CLINICAL REPORT Guidance for the Clinician in Rendering Pediatric Care

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The Metabolic Syndrome in Children and Adolescents: Shifting the Focus to Cardiometabolic Risk Factor Clustering

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Metabolic syndrome (MetS) was developed by the National Cholesterol Education Program Adult Treatment Panel III, identifying adults with at least 3 of 5 cardiometabolic risk factors (hyperglycemia, increased central adiposity, elevated triglycerides, decreased high-density lipoprotein cholesterol, and elevated blood pressure) who are at increased risk of diabetes and cardiovascular disease. The constellation of MetS component risk factors has a shared pathophysiology and many common treatment approaches grounded in lifestyle modification. Several attempts have been made to define MetS in the pediatric population. However, in children, the construct is difficult to define and has unclear implications for clinical care. In this Clinical Report, we focus on the importance of screening for and treating the individual risk factor components of MetS. Focusing attention on children with cardiometabolic risk factor clustering is emphasized over the need to define a pediatric MetS.

INTRODUCTION

Cardiovascular disease (CVD) risk factor clustering has been well recognized for decades in both children and adults, but it was not until 1988 when Gerald Reaven described a specific clustering of cardiometabolic risks as "syndrome X" that the concept that evolved into "the metabolic syndrome" (MetS) was born. Reaven's syndrome X was an explanatory framework to understand the myriad effects of hyperinsulinemia and insulin resistance on physiology, not a diagnostic category.[1] His formulation of syndrome X described mechanisms underlying insulin resistance and the effects of hyperinsulinemia on glucose and lipid metabolism, blood pressure, and coronary artery disease risk. Over time, the risk factors associated with syndrome X grew to include other factors, such as central obesity, microalbuminuria, abnormalities in fibrinolysis, and inflammation.[1,2] Dissemination of the

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concept of syndrome X promulgated the idea of insulin resistance causing a constellation of factors that increased diabetes and CVD risk.

After publication of Reaven's landmark article, clustering of CVD risks was variously described as insulin resistance syndrome, syndrome X, and the dysmetabolic syndrome. In 2001, the National Cholesterol Education Program (NCEP) Adult Treatment Panel III (ATP III) coined the term "metabolic syndrome" to describe the presence of any 3 of 5 particular risks: hyperglycemia, hypertriglyceridemia, central adiposity, elevated blood pressure, and low high-density lipoprotein cholesterol (HDL-C). Research on MetS has increased dramatically since 2001, with more than 1000 articles per year published on this topic since 2006. MetS has been associated with both diabetes and CVD in adults. Insulin resistance, obesity, aging, inflammation, hormonal factors, sedentary lifestyle, dietary sugar intake, and genetics all have been implicated in the pathogenesis of MetS.[1–6]

Despite this vast literature, MetS remains a controversial topic in pediatrics for several reasons. First, MetS is challenging to define in pediatric populations. MetS in adults consists of a subset of at least 3 out of 5 risk factors: increased central adiposity, elevated triglycerides, decreased HDL-C, elevated blood pressure, and hyperglycemia. In adults, MetS (the presence of 3 or more of these risks) is predictive of CVD and type 2 diabetes mellitus.[3,7] In children and adolescents, however, many different definitions of MetS have been proposed (Table 1), and there is no clear consensus on which to use.[8,9] In addition, because the majority of MetS cases in childhood and adolescence occur in individuals with obesity, the utility of MetS as a construct above and beyond obesity itself has been questioned.[8,10–12] Regardless of the definition used, there is no uniform way to treat MetS when it is diagnosed other than weight management. Instead, each risk factor must be treated individually, which leaves pediatricians wondering whether they should (and how to) define MetS in their patients. Our purpose with this Clinical Report is to provide an overview of the current state of the field in relation to MetS in pediatric populations. Given its name recognition, MetS terminology will be used in this report. However, the clinical relevance of MetS lies in its ability to be used as an organizational framework for the identification of cardiometabolic risk factor clustering. Recommendations for pediatricians regarding how to approach the concept of MetS in children and adolescents are provided.

PATHOPHYSIOLOGY

The pathophysiologic origins of MetS are in insulin resistance, a physiologic state associated with obesity. Insulin binds to receptors on multiple tissues of the body, including liver, fat, muscle, and blood vessels, with a myriad of effects (Fig 1). Insulin secreted by the pancreatic β cells travels to the liver via the portal system, where it normally acts to suppress glucose production. In the insulin-resistant state, the suppression of hepatic glucose production is impaired, resulting in abnormal glucose homeostasis. However, even in an insulin-resistant state, not all insulin effects are impaired; there is "selective" insulin resistance.[17] For unknown reasons, insulin action stimulating hepatic lipogenesis is not impaired, causing the release of free fatty acids and triglycerides into the circulation. This results in dyslipidemia and ectopic adipose deposition.[6] The MetS dyslipidemia pattern consists of elevated triglycerides, low HDL-C, relatively normal low-density lipoprotein cholesterol, and increased small, dense low-density lipoprotein particles,[18] which are known to be atherogenic and to increase cardiovascular risk.

One of the major clinical consequences of insulin resistance is adipose tissue dysfunction, or "adiposopathy." As adipose expands, the cells hypertrophy, and these hypertrophic adipose cells are more resistant to insulin's action to suppress lipolysis. These large adipocytes also secrete increased proinflammatory chemokine monocyte chemoattractant protein-1.[19] As stated previously, insulin action stimulating fatty acid synthesis is preserved, promoting adipose tissue expansion. MetS is characterized by increased visceral as opposed to subcutaneous fat as well as ectopic fat deposited in abnormal locations, such as the liver.[6] Ectopic fat distribution results in the release of adipocytokines, causing a state of low-grade inflammation, with increased inflammatory factors, such as plasminogen activator inhibitor-1, tumor necrosis factor α, interleukin 6, and acute phase reactants such as high-sensitivity C-reactive protein and fibrinogen.[20] The endoplasmic reticulum acts as a nutrient sensor. Energy or nutrient excess can trigger endoplasmic reticulum stress, resulting in activation of inflammatory pathways, increased reactive oxygen species production, and mitochondrial dysfunction.[21] Some emphasize the importance of the inflammatory state, with insulin resistance being a consequence of inflammation.[20] Irrespective of what is the consequence or cause, insulin resistance, ectopic fat distribution, and inflammation are all key pathologic players in the components of MetS.

DEFINING MetS IN ADULTS

At least 5 health organizations have created clinical criteria for

TABLE 1 Comparison of Key Published MetS Definitions for Pediatric and Adult Populations

	Pediatric Definitions			Adult Definitions	
	Cook et al[13]	de Ferranti et al[14]	Zimmet et al[9] (IDF Definition Ages 10–16)	Alberti et al[15] (IDF Definition Ages 16+)	Grundy et al[16] (AHA/NHLBI Consensus Statement)
Defining criterion	≥3 criteria	≥3 criteria	Obesity and at least 2 of remaining 4 criteria	Obesity and at least 2 of remaining 4 criteria	≥3 criteria
Obesity	WC ≥90th percentile (age and sex specific, NHANES III)	WC >75th percentile	WC ≥90th percentile or adult cutoff if lower	WC ≥94 cm for white men and ≥80 cm for white women	WC ≥102 cm (≥40 in) in men and WC ≥88 cm (≥35 in) in women
Glucose intolerance	Fasting glucose ≥110 mg/dL (≥6.1 mmol/L)	Fasting glucose ≥110 mg/dL (≥6.1 mmol/L)	Fasting glucose ≥100 mg/dL (>5.6 mmol/L) or known type 2 diabetes mellitus	Fasting glucose ≥100 mg/dL (>5.6 mmol/L) or known type 2 diabetes mellitus	Fasting glucose ≥100 mg/dL or drug treatment of elevated glucose
Dyslipidemia (triglycerides)	Triglycerides ≥110 mg/dL	Triglycerides ≥100 mg/dL	Triglycerides ≥150 mg/dL	Triglycerides ≥150 mg/dL (1.7 mmol/L) or treatment of elevated triglycerides	Triglycerides ≥150 mg/dL (1.7 mmol/L) or treatment of elevated triglycerides
Dyslipidemia (HDL-C)	HDL-C ≤40 mg/dL (1.03 mmol/L; all ages and sexes, NCEP)	HDL-C ≤50 mg/dL (1.3 mmol/L)	HDL-C <40 mg/dL (1.03 mmol/L)	HDL-C <40 mg/dL (1.03 mmol/L) in men and <50 mg/dL (<1.29 mmol/L) in women or specific treatment of low high-density lipoprotein	HDL-C <40 mg/dL (1.03 mmol/L) in men and <50 mg/dL (1.3 mmol/L) in women or on drug treatment of reduced HDL-C
High BP	BP ≥90th percentile (age, sex, and height specific)	BP >90th percentile	Systolic BP ≥130 mm Hg or diastolic BP ≥85 mm Hg or treatment of previously diagnosed hypertension	Systolic BP ≥130 mm Hg or diastolic BP ≥85 mm Hg or treatment of previously diagnosed hypertension	Systolic BP ≥130 mm Hg or diastolic BP ≥85 mm Hg or treatment of previously diagnosed hypertension

BP, blood pressure; HDL-C, high-density lipoprotein cholesterol; WC, waist circumference.

defining either the insulin resistance syndrome or MetS among adults: the World Health Organization (WHO),[22] the NCEP's ATP III,[23] the American Association of Clinical Endocrinologists/American College of Endocrinology,[24] the International Diabetes Federation (IDF),[25] and the American Heart Association (AHA) in conjunction with the National Heart, Lung, and Blood Institute (NHLBI) of the National Institutes of Health.[16] A detailed comparison of these definitions is beyond the scope of this report. The definitions differ significantly, with most but not all requiring a minimum number of risk factors, some excluding those with a diagnosis of type 2 diabetes mellitus, and most differing in the types, required number, and specific cut points for the criterion risk factors. As noted previously, in 2001, the NCEP first developed the "any 3 of 5" risk criteria definition. The 5 risks included in the NCEP ATP III definition are (1) hyperglycemia, (2) hypertriglyceridemia, (3) low HDL-C, (4) hypertension, and (5) increased waist circumference. In 2005, the AHA/NHLBI modified this definition by revising the glucose cut point down and adding allowance for drug treatment of dyslipidemia and impaired fasting glucose. That same year, the IDF introduced its "worldwide" definition of MetS,[25] lowering the waist circumference cut points for certain racial and ethnic groups and putting greater emphasis on abdominal obesity by making it a necessary criterion for MetS diagnosis.

Although the AHA/NHLBI and IDF definitions have many similarities, there are important differences between them with respect to cut points of the various component risks (Table 1). The differences in these definitions have important implications for case identification. For example, an adult with hyperglycemia, hypertriglyceridemia, and low HDL-C but with a normal waist circumference would have MetS according the NCEP but not the IDF. In contrast, a person with hyperinsulinemia, low HDL-C, and obesity would have MetS according to the WHO criteria but not per the NCEP guidelines because hyperinsulinemia is not a risk factor used by the NCEP. These differences between definitions lead to differences in their prognostic ability and case identification.[3,26] For example, in one of the earliest articles on MetS in adolescents, Goodman et al[27] found a greater than twofold

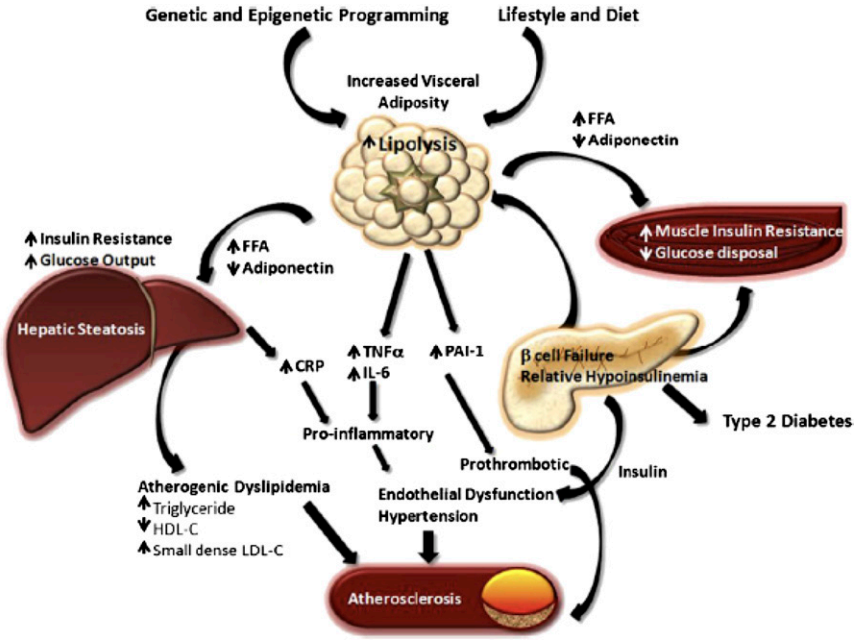

FIGURE 1

Proposed mechanisms for the clustering of MetS traits and the increased risk of type 2 diabetes mellitus and CVD. CRP, C-reactive protein; FFA, free fatty acids; IL-6, interleukin 6; LDL-C, low-density lipoprotein cholesterol; PAI-1, plasminogen activator inhibitor 1; TNF α, tumor necrosis factor α. (Reprinted with permission from Samson SL, Garber AJ. Metabolic syndrome. *Endocrinol Metab Clin North Am.* 2014;43[1]:23.)

difference in the prevalence of WHO-defined MetS compared with NCEP-defined MetS in the Princeton School District Study.

DEFINING MetS IN PEDIATRICS

Definitions of MetS for children and adolescents have been even more varied than the definitions used for adults. The first researchers addressing MetS in a pediatric population focused on adolescents.[13,14,27–29] Even researchers that used the same database (the National Health and Nutrition Examination Survey III) had divergent prevalence estimates, ranging from 4.2%[13] to 9.2%,[14] a difference of greater than twofold. More than 40 different pediatric definitions of MetS have been used.[30] In 2007, the IDF brought together an international group of experts and developed a consensus definition.[9] In that report, the IDF recommended that pediatric MetS be based on the adult IDF definition but that it should only apply to children 10 years and older and that, among those between 10 and 16 years of age, the 90th percentile for waist circumference or adult cut point (whichever was lower) should define abdominal obesity. The IDF stated that for those 16 years and older, adult criteria should apply. Two years later, the AHA published its scientific statement on MetS in children and adolescents,[8] which emphasized the need to identify pediatric cardiometabolic risks and noted that only some of these were found in the criteria used to define MetS. The AHA did not include a definition of MetS for use in pediatric populations and indeed made particular note of the limitations of adapting definitions derived for adults to pediatric populations. To date, there is no clear consensus on whether MetS should be defined in pediatric populations and, if defined, which definition to use.[8,9]

The controversy over the utility of MetS in pediatrics goes beyond its definition. In adulthood, MetS predicts CVD and type 2 diabetes mellitus.[2,31] Malik et al[7] found that compared with those who have no MetS risk factors, the hazard ratio for coronary heart disease mortality was 2.87 for those with MetS without diabetes and 5.02 for those with MetS and diabetes. Depending on the definition used, Laaksonen et al[3] found that the odds ratio (OR) for men with MetS developing diabetes in the 4-year follow-up period was 5 to 8.8. Data from the Princeton Prevalence and Follow-up Studies demonstrated that pediatric MetS predicted adult MetS with an OR of 9.4 and adult type 2 diabetes mellitus with an OR of 11.5; this study arbitrarily used 2 different MetS definitions.[32] However, the utility of the syndrome in adolescents has also been questioned, given studies indicating instability of the definition when transitioning from adolescence to adulthood.[10,33–35] Large proportions of children defined as having MetS during childhood do not meet the diagnostic criteria on follow-up 3 to 6 years later.[10,34] In multiple observational longitudinal studies, although population-level prevalence has increased, within-person variation in presence or absence of MetS has been large, with many studies showing 50% or more of MetS-positive subjects becoming MetS-negative over time, whether that be with short-term (~3 weeks)[36] or longer-term (9 years)[35] follow-up. The instability was not related to change in weight status.[35] Thus, MetS is highly unstable throughout childhood. A child can meet the criteria at 1 point in time and not meet it at another point in time, and it is unclear whether this variation represents an improvement or deterioration in health status.[35]

Ethnic or racial differences in rates of obesity and MetS components also exist. Hispanic and black non-Hispanic children demonstrate higher rates of obesity than white non-Hispanic

children across age categories.[37] However, similar to adults, black non-Hispanic youth demonstrate lower rates of dyslipidemia,[38] greater insulin resistance, and higher blood pressure than white non-Hispanic and Hispanic youth.[8] Hispanic children have increased dyslipidemia (elevated total cholesterol, low HDL-C, or high non–HDL-C) compared with black non-Hispanic and white non-Hispanic children.[39] Because of the racial and/or ethnic differences in dyslipidemia, and despite increased prevalence of obesity and greater risk for type 2 diabetes mellitus, black non-Hispanic youth have a lower prevalence of MetS than white non-Hispanic or Hispanic youth,[28] which can lead to an underestimation of cardiometabolic risk.[40]

Given the absence of a consensus on the definition of MetS, the unstable nature of MetS, and the lack of clarity about the predictive value of MetS for future health in pediatric populations, pediatricians are rightly confused about MetS. The high prevalence of pediatric obesity and limited resources to address the obesity problem in pediatrics reveal the need to identify a subset of children with obesity or who are overweight and at increased risk for cardiovascular and metabolic complications beyond the physical complications of obesity. Although obesity is, in general, associated with increased mechanical stress and potential orthopedic complications, not all children with obesity manifest metabolic dysregulation as a consequence of their obesity. Identifying children with multiple metabolic derangements allows targeting of focused interventions toward children at the highest risk for cardiometabolic disease. Thus, rather than focus on defining MetS in youth, the American Academy of Pediatrics (AAP) recommends that pediatricians focus on the concept of cardiovascular risk factor clustering and associated risk factor screening. This concept is especially important because the Bogalusa Heart Study demonstrated substantially increased development and severity of atherosclerotic lesions associated with increased clustering of atherosclerotic CVD risk factors.[41] Furthermore, the AAP recommends that pediatricians do not need to use cut points based on MetS definitions. The MetS construct identifies multiple component risk factors that appear to cluster together and whose pathologic origins arise from insulin resistance and adiposopathy. Much of the discrepancy in definitions derives from differences in these thresholds. Moreover, for many risk factors, the risk is a continuum. Continuous variables may be more reliable in predicting young adult risk from early adolescence and might help determine future risk.[42] A number of researchers have used factor analysis of MetS components to develop a continuous risk score measure to identify children at higher risk for developing a chronic disease related to MetS into adulthood.[43,44] Although such work currently is not clinically applicable, with advances in research and development of clinically applicable risk score guidelines, a continuous risk score approach may be created for use in general pediatric practice in the future. At the moment, however, risk factor screening and identification of youth with MetS risk factor abnormalities allow providers to target scarce resources to children at increased cardiometabolic risk, particularly those with multiple component abnormalities. Such screening and associated treatment (see below) is an important component of preventive pediatric care.

DETERMINANTS OF METABOLIC RISK FACTOR CLUSTERING

There are multiple determinants of the 5 risk factors currently used to define MetS in adolescents or in adults. Familial influences include shared genetic and environmental factors, which combine to make heritability of these individual MetS components strong. Twin and family studies have revealed substantial familial aggregation of MetS risk factors. Family history of atherosclerotic CVD is a well-known genetic risk for high lipid concentrations, high blood pressure, and high glucose concentration.[45] Obesity, at the core of MetS, is itself highly heritable through shared genetic and environmental factors. If a parent is obese, his or her child is twice as likely to be obese, and conversely, more than half of children with obesity have at least 1 parent with obesity.[46]

Several MetS risk factors have origins during the prenatal and early postnatal period. The presence of maternal gestational diabetes; low birth weight, especially with rapid catch-up growth; infant feeding practices (restrictive and pressuring); and early adiposity rebound are associated with later development of obesity and other MetS components.[8,9] Throughout childhood and adolescence, socioeconomic factors and parental obesity also affect development of the 5 MetS component risk factors.[8,9]

Health behavioral factors also are associated with and can predict the presence of MetS risks, particularly obesity, in youth. Specific behaviors include short duration of sleep, excessive screen time, specific dietary factors, low physical activity, and tobacco smoke exposure.[47,48] Even after controlling for demographic factors, the number of hours a child spends each day in front of a screen is directly related to BMI and calories consumed per day and inversely related to minutes of physical activity.[49] New AAP policies discourage screen use except for video chatting before 18 to 24 months of age and recommend that pediatricians help families develop a Family Media Use Plan specific for each child that ensures entertainment screen time does not displace healthy behavioral factors, such as adequate sleep and physical activity. (The AAP

Family Media Use plan is available at www.healthychildren.org/MediaUsePlan.)[50,51] Physical activity is beneficial for weight management, and it has also been negatively associated with MetS and factors that overlap with MetS, independent of weight status. Short sleep duration inversely predicts cardiometabolic risk in adolescents with obesity, even when controlling for degree of obesity and levels of physical activity.[52] Some studies in adults and children have found a U-shaped relationship between sleep duration and cardiometabolic risk, with either too much or too little sleep being problematic.[53–55] Although exact mechanisms remain unknown, factors related to inflammation, oxidative stress, and antioxidant status are thought to mediate the sleep duration–cardiometabolic health relationship.[56]

Among the multiple dietary factors associated with obesity, lack of whole grain and fiber intake is most strongly correlated with the development of insulin resistance even after adjusting for BMI.[57] Higher consumption of fruits and vegetables, which contribute dietary fiber as well as micronutrients, is known to reduce risk of atherosclerotic CVD, an end point of MetS in adulthood.[58]

COMORBIDITIES

Comorbidities of MetS, insulin resistance, and obesity include nonalcoholic fatty liver disease (NAFLD), polycystic ovary syndrome (PCOS), obstructive sleep apnea (OSA), and mental health disorders. NAFLD represents a spectrum of damage to the liver, from steatosis to fibrosis and cirrhosis. NAFLD is defined by having liver fat >5% liver weight (not caused by alcohol consumption) and is strongly associated with insulin resistance.[59] Although there is not a consensus about testing frequency among professional organizations, current AAP recommendations, published in 2007, suggest biannual screening for NAFLD by measuring aspartate aminotransferase and alanine aminotransferase among children with BMI at or greater than the 85th percentile.[60]

The risk for PCOS is increased in girls with obesity. PCOS is characterized by hyperandrogenism (elevated free testosterone), menstrual irregularities and/or ovulatory dysfunction, and polycystic ovaries. Obesity and insulin resistance (with resulting hyperinsulinemia) are associated with PCOS as well as with increased free testosterone and ovarian and adrenal hyperandrogenism. The increased luteinizing hormone pulse frequency and increased luteinizing hormone–follicle-stimulating hormone ratio observed in PCOS (although not part of diagnostic criteria) result in increased androgen secretion from theca cells in the ovaries.[61]

Obesity and type 2 diabetes mellitus have been associated with worse mental health, including increased risk for anxiety and depression.[60,62,63] Chronic disease is a well-recognized stressor, and obesity is associated with social stigma and discrimination. Thus, obesity and diabetes screening guidelines often recommend mental health screening, as do the current AAP recommendations for children who are overweight or children with obesity.[60]

OSA is a condition characterized by complete or partial obstruction of the upper airway and is associated with obesity. OSA causes sleep fragmentation, intermittent hypoxia, and increased negative airway pressure in the thoracic cavity.[64] Obesity increases the risk for OSA because of enlarged soft tissues in and around the airway as well as decreased lung volumes because of increased abdominal fat.[64] Interestingly, OSA is independently associated with CVD, insulin resistance, type 2 diabetes mellitus, and endothelial dysfunction and is related to hypertension. Moreover, studies have revealed that treatment of OSA improves multiple components of MetS, such as blood pressure, lipids, and glucose control.[65,66] As in MetS, the comorbid conditions mentioned here share associations with insulin resistance and obesity, which potentially play a role in their pathology as well.

SCREENING

Given the complexity of defining MetS in adolescence, the evolving understanding of MetS, and the lack of consensus regarding definition, it is not surprising that there is no consensus as to whether or how MetS should be identified in pediatric populations, particularly adolescents. However, there is a consensus among the American Diabetes Association and AHA that obesity prevention and treatment in childhood and adolescence should be the first-line approach to alleviating cardiometabolic risk.[67] Published guidelines recommend that primary care clinicians perform annual obesity screening for all children by using BMI and refer children with BMI at or greater than the 95th percentile to a comprehensive weight-management program.[60,68,69] In practice, it is sometimes not possible to refer all such children to a comprehensive program. Pediatricians can develop the expertise and resources necessary to manage these patients themselves, especially when no comprehensive program exists in their catchment area.

In addition to obesity screening with BMI, children should be screened annually for elevated blood pressure in primary care by using auscultatory methods for obtaining blood pressure.[69] Nonfasting non–HDL-C or fasting lipid screening should be performed in all children between the ages of 9 and 11 years.[69] This approach will help to identify children with genetic forms of dyslipidemia

and will also identify those with high triglycerides and low HDL-C because of metabolic problems. Although insulin resistance is the key to the etiology of MetS, the Insulin Resistance Consensus group did not recommend screening for insulin resistance with fasting insulin.[70] Screening for glucose intolerance and type 2 diabetes mellitus is important because hyperglycemia is one of the MetS component risks. Risk factors for type 2 diabetes mellitus include overweight or obesity, belonging to a high-risk racial and/or ethnic group, family history of type 2 diabetes mellitus, physical signs of insulin resistance (acanthosis nigricans), PCOS, dyslipidemia, or hypertension. Methods of screening have included the oral glucose tolerance, hemoglobin A1c, fasting glucose, and random glucose tests.[67,71] The authors of the expert committee obesity guidelines from 2007 recommended that children 10 years or older (or pubertal) with a BMI at or greater than the 85th percentile and 2 additional risk factors be screened with a fasting glucose test every 2 years.[60]

TREATMENT

Treatment of MetS involves both behavioral and pharmacotherapeutic interventions aimed at reducing obesity, glucose abnormalities, hypertension, and dyslipidemia. Once identified, pediatricians should treat these component risk factors by using current best practices (summarized or referenced later in this report) to reduce future risk for cardiometabolic disease.

Obesity treatment is grounded in lifestyle modification, and early treatment of obesity in childhood and adolescence is recommended as the first-line approach to reducing cardiometabolic risk.[60,67,69] Obesity is a more stable trait than MetS, more likely to be present at multiple points in time, and more likely to persist into adulthood. Furthermore, treatment of obesity and treatment of MetS components share many common elements, and interventions that improve 1 condition are likely to ameliorate the other. Meta-analyses of pediatric lifestyle intervention studies have revealed that dietary modification and increased physical activity decrease weight and also improve cardiometabolic risk factors such as dyslipidemia and hypertension.[68,72] Decreased obesity also results in decreases in insulin resistance and inflammatory markers.[73] Good evidence suggests that moderate- to high-intensity weight-loss programs combined with behavioral counseling, negative energy balance diets, and increased physical activity, can successfully address obesity.[68] Combining diet and exercise is more effective at achieving decreases in BMI than either intervention in isolation. No researchers have demonstrated evidence for recommending a specific dietary plan because appropriate restriction of calories is the main issue. Low-glycemic-load diets and low-carbohydrate diets may be more effective than low-fat diets in reducing weight and improving CVD risk, at least in the short-term.[69] Specific lifestyle targets that have demonstrated efficacy in reducing BMI include substitution of sugar-sweetened beverages with water, milk, or artificially sweetened beverages[74–77] and reducing television or screen time.[77–79] It is important to note that achieving a normal BMI is not necessary to decrease cardiometabolic risk. Studies have revealed that weight loss and improvement in BMI by 5% to 10% can have metabolic benefits.[80]

The mechanisms that explain the association between lifestyle modification and effects on MetS components are not fully understood. Dietary interventions that lower intake of simple sugars may reduce stimulus for insulin production. Reducing mitochondrial substrate by caloric restriction, particularly lipogenic substrates,[6] could also be effective. In addition, increased dietary fiber intake decreases the glycemic load to the liver. Increased physical activity improves mitochondrial efficiency, which is preventive against MetS,[6] and improves insulin sensitivity. As activity levels increase, inflammatory cytokines and markers of oxidative stress decrease, insulin sensitivity increases, endothelial function improves, and HDL-C concentrations increase.[81] Time spent in moderate to vigorous physical activity is inversely associated with a MetS continuous risk score, and those who spent at least 88 minutes per day in moderate to vigorous physical activity were least likely to have MetS.[82]

Pharmacotherapeutic options to treat obesity in children are limited.[83] Currently, only orlistat has an FDA indication for weight loss in adolescents as young as 12 years of age. Orlistat, an intestinal lipase inhibitor, results in a mean 3% weight loss (on the basis of starting weight) at 6 months.[84,85] Adverse effects include steatorrhea and flatulence, making it difficult to use in practice. Insurance coverage for orlistat is variable.[85] Bariatric surgery in adolescents is effective[86] and reserved for the most severely affected.

Treatment of MetS risk factor components is well described in several evidence-based guidelines. The authors of the NHLBI Expert Panel guidelines, published in 2011, provide evidence-based guidance for dietary and pharmacotherapeutic treatment of dyslipidemia and hypertension in children and adolescents. The type of dyslipidemia associated with MetS usually is treated with lifestyle intervention only, not with pharmacologic agents.[69] Treatment of insulin resistance involves lifestyle modification only. Anecdotally, some providers are using metformin to

treat children and adolescents who have insulin resistance with normal glucose concentrations. Although some studies have revealed beneficial effects of metformin on BMI and homeostatic model assessment of insulin resistance score in adolescents with insulin resistance, these trials were only 6 months in length and involved small numbers of subjects.[87] Thus, metformin is not currently recommended for treatment of insulin resistance.[70] No consensus exists in the pediatric diabetes community as to treatment of prediabetes in children, other than lifestyle management. Children found to have prediabetes or type 2 diabetes mellitus on screening can be referred to a pediatric endocrinologist for management and/or monitoring.[88] It is also critical to screen for and address any comorbid conditions, such as PCOS or OSA, which often share the causal link of insulin resistance with MetS component risk factors.

SUMMARY

MetS evolved from Reaven's concept of syndrome X, a tool used to understand the many effects of insulin resistance on human physiology. In adults, a diagnosis of MetS is associated with an increased risk for CVD and diabetes. In pediatrics, there remain many unanswered questions regarding the definition of and utility of the diagnosis of MetS. Therefore,

1. although pediatricians can use MetS as an organizing frame, the focus for clinical screening and treatment should be on cardiometabolic risk factors, many of which cluster together and are associated with obesity;
2. pediatricians should not focus the specific levels of cardiometabolic risk factors from the multitude of MetS definitions because the risk lies on a continuum and in the context of the whole child;
3. by following current recommendations to screen for and treat obesity, glucose abnormalities, hypertension, and dyslipidemia, pediatricians are addressing the major MetS-associated cardiometabolic risks in pediatric populations;
4. identification of children with multiple component risks enables pediatricians to apply their most intensive intervention efforts to the children and adolescents in greatest need of risk reduction; and
5. increasing awareness of comorbid conditions such as NAFLD, mental health disorders, PCOS, and OSA enables pediatricians to address and refer to specialists, as needed.

Continued efforts to prevent and treat obesity and its associated metabolic abnormalities among children and adolescents and vigilant attention to the early diagnosis of diabetes provide the pediatrician with the most evidence-based methods for addressing cardiometabolic risk factor clustering (MetS) in adolescence.

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ABBREVIATIONS

AAP: American Academy of Pediatrics
AHA: American Heart Association
ATP III: Adult Treatment Panel III
CVD: cardiovascular disease
HDL-C: high-density lipoprotein cholesterol
IDF: International Diabetes Federation
MetS: metabolic syndrome
NAFLD: nonalcoholic fatty liver disease
NCEP: National Cholesterol Education Program
NHLBI: National Heart, Lung, and Blood Institute
OR: odds ratio
OSA: obstructive sleep apnea
PCOS: polycystic ovary syndrome
WHO: World Health Organization

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