Metabolic Syndrome in Children and Adolescents

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Educational Gap

Metabolic syndrome in obese children is associated with increased risk for the development of type 2 diabetes and cardiovascular disease. Currently, no unifying definition exists and the impact of metabolic syndrome on other obesity-related comorbidities continues to be poorly understood.

Objectives

After completing this article, the reader should be able to:

1. Describe the relationship between obesity and metabolic syndrome (MetS).
2. Recognize the difficulty in defining MetS in the pediatric population.
3. Recognize the multiple risk factors associated with MetS in the pediatric population.
4. Describe the importance of various clinical features associated with MetS.
5. Initiate screening for MetS in appropriate patients and develop treatment strategies for those patients.

INTRODUCTION

As the prevalence of obesity in adults and youth continues at historically high rates, so does the occurrence of obesity-related comorbidities. Many chronic diseases that were once believed to be conditions of adults alone are now being seen commonly in the pediatric population. The combination of dyslipidemia, abnormal glucose regulation, central adiposity, and hypertension, known collectively as metabolic syndrome (MetS), has long been recognized in the obese adult population and is associated with an increased risk for the development of cardiovascular disease (CVD) and type 2 diabetes (T2D). The definitive criteria for MetS have not been firmly established; many criteria have small differences that can alter the risk stratification for progression to CVD and T2D. (1)(2) What is clear is that the risk of developing CVD or T2D increases substantially in the presence of MetS, with a twofold increase for the former and fivefold increase for the latter in adult populations. (3) In the pediatric population, only 1 set of criteria is available, and its use as an assessment for CVD and T2D risk continues to be a subject of debate. (1)(4)

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DEFINITION

The description of MetS dates back to World War I, when Hitzenberger and Richter-Quittner in Austria discussed the relationship between blood pressure and diabetes mellitus. (1) Kylin of Sweden and Maranon of Spain also published articles at approximately the same time that described the coexistence of hypertension and hyperglycemia. (1) In the 1940s, Vague described the connection between abdominal obesity and diabetes, hypertension, and atherosclerosis. From the 1960s until the late 1980s, researchers from several countries independently described the constellation of findings that are observed in MetS, giving the syndrome a number of names, including syndrome of affluence (Mehnert and Kuhlmann), plurimetabolic syndrome (Avogaro and Crepaldi), and insulin resistance syndrome (DeFronzo and Ferrannini, Haffner). (1) In 1981, Hanefeld and Leonhardt called a constellation of findings that included T2D, hypertension, and hyperlipidemia "metabolic syndrome," noting that the development of these conditions occurred in the setting of genetic predisposition, excessive food intake, and lack of physical activity. In the late 1980s, Reaven published his findings that the common denominator for these conditions was insulin resistance and coined the term syndrome X to describe them. (1) Shortly thereafter, Kaplan described the importance of central adiposity as a common factor in this constellation of findings and called the combination of central adiposity, hypertriglyceridemia, impaired glucose tolerance, and hypertension "the deadly quartet." Since then, a multitude of researchers has contributed to our understanding of the development of MetS and the impact of its individual components. (2) Although most of the terms used to describe the constellation of findings of central obesity, dyslipidemia, impaired glucose regulation, and increased risk of CVD and T2D are interchangeable, today this condition is most well known as metabolic syndrome.

Just as many terms have been ascribed to MetS, many definitions also have been used to describe it. Adult definitions have been published by the World Health Organization (WHO), International Diabetes Foundation (IDF), National Cholesterol Education Program III, National Heart, Lung and Blood Institute (NHLBI), and the American Association of Clinical Endocrinologists (Table 1). (2) Differences include the presence or absence of microalbuminuria, the use of waist-to-hip ratios, and the use of hyperinsulinemic euglycemic clamp studies. (2) The subtle differences in criteria led to the publication of a statement from the Joint Task Force of all groups stating that the criteria for MetS in adults should be 3 of the following 5 criteria (2):

- Elevated waist circumference (WC) based on population- and country-specific definitions
- Triglycerides of 150 mg/dL (1.7 mmol/L) or more or receiving treatment for elevated triglycerides
- High-density lipoprotein (HDL) cholesterol less than 40 mg/dL (1.0 mmol/L) in males and less than 50 mg/dL (1.3 mmol/L) in females or receiving treatment for reduced HDL cholesterol
- Systolic blood pressure of 130 mm Hg or more and/or diastolic blood pressure of 85 mm/Hg or more or receiving treatment for hypertension
- Fasting blood glucose of 100 mg/dL (5.6 mmol/L) or more or receiving treatment for hyperglycemia

There is currently no consensus guideline for the diagnostic criteria for pediatric MetS in the pediatric literature. In fact, more than 40 definitions have been reported in the pediatric population. (3) In 2007, the IDF provided a definition for MetS in the pediatric population using pediatric-specific criteria (Table 2). A number of researchers have published their proposed definitions in addition to risk stratification for CVD and T2D using these definitions. Other published criteria for MetS in children and adolescents have used waist-to-hip ratio, fasting insulin levels, low-density lipoprotein (LDL) cholesterol, cholesterol-to-HDL cholesterol ratios as well as skinfold thickness. (3) Defining MetS in the pediatric population is difficult for a number of reasons:

- The lack of a unifying definition in adults makes it less likely that a unifying definition can be developed in the pediatric population
- The increase in insulin resistance during puberty can potentially affect metabolism and weight gain
- The change in lipid profiles at different ages makes using one set of values for all age groups difficult
- The lack of consensus on cutoffs for WC to define central adiposity, which changes based on age

EPIDEMIOLOGY

Use of adult definitions for MetS in the pediatric population has led to substantial discrepancies in determining prevalence, which is not unlike the discrepancies noted in the adult population. Discrepancies have been up to 50% in some cases. For example, one study noted a prevalence of MetS in junior high and high school students of 4.8% using IDF criteria and 12.7% using NHLBI criteria. (5) Most studies to date have used the Adult Treatment Panel III (ATPIII) and WHO criteria to describe MetS in the pediatric population. Various publications have noted prevalence numbers using different definitions ranging from 0.2% to 38.9%. (4) Data from 2010 show

TABLE 1. **Definitions of Metabolic Syndrome in Adults**

WORLD HEALTH ORGANIZATION	INTERNATIONAL DIABETES FEDERATION	NATIONAL HEART, LUNG AND BLOOD INSTITUTE	NATIONAL CHOLESTEROL EDUCATION PROGRAM III
■ Type 2 diabetes (fasting blood glucose ≥126 mg/dL [7 mmol/L] or OGTT 2 hour ≥200 mg/dL [11.1 mmol/L])	■ Central obesity: waist circumference >94 cm (men) or 80 cm (women)	3 of the following:	3 of the following:
■ Insulin resistance (determined by hyperinsulinemic euglycemic clamp method)		■ Fasting blood glucose ≥110 mg/dL (6.1 mmol/L) or treatment for hyperglycemia	■ Fasting blood glucose ≥100 mg/dL (5.6 mmol/L) or treatment for hyperglycemia
■ Impaired fasting glucose (fasting blood glucose 110–125 mg/dL [6.1–6.9 mmol/L])	Plus 2 of the following:	■ SBP ≥130 mm Hg or DBP ≥85 mm Hg or antihypertensive medication	■ SBP ≥130 mm Hg or DBP ≥85 mm Hg or treatment for hypertension
Plus 2 of the following:	■ Fasting blood glucose ≥100 mg/dL (5.5 mmol/L) or previously diagnosed type 2 diabetes	■ Fasting TG ≥150 mg/dL (1.7 mmol/L) or treatment for hyperlipidemia	■ TG ≥150 mg/dL (1.7 mmol/L) or treatment for hyperlipidemia
■ SBP ≥140 mm Hg or DBP ≥90 mm Hg and/or antihypertensive medication	■ SBP ≥130 mm Hg or DBP ≥85 mm Hg or antihypertensive medication	■ HDL <40 mg/dL (1.0 mmol/L) (men) or <50 mg/dL (1.3 mmol/L) (women) or treatment for hyperlipidemia	■ HDL <40 mg/dL (1.0 mmol/L) (men) or <50 mg/dL (1.3 mmol/L) (women) or treatment for hyperlipidemia
■ Fasting TG ≥150 mg/dL (1.7 mmol/L) and/or HDL <35 mg/dL (0.9 mmol/L) (men) or <39 mg/dL (1.0 mmol/L) (women)	■ Fasting TG ≥150 mg/dL (1.7 mmol/L) or treatment for hyperlipidemia	■ Waist circumference ≥102 cm (men) or ≥88 cm (women), with lower thresholds for ethnic groups or individuals prone to insulin resistance	■ Waist circumference ≥102 cm (men) or ≥88 cm (women)
■ BMI ≥30 and/or waist-to-hip ratio >0.9 (men) or >0.85 (women)	■ HDL <40 mg/dL (1.0 mmol/L) (men) or <50 mg/dL (1.3 mmol/L) (women) or treatment for hyperlipidemia		
■ Urinary albumin excretion rate ≥20 μg/min or albumin-to-creatinine ratio >30 mg/g			

BMI=body mass index, DBP=diastolic blood pressure, HDL=high-density lipoprotein cholesterol, OGTT=oral glucose tolerance test, SBP=systolic blood pressure, TG=triglycerides

Alberti KGMM, Eckel RH, Grundy SM, et al; International Diabetes Federation Task Force on Epidemiology and Prevention; National Heart, Lung, and Blood Institute; American Heart Association; World Heart Federation; International Atherosclerosis Society; International Association for the Study of Obesity. Harmonizing the metabolic syndrome: a joint interim statement of the International Diabetes Federation Task Force on Epidemiology and Prevention; National Heart, Lung, and Blood Institute; American Heart Association; World Heart Federation; International Atherosclerosis Society; and International Association for the Study of Obesity. Circulation. *2009;120(16):1640–1645, http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=19805654&dopt=Abstract (2)*

that the prevalence of MetS among children and adolescents in the United States is 4.2% by ATPIII criteria and 8.4% by WHO criteria, (6) with a higher percent of obese and Hispanic patients compared to normal-weight, Caucasian, or African American patients. The prevalence of MetS in overweight individuals has been quoted as 7.1% to 11.9%, compared with 29.2% to 32.1% in obese individuals. (7)

PATHOGENESIS

The pathogenesis of MetS is not fully understood, but insulin resistance is believed to play a key role in the development of the syndrome as well as its individual components. The phenomenon of insulin resistance is most often seen in the setting of obesity and is believed to be due to free fatty acid accumulation in the liver, skeletal muscle, adipocytes, and pancreas, which interferes with normal insulin signaling. (8) Free fatty acid buildup in the liver leads to a decreased ability to regulate gluconeogenesis, which increases insulin levels further as well as triglyceride (TG) production. The insulin resistance at the level of the adipocyte leads to increased lipolysis and lipid deposition into the bloodstream. Muscle fatty acid buildup and insulin resistance

TABLE 2. **Definition of Metabolic Syndrome in Children and Adolescents by the International Diabetes Federation**

6-<10 YEARS	10-<16 YEARS	>16 YEARS
• Cannot diagnose in this age group	• Obesity ≥90th percentile by waist circumference • 2 or more of the following: - Fasting glucose >100 mg/dL (5.6 mmol/L) or known type 2 diabetes -SBP ≥130 mm Hg or DBP ≥85 mm Hg -Fasting TG ≥150 mg/dL (1.7 mmol/L) -HDL <40 mg/dL (1.0 mmol/L)	• Central obesity: waist circumference >94 cm (men) or >80 cm (women) • 2 of the following: -Fasting glucose >100 mg/dL (5.6 mmol/L) or previously diagnosed type 2 diabetes -SBP ≥130 mm Hg or DBP ≥85 mm Hg or treatment for hypertension - Fasting TG ≥150 mg/dL (1.7 mmol/L) or treatment for hyperlipidemia -HDL <40 mg/dL (1.0 mmol/L) (men) or <50 mg/dL (1.3 mmol/L) (women) or treatment for hyperlipidemia

DBP=diastolic blood pressure, HDL=high-density lipoprotein cholesterol, SBP=systolic blood pressure, TG=triglycerides
The IDF Consensus Definition of the Metabolic Syndrome in Children and Adolescents. International Diabetes Foundation. *Accessed 4/1/2016 at http://www.idf.org/webdata/docs/Mets_definition_children.pdf. (c) 2007, International Diabetes Foundation*

result in decreased glucose uptake as well as increased inflammation. (4)

Adipocyte dysfunction is an essential contributor to the pathogenesis of obesity and T2D. The pathogenesis is believed to be due, in part, to the release of inflammatory cytokines in response to excess fat stores in adipocytes, such as interleukin-6, monocyte chemoattractant protein-1, and tumor necrosis factor-α, which subsequently promotes macrophage migration to the adipose tissue that further increases cytokine production. (7) The decrease in adiponectin has been shown to increase inflammatory mediators from adipose tissue. Changes in the gut microbiome in normal-weight mice when fed high-fat diets and in obese versus nonobese mice have been observed; the altered gut microbacteria that are present in states of obesity are associated with increased markers of inflammation and may be linked to the development of insulin resistance. (9) Other factors, including retinol-binding protein 4 and leptin, have also been implicated in the link between obesity and insulin resistance. (7)

Considerable data link insulin resistance and inflammation. (8) Possible mechanisms of action include insulin stimulation of inflammatory cytokines and growth factors in the vascular smooth muscle.

Thus, data support a strong interplay among obesity, insulin resistance, and inflammation, and this interplay is of importance in the pathogenesis of MetS. The links connecting obesity, insulin resistance, and inflammation and their association with MetS continue to be elucidated.

RISK FACTORS

Both genetic and environmental factors play roles in modifying the risk of developing MetS. Children of parents with MetS are at higher risk of developing it themselves. Recent studies have documented genes linked to the development of MetS in clusters of family members (10) as well as gene polymorphisms that may be associated with increased risk of developing the syndrome. (11)

Gender confers a minimally increased risk in adolescents, with males at higher risk than females, but this gender difference seems to disappear in the adult population. (7)

A risk is conferred based on ethnic background in adolescents in a number of studies. The prevalence of MetS is higher in Hispanics than in Caucasians and African Americans. (7) Some of the disparity in ethnic prevalence is related to the lower TG concentrations in African Americans due to lower apolipoprotein CIII levels. (12) Some have suggested redefining criteria for MetS in African American adults and children because of this difference, but no new definitions have been proposed to date. Data in adults show variations in ethnic predisposition, with the National Health and Nutrition Examination Survey data noting no ethnic difference in MetS prevalence between African Americans and Caucasians. (7)(13)

A number of studies in adults and some in children have assessed the impact of physical activity on the risk of developing MetS. Increased television viewing in adolescence has been associated with increased risk of developing MetS in adulthood. (14) Inactivity has been associated with a decrease in insulin sensitivity in the skeletal muscle that

can be regained with resumption of activity. Moderate and vigorous physical activity in both adults and adolescents has conferred a lower risk of developing MetS. (15) The presence or absence of gender and ethnic differences with respect to risk and activity are not clear. Nevertheless, sedentary behavior is a clear risk factor for the development of MetS.

Smoking has been linked to an increased risk of MetS. Cessation of the habit significantly reduces risk. (16)

Nonalcoholic fatty liver disease (NAFLD) has been implicated in the progression to MetS, possibly through liver cell inflammation increasing cytokine production as well as hepatic insulin resistance. (17) Insulin resistance in the liver leads to disinhibition of very low-density lipoprotein cholesterol production, which accumulates in the liver and leads to elevations in TGs. Thus, fat accumulation in the liver can be considered a risk factor for MetS. (17)

Both early and late menarche has been predictive of MetS in adulthood, (18) independent of weight. Further studies are needed to confirm these findings and understand the mechanisms by which time of menarche can affect development of metabolic abnormalities.

A small number of studies have suggested that high fructose consumption (amounts seen in soda and processed foods) leads to higher risk of MetS. (19) Fructose consumption has been associated with a decrease in insulin sensitivity in young adults compared to glucose consumption. (20) Fructose metabolism to fatty acids is more rapid than glucose metabolism, leading to a faster accumulation of fatty acids in the circulation. In addition, TGs can accumulate in the circulation following fructose-mediated decreases in lipoprotein lipase activity.

The use of antipsychotics to treat mood disorders such as bipolar disorder as well as anxiety and depression has been associated with an increased risk for the development of MetS. Bipolar disorder, irrespective of antipsychotic use, has also been linked to MetS, and both have been noticed irrespective of weight.

Any obesity syndrome confers an increased risk of obesity-related comorbidities, including MetS. However, Klinefelter syndrome has a notably increased risk for the development of MetS, with most studies suggesting a fivefold higher chance of developing the syndrome in affected boys compared to boys without Klinefelter syndrome. Klinefelter syndrome is heralded by a 47 XXY genotype with associated testicular failure, infertility, pubertal delay, tall stature, and social and behavioral dysfunction. The cause of this higher risk is not fully understood but is believed to be related to the increase in central obesity that these boys develop, leading to insulin resistance, even when body mass index (BMI) is in the normal or overweight range.

CLINICAL FEATURES

Obesity

Obesity is a crucial factor for the development of MetS, T2D, and adverse CVD outcomes. In addition, data from multiracial cohorts of children have shown that the degree of obesity and the prevalence of MetS are strongly associated. (21) Calculating a BMI and plotting it on standard growth curves is the gold standard for diagnosing obesity in children, with a BMI above the 95th percentile for age and gender considered obese. Obtaining an accurate height and weight as well as calculating and plotting a BMI yearly are crucial for identifying children at risk for MetS.

In addition to the degree of obesity, fat distribution also appears to be important. Visceral fat accumulation, independent of BMI, has been shown to be strongly associated with both childhood MetS (22) and CVD later in life (23). This clustering of risk factors is most likely related to increased insulin resistance that is known to be associated with increased visceral adiposity. Different methods can be used to assess visceral fat accumulation, including magnetic resonance imaging, waist-to-hip ratios, and WC. Of these, WC is often recognized as the best clinical predictor of visceral fat accumulation in both children and adults. (24)(25) Increased WC in children and adolescents, independent of BMI, is a predictor of insulin resistance and is associated with elevated CVD risk factors. (25) However, due to lack of childhood-specific data, WC measurements are not currently recommended as part of routine assessment of the obese child.

An additional clinical tool for assessing adiposity in children is the waist-to-height ratio. A waist-to-height ratio greater than 0.6 has been shown to be a significant predictor of both MetS and CVD risk in obese children. (26)(27) The clinical application of this index needs to be explored further before making any recommendations for its routine use.

Dyslipidemia

Dyslipidemia, as defined by an increase in TGs and a decrease in HDL cholesterol, is found in children with obesity and insulin resistance and is an important criterion for the diagnosis of MetS. Insulin resistance and resultant hyperinsulinemia appear to increase the transcription of genes for lipogenic enzymes in the liver and stimulate the production of TGs. Elevated TGs in association with low HDL cholesterol has been shown to be a marker for small dense low-density lipoproteins (LDLs) in obese children. A TG/HDL cholesterol ratio of 3 or greater is associated with a markedly higher concentration of small LDLs than a ratio of less than 3. (28) The small dense LDL particles are very

atherogenic and may confer an added risk for CVD in obese children with MetS. (29)

Hypertension

Elevated blood pressure is an important component of the MetS and one of the most modifiable risk factors for CVD. Although understanding the effects of obesity and insulin on blood pressure has been difficult, there does appear to be a direct effect of hyperinsulinemia on blood pressure in children and adolescents. Studies not only have shown a direct correlation between fasting insulin and blood pressure in children and adolescents, but the level of insulin was predictive of blood pressure 6 years later. (30) This has been ascribed to various mechanisms, including sympathetic nervous system activity, sodium retention by the kidney, and insulin-stimulated smooth muscle growth. There also is a strong association between childhood hypertension and the development of MetS in adulthood. (31)

Glucose Intolerance and Type 2 Diabetes

Insulin resistance is well documented in obese children and is believed to be a normal reaction of tissues to maintain adequate insulin sensitivity against increased fat deposition. In some individuals with insulin resistance, B-cell function deteriorates and subsequently insulin decreases, which leads to progression from insulin resistance to glucose intolerance and T2D. Glucose intolerance is defined as either impaired fasting glucose or impaired glucose tolerance. Most individuals with glucose intolerance have either impaired fasting glucose or impaired glucose tolerance but not both. The Expert Committee on the Diagnosis and Classification of Diabetes Mellitus categorizes impaired fasting glucose as equal to or greater than 100 mg/dL (5.6 mmol/L) but less than 126 mg/dL (7.0 mmol/L) and impaired glucose tolerance as a 2-hour oral glucose tolerance test value equal to or greater than 140 mg/dL (7.8 mmol/L). Diabetes is defined by the American Diabetes Association as meeting any 1 of 4 criteria in the presence of symptoms of hyperglycemia or 1 of 4 criteria on two separate occasions in the absence of symptoms: hemoglobin A1c equal to or greater than 6.5%, fasting glucose equal to or greater than 126 mg/dL (7.0 mmol/L), 2-hour oral glucose tolerance test value equal to or greater than 200 mg/dL (11.1 mmol/L), or a random glucose value equal to or greater than 200 mg/dL (11.1 mmol/L). Not all individuals with insulin resistance develop glucose intolerance, and although children and adolescents with glucose intolerance are at higher risk for developing T2D, not all progress to diabetes. T2D is an additional CVD risk factor for individuals with MetS. Given the concern for adverse outcomes in individuals with T2D, it is imperative to monitor obese children with glucose intolerance regularly for signs and symptoms of overt diabetes such as polyuria, polydipsia, polyphagia, and weight loss.

Nonalcoholic Fatty Liver Disease

NAFLD is an important metabolic complication in the obese pediatric population. It includes a range of liver conditions from asymptomatic steatosis to nonalcoholic steatohepatitis to advanced fibrosis with cirrhosis. The intrahepatic fat accumulation that is apparent in this disease is believed to be associated directly with insulin resistance and, therefore, is also strongly associated with MetS. Children with a diagnosis of NAFLD often have many clinical features that overlap with MetS, increasing their risk for CVD. Definitive diagnosis can be difficult and requires a liver biopsy, but elevated aminotransferase values in an obese child should prompt the clinician to investigate further for NAFLD.

Polycystic Ovary Syndrome

Polycystic ovary syndrome (PCOS) is a common disorder affecting obese adolescent girls that is characterized by hyperandrogenism and associated with insulin resistance. Adolescent girls with PCOS have an increased risk of MetS independent of obesity or insulin resistance, (32) and the combination of PCOS and MetS may increase the risk for CVD and T2D more than just MetS alone. (33) Young women with PCOS should be screened routinely for the components of MetS and impaired glucose metabolism.

Inflammatory Markers

Obesity is associated with a proinflammatory state. Adipocytes, especially visceral adipocytes, respond to excess lipid stores by secreting increased amounts of inflammatory cytokines, thus triggering an inflammatory cascade. Levels of several circulating inflammatory markers, including interleukin-6, tumor necrosis factor-α, and C-reactive protein (CRP), have been shown to be elevated in obese children. (34) The marker most commonly used to assess systemic inflammation is CRP. High-sensitivity CRP, in particular, is associated with increased cardiovascular risk and is used for CVD risk stratification in adults. CRP has been shown in children and adolescents to be associated with insulin resistance and the components of MetS and, therefore, may be an additional risk factor in obese children. (35)(36) However, the exact relationship between CRP and MetS is not well delineated, and longitudinal data on its predictive importance in children are lacking.

SCREENING

Children who have MetS that continues into adulthood have a severalfold higher risk of CVD and T2D. (30)(37) Given the ongoing obesity epidemic, it is critical for clinicians to identify overweight and obese children who are at high risk for CVD and T2D. Once identified, children with MetS should be tracked and treated using a systematic, patient-centered medical home model that focuses on chronic disease management.

Although no specific screening guidelines exist for MetS in children, the evidence-based 2007 American Academy of Pediatrics (AAP) Expert Committee recommendations propose screening for several of the CVD risk factors that encompass the components of MetS in overweight and obese children. (38) Physical examination should include pulse, blood pressure, and a search for signs commonly associated with obesity, such as hepatomegaly (NAFLD) and acanthosis nigricans (associated with insulin resistance). Laboratory testing is recommended based on the patient's BMI percentile and any known risk factors for CVD, such as hypertension, dyslipidemia, a strong family history of diabetes, or other obesity-related disease. A fasting lipid profile should be obtained in children who have no risk factors with a BMI between the 85th and 94th percentiles. A fasting lipid profile, serum alanine transaminase and aspartate transaminase assessment, and fasting blood glucose should be obtained for children with a BMI between the 85th and 94th percentiles and risk factors. Children with a BMI above the 95th percentile should have the same tests plus measurement of blood urea nitrogen and creatinine. In addition, the summary report from 2011 NHLBI Expert Panel states "The presence of obesity should prompt specific evaluation for all other cardiovascular risk factors, including family history of premature CVD, hypertension, dyslipidemia, DM, and tobacco exposure." (39)

TREATMENT

The optimal strategies for treating MetS in children and adolescents are yet to be determined. Currently, treatment of childhood MetS focuses on several areas that include weight reduction through dietary modification and increased physical activity and disease-specific management of its various components.

Weight reduction or, in younger children, a decrease in BMI percentile, is a critical component of MetS treatment. Even a small reduction in BMI percentile can have beneficial effects. However, before engaging a patient and family in a weight reduction program, clinicians should assess them for readiness to change. This information can guide the degree of intervention and may help the clinician avoid investing excess time and energy in patients who are not ready for change. For patients and families who are ready, lifestyle changes have been shown to reduce weight and improve many of the components of MetS. Dietary recommendations continue to focus on a moderately reduced calorie intake while maintaining a well-balanced diet. Obese children with the components of MetS should be engaged in comprehensive behavioral modification programs that focus on nutrition and physical activity. Interventions that offer more contact hours (>26 hours) have more success with weight loss over both the short and long term. (40) The recent US Preventive Services Task Force Recommendations found "adequate evidence that multi-component, moderate- to high-intensity behavioral interventions for obese children and adolescents aged 6 years and older can effectively yield short-term (up to 12 months) improvements in weight status." (41). Because of the high prevalence of depression and mood disorders in obese children, such treatment programs also should actively screen for mental health disorders and offer appropriate behavioral health resources.

An increase in physical activity, independent of a change in weight status, may be an important treatment strategy for children with MetS. A 2011 systematic review found evidence supporting a conclusion that increased physical activity improved insulin sensitivity in obese children. (42) However, relatively few of the reviewed studies specifically examined the impact of physical activity on MetS as a whole. Adult studies have shown up to a 30% reduction in MetS after supervised aerobic training. (3)

Appropriate management of the diseases that are part of MetS, such as hypertension, dyslipidemia, and impaired glucose homeostasis, is essential to decrease the risk of CVD in affected children. Management should be evidence-based and follow the guidelines outlined by the 2011 NHLBI Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents. (39)

For adolescents with MetS in whom lifestyle management of obesity has not resulted in improvements, less traditional methods have been employed. Medications have been suggested as adjunctive therapy. Several small-scale studies have reported beneficial effects on body weight and insulin resistance from the use of metformin in obese children and adolescents with hyperinsulinemia. (43)(44)(45) These studies have not examined overall resolution of MetS and have documented only short-term efficacy. Further large-scale trials are needed before making recommendations involving the routine use of metformin in children with MetS.

Bariatric surgery has become a successful method of reducing weight and eliminating a number of comorbid conditions in both the morbidly obese adult and pediatric populations. Pediatric data are still limited, but results to date have been consistent with those observed in the adult population. A recent study that specifically assessed the status of MetS in morbidly obese adolescents pre- and postlaparoscopic gastric banding noted a 59% decrease in the presence of MetS after 6 months and a 69% decrease after 12 months. (46) Further studies with long-term data on pediatric patients undergoing bariatric surgery are still necessary to determine if the initial decrease seen in CVD risks translates to decreased morbidity in adulthood.

CONCLUSION

MetS in children and adolescents continues to be a challenge for clinicians, patients, and families. Although further research is needed to gain a better understanding of this syndrome, clearly childhood obesity can dramatically impair cardiovascular health, and the potential long-term impacts on health are very concerning. Given the large percentage of children and adolescents who are at high risk for the development of T2D and CVD, clinicians must screen all overweight and obese patients for the components of MetS and provide guidance during health supervision visits about the importance of exercise and healthy eating habits to prevent the condition from developing. Clinicians should identify individuals who have components of MetS and not focus on whether they meet a certain definition. For patients who have components of MetS, the primary care clinician should address these components using a chronic disease model that includes close, regular follow-up visits. In addition, it is imperative that clinicians use the primary care setting to begin counseling patients and their caregivers on healthy eating and exercise habits before overweight and obesity occur, employing guidelines set forth by the AAP for the treatment and prevention of obesity. These include limiting screen time to 2 hours daily; increasing fruit and vegetable consumption; limiting fast food; monitoring portions; and avoiding grazing, eating in front of the TV, and skipping meals. By establishing healthful habits early, clinicians can help prevent the development of obesity, MetS, and other related comorbidities in the pediatric population.

Summary

- On the basis of strong research evidence, metabolic syndrome (MetS) has increased in prevalence along with the increase in the prevalence of obesity.
- On the basis of expert opinion and consensus, the definitions of MetS in both adults and children have been challenged, leading to a unifying definition of MetS in adults but still leaving the definition of the condition unclear in children. The only group that has established a definition of MetS in children is the International Diabetes Federation. (2)(4)
- On the basis of strong research evidence, risk factors for MetS can be both genetic and environmental, including gender, ethnicity, obesity, inactivity, smoking, menarchal age, nonalcoholic fatty liver disease (NAFLD), and fructose consumption. (10)(11)(13)(14)(15)(18)(19)(20)
- On the basis of consensus, the components of MetS, as defined in the pediatric population, include obesity (determined by waist circumference and body mass index), hypertension, dyslipidemia, and either impaired fasting glucose, impaired glucose tolerance, or frank type 2 diabetes. (12)
- Based on research evidence, inflammation and NAFLD have been linked to MetS, and the presence of NAFLD portends greater risk for the development of MetS. (17)(34)
- On the basis of consensus and expert opinion, no specific screening guidelines for MetS exist, but all obese children and adolescents should be screened yearly for MetS as well as other cardiovascular risk factors. (40)(41)
- On the basis of research evidence, expert opinion, and consensus, treatment of MetS involves weight loss as well as treatment of its individual components. (39)(40)

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1. The definition, epidemiology, risk stratification, and health outcomes of metabolic syndrome (MetS) require further clarification in both adult and pediatric populations. Nevertheless, research has clearly established that:
   A. Adults with MetS experience an elevated risk of cardiovascular disease.
   B. An age-independent definition of MetS is readily achievable.
   C. Central adiposity rates do not vary with age or ethnic background.
   D. Insulin resistance is unrelated to Sexual Maturity Rating.
   E. Lipid profiles in healthy individuals are constant across the lifespan.

2. MetS was first recognized near the beginning of the 20th century. It describes the health-threatening combination of dyslipidemia, abnormal glucose regulation, central adiposity, and hypertension. Although it has had many different names, MetS has endured. An older name for the syndrome, which Kaplan coined to help define and diagnose it, is:
   A. Insulin sensitivity syndrome.
   B. Poverty syndrome.
   C. Syndrome XY.
   D. The deadly quartet.
   E. Vague syndrome.

3. Which of the following overweight but otherwise healthy 9-year-old children has the highest risk of developing MetS as a sedentary adult?
   A. African American female.
   B. African American male.
   C. Caucasian female.
   D. Caucasian male.
   E. Hispanic male.

4. Obesity in childhood is a risk factor for the development of MetS, type 2 diabetes, and adverse cardiovascular outcomes. A 10-year-old Caucasian boy comes in for his annual health supervision visit. You determine that his body mass index (BMI) has risen in 1 year from the 84th to the 97th percentile for age. His blood pressure is 103/61 mm Hg. Results of laboratory studies include: fasting blood glucose of 90 mg/dL (5 mmol/L), serum alanine aminotransferase of 25 U/L (0.42 μkat/L), serum aspartate aminotransferase of 26 U/L (0.43 μkat/L), and total cholesterol of 160 mg/dL (4.14 mmol/L). His actual risk for cardiovascular disease as an adult is best reflected in his current:
   A. Blood pressure.
   B. Fasting blood glucose.
   C. Serum aminotransferases.
   D. Serum cholesterol.
   E. Visceral fat accumulation.

5. You are examining an obese 10-year-old African American boy. His father is obese and is currently being treated for type 2 diabetes mellitus and hypertension. The boy's BMI is at the 97th percentile for age and his central adiposity is readily apparent. His height has increased 2 inches in the past year and he continues to track along the 75th percentile. The remainder of his physical examination findings are unremarkable. You are planning to discuss the need for weight reduction and increased physical activity with the boy and his father. According

REQUIREMENTS: Learners can take *Pediatrics in Review* quizzes and claim credit online only at: http://pedsinreview.org.

To successfully complete 2016 *Pediatrics in Review* articles for *AMA PRA Category 1 Credit*^{TM}, 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. 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.

This journal-based CME activity is available through Dec. 31, 2018, however, credit will be recorded in the year in which the learner completes the quiz.

to the American Academy of Pediatrics, what type of laboratory investigations would be most appropriate at this time?

A. Defer studies until next year.
B. Fasting blood glucose, fasting lipid profile, serum aminotransferases.
C. Fasting blood glucose, fasting lipid profile, serum aminotransferases, blood urea nitrogen, serum creatinine.
D. Fasting lipid profile alone.
E. Hemoglobin A1C, fasting lipid profile, thyrotropin and free thyroxine, serum aminotransferases.

Parent Resources from the AAP at HealthyChildren.org

- https://www.healthychildren.org/English/health-issues/conditions/obesity/Pages/Your-Overweight-Child-and-the-Risk-of-Disease.aspx
- Spanish: https://www.healthychildren.org/spanish/health-issues/conditions/obesity/paginas/your-overweight-child-and-the-risk-of-disease.aspx

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