Diagnosis of the metabolic syndrome in children

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Purpose of review

The metabolic syndrome, a cluster of potent risk factors for atherosclerotic cardiovascular disease and type 2 diabetes mellitus in adults, is composed of insulin resistance, obesity, hypertension and hyperlipidemia. Of significant impact in the adult population, atherosclerotic cardiovascular disease and death are rarely seen in the young, but the pathologic processes and risk factors associated with its development have been shown to begin during childhood. The current review summarizes the work published during the past year in the following areas: childhood obesity, insulin resistance, dyslipidemia, hypertension and type 2 diabetes mellitus.

Recent findings

Recent studies have revealed the presence of components of the metabolic syndrome in children and adolescents. Obesity has a central role in the syndrome. There is an increasing amount of data to show that being overweight during childhood and adolescence is significantly associated with insulin resistance, abnormal lipids, and elevated blood pressure in young adulthood. Weight loss in these situations results in a decrease in insulin concentration and an increase in insulin sensitivity toward normalcy. With cardiovascular disease, obesity, and type 2 diabetes reaching epidemic proportions, it is of great importance to understand and control the risk factors at an early age.

Summary

The information obtained during the past year has improved our understanding of the pathogenesis, diagnosis and treatment of components of the metabolic syndrome in children, and potentially could improve the risk profiles for cardiovascular disease as children make the transition toward adolescence and young adulthood.

Keywords

obesity, lipids, insulin, diabetes, children

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Introduction

Atherosclerotic cardiovascular disease, the number one killer in the adult population of Western societies [1], is strongly associated with the metabolic syndrome and type 2 diabetes mellitus [1,2]. Obesity plays a central role in the metabolic syndrome, which also includes hyperinsulinemia/insulin resistance, hypertension and hyperlipidemia. Recent studies in children and adolescents indicate that the process of atherosclerosis starts at an early age and is linked to obesity and other components of the syndrome already in childhood [3]. Being overweight and suffering with obesity have been increasing and continue to increase in children and adolescents [4] and, in addition to their health burden, they are also associated with a large economic burden in terms of hospital cost for obesity-related disease [5•]. As a result of the obesity epidemic, the incidence of type 2 diabetes in children has increased alarmingly and has emerged as a critical health issue [6,7••]. Type 2 diabetes mellitus (formerly known as non-insulin dependent diabetes mellitus) results from insulin resistance, a state in which the tissues are less sensitive to insulin. The pancreatic cells are driven to work harder to overcome the resistance, resulting in hyperinsulinemia. Obesity beginning in childhood often precedes the hyperinsulinemic state. Other components of the metabolic syndrome are also present in children and adolescents [8,9,10••]. The association between obesity and insulin resistance has been reported in the young, as has the link between insulin resistance, hypertension, and abnormal lipid profile [11••]. Being overweight during childhood and adolescence is significantly associated with insulin resistance, dyslipidemia, and elevated blood pressure in young adulthood [12•]. The specifics of the change from risk factors in childhood to diabetes and cardiovascular disease are not clear, but there is compelling evidence of their association with overt disease in adults. Based on current knowledge, and by extrapolation from studies in adults, it is reasonable to suggest that lifestyle modification and weight control in childhood could reduce the risk for developing the metabolic 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. Data from the Framingham and other studies have established an increased incidence of cardiovascular events with increasing weight in both men and women [13]. The proportion of children and

adolescents who are overweight (defined as a body mass index >95 percentile) has tripled in the past three decades [14•]. Greater body weight predisposes children to many of the medical complications of obesity found in adults, in particular components of the metabolic syndrome: hypertension [15•], dyslipidemia, and impaired glucose metabolism/hyperinsulinemia [16••,17]. As these children age, the obesity epidemic will lead to epidemics of diabetes, hypertension, and cardiovascular disease.

The association of obesity with the insulin resistance syndrome and cardiovascular risk is not only related to the degree of obesity, but also appears to be critically dependent on the body fat distribution. Similar to adults, it has recently been shown that children with greater degrees of central adiposity develop this syndrome more frequently than do those with a peripheral body fat distribution [18•]. Weight loss is associated with a decrease in insulin concentration and an increase in insulin sensitivity in adults and adolescents. In a study of 122 adolescents, obese individuals were significantly more insulin resistant, and had an abnormal lipid profile when compared with lean individuals [8]; 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. In a recent study of pathobiological determinants of atherosclerosis, obesity was associated with dyslipidemia and accelerated coronary atherosclerosis in 3000 adolescents and young adults [19••].

Hypertension and the insulin resistance syndrome

Essential hypertension is the clinical expression of a disordered interaction between genetic, physiologic 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 others. In concert with the increasing prevalence of obesity in children, pediatric essential hypertension has become far more common than previously noted [20•]. Most studies of children have focused on three main pathophysiologic mechanisms: disturbances of autonomic function, insulin resistance, and abnormalities of vascular structure and function. Obesity induced hypertension is likely due to a combination of these factors [21].

Insulin increases renal sodium retention, while increasing free water clearance. Insulin resistance is also associated with increased sympathetic nervous system activity, and stimulation of vascular smooth muscle growth. Insulin levels have been found to be significantly higher in patients with essential hypertension and borderline hypertension (than in normotensive control patients). 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. 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. There is substantial evidence from genetic and epidemiologic studies to confirm that blood pressure tracks over time and that the roots of essential hypertension extend into the first and second decades of life.

There is a strong genetic influence on blood pressure that in some can be identified early in childhood and that is intensified in the presence of other risk factors [22••]. A number of studies have addressed the association between insulin and blood pressure in children and adolescents. Interactions similar to those identified in adults may also be found at a young age. Because multiple mechanisms contribute to the development of hypertension, it is difficult to isolate the contribution of obesity or hyperinsulinemia. In a study by Sinaiko *et al.* [23•], blood pressure was not related to insulin resistance proper measured by the euglycemic insulin clamp (the most sensitive technique available to date to estimate insulin resistance); however, there was a significant clustering effect for other components of the metabolic syndrome (insulin, adiposity, triglycerides, HDL-cholesterol), which were related to blood pressure. The authors concluded that the level of blood pressure in children is mediated through body fat, and that insulin resistance *per se* does not play a primary role in blood pressure control at this age.

Lipid abnormalities and the insulin resistance syndrome

Obesity and insulin resistance have 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. The association between obesity and dyslipidemia observed in adults has also been documented 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 comparing 82 normoglycemic, obese adolescents with 40 lean adolescents, abnormalities consistent with an 'atherogenic' lipid profile were present in the obese adolescents. 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 [8]. Investigators from the Bogalusa Heart Study reported that overweight schoolchildren in comparison with their lean counterparts were between 2.4 and 7.1 times more likely to have elevated total cholesterol, LDL-cholesterol and triglycerides and 12.6 times more likely to have hyperinsulinemia [24].

Several mechanisms whereby insulin resistance could cause an alteration in lipid metabolism have been described [25]: (1) hyperinsulinemia is known to enhance hepatic VLDL synthesis and thus directly contributes to the increased plasma triglyceride and LDL-cholesterol levels; (2) resistance to the action of insulin on lipoprotein lipase in peripheral tissues may also contribute to elevated triglyceride and LDL-cholesterol levels; (3) insulin resistance may be responsible for the reduced levels of HDL-cholesterol observed in type 2 diabetes patients, accounted for by an increase in the rate of apolipoprotein A1/HDL-cholesterol degradation, in excess of the rate of its synthesis. In addition, Caprio [26•] has shown that hyperinsulinemia in children results in impaired suppression of total body lipid oxidation and plasma free fatty acid concentration.

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.

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 (~90%) and is associated with increased risk of cardiovascular disease morbidity and mortality [27••]. However, during the last 10 years an increasing frequency in the occurrence of type 2 diabetes mellitus has been reported in adolescents [28]. There are now reports in the literature of type 2 diabetes in Native American, Hispanic, African-American, South Asian and Caucasian youth [29]. This increase in frequency of type 2 diabetes appears to parallel the increase in prevalence and severity of obesity in children and adolescents [30•].

Among adults, the best predictor of type 2 diabetes and the metabolic syndrome is the quantity of visceral fat [31]. Similar findings were reported in obese Hispanic children [32]. In a study of 710 obese children, both insulin resistance and impaired insulin secretion contributed to the development of type 2 diabetes, and the degree of obesity was related to cardiovascular risk factors independent of insulin resistance [33••].

Some patients are diagnosed with the typical symptoms of polyuria and polydipsia, and some develop ketoacidosis. However, type 2 diabetes is often asymptomatic in its early stages. This makes the diagnosis difficult unless there is an awareness of the subtle characteristics, which should prompt further work-up. In a recent study by Sinha *et al.* [16••] impaired glucose tolerance and insulin resistance were highly prevalent in obese children and adolescents, and 4% of the obese children were found to have previously undiagnosed type 2 diabetes. 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. Glycosylated hemoglobin concentrations may be elevated but variable, depending on how early in the course of the disease the diagnosis is made. Children with type 2 diabetes are usually diagnosed after age 10 years. This may in part be due to the physiologic 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/m^2 [29]. 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% [29]. In one study, 6% had a clinical diagnosis of sleep apnea [28].

Because type 2 diabetes is a relatively recent problem in adolescents, there are few data on long-term follow-up. Recently, Srinivasan *et al.* [34••] described the longitudinal changes in risk variables of the metabolic syndrome in a cohort with and without a parental history of type 2 diabetes, as they grew from childhood to adulthood. The authors reported that offspring of parents with type 2 diabetes displayed excess body fatness beginning in childhood and accelerated risk profile of the metabolic syndrome as they progressed into young adulthood.

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 appears 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 at 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 appears that a 10–15% weight loss has substantial benefit. Patients may also be treated with oral agents [35,36]. Future studies may answer questions regarding the safety and efficacy of oral agents in general, and specifically medications which increase insulin sensitivity such as glitazones, in children. Some adolescents with type 2 diabetes mellitus may require administration of insulin to achieve control of their diabetes.

Type 2 diabetes mellitus appears 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 will also increase in the pediatric age group.

Conclusion

In the face of the major impact that adult cardiovascular disease has in westernized societies, it seems crucial to examine further the relationships among cardiovascular risk factors at the childhood–adolescent–adult transition, that is 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 metabolic 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 pharmacologic and surgical approaches in the appropriate patients. Clinicians should be vigilant for the subtle signs indicating the development of insulin resistance, glucose intolerance and type 2 diabetes. Early recognition of these problems can lead to better treatment. Detailed and specific guidelines for health care providers for cardiovascular risk identification and reduction in children were recently outlined by the American Heart Association [11••,37•].

Thus, the best approach to prevention of future cardiovascular disease in these young patients is early recognition and aggressive therapy. Without this approach it is likely that this patient population is destined to develop cardiovascular complications, requiring substantial resources for future management.

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