Dysmetabolic Syndrome: Multiple Risk Factors for Premature Adult Disease in an Adolescent Girl

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ABSTRACT. The clinical diagnosis of dysmetabolic syndrome in an adult defines a patient with abnormal glucose metabolism (or diabetes), hypertension, hyperlipidemia, and obesity. This disorder accelerates atherosclerosis and significantly raises the risk for cardiovascular events. With the marked rise in the prevalence of obesity in childhood, obesity-linked risk factors are being expressed at young ages. The case of a 12-year-old girl with dysmetabolic syndrome is described and discussed. Emerging clinical data now indicate that the presence of 1 risk factor for cardiovascular disease in an overweight child should prompt screening for additional clinical abnormalities, with the aim of finding treatable disorders. *Pediatrics* 2002;110(1). URL: http://www.pediatrics.org/cgi/content/full/110/1/e14; *obesity, hypertension, insulin resistance, diabetes, lipids, children.*

ABBREVIATIONS. BMI, body mass index; HDL, high-density lipoprotein; LDL, low-density lipoprotein.

The concept that atherosclerosis is a clinical problem that requires attention and intervention by pediatricians has received little consideration because symptomatic atherosclerotic cardiovascular disease in childhood has been extremely rare. Cardiovascular disease, with target organ and vessel injury, is generally a consequence of dyslipidemia, hypertension, diabetes, and smoking.[1] Full clinical expression of dyslipidemia, hypertension, and diabetes generally occurs in middle to late adulthood and is related to a combination of genetic and environmental/behavioral factors. Because of gene–environment interaction, the origins of hypertension, diabetes, and dyslipidemia are now considered to begin in childhood and are often related to obesity.[2–4] In many individuals, there is overlap in the expression of these disorders.

The presence within an individual patient of elevated blood pressure, abnormalities in glucose metabolism, alterations in plasma lipid concentration, and abdominal obesity has been clinically described as the insulin resistance syndrome or a mixed metabolic syndrome. This condition is now termed dysmetabolic syndrome.[5] The syndrome emanates from a core abnormality of insulin resistance, wherein there is a suboptimal response to insulin action in cellular glucose regulation. As a consequence, there is compensatory hyperinsulinemia, along with the other alterations in plasma lipids, glucose concentration, and blood pressure level.[6] Dysmetabolic syndrome is now considered a clinical diagnosis and has an *International Classification of Diseases, Ninth Revision* code of 277.7. A recent analysis of existing United States population data indicates that the prevalence of dysmetabolic syndrome is at least 23.7% in adults, with rates increasing with age. The current rate may actually be greater because of the recent rise in the rates of obesity.[7] In the evaluation and treatment of adults with 1 of the components such as hypertension, diabetes, or lipid abnormalities, there is now emphasis on assessing and managing the related disorders, as well as controlling the presenting condition.[8,9]

The following case describes a child with dysmetabolic syndrome and demonstrates the detection in childhood of substantial and multiple risk factors for cardiovascular disease, raising the question of when risk factors become disease. Until the most recent decade, little attention has been given to this issue in childhood because of its rarity. Thus, pediatricians are less familiar with the importance of a comprehensive work-up and need for aggressive management.[2,3]

CLINCIAL CASE DESCRIPTION

A 13-year-old white girl was referred for evaluation of high blood pressure. Previous blood pressure measurements averaged 122/72 mm Hg, and the child's parents were told that her blood pressure measurements were elevated for her age. She denied having any current symptoms but had previous complaints of headache and of abdominal pain relieved by ranitidine. Menarche was at 12 years of age, and her menstrual periods were described as normal. Birth weight was 7 lb 14 oz (3580 g). The mother had gestational diabetes during this pregnancy. The patient's diet included fruits and nonfat milk, but she also consumed several glasses of soda or sugar-sweetened punch daily, as well as processed foods. She did not participate in sports or other physical activities. She denied tobacco or alcohol use. She did not take any other prescribed or over-the-counter medications. The mother, 52 years of age, had type 2 diabetes and elevated blood lipids. The mother reported her weight at 190 lb and height at 5 feet 7 inches. (She subsequently had a myocardial infarction during the course of the child's follow-up.) The father, 51 years of age, had hypertension and elevated lipids. The father's reported weight was 209 lb and height was 5 feet 8 inches. A 31-year-old brother was in good health. A 14-year-old brother was stated to be healthy but with elevated lipids. The maternal grandfather died at 62 years of age from a myocardial infarction. The maternal grandmother died at 67 years of age after a stroke. The paternal grandfather had hypertension and died at the age of 77 years from cancer.

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On physical examination, the girl's weight was 67.1 kg (95th percentile), her height was 149.3 cm (10th percentile), and her calculated body mass index (BMI) was 30.1 kg/m^2 (>97th percentile). Her blood pressure was measured at 122/80 mm Hg. The 95th percentile for blood pressure at her age and height is 120/79 mm Hg. Her leg blood pressure was 126/82 mm Hg. The ratio of her waist:hip circumference was 0.98. Complete physical examination including assessment of the head, eyes (with fundoscopic examination), ears, nose, throat, neck, skin, heart, chest, abdomen, and neurologic system was normal. She was Tanner stage IV. Heart rate was 108 beats per minute. An office urinalysis, including microscopic sediment examination, was normal.

The child had blood pressure measurements that approximated the 95th percentile for age and height on 2 separate measurements. She was also obese and had a strong family history of cardiovascular diseases. She then had a complete blood count and a serum chemistry panel. In view of the family history, she also had fasting plasma lipids measured and an oral glucose tolerance test. The results of these tests are presented in Table 1.

At a visit 4 weeks later, her weight was unchanged. An average of 2 blood pressure measurements was 122/78 mm Hg. Her systolic blood pressure measurements had approximated the 95th percentile for age and height on 3 separate occasions, which meets the criteria for hypertension.[10] Her oral glucose tolerance test indicated the presence of impaired glucose tolerance[11] with marked hyperinsulinemia. Her high-density lipoprotein (HDL) cholesterol was low, and she had elevated serum triglyceride levels—a pattern consistent with the obesity-associated combined dyslipidemia.

The results of the girl's blood tests were reviewed with her and her parents. To determine whether there was any evidence of target organ injury related to the high blood pressure, an echocardiogram was recommended. Lifestyle changes were advised, including body weight control with diet modification to reduce her intake of sodium, refined sugars, and fat. She was also strongly encouraged to increase her physical activity. The echocardiogram reported her left ventricular mass (adjusted for height) at 42 g/m$^{2.7}$, a value that is at the reference cutpoint for left ventricular hypertrophy.[12]

Subsequent follow-up has shown improved weight control with a 5 mm Hg reduction in blood pressure, no change in blood lipids, and a reduction in BMI to under 30 kg/m^2.

CLINICAL DISCUSSION

This child had hypertension, obesity, impaired glucose tolerance with marked hyperinsulinemia, borderline left ventricular hypertrophy, and dyslipidemia. The dysmetabolic syndrome is the best clinical characterization of this child's multiple metabolic and hemodynamic abnormalities. There is a significant family history for all components of the syndrome, including diabetes and cardiovascular events. Obesity may either be the origin or the trigger of this constellation of clinical findings and risk factors. The leading question for the child and her family is the medical management of her overall clinical condition, including the types of intervention that are likely to provide benefit and succeed in modifying her disease risk. The treatment approach should attend to the range of related but distinct medical conditions.

TABLE 1. Patient's Blood Count, Oral Glucose Tolerance Test, and Plasma Lipid Concentration

Blood count		
Hemoglobin	13.9 g/dL	
White blood cells	5700 c/mL	
Platelets	310 000/mL	
Serum chemistry	Normal	
Oral glucose tolerance		
Glucose: fasting	116 mg/dL	
Insulin: fasting	38 uU/mL	
Glucose: 30′	186 mg/dL	
Insulin: 30′	298 uU/mL	
Glucose: 60′	177 mg/dL	
Insulin: 60′	436 uU/mL	
Glucose: 120′	150 mg/dL	
Insulin: 120	403 uU/mL	
Fasting plasma lipids		Normal values
Cholesterol	194 mg/dL	
HDL cholesterol	24 mg/dL	>40 mg/dL
LDL cholesterol	89 mg/dL	<130 mg/dL
Triglycerides	253 mg/dL	<150 mg/dL

Obesity

Although obesity was not this patient's primary complaint, obesity is known to increase risk for each of this child's clinical abnormalities including high blood pressure, abnormal lipid pattern, hyperinsulinemia, and impaired glucose tolerance.[13] This patient's weight is at the 95th percentile, with her height at the 10th percentile for age. Her calculated body mass index exceeds the 97th percentile for age, a level that places her in a high-risk group for complications of obesity. Modifying obesity in childhood has been shown to reduce hyperinsulinemia, lower blood pressure, and improve lipid abnormalities.[13,14]

The mainstay of obesity treatment is alteration of energy balance through lifestyle change. This involves intervention in dietary intake and increasing physical activity. In children and adolescents, family-based change is most successful, and it is important to engage the family in supporting lifestyle changes.[15] By adolescence, eating and activity patterns have become established and frequently children have taken over decision-making about food and activity. This patient's nutritional intake is typical of most adolescents favoring a high-carbohydrate diet, sweetened beverages, and a limited variety of foods. Dietary strategies should include emphasis on regular structured meals, increase in fiber and protein, and elimination of sugared beverages between meals. Snacking and overconsumption of "fast food" can sabotage adequate nutrition and should be discouraged.

The patient is also sedentary, with no regular physical activity. Additional history on time spent watching television, using the computer, and watching movies can be quantified. Time limits can be set on sedentary activities, and guidelines for participation in regular physical activity (walking, bicycling, swimming, rollerblading) can be given. Community resources can be investigated. A useful recommendation is participation in 30 to 60 minutes of large muscle activity at least 5 days a week.

Often, obese patients have increased motivation for change when significant medical issues are present; in this case the mother had a myocardial infarction during follow-up. Hypertension, hyperinsulinemia, and hyperlipidemia, all documented in this child, can improve with lifestyle changes. Measuring blood pressure, insulin/glucose and lipids, in addition to weight, as a way of monitoring progress is often reinforcing for patients and families. Specific weight-loss drugs are not recommended for children because of limited data on both efficacy and safety. Patients and families require reassurances that overall health and well-being are the goals of treatment,

and long-term change rather than more rapid approaches have the best chance of success.

Hypertension

The blood pressure level according to age and height that designates hypertension for this 12-year-old girl is 120/79 mm Hg. Her blood pressure on repeated measurement was 122/80 mm Hg. Therefore, her blood pressure measurements met the criteria for hypertension in childhood.[10] Her history and physical examination did not detect any findings to suggest an underlying, or secondary, cause for her hypertension. The normal urinalysis and normal plasma creatinine level make it unlikely that there is an underlying renal disorder causing hypertension in this child. Although patients with renal dysplasia or renal-vascular lesions can have a normal urinalysis and normal plasma creatinine, these lesions usually cause very severe blood pressure elevation, in the range of 20 mm Hg above the 95th percentile. The blood pressure elevation in this child just approximates the 95th percentile.

On the other hand, this child has several of the risk factors associated with primary or essential hypertension in the young. The degree of blood pressure elevation is mild, and she has a relatively high resting heart rate. She is obese as confirmed by her calculated BMI. A striking aspect of the evaluation is the very strong family history of hypertension, as well as of other cardiovascular disorders, and the history of cardiac events among her mother and grandparents. Together these characteristics fit best with childhood expression of essential hypertension. Treatment to lower the blood pressure is indicated for this child. If left untreated, the blood pressure level will remain elevated and trend to higher levels. An appropriate treatment goal is to lower her average blood pressure to less than the 90th percentile for age and height (<116/75 mm Hg).

The first steps in the treatment of children and adolescents with mild hypertension, in the absence of renal disease or type 1 diabetes, are nonpharmacologic approaches to achieve lifestyle changes. Efforts to achieve lifestyle changes in diet, physical activity, and weight control, to effect a reduction in her blood pressure are concurrent with those described above for treatment of obesity. Moreover, the results of the Dietary Approach to Stop Hypertension study[16] have demonstrated the benefits in blood pressure reduction from diets that are enriched with multiple nutrients. Therefore, a diet that is rich in fruits, vegetables, and low-fat dairy products would be appropriate for children with mild hypertension as well as adults. In addition, sodium intake should be moderated by avoidance of salted and processed food products. From the information provided on this child's current diet, these changes along with avoiding sugar-sweetened drinks could be sufficient to reduce both her body weight and her blood pressure.

If efforts to modify diet, reduce weight, and increase physical activity are not achieved and the blood pressure remains elevated, alternative treatments are appropriate. Despite limited data from clinical trials in children, there is sufficient clinical experience in the use of antihypertensive medications in children and adolescents to guide treatment. If this child has no reduction in her blood pressure level after 6 months of efforts to achieve lifestyle change, then additional treatment with medication to lower her blood pressure is indicated, particularly because borderline left ventricular hypertrophy is already present. A reasonable choice to begin therapy would be the angiotensin-converting enzyme inhibitors. A recent report on data from a large clinical trial in adults indicated that these agents may also have some effect in attenuating the progression to type 2 diabetes.[17]

Impaired Glucose Tolerance

The results of the oral glucose tolerance test in this child confirm that she has impaired glucose tolerance with marked hyperinsulinemia. She has insulin resistance and, particularly in view of the type 2 diabetes in the mother, this girl is likely to develop type 2 diabetes at a young age. The presence of diabetes in young women greatly augments the risk for early onset cardiac, renal, and vascular disease, and there are also substantial reproductive risks associated with pregnancy. In girls and young women, there is also often overlap of impaired glucose with the condition of polycystic ovary syndrome. This girl did not have evidence of hyperandrogenism, such as hirsuitism, acne, or reported menstrual irregularity. Acanthrosis nigricans, described as velvet-like thickening with increased pigmentation of the skin around the neck and axilla, can be found in obese girls and young women. Although absent in this child, the detection of this skin anomaly on physical examination in girls may be significant because of its association with impaired glucose tolerance and hyperandrogenism.

The extent to which significant underlying metabolic and endocrine disorders are present in obese children and adolescents is uncertain. From a recent study on glucose tolerance in obese children and adolescents by Sinha et al,[18] impaired glucose was detected in 25% of obese children and in 21% of obese adolescents. Basic research and some clinical data have detected possible regulatory roles of factors such as leptin and resistin.[19] The importance of these factors has not yet been translated to clinical practice. Screening for treatable conditions should be performed. Obese children, as well as children with acanthrosis nigricans (with or without obesity), should have fasting measurement of C-peptide, HbA_1C, and a lipid profile. Those with abnormal levels of these screening tests should have additional evaluation, including an oral glucose tolerance test.

Treatment is very important to prevent additional deterioration in glucose tolerance. There is now data in adults that demonstrate that nonpharmacologic interventions to achieve weight reduction and increase physical activity can improve glucose tolerance and attenuate the progression to diabetes.[20] The class of pharmacologic agents that have rationale for use in patients with severe insulin resistance and impaired glucose tolerance are the insulin sensitizers

such as Metformin. Other insulin-sensitizing agents are being used in adults. Additional data and clinical experience are needed to determine the specific indications and appropriate use of these agents in children and adolescents, particularly those with impaired glucose tolerance. In this case, insulin-sensitizing agents are not advised unless the child's glucose tolerance continues to deteriorate.

Dyslipidemia

This child's lipid pattern of low HDL cholesterol and elevated triglycerides reflects the typical dyslipidemia associated with overweight.[21] Pathologic studies have shown a relationship between HDL cholesterol measured in youth (or postmortem) to atherosclerosis, but the relationship is generally weaker than for low-density lipoprotein (LDL) cholesterol.[2,3] Because of its high-population prevalence, the high triglyceride/low HDL phenotype is commonly associated with myocardial infarction. An HDL cholesterol of <40 μg/dL is now considered a major coronary risk factor in adults.[21] Familial combined hyperlipidemia is often associated with obesity. This term encompasses a large number of metabolic and biochemical abnormalities all of which result in the characteristic high triglyceride/low HDL phenotype and also have elevated apolipoprotein B levels. They are usually but not always associated with obesity and/or insulin resistance. Assessment of parental lipid levels can be helpful and the diagnosis is made by finding multiple family members with abnormal lipoprotein profiles or elevated levels of apolipoprotein B.

The primary approach in treating the high triglyceride/low HDL cholesterol phenotype is controlling obesity by applying the Step I American Heart Association diet, and increasing physical activity. This diet is consistent with the dietary recommendations discussed above. Even modest weight reduction can improve the lipid profile.[13]

Current guidelines do not recommend pharmacologic treatment in childhood unless the patient is over 10 years of age and the LDL cholesterol is above 190 μg/dL (or above 160 μg/dL with 2 additional risk factors).[22] Medications commonly used in children are directed toward lowering LDL cholesterol. Niacin can lower triglycerides and raise HDL cholesterol, but is poorly tolerated. The fibrates have not been used in children and may have unacceptable long-term toxicity. Of the statins, atorvastatin has positive effects on HDL cholesterol and lowers triglycerides but is primarily used to lower LDL cholesterol. Drugs that effect bile acid reabsorption tend to raise triglycerides and occasionally lower HDL cholesterol. Thus, current pharmacologic options for improving this child's dyslipidemia are inadequate.

Summary

This child is representative of an extreme but increasingly common condition in the pediatrician's office: the child with multiple cardiovascular risk factors precipitated by excessive weight gain. The clinical profile had been previously considered a problem in middle age to older adults, but this pattern is detectable at much younger ages.[23,24] In adults, the dysmetabolic syndrome is defined as the presence of 3 or more of the following criteria: 1) abdominal obesity; 2) hypertriglyceridemia: >150 μg/dL; 3) low HDL (HDL cholesterol: < 40 μg/dL in men and <50 μg/dL in women; 4) high blood pressure $>130/85$ (in adults); and 5) high fasting glucose >110 μg/dL.[5] This case fulfills the criteria for the diagnosis of dysmetabolic syndrome and highlights the significant abnormalities that can be detected from a thorough medical evaluation on a child with 1 identified cardiovascular risk factor (hypertension) and obesity. Family history, lipid determination, echocardiography, and study of glucose metabolism uncovered a scenario where the development of full-blown diabetes mellitus and accelerated atherosclerosis are imminent.

Although most obese adolescents will not manifest all features of the dysmetabolic syndrome, many will have some positive findings on complete evaluation. A careful medical history of cardiovascular disease and physical examination can provide some guidance to determine which children with obesity require additional evaluations for medically treatable disorders linked with obesity. In general, when 1 risk factor is detected in an obese child, an evaluation for other risk parameters is indicated.

Current management strategies for treating obesity are difficult and require long-term efforts. Both public health and medical treatment strategies will be essential as the prevalence of childhood obesity continues to rise. Currently, the prevailing body of clinical information indicates that, in children and adolescents, the presence of 1 risk factor for cardiovascular disease in an overweight child should prompt screening for additional clinical abnormalities, with the aim of finding treatable disorders.

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