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Obesity, Insulin Resistance, Diabetes, and Cardiovascular Risk in Children

An American Heart Association Scientific Statement From the Atherosclerosis, Hypertension, and Obesity in the Young Committee (Council on Cardiovascular Disease in the Young) and the Diabetes Committee (Council on Nutrition, Physical Activity, and Metabolism)

This statement was reviewed by the American Diabetes Association. The recommendations contained herein are consistent with the American Diabetes Association's Clinical Practice Recommendations.

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Atherosclerotic cardiovascular disease is the No. 1 killer in the adult population of Western societies,¹ but the pathological processes and risk factors associated with its development have been shown to begin during childhood.² Obesity plays a central role in the insulin resistance syndrome, which includes hyperinsulinemia, hypertension, hyperlipidemia, type 2 diabetes mellitus, and an increased risk of atherosclerotic cardiovascular disease. The incidence of type 2 diabetes reported in children has increased alarmingly.^{3,4}

Resistance of the body to the actions of insulin results in increased production of this hormone by the pancreas and ensuing hyperinsulinemia. Obesity beginning in childhood often precedes the hyperinsulinemic state. Other components of the insulin resistance syndrome are also present in children and adolescents.^{5,6} An association between obesity and insulin resistance has been reported in the young, as has the link between insulin resistance, hypertension, and abnormal lipid profile. There is an increasing amount of data showing that being overweight during childhood and adolescence is significantly associated with insulin resistance, dyslipidemia, and elevated blood pressure in young adulthood. Weight loss by obese youngsters results in a decrease in insulin concentration and improvement in insulin sensitivity. Moreover, it has been determined that increased left ventricular mass, which is an independent risk factor for cardiovascular disease in adults, is present in childhood. Recent research has found that left ventricular hypertrophy is related to other risk factors, including obesity and insulin resistance in children and adolescents.⁷ The specifics of the transition from risk

factors in childhood to diabetes and cardiovascular disease are not clear, but compelling evidence points to their association with overt disease in adults. On the basis of current knowledge and extrapolation from studies in adults, it is reasonable to suggest that lifestyle modification and weight control in childhood could reduce the risk of developing the insulin resistance syndrome, type 2 diabetes mellitus, and cardiovascular disease.

Obesity and the Insulin Resistance Syndrome

Obesity increases the risk of cardiovascular disease in adults and has been strongly associated with insulin resistance in normoglycemic persons and in individuals with type 2 diabetes.^{8,9}

Data from the Framingham study have established an increased incidence of cardiovascular events with increasing weight in both men and women.¹⁰ Body weight and mortality were directly related in the Harvard Alumni Health Study,¹¹ and weight gain was a significant risk factor for development of diabetes mellitus in women.¹² The association of obesity with the insulin resistance syndrome and cardiovascular risk is not only related to the degree of obesity but also seems to be critically dependent on body fat distribution. Thus, individuals with greater degrees of central adiposity develop this syndrome more frequently than do those with a peripheral body fat distribution.¹³

Studies in obese adults have shown sustained improvement in cardiovascular risk in association with a 10% to 15% weight loss maintained over time.¹⁴ One other report, however, suggested that a weight loss of 16% resulted in a

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differential risk factor response, including a dramatic reduction in the incidence of type 2 diabetes but not in the 8-year incidence of hypertension.¹⁵

An association between adiposity and insulin resistance has been reported in adults and children.^{16,17} Weight loss is associated with a decrease in insulin concentration and an increase in insulin sensitivity in adults¹⁸ and adolescents.¹⁹ In a study of 122 adolescents, obese individuals were significantly more insulin resistant and had an abnormal lipid profile when compared with lean subjects⁵; in this study, insulin resistance was significantly related to an abnormal lipid profile in heavy children but not in thin children, and insulin resistance varied directly with the degree of adiposity. Obesity and insulin resistance have also been shown to be associated with other risk factors, such as elevated blood pressure. Ethnic and sex differences occur in the insulin resistance syndrome in the United States, with a greater prevalence demonstrated in men and in African Americans.²⁰

Hypertension and the Insulin Resistance Syndrome

Essential hypertension is the clinical expression of a disordered interaction between the genetic, physiological, and biochemical systems that under usual conditions maintain cardiovascular homeostasis. The multifactorial nature of essential hypertension has made it difficult to completely isolate the action of any one of these systems from the actions of the others.

The relation between insulin metabolism/resistance and essential hypertension has the potential to provide insight into the mechanisms that operate this complex interaction.^{21–25} Insulin increases renal sodium retention^{26–29} while increasing free water clearance. Insulin resistance is also associated with increased sympathetic nervous system activity³⁰ and stimulation of vascular smooth muscle growth.³¹ Insulin levels have been found to be significantly higher in adult patients with essential hypertension^{32–34} and borderline hypertension³⁵ than in normotensive control patients. This is true whether insulin is measured in the fasting state^{32–34,35} or in response to the oral glucose tolerance test,^{32–34} the insulin suppression test, or the euglycemic insulin clamp technique.^{33,35} Moreover, these differences have been reported to be independent of age, sex, and ethnic group.^{32–35} A confounding factor in the insulin–hypertension link is obesity. In most of the world's populations, blood pressure is directly correlated with body weight. Numerous studies have confirmed the association between weight gain, percent body fat, and insulin resistance.^{21,36–39} Other studies, however, have indicated that an interaction exists between insulin and hypertension that is independent of their interaction with obesity.⁴⁰ The Coronary Artery Risk Development In young Adults (CARDIA) study of 4576 young adults reported a weight-independent association between fasting insulin concentration and hypertension.⁴¹ Thus, it is clear that several questions about the association between blood pressure and the syndrome of insulin resistance remain unanswered. Although the prevalence of essential hypertension in children is low, the precursors of this disease are present long before clinically accepted levels of hypertension are recognized. Substantial evidence from genetic and epidemiological studies confirms that blood pressure tracks over

time and that the roots of essential hypertension extend into the first and second decades of life.^{42,43}

There is a strong genetic influence on blood pressure that in some can be identified early in childhood⁴⁴ and that is intensified in the presence of other risk factors.⁴⁵ Several studies have addressed the association between insulin and blood pressure in children and adolescents. Interactions similar to those identified in adults also may be found at a young age. The Bogalusa Heart Study has shown a positive correlation between blood pressure and fasting insulin, even after adjustment for body mass index, as early as 5 years of age.⁴⁶ Insulin resistance has been found in young black men (early twenties) with only borderline hypertension, independent of body mass index.³⁵ Several mechanisms through which blood pressure may be linked with insulin resistance have been proposed. In adolescents, the resistance to insulin has been associated with chronic sodium retention⁴⁷ and sodium sensitivity,⁴⁸ and this is reversible with weight loss and exercise.¹⁸ Moreover, obese, insulin-resistant adolescents have increased forearm vascular resistance that is reversible with weight loss.⁴⁹ Of particular interest, normotensive adolescent offspring (mean age of 13 years) of hypertensive parents were found to have significantly higher serum insulin levels after an overnight fast and an intravenous glucose load, which suggests that insulin resistance predates an increase in blood pressure in subjects with a genetic predisposition to hypertension.⁵⁰ Because multiple mechanisms contribute to the development of hypertension, it is difficult to isolate the contribution of obesity and/or hyperinsulinemia.

Lipid Abnormalities and the Insulin Resistance Syndrome

Insulin resistance has been hypothesized to play a major role in dyslipidemia in individuals with normal glucose tolerance, as well as in those with impaired glucose tolerance and type 2 diabetes.^{51,52} Lipid abnormalities have also been reported in obese adults, who have elevated triglycerides and LDL cholesterol and low levels of HDL cholesterol.^{53,54} Similar lipid profiles have been reported in obese and nonobese adults with type 2 diabetes, in obese normoglycemic adults, and in nonobese adults with impaired glucose tolerance.^{55–57} The association between obesity and dyslipidemia observed in adults also has been documented also in children and adolescents. In the Lipid Research Clinics Population Studies Data Book, obese adolescents had an abnormal “atherogenic” lipid profile consisting of elevated LDL cholesterol and triglycerides and low HDL cholesterol. In more recent studies in children, insulin resistance was also implicated in the association between obesity and dyslipidemia. In a study of insulin resistance and lipids that compared 82 normoglycemic, obese adolescents with 40 lean adolescents, abnormalities consistent with an atherogenic lipid profile were present in the obese subjects. The dyslipidemia correlated with the degree of insulin resistance in the obese children, and it was shown that the degree of insulin resistance explained a significant portion of the variance in the levels of triglycerides, LDL cholesterol, and HDL cholesterol.⁵ Investigators from the Bogalusa Heart Study reported that overweight schoolchildren, in comparison with their lean counterparts,

were 2.4 to 7.1 times more likely to have elevated total cholesterol, LDL cholesterol, and triglycerides, and 12.6 times more likely to have hyperinsulinemia.⁵⁸

Several mechanisms whereby insulin resistance could cause an alteration in lipid metabolism have been described. Hyperinsulinemia is known to enhance hepatic very-low-density lipoprotein synthesis and thus may directly contribute to the increased plasma triglyceride and LDL cholesterol levels.⁵⁹ Resistance to the action of insulin on lipoprotein lipase in peripheral tissues may also contribute to elevated triglyceride and LDL cholesterol levels.^{60,61} It has been suggested that insulin resistance may be responsible for the reduced levels of HDL cholesterol observed in type 2 diabetes patients and that despite enhanced HDL cholesterol synthesis, the plasma HDL cholesterol concentration was significantly reduced in patients with type 2 diabetes versus control subjects; this decrease in plasma HDL cholesterol was accounted for entirely by an increase in the rate of apolipoprotein A1/HDL cholesterol degradation, which exceeded the enhanced rate of its synthesis.⁶²

Other intrinsic metabolic factors, such as apolipoproteins, lipoprotein A, and homocysteine, are known to influence the development of cardiovascular disease; their potential relationship to the insulin resistance syndrome remains to be clarified.

Assessment

Our understanding of the insulin resistance syndrome in children is evolving, and there is no general agreement about the overall assessment and treatment of this syndrome. Although the end points for cardiovascular risk are not seen in childhood, the components of the insulin resistance syndrome (obesity, hypertension, dyslipidemia, and hyperinsulinemia) track from childhood into adulthood, which supports the conclusion that the precursors of cardiovascular disease are present early in life.^{63,64} Because insulin resistance often is associated with type 2 diabetes, the first step in assessment is to identify children who would benefit from intervention. Testing has been recommended for children at significant risk for the presence or development of type 2 diabetes.⁶⁵ These are children who in general: (1) are overweight; (2) have a family history of type 2 diabetes; (3) have a predisposition based on race/ethnicity (American Indian, African American, Hispanic, Asian/Pacific Islander); and (4) have signs of insulin resistance or conditions associated with insulin resistance (eg, acanthosis nigricans, hypertension, dyslipidemia, polycystic ovary syndrome). The diagnosis of diabetes can be made by using either the fasting plasma glucose or the 2-hour value on an oral glucose tolerance test. The fasting glucose determination is preferred. At this time, sufficient data are not available to support the use of the HbA_{1c} in the diagnosis of diabetes. It is important to remember that even in the face of a normal fasting glucose level, the child may have diabetes or remain at risk for developing type 2 diabetes.

Children who do not have elevated blood glucose concentrations may exhibit other features of the insulin resistance syndrome, such as obesity, hypertension, and high cholesterol, and they remain at risk for cardiovascular disease and diabetes. Body size measurements (expressed by body mass

index, waist circumference [a measure of central adiposity], or other methods) and determination of blood pressure and cholesterol should become part of the evaluation of any child with the risk profile described above. Insulin resistance is measured by an accurate but rather complicated method: the euglycemic insulin clamp. This technique involves the continuous intravenous administration of insulin and glucose over 3 hours and the calculation of insulin sensitivity (the inverse of insulin resistance) by measuring the amount of glucose required to maintain normal glucose levels (euglycemia).⁶⁶ The euglycemic clamp currently is used for research purposes only. Although less accurate than the euglycemic clamp method, assessment of hyperinsulinemia from fasting plasma insulin levels and estimation of insulin resistance from indices based on fasting glucose and insulin levels have been proposed as reasonable alternative methods for evaluating insulin resistance.

Type 2 Diabetes Mellitus in Children and Adolescents

Type 2 diabetes mellitus has long been considered a disease of adults, in whom it is the most prevalent form of diabetes ($\approx 90\%$) and is associated with increased risk of cardiovascular disease morbidity and mortality.⁶⁷ During the past 10 years, however, an increasing frequency in the occurrence of type 2 diabetes mellitus has been reported in adolescents.³ There are now reports in the literature of type 2 diabetes in Native American, Hispanic, African-American, South Asian, and white youth.⁴ This increase in frequency of type 2 diabetes seems to parallel the increase in prevalence and severity of obesity in children and adolescents.⁶⁸

Type 2 diabetes is often asymptomatic in its early stages. This makes the diagnosis difficult without an awareness of the subtle characteristics that should prompt further work-up. Some patients are diagnosed with the typical symptoms of polyuria and polydipsia, and some develop ketoacidosis.⁶⁹ Others are asymptomatic or may have nonspecific findings, such as vaginal moniliasis.³ Some patients are identified when glycosuria is found on routine testing for sports, school, or employment examinations.⁴ Obesity, acanthosis nigricans, and a positive family history of diabetes are common in adolescents with type 2 diabetes. At diagnosis, the fasting C peptide and insulin concentrations are often elevated, and antibodies to pancreatic islet cells are generally absent.⁷⁰ Glycosylated hemoglobin concentrations may be elevated but variable according to how early in the course of the disease the diagnosis is made.^{71,72} Children with type 2 diabetes are usually diagnosed after age 10 years. This may be in part due to the physiological insulin resistance seen with the hypersomatotropic state of puberty, which may contribute to the exacerbation of the disease. Adolescents with type 2 diabetes mellitus are almost always obese. The mean body mass index in clinical series has ranged from 26 to 38 kg/m².⁴ Patients with type 2 diabetes often have other risk factors for cardiovascular disease. The prevalence of elevated blood pressure has ranged from 17% to 32%. The prevalence of hypertriglyceridemia has ranged from 4% to 32%.⁴ In one study, 6% had a clinical diagnosis of sleep apnea.³

Because type 2 diabetes is a relatively recent problem in adolescents, few data on long-term follow-up exist. One study of Pima Indians monitored 36 individuals for a mean of 10 years until they reached a median age of 26 years. In this cohort, at baseline (age 5 to 19 years), 85% were obese, 14% had hypertension, 30% had total cholesterol >200 mg/dL, and 55% had triglyceride concentrations >200 mg/dL. Fifty-eight percent of the patients had microalbuminuria and 16% a urinary albumin/creatinine ratio >300 mg/g, which indicated that the renal effects of diabetes were already present at diagnosis. After 10 years of follow-up, the number of patients with increased urinary albumin excretion was significantly increased, as was the magnitude of albuminuria.⁷³ Thus, these patients have a constellation of risk factors that place them at increased risk of cardiovascular disease at an early age.

The pathophysiology of the development of type 2 diabetes mellitus is complex and multifactorial. It is believed that obesity leads to insulin resistance and increased circulating insulin concentrations over time. It seems that at some point a loss of control of blood glucose begins to emerge, resulting in dietary glucose intolerance. This ultimately results in type 2 diabetes. It is known that obese individuals may develop different degrees of insulin resistance, and not all individuals develop glucose intolerance. The factors that make some individuals more likely to progress to type 2 diabetes mellitus are not well understood at the present time. A strong family predisposition is known to exist; therefore, parental history is important in risk assessment. In the future, genetic markers may help identify those offspring of diabetic parents who are greatest risk of developing diabetes.

The treatment of type 2 diabetes mellitus in adolescents is similar to the treatment in adults. Because obesity is the major underlying factor, patients are counseled on an improved, calorie-restricted diet and increased physical activity to achieve better energy balance and weight loss. It is not currently known what level of weight loss is necessary for adolescents to achieve improved glucose handling. In adults, it seems that a 10% to 15% weight loss has substantial benefit. Patients may also be treated with oral agents. Future studies may answer questions about the safety and efficacy of oral agents in children in general, and specifically about the safety and efficacy of medications that increase insulin sensitivity, such as glitazones. Some adolescents with type 2 diabetes mellitus may require administration of insulin to achieve control of their diabetes.

Type 2 diabetes mellitus seems to be emerging as a major public health problem for adolescents. The early onset of type 2 diabetes suggests that these patients will be at risk for the development of cardiovascular disease at a young age. If the secular trend seen with increasing prevalence and severity of obesity in childhood and adolescence continues, it is likely that the problem of type 2 diabetes also will increase in the pediatric age group.⁷⁴

Significance

In the face of the major impact that adult cardiovascular disease has in the westernized societies, it seems crucial to examine further the relationships among cardiovascular risk factors at the childhood–adolescence–adulthood transition, ie,

the putative earliest point in the development of cardiovascular risk. This may result in important information on the etiologic relations between early indicators of the insulin resistance syndrome, type 2 diabetes, and establishment of risk in young adulthood.

As more research evidence is accumulated, it is also important to deal with the problems of insulin resistance and type 2 diabetes in children and adolescents from a clinical standpoint. The first approach should focus on prevention of obesity in childhood. More attention should be paid to increasing physical activity and decreasing calorie consumption in this age group. Once obesity is established in a child or adolescent, vigorous clinical efforts should be directed at treating it. At present, this involves therapy directed at behavior change, but in the future it may include pharmacological and surgical approaches in the appropriate patients. Clinicians should watch vigilantly for the subtle signs that indicate the development of insulin resistance, glucose intolerance, and type 2 diabetes. Early recognition of these problems can lead to better treatment. On the basis of current knowledge, it seems that better control of blood glucose is likely to lead to improved long-term microvascular and macrovascular outcomes. Thus, the best approach to prevention of future cardiovascular disease in these young patients is early recognition and aggressive therapy. Without this, it is likely that this patient population is destined to develop cardiovascular complications and require substantial resources for future management.

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