- and gender-specific, NHANES III) | IGT: http://www.sciencedirect.com.proxy3.library.jhu.edu/science/article/pii/S0022347607007494 - bib20 (ADA) |
| Goodman et al, 2004 (13) | ≥3 risk factors | WC ≥102 cm, male; WC ≥88 cm, female (ATPIII) | ≥130/85 mm Hg BP (ATPIII) | ≥150 mg/dL (ATPIII) | ≤40 mg/dL, male; ≤50 mg/dL, female (ATPIII) | FPG ≥110 mg/dL or IGT (ADA) |
| Weiss et al, 2004 (44) | ≥3 risk factors | >97th percentile BMI (CDC[b] growth chart) or BMI *z* score ≥2 (age- and gender-specific) | >95th percentile (age-, gender-, and height-specific, NHBPEP) | >95th percentile (age-, gender-, and race-specific, NGHS) | <5th percentile (age-, gender-, and race-specific, NGHS) | IGT (ADA) |
| Cook et al, 2003 (104); Ford et al, 2005 (105) | ≥3 risk factors | WC ≥90th percentile (age- and gender-specific, NHANES III) | ≥90th percentile (age-, gender-, and height-specific, NHBPEP) | ≥110 mg/dL (age-specific NCEP) | ≤40 mg/dL (all ages/gender, NCEP) | FPG ≥110 mg/dL or IGT (ADA) |

ADA=American Diabetes Association; ATP=Adult Treatment Panel III of the NCEP; BP=blood pressure; HDL=high-density lipoprotein; IDF=International Diabetes Foundation; IFG=impaired fasting glucose defined as fasting plasma glucose concentration 110–125 mg/dL; IGT=impaired glucose tolerance defined as 2-hour oral glucose tolerance values >140 mg/dL; NCEP=National Cholesterol Education Program; NGHS=National Growth and Health Survey; NHBPEP=National High Blood Pressure Education Program; TG=triglycerides; T2DM=type 2 diabetes mellitus; WC=waist circumference.

[a]IDF suggests that below age 10 years, metabolic syndrome cannot be diagnosed, but a strong message for weight reduction should be encouraged for children age 6 to <10 with evidence of central obesity.

[b]Centers for Disease Control and Prevention growth chart used to define BMI.

The lack of stability in the diagnosis of pediatric MetS raises several questions regarding the optimal approach for screening, in particular, when and how to screen children at risk for MetS. In addition, this diagnostic uncertainty affects the ability to devise appropriate strategies for the management of MetS in the clinical setting.

Although studies in adults show strong evidence that those who have MetS are at increased risk of developing both T2DM and atherosclerotic cardiovascular disease, (18) as well as other obesity-related conditions such as nonalcoholic fatty liver disease (NAFLD), (19) polycystic ovarian syndrome, (20) and obstructive sleep apnea, (21) the long-term outcomes of children and adolescents who have or are at risk for pediatric MetS are not well established. Studies do suggest that pediatric MetS predicts adult MetS, (22)(23) and that obesity, particularly central obesity, correlates strongly with cardiovascular risk among youth; (24)(25)(26) but limited data exist to support the direct relationship between pediatric MetS and subsequent progression to adult cardiovascular outcomes such as atherosclerotic cardiovascular disease and T2DM.

Recognizing pediatric MetS as a unique cardiovascular risk predictor compared with its individual components remains controversial. Analysis of data from the Bogalusa Heart and Cardiovascular Risk in Young Finns studies reveals that the categorical definition of MetS is no better than screening with high BMI to identify youth at risk of developing long-term outcomes such as adult MetS, subclinical atherosclerosis, and T2DM. (27) However, in another analysis from the Bogalusa Heart Study, the authors report a stronger correlation of pediatric MetS with the persistence of multiple cardiovascular risk clustering over an 8-year period, compared with individual risk factors alone (systolic BP, insulin level, and total-to-HDL cholesterol ratio), suggesting that these risk factors may reinforce each other and track together as a group. (22) Studies also appear to indicate an association between pediatric MetS with both subclinical cardiovascular disease in young adults (23)(28) and T2DM. (29) More longitudinal studies are needed to clarify these relationships and evaluate the effectiveness of preventive and therapeutic interventions for pediatric MetS.

## Pathogenesis

The etiology of MetS is incompletely understood; however, insulin resistance and hyperinsulinemia are thought to be central to the development of MetS and may play a role in the pathogenesis of its individual metabolic components. Peripheral effects of insulin resistance on various organ systems is thought to explain some of the differences in the expression of MetS and its associated conditions such polycystic ovary syndrome (PCOS), NAFLD, and obstructive sleep apnea. (10)(30) Although insulin resistance appears to have an important role in the underlying mechanism of MetS, not all individuals who have insulin resistance proceed to develop MetS, (31) suggesting that other factors may be contributing to the pathogenesis of MetS. Obesity, particularly abdominal or visceral obesity, inflammatory mediators, adipocytokines, cortisol, oxidative stress, genetic predisposition, and lifestyle characteristics such as physical activity and diet are all thought to be involved in the pathophysiologic framework for MetS. (10)(32)(33)

## Risk Factors

### Heredity

Genetic and environmental factors appear to influence an individual's risk of developing MetS. Familial clustering for MetS risk factors is seen in several studies, suggesting that genetic effects or shared environments may contribute to development of MetS. (34)(35)(36) Children of parents who have early coronary artery disease in the Bogalusa Heart Study were more likely to be overweight beginning in childhood and commonly presented with components of MetS, including elevated levels of total cholesterol, low-density lipoprotein (LDL), and plasma glucose. (37) Furthermore, children having at least 1 parent who has MetS have significantly higher levels of central obesity and insulin resistance than children in whom neither parent has MetS. (38)

### Ethnicity

Components of MetS, including obesity, insulin resistance, cardiovascular disease, and T2DM, continue to affect black and Hispanic children disproportionately more than white children; (39)(40)(41) however, the rates of MetS in black youth are lower than in non-Hispanic white or Hispanic children. (42)(43) In contrast, when using lipid thresholds specific to black individuals, the prevalence of MetS among black youth was similar to non-Hispanic white and Hispanic children. (44) These disparities and inconsistencies have prompted a call for developing criteria specific to race and ethnicity in the evaluation of MetS to ensure appropriate identification of youth at risk for MetS and development of future adverse cardiovascular outcomes. (15)

### Physical Inactivity

In addition to physical activity being beneficial for weight management and obesity prevention, (45) physical activity alone improves several cardiovascular risks. Studies demonstrate that physical activity appears to be associated independently with improved insulin sensitivity; (46) lower LDL and TG and higher HDL concentrations; (47) and improved endothelial function, such as reduced systolic and diastolic BPs, arterial stiffness, and arterial wall remodeling in prepubertal obese children. (48) Additionally, increased physical activity appears to have an anti-inflammatory effect. (49)(50)

### Tobacco Exposure

Tobacco use has long been recognized as a significant risk factor for cardiovascular disease and also may be associated independently as a risk factor for MetS. One observational study reported a dose–response relationship between tobacco smoke and MetS among adolescents and speculated an association between tobacco and insulin resistance. (51)

## Clinical Features

### Obesity

There is strong evidence supporting the association between obesity with insulin resistance, T2DM, and atherosclerotic cardiovascular disease. (52)(53) Specifically, abdominal obesity due to accumulation of visceral fat is associated with increased cardiovascular risk independent of total body fat in adult populations. (54) Although BMI is used widely as a standard measure for obesity, BMI does not always reflect central adiposity and cannot differentiate the contributions made by muscle, bone, and fat. (55)(56) WC and waist-to-hip ratio have been suggested frequently as potential surrogates to determine the degree of visceral fat. (57) WC is an independent predictor of insulin resistance in youth, (58) and is associated with hypertension and dyslipidemia. (59) For these reasons, WC has been suggested as a more reliable measure for predicting MetS than BMI alone.

At this time, however, routine use of WC to measure central adiposity in children is not recommended because of insufficient information and lack of specific guidance for clinical application, according to an expert panel of the American Medical Association and the Centers for Disease Control and Prevention Task Force on Assessment, Prevention, and Treatment of Childhood Obesity. (60)

### Dyslipidemia

Dyslipidemias, especially high TG and low HDL cholesterol levels, are strongly associated with insulin resistance in children and adolescents. (22)(61) In general, the lipid abnormalities associated with insulin resistance are thought to result from an increased flux in free fatty acid delivery to the liver, resulting in hepatic insensitivity to the inhibitory effects of insulin on VLDL secretion and overproduction of TG-rich VLDL particles. (62)(63)(64) This process may be mediated by abnormal levels of inflammatory markers, such as adipokines and cytokines, associated with visceral obesity. (62)

HDL cholesterol metabolism also is altered by the increased levels of VLDL through the activation of hepatic lipase, forming small dense HDL and increasing clearance of HDL from the circulation. (63) Small dense LDL, which is believed to have increased atherogenic potential, is associated with abdominal obesity, visceral fat, and insulin resistance in adults and children. (65)(66)

## Hypertension

The association between insulin resistance and essential hypertension is well established, (67) and several mechanisms appear to be involved in this process. Insulin has vasodilatory effects on the endothelium, resulting from complex pathways that stimulate endothelial production of nitric oxide, a potent vasodilator. (68)(69) However, in individuals who have insulin resistance, even before any evidence of glucose intolerance, endothelial dysfunction and the vasodilatory response frequently are blunted. (35) These effects may occur because of the role of insulin in sodium reabsorption, (70)(71) the increased sympathetic tone due to hyperinsulinemia and obesity, (72)(73) and indirect impairment of vasodilation from the presence of fatty acids. (74)

The cluster of metabolic abnormalities associated with MetS may have an effect on BP greater than each of the individual factors alone. In one study examining the relationship between insulin resistance and BP in 11- to 15-year-olds, correlations were found when metabolic factors (fasting insulin, insulin resistance, TG, HDL cholesterol, or LDL cholesterol ) were considered as a group; but no correlations were seen when each factor was considered independently. (75) This clustering effect supports the importance of considering MetS as a unique collective entity rather than just considering independent risk factors to determine cardiovascular risk.

### Glucose Intolerance, Type 2 Diabetes Mellitus

The spectrum of diseases related to impairments in glucose metabolism and hyperglycemia results from either

defects in insulin action, ineffective secretion or clearance of insulin, or a combination of those pathophysiologic causes. The development of insulin resistance leading to an impaired fasting glucose level or IGT and on to T2DM is documented in both adult (76) and pediatric populations. (77)(78) However, all children who have impaired glucose tolerance are not certain to progress to a diagnosis of T2DM.

To examine this question, Weiss et al followed obese youth who have IGT over a 12-month period and illustrated the dynamic variations of their glucose tolerance status: 46% reverted to normal glucose tolerance, 30% continued to have IGT, and 24% progressed to T2DM. (79) On the other hand, the same study demonstrated that all of the children who did eventually develop T2DM had started initially from an IGT state, suggesting that IGT could be considered a "prediabetic" state. With the growing prevalence of childhood obesity and T2DM in adolescents and the risk of accelerated cardiovascular outcomes in youth who have T2DM, (80) early identification of children who have evidence of hyperglycemia who may be asymptomatic and yet have signs of the other components of MetS is an important step in managing those children who may require more aggressive monitoring and interventions.

### Inflammation

Increasing recognition of obesity as a chronic, low-level proinflammatory state (44)(81) and the association of MetS with inflammation has been reported. (82) Elevations of C-reactive protein, a biomarker that has been implicated in negative cardiovascular outcomes, (83)(84) is observed in obese children but has not been linked conclusively to insulin resistance or MetS. (44)(85) Several studies have examined other potential inflammatory markers, including adipocytokines, interleukin-6, tumor necrosis factor-alpha, and interleukin-18, with some evidence for a direct association with obesity, insulin resistance, and dyslipidemia. (81)(86)(87) Although inflammatory biomarkers are not a component of any current diagnostic criteria definitions, the recognition of the role of inflammation and its associations with MetS and cardiovascular disease is important to note among the clinical features of MetS.

### Other Clinical Considerations

In addition to atherosclerotic cardiovascular disease and T2DM, conditions such as PCOS and NAFLD are associated with MetS and frequently share overlapping features with its individual components.

PCOS is a common heterogeneous endocrine disorder in women primarily characterized by menstrual dysfunction, hyperandrogenism, or polycystic ovaries. (88)(89) Hyperandrogenism is a risk factor for MetS independent of insulin resistance and obesity, (90) and there is a fourfold increase in the prevalence of MetS in women who have PCOS. (91) Adolescent girls who have PCOS should therefore be screened for other metabolic abnormalities, including high BP, dyslipidemia, and impaired glucose metabolism.

In addition, NAFLD, a clinicopathologic syndrome ranging from simple steatosis to steatohepatitis, fibrosis, or cirrhosis of the liver, (92) is associated with dyslipidemia, obesity, and insulin resistance, and is considered a strong predictor of MetS and future cardiovascular disease and T2DM, as well. (93)(94) Diagnosis is challenging because a liver biopsy is required; however, noninvasive measurement of biochemical markers and ultrasonographic imaging of the liver may indicate the diagnosis in children, although the absence of abnormalities in these markers and imaging results would not be sufficient to exclude the diagnosis of NAFLD. (95)

## Screening, Management, and Treatment

Despite the challenges and difficulties of defining the clinical parameters for pediatric MetS, it is clear that the prevalence of the individual components of MetS, such as obesity, prediabetes, and T2DM, is on the rise among children and adolescents. Although clarification of the nature of the MetS and its management continues, the clinician must deal with this at-risk population in the hopes of helping them to have a healthier future.

Although standardized universal screening guidelines do not exist currently for the MetS in the pediatric population, evaluation and screening should aim to identify those youth who are at increased risk of developing MetS, particularly children and adolescents who are overweight or obese. Findings from the Bogalusa Heart Study have shown that the presence of an increasing number of cardiovascular risk factors is associated with an increased risk of developing precursors of atherosclerotic cardiovascular disease, such as fatty streaks and fibrous plaques in the aorta and coronary arteries. (96) Therefore, screening may help to identify children and adolescents who require more aggressive monitoring and treatment to prevent or slow the progression of developing atherosclerotic cardiovascular disease.

Screening in the pediatric population encompasses a multifaceted and comprehensive approach to assess cardiovascular risk. In the recently released NHLBI *Expert Panel on Integrated Guidelines for Cardiovascular*

*Health and Risk Reduction in Children and Adolescents*, children who are obese should have further evaluation for other specific cardiovascular risk factors, including evaluation of family history, growth and development, nutritional intake, assessment of physical activity, BP, lipid profile, and evidence of insulin resistance and DM, as well as tobacco exposure (97) (See Table 2 for summary).

## Table 2. Summary of Screening Guidelines by Component Cardiovascular Risk Factors for Metabolic Syndrome

<table>
<tr><th></th><th colspan="21">Age in Years</th></tr>
<tr><th></th><th>Birth to 2</th><th>3</th><th>4</th><th>5</th><th>6</th><th>7</th><th>8</th><th>9</th><th>10</th><th>11</th><th>12</th><th>13</th><th>14</th><th>15</th><th>16</th><th>17</th><th>18</th><th>19</th><th>20</th><th>21</th></tr>
<tr><td>Tobacco exposure</td><td colspan="3">Smoke-free environment</td><td colspan="6">Obtain smoke exposure history from child, including personal use</td><td colspan="12">Assess personal smoking history, specifically recommend against smoking, and promote smoking cessation</td></tr>
<tr><td>Physical Activity</td><td colspan="3">Environment promoting physical activity</td><td colspan="18">Moderate to vigorous daily physical activity</td></tr>
<tr><td>Blood Pressure[a]</td><td colspan="3">No routine BP monitoring</td><td colspan="18">Routine annual BP monitoring</td></tr>
<tr><td>Lipid Screening</td><td colspan="3">No routine lipid screening</td><td colspan="5">No routine lipid screening<br><br>Measure fasting lipid profile x 2 in certain higher risk groups[b]</td><td colspan="3">Universal screening (non-fasting or fasting lipid profile)</td><td colspan="5">No routine lipid screening<br><br>Measure fasting lipid profile x 2 in certain higher risk groups[b]</td><td colspan="5">Universal screening (non-fasting or fasting lipid profile)</td></tr>
<tr><td>Overweight and Obesity</td><td colspan="3">No weight-for-height specific recommendations</td><td colspan="3">Identify children at high risk for obesity (parental obesity, excessive gain in BMI)</td><td colspan="6">Identify children at increased risk for obesity (parental obesity, change in physical activity +\- excessive gain in BMI) for focused diet/physical activity education</td><td colspan="10">Identify children at increased risk for obesity (parental obesity, change in physical activity +\- excessive gain in BMI) for focused diet/physical activity education</td></tr>
<tr><td>Type 2 Diabetes Mellitus</td><td colspan="9"></td><td colspan="13">Overweight[c] PLUS, any 2 of the following risk factors:<br>1) Family history of T2 DM in first- or second-degree relative<br>2) Race/ethnicity (Native American, African-American, Latino, Asian-American/Pacific Islander<br>3) Signs of insulin resistance or conditions associated with insulin resistance (acanthosis nigricans, hypertension, dyslipidemia, or polycystic ovary syndrome)<br>Start: ≥10 years or at onset of puberty if occuring at younger age<br>Frequency: Every 2 years<br>Test: Fasting plasma glucose</td></tr>
</table>

BP=blood pressure; DM=diabetes mellitus; NHLBI=National Heart, Lung, and Blood Institute; TC=total cholesterol; T2DM=type 2 diabetes mellitus.
[a]Measure BP from birth if history (+) for neonatal complications, congenital heart disease, urinary/renal abnormality, solid organ transplant, malignancy, drug treatment, or other condition known to raise BP or intracranial pressure.
[b]Parent, grandparent, aunt/uncle, or sibling with myocardial infarction, angina, stroke, coronary artery bypass graft/stent/angioplasty <55 years in males,<65 years in females, parents with known dyslipidemia or TC ≥240 mg/dL; child has DM, hypertension, BMI ≥95%, or smokes cigarettes; child has moderate- or high-risk medical condition.
[c]Overweight defined by BMI >85th percentile for age and gender, or weight for height >85th percentile, or weight >120% of ideal for height.
(Adapted from NHLBI, *Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents: Summary Report* [97].)

Currently, treatment targets overweight and physical inactivity in the management of obesity. The 2011 NHLBI report also recommends prompt intensification of weight loss in the presence of any combination of multiple individual risk factors for MetS, in addition to management of any coexisting associated cardiovascular risk factors. Components of the MetS can improve with effective weight management, (98) and improvements can be seen even with relatively small weight changes. (99) Lifestyle modifications, including appropriate caloric nutritional intake, avoiding atherogenic and diabetogenic foods, increasing physical activity, and smoking cessation, are the primary recommendations from both the AHA and the IDF. (10)(44)

Assessing patient and family motivation and willingness to adopt healthier lifestyles is an important step at the onset of any weight management plan. Engaging youth and their families through frequent scheduled visits and helping them to identify creative strategies, such as increasing family meals together, writing exercise prescriptions, and scheduling activities with friends may encourage youth and families to work toward small, manageable changes. (100)

Currently, there are no specific indications or guidelines on the use of pharmacologic agents for treatment of MetS. However, medications for treatment of hypertension, dyslipidemia, and DM should be considered where appropriate. Although pharmacologic agents such as metformin have been used effectively for weight reduction and improving glucose tolerance for children who have T2DM in small studies, (101) there are no existing recommendations for the use of metformin in treating MetS. Rosiglitazone, a thiazolidinedione derivative, also has shown promise in restoring normal glucose tolerance in obese children who have IGT in a recently published pilot study. (102) Further studies are necessary to determine if there may be a role for pharmacologic treatment in the management of pediatric MetS as an adjunct to lifestyle modifications, but routine use of medications in the clinical setting is not recommended at this time.

## Future Research

Much still needs to be explored to understand and define the MetS in children and adolescents. Priorities include identification of better definitions of obesity in children; development of age-, gender-, and ethnic-specific ranges for the categorical criteria used to define MetS; initiation of long-term cohorts of children from diverse backgrounds to understand better the natural history and outcomes of MetS; and assessment of the effectiveness of prevention and intervention strategies.

## Summary

- Pediatric metabolic syndrome (MetS) represents a cluster of risk factors associated with cardiovascular disease, with features that include insulin resistance, obesity, hyperlipidemia, and hypertension.
- Currently, there are no consensus definitions to define the MetS in youth; however, identification of children at risk for developing MetS remains an important task because of the presence of multiple cardiovascular risks and the evidence that the clustering of these conditions persists in adulthood.
- Screening recommendations should aim at identifying children who are overweight or obese and have additional risk factors associated with MetS
- Management and treatment prioritizes intensive weight management programs in addition to other lifestyle modifications and management of other clinical risk factors associated with cardiovascular disease.

***Note: To view the references for this article, visit the October issue at http://pedsinreview.aappublications.org and click on the "Metabolic Syndrome" article.***

### HealthyChildren.org Parent Resources From the AAP

The reader is likely to find material to share with parents that is relevant to this article by visiting this link: http://www.healthychildren.org/English/health-issues/conditions/obesity/Pages/Your-Overweight-Child-and-the-Risk-of-Disease.aspx.

## PIR Quiz

This quiz is available online at http://www.pedsinreview.aappublications.org. NOTE: Since January 2012, learners can take *Pediatrics in Review* quizzes and claim credit online *only*. No paper answer form will be printed in the journal.

## New Minimum Performance Level Requirements

Per the 2010 revision of the American Medical Association (AMA) Physician's Recognition Award (PRA) and credit system, a minimum performance level must be established on enduring material and journal-based CME activities that are certified for *AMA PRA Category 1 Credit™*. To successfully complete 2012 *Pediatrics in Review* articles for *AMA PRA Category 1 Credit™*, learners must demonstrate a minimum performance level of 60% or higher on this assessment, which measures achievement of the educational purpose and/or objectives of this activity.

Starting with the 2012 issues of *Pediatrics in Review*, *AMA PRA Category 1 Credit™* can be claimed only if 60% or more of the questions are answered correctly. If you score less than 60% on the assessment, you will be given additional opportunities to answer questions until an overall 60% or greater score is achieved.

1. You are discussing the obesity epidemic with a group of medical students on morning rounds. Of the following groups of findings, which are used by epidemiologists as diagnostic criteria for metabolic syndrome?
   A. Elevated high-density lipoproteins, family history of heart disease, hypertriglyceridemia.
   B. Fasting hyperglycemia, hypertension, obesity.
   C. Hypertension, obesity, smoking history.
   D. Hypertension, obesity, polycystic ovaries.
   E. Family history of heart disease, obesity, type 1 diabetes.

2. You are caring for a 15-year-old boy who is obese and has an abnormal lipid profile and impaired glucose metabolism. You are concerned that he might have nonalcoholic fatty liver disease. Of the following tests, which is necessary to make a definitive diagnosis?
   A. Alanine transaminase (ALT) level.
   B. Aspartate transaminase (AST) level.
   C. Hepatobiliary iminodiacetic acid (HIDA) scan.
   D. Liver biopsy.
   E. Ultrasonography of the liver.

3. An overweight 17-year-old boy is seen in a follow-up visit. He has had a history of elevated blood pressure, and today his blood pressure is 145/95. You are concerned that he may be developing metabolic syndrome. Of the following factors, which may be an independent risk factor for metabolic syndrome?
   A. Alcohol consumption.
   B. Decreased intake of fish oil.
   C. Hashimoto thyroiditis.
   D. Low vitamin D level.
   E. Smoking.

4. An obese child comes in with a history of polyuria. You obtain a chemistry panel, including fasting blood glucose. Of the following levels of fasting blood glucose, which is the lowest level that would warrant further evaluation for glucose intolerance?
   A. 90 mg/dL.
   B. 110 mg/dL.
   C. 130 mg/dL.
   D. 150 mg/dL.
   E. 170 mg/dL.

5. A 16-year-old girl with a body mass index of 35 comes in for her initial evaluation to your practice. Fasting serum triglycerides levels are elevated (170 mg/dL). Your initial management of this patient should include:
   A. Lifestyle modifications (calorie restriction and exercise) only.
   B. Lifestyle modifications plus lovastatin.
   C. Lifestyle modifications plus metformin.
   D. Lifestyle modifications plus niacin.
   E. Lifestyle modifications plus rosiglitazone.

## Corrections

In the June 2012 article "Index of Suspicion Case 2: Abnormal Behavior, Seizures, and Altered Sensorium in a 7-year-old Boy" (Patra KP, Sankararaman S, Ray M. *Pediatr Rev.* 2012;33(6):279-284), the second paragraph in the Case 2 Presentation section (page 279) says, "His temperature is 36.5˚F…". This should be 36.5˚C. The journal regrets the error.

In the February 2012 article "Index of Suspicion Case 3: Ptosis and Diplopia After a Respiratory Infection in a 7-year-old Girl" (Nguyen L, Kansagra S, Shaw A, McLean H. *Pediatr Rev.* 2012;33(2):89-94), one of the co-authors was misidentified. The correct name should be Andrea Shaw, MD. The journal regrets the error.