

The Metabolic Syndrome: Look for It in Children and Adolescents, Too!

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The third National Cholesterol Education Program Adult Treatment Panel (ATP III)¹ defines the metabolic (or insulin resistance) syndrome as the presence in an individual of at least three of the following five risk factors: central or abdominal obesity, hypertriglyceridemia, hypertension, low HDL cholesterol, and high fasting glucose levels. The metabolic syndrome is a major risk factor for cardiovascular disease (CVD) and type 2 diabetes. Although insulin resistance is also a key risk factor for CVD and type 2 diabetes, hyperinsulinemia is not included as a potential risk factor by the ATP III; its definition was designed for use in clinical practice with adults, and insulin levels are not usually assessed in clinical practice.

IDENTIFYING THE METABOLIC SYNDROME IN CHILDREN AND ADOLESCENTS

Components of the metabolic syndrome are present in children and adolescents as well as in adults,²⁻⁵ but there is no agreement on the definition of the metabolic syndrome as a whole in this population. Some researchers use definitions that follow the ATP III guidelines (having at least three or five components),⁶⁻⁸ whereas others have added an elevated fasting insulin level as a component of the syndrome.¹

This variability of definition is at least in part because of the growth and

developmental changes that occur during childhood and adolescence and complicates the choice of cut-off points for risk factors. Norms for several of the factors, such as blood pressure, height, weight, and BMI, differ between males and females and are age-specific in that most increase normally with age.

In addition, overweight is defined differently in children than it is in adults. Because children are growing and thus changing in height and weight over time, it is not possible to provide a simple cut-point to define overweight or obesity, as is done for adults. In fact, the recent Centers for Disease Control and Prevention (CDC) definitions of overweight in children do not even use the term "obesity," in part to avoid labeling children with a pejorative term. The preferred terms are "overweight" (defined as a BMI \geq 95th percentile for age and sex) and "at risk of overweight" (reserved for children with a BMI \geq 85th percentile but $<$ 95th percentile for age and sex).⁹

Central obesity, considered a key component of the metabolic syndrome, is a good example of the problem of defining risk levels in children. Although there are accepted risk cut points for waist circumference in adults, there are no accepted normative values for children. Some researchers have used BMI z-score, a measure of overall overweight, rather than a more specific indicator of central overweight, such as waist circumference.⁷ Still others have used data from children in their studies to define age- and sex-specific percentiles, using the 90th percentile as a cut point for increased waist circumference.⁶ More recently, Katzmarzyk et

al.¹⁰ developed risk-based, age- and sex-specific thresholds for increased waist circumference in their study of almost 3,000 African-American and white children aged 5–18 years. They used receiver operator characteristic curves to develop thresholds that predicted the presence of three or more of the other metabolic syndrome risk factors, such as low HDL cholesterol, high glucose levels, or hypertension.

PUBERTY AND THE METABOLIC SYNDROME

Puberty presents a unique challenge to insulin-glucose homeostasis. During puberty, insulin resistance is increased, and insulin sensitivity is reduced in both nondiabetic and diabetic children. This insulin resistance is normally compensated for by increased insulin secretion.¹¹⁻¹³ Caprio et al.¹² suggested that the insulin hypersecretion they found in adolescents may reflect the puberty-associated increase in the amount of circulating growth hormone. Travers et al.¹⁴ found that changes in insulin sensitivity during puberty were sex-dependent and suggested that they are related to changes in body composition.

Body fat, blood pressure, and lipids are all affected by puberty. The percentage of body fat increases strikingly in females through adolescence, but changes in body fat in males are not consistent.¹⁵ Systolic blood pressure also rises with pubertal stage independent of age, particularly in girls.¹⁶⁻¹⁸ Lipids vary by pubertal stage in youth.¹⁹⁻²¹ For example, total cholesterol drops in mid-puberty and begins rising toward adult levels at the end of puberty.^{21,22} These

lipid changes through puberty complicate the definition of cut-off points for dyslipidemia in youth. In addition, the changes in body fat, blood pressure, and lipid profiles during puberty may be influenced by the decrease in physical activity and changes in eating habits that are commonly seen during adolescence.^{23,24} Thus, puberty is a crucial time for the development of the metabolic syndrome, and yet it is a difficult time during which to identify it.

PREVALENCE OF THE METABOLIC SYNDROME IN CHILDREN AND ADOLESCENTS

The prevalence of the metabolic syndrome varies by the definitions used for the components and by the weight status of the subjects. Cook et al.,⁶ who studied children and adolescents 12–19 years of age in the third National Health and Nutrition Examination Survey (NHANES III) data set, reported a prevalence of 4.2%. Investigators from the Bogalusa Heart Study²⁵ reported a prevalence of 3.6% in youth 8–17 years of age. However, researchers reported much higher prevalence rates in children who are overweight or obese.^{6,7} In a study of 490 subjects aged 4–20 years, 89% of whom had a BMI \geq 97th percentile, the prevalence of the metabolic syndrome in moderately obese subjects (defined as a BMI *z*-score of 2.0–2.5) was 38.7%, whereas almost half (49.7%) of severely obese subjects (defined as a BMI *z*-score $>$ 2.5) had the syndrome.⁷ In another study among children and adolescents 8–19 years of age, the prevalence was 6.8% in those who were at risk for overweight (85–95th percentile of BMI) and 28.7% in those who were overweight (BMI \geq 95th percentile).⁸

The prevalence of the metabolic syndrome in youth may vary by sex and ethnicity, as it does in adults, but data on this are conflicting. In a national multiethnic study, the metabolic syndrome was significantly more prevalent in males (6.1%) than in females (2.1%),⁶ but other researchers reported no signifi-

cant sex differences.⁸ Cook et al.⁶ reported the prevalence of the metabolic syndrome was higher in whites (4.8%) and Mexican Americans (5.6%) than in African Americans (2.0%). Weiss et al.⁷ also found that white children were at greater risk for metabolic syndrome than were African-American children when they used the same cut points for lipids. However, when they used race-specific norms for lipids, the prevalence of the metabolic syndrome risk did not differ between African-American and white youth, likely because the African-American youth had better lipid profiles. More large, multiethnic studies with boys and girls are needed to learn whether the ethnic and sex differences seen in the metabolic syndrome in adults are also present during childhood and adolescence.

RELATIONSHIPS AMONG METABOLIC SYNDROME COMPONENTS

Overweight and increased plasma insulin values are key components of the metabolic syndrome.^{26,27} Bao et al.²⁷ studied $>$ 1,500 individuals in the Bogalusa Heart Study initially when they were 5–23 years of age and then again 8 years later. They found that subjects with consistently high insulin levels had 36 times more overweight, 2.5 times more hypertension, and 3 times more dyslipidemia than those with low insulin levels. Other studies also support a link among obesity, hyperinsulinemia, and other metabolic syndrome components in youth.^{4,7,28} These links indicate the importance of clarifying the origins of insulin resistance while examining factors such as energy intake and output, which may be modified via diet and physical activity. Lifestyle habits certainly influence obesity and most of the metabolic syndrome components.

Not only are overweight and hyperinsulinemia associated, but the two factors are also related to dyslipidemia, especially low HDL cholesterol and high triglyceride levels.^{4,8,29,30} In several studies, overweight youth had higher serum insulin (with normal glucose), higher

triglycerides and blood pressure, and lower HDL cholesterol than nonoverweight subjects.^{4,7}

Hypertension is recognized as an important component of the metabolic syndrome in adults, but its role in the syndrome in children and adolescents is not clear. Few studies of youth have examined the relationship of blood pressure and insulin values, and their results are conflicting. Some investigators found a positive association between insulin levels and blood pressure,^{8,31,32} whereas others have not.^{33,34}

Definitions of the metabolic syndrome often include impaired glucose tolerance or high fasting glucose, now called prediabetes.³⁵ However, in several studies, overweight children had low HDL cholesterol and high triglycerides and insulin, but normal glucose levels,^{4,7} suggesting that glucose intolerance may develop later than other syndrome abnormalities. Thus, it may be important to assess insulin levels as well as glucose in children, because many with the cluster of metabolic syndrome factors will have normal glucose levels.

Several longitudinal studies of adults have demonstrated that hyperinsulinemia can precede the development of type 2 diabetes by $>$ 10 years.^{36,37} Beck-Nielsen and Groop³⁸ proposed a three-stage model for the development of type 2 diabetes. Stage 1 includes fasting hyperinsulinemia with normal or slightly increased blood glucose. Stage 2 is characterized by prediabetic glucose intolerance with insulin resistance, and stage 3 is development of type 2 diabetes. Unfortunately, many of the macrovascular changes associated with diabetes and related to CVD begin in stages 1 and 2, well before diagnosis. Thus, if the metabolic syndrome is identified early, the hope is that lifestyle changes can prevent the development of prediabetes or full type 2 diabetes.

IMPLICATIONS FOR PRACTICE Screening

Primary care providers must be aware that, as in adults, risk factors for CVD

and type 2 diabetes may cluster in children and adolescents. That is, children who have one risk factor are likely to have others as well, especially if they are overweight. Early identification of children at risk will be crucial to the prevention of chronic disease during childhood and in later life.

At present, there are no guidelines for the screening and management of children or adolescents for the metabolic syndrome when defined as a separate entity, but there is guidance related to its individual components and the prevention of atherosclerosis or type 2 diabetes.^{39–41} The components of the metabolic syndrome and the risk factor levels that indicate increased risk are shown in Table 1.

Overweight in children is a key component of the metabolic syndrome and is recognized as a risk factor for type 2 diabetes and CVD.^{39,40} Childhood overweight has increased in all age groups;⁴²

the prevalence in adolescents almost tripled during the time between the NHANES of 1971–1974 and that of 1999–2000.⁴³ The most recent national data show that in 1999–2002, 16.0% of all children aged 6–19 were overweight; the prevalence of overweight was significantly higher in non-Hispanic black (20.5%) and Mexican-American (22.2%) than in non-Hispanic white youth (13.6%).⁴³

BMI is the most widely used and efficient measure of overweight in children, and age- and sex-specific norms are available for children from 2 to 20 years of age. Tables that allow for easy identification of BMI in youth are available on the CDC website at www.cdc.gov/nccdphp/dnpa/bmi/00binaries/bmi-tables.pdf, and charts for plotting a child's BMI over time may be found at www.cdc.gov/nchs/about/major/nhanes/growthcharts/clinical_charts.htm. All children should be

screened yearly for overweight per recommendations of the American Academy of Pediatrics (AAP).⁴⁴

A child or adolescent who is overweight is likely to have multiple risk factors, and a thorough screening for any and all factors is necessary. Findings from an initial screening may necessitate further investigation. For example, children or adolescents with a diagnosis of hypertension will need to be screened for secondary causes of hypertension. The appropriate screening for secondary comorbidities in children is detailed in a recent report by the National High Blood Pressure Program (NHBPP) Working Group.⁴⁵ A link to the reference is available online at www.nhlbi.nih.gov/health/heart/hbp/hbp_ped.htm.

Biennial screening for diabetes with a fasting plasma glucose is recommended by the American Diabetes Association³⁵ for children who are either overweight or at risk for overweight (\geq 85th percentile for age and sex) and have at least two of the following risk factors: family history of type 2 diabetes in first- and second-degree relatives; membership in certain race/ethnic groups (Native Americans, African Americans, Hispanic Americans, Asians/South Pacific Islanders); and signs of insulin resistance or conditions associated with insulin resistance (acanthosis nigricans, hypertension, dyslipidemia, polycystic ovary syndrome). This testing should begin by the age of 10 years, or sooner if puberty has already begun.

American Heart Association (AHA) recommendations add the assessment of fasting insulin to the evaluation of children at risk for insulin resistance.⁴⁰ The AAP Expert Committee on Evaluation and Treatment of Obesity in Children recommends measurement of both fasting glucose and insulin.⁴¹ In addition, measurement of glucose and insulin may also be warranted in girls who enter puberty early. Girls with early menarche tend to have excess body fat and higher insulin starting in early childhood and have a higher prevalence of the metabolic syndrome in young adulthood.⁴⁶

Table 1. Definitions of Risk for Metabolic Syndrome Components

Component	Risk Category Definition
BMI ⁹	Not at risk: < 85th percentile* At risk of overweight: \geq 85th to < 95th percentile* Overweight: \geq 95th percentile*
HDL cholesterol ⁷³	Normal: > 35 mg/dl Low: \leq 35 mg/dl
Triglycerides ⁶	Normal: \leq 110 mg/dl High: >110 mg/dl
Insulin ⁴⁰	Normal: < 15 μ U/l Borderline high: 15–20: μ U/l High: > 20 μ U/l
Glucose ⁵	Normal: <100 mg/dl Impaired Glucose Tolerance: 100–125 mg/dl Diabetes: \geq 126 mg/dl
Systolic Blood Pressure ⁴⁵	Normal: < 90th percentile† Prehypertension: \geq 90th to < 95th percentile† Hypertension: \geq 95th percentile†
Diastolic Blood Pressure ⁴⁵	Normal: < 90th percentile† Prehypertension: \geq 90th to < 95th percentile† Hypertension: \geq 95th percentile†

*All percentiles specific to age and sex; †All percentiles appropriate for age and sex and are available in Table 3 and 4 of Ref. 45.

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Children with a family history of early CVD or parental hypercholesterolemia (≥ 240 mg/dl) should be tested for dyslipidemias including low HDL cholesterol, high LDL cholesterol, and hypertriglyceridemia with a fasting lipid profile per AHA recommendations.⁴⁰ In addition, the AHA recommends screening for children with any of the following conditions: “hypertension, smoking, sedentary lifestyle, obesity, excessive alcohol intake, . . . medications associated with hyperlipidemias . . . or disease states such as diabetes mellitus or nephritic syndrome.” Similar recommendations have been made by the AAP Expert Committee.⁴¹

Finally, children who are overweight must also be screened for hypertension. The NHBPP Working Group⁴⁵ recommends blood pressure screening for all children > 3 years of age at all medical visits. A cuff of appropriate size should be used for measuring blood pressure in children. The recommendations state that the appropriate cuff has “an inflatable bladder width of 40% of the arm circumference at a point midway between the olecranon and the acromion” and “the cuff bladder length should cover 80–100% of the circumference of the arm.”

As in adults, elevated blood pressure on three separate occasions is necessary for diagnosis of prehypertension or hypertension. Cut points for prehypertension and hypertension in children are found in Table 1. In addition, the NHBPP Working Group⁴⁵ recommends that overweight children with prehypertension and all children with hypertension be screened with a lipid profile and fasting glucose because of the probability of risk factor clustering.

Management and Prevention

Ten and McLaren⁴⁷ state that “attention must be urgently given to the children who are becoming more obese and more insulin resistant with time.” Currently, there are no practice guidelines for management of the metabolic syndrome in children, but recommenda-

tions exist for management of components of the syndrome.

The AAP Expert Committee⁴¹ has outlined goals for childhood weight maintenance or loss that are dependent on the child’s age and weight and the presence of any secondary complications. It recommends that children ≤ 7 years of age with a BMI ≥ 95 th percentile for age and sex maintain their weight unless they have secondary complications, such as hypertension; it recommends weight loss to ≤ 85 th percentile for those with secondary complications. Weight loss is also recommended for older children who have a BMI “between the 85 and 95th percentile and a nonacute secondary complication of obesity” and for any child > 7 years of age with a BMI ≥ 95 th percentile. Lifestyle changes in diet, physical activity, and sedentary activity are recommended as first-line therapy for overweight, hypertension, insulin resistance, and dyslipidemia by several expert authors.^{40,41,45}

Physical inactivity fosters the development of obesity, the metabolic syndrome abnormalities,^{48,49} and diabetes.^{50,51} Exercise can improve responses to a 2-hour glucose tolerance test⁵² and improve insulin sensitivity even without weight loss,⁵³ apparently through activation of cellular glucose uptake independent of insulin.⁵⁴ Several recent studies have shown that physical activity is also associated with lower fasting insulin and greater insulin sensitivity in children.^{55,56} Exercise can also improve blood pressure, both directly and by increasing insulin sensitivity.⁵⁷

Fewer studies have reported the association of cardiovascular fitness with the metabolic syndrome in adults or youth. In their study of $\sim 1,500$ youth aged 8–15 years, Ribeiro et al.⁵⁸ found that male children and adolescents in the lowest quartile for physical activity had more metabolic syndrome risk factors, such as high blood pressure and hypercholesterolemia.

Recommendations for dietary intake in children and adolescents include con-

sumption of at least five fruits and vegetables a day; increased consumption of whole grains; avoidance of sweets, sodas, and other empty-calorie foods; and a dietary fat content of no more than 30% of total calories per day. These guidelines are available online at www.health.gov/dietaryguidelines/dga2000/document/frontcover.htm.

Unfortunately, studies verify that the diet of adolescents is poor.^{59–61} A longitudinal study of children 6–13 years of age showed that drinking excessive amounts of sweetened drinks (defined as > 12 oz/day) was associated with a higher daily energy intake, greater weight gain, and displacement of milk from the diet.⁶⁰ Investigators in England reported that a school-based program to decrease the consumption of carbonated beverages was successful in producing a small reduction in the amount of consumption of these drinks and was associated with a reduction in the number of overweight children.⁶¹ The AAP issued a statement in January 2004 expressing concern over the negative health implications of providing soft drinks in schools. It recommended that school districts adopt a “clearly defined, district-wide policy that restricts the sale of soft drinks.”⁶²

The AAP Expert Committee⁴¹ provides a comprehensive summary of strategies for helping families of overweight children and stresses the need for health professionals to assess the parents’ and adolescents’ readiness to participate in lifestyle changes or treatment. The strategies include suggestions for helping parents develop parenting skills that promote healthy eating behaviors in children and ideas for increasing physical activity for children and families, such as walking to school or decreasing time spent watching television.

Suggestions are also provided to promote dietary change, for example, use of the “stoplight diet” developed by Epstein and Squires.⁶³ In this dietary plan, children and families may choose foods from three categories that correspond to the three colors on a stoplight: “green” foods may be eaten anytime; “yellow”

foods are to be consumed less often; and “red” foods should be avoided. Families may also benefit from referral to a registered dietitian for more in-depth dietary counseling.

Guidelines are also available that go beyond encouragement for lifestyle change. The AHA Expert Committee recommends a diet low in saturated fat and cholesterol for the initial management of childhood hypercholesterolemia, but it also advises referral to physicians with experience managing lipid disorders in children for children whose cholesterol levels remain elevated.⁴⁰ Medications for children with hypercholesterolemia may include bile acid sequestrants, such as cholestyramine or cholestipol,⁴¹ and research on the use of statins for more severe familial hypercholesterolemia is promising.^{64,65} The management of hypertension in children and adolescents is described in detail by the NHBPP Working Group.⁴⁵ Other than encouragement of increased physical activity and healthy dietary choices, and careful monitoring for related complications, there are no currently accepted recommendations for the management of increased glucose levels and hyperinsulinemia in children who are otherwise well. An exception would be the child with a fasting glucose measure that is indicative of diabetes (> 126 mg/dl).

This child should be referred to the care of a pediatric endocrinologist.⁴¹ Children with multiple components of the metabolic syndrome may benefit from referral to specialists who have experience with the management of obesity, hypertension, dyslipidemia or insulin resistance.⁴⁰

The best approach to decreasing the incidence of metabolic syndrome in children may be prevention.^{40,45,66} Primary care providers can encourage children, adolescents, and their parents to adopt lifestyle changes such as healthier diets, increased physical activity, and decreased sedentary activities. For example, parents can be encouraged to simply decrease the time their children and ado-

lescents spend watching TV. Dennison et al.⁶⁷ found that in children, both increased TV watching and the presence of a TV in the bedroom is associated with an increased risk of having a BMI \geq 85th percentile for age and sex. In addition, watching TV while eating meals has been associated with a less nutritious dietary intake in children.⁶⁸

Primary care providers can also help in the effort to prevent obesity in children by supporting public policy changes that promote increased physical activity, such as the planning of neighborhoods that provide safe activity areas and increases in physical education (PE) time in schools. Decreased neighborhood safety is associated with decreased physical activity in children.⁶⁹ PE programs in schools provide a mechanism for reaching a great number of children on a daily basis to promote increased physical activity and to provide education on healthier lifestyle choices. Programs that provide health education and modify PE in elementary and middle schools to increase noncompetitive physical activity and decrease down time have been shown to improve fitness and cardiovascular risk profiles,^{70,71} but few schools provide daily PE. Only 6.4% of middle schools and 5.8% of high schools provided such an opportunity in one nationwide study.⁷²

CONCLUSION

At present, the metabolic syndrome is found in ~ 4–5% of children and adolescents in population-based studies,⁶ and in up to 49% of severely obese youth.⁷ This presents a serious threat to the current and future health of American youth. The metabolic syndrome and its many consequences, including CVD and type 2 diabetes, will continue to increase unless we can find ways to prevent obesity and the metabolic syndrome in childhood and adolescence.

We must be diligent in screening for and identifying children and adolescents with metabolic syndrome and supporting and encouraging them and their families through healthy lifestyle changes. Prima-

ry care providers can join other health care providers in developing and testing primary prevention strategies that will change the environment to provide access to safe places where our children can be active and play and to promote an atmosphere conducive to making healthier food choices.

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