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Metabolic syndrome: definition and prevalence in children

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Metabolic syndrome, a concurrence of disorders including obesity, insulin resistance, dyslipidemia and hypertension, has gained importance because of its association with subsequent development of cardiovascular disease and type 2 diabetes. The extent of coronary atherosclerosis in children and young adults increases markedly with the increasing number of multiple risk factors.[1] The metabolic syndrome is highly prevalent in adults, and the coexistence of these multiple cardiovascular risk variables also occurs commonly in children.[2,3] Importantly, multiple risk factors reinforce each other and persist (track) from childhood into adulthood.[3] Recent studies suggest that metabolic syndrome may even originate in the embryonic and fetal stages.

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In this month's issue of Jornal de Pediatria, Ferreira et al.[4] reported the results of their study on the prevalence of the metabolic syndrome and the relationships between its components and insulin resistance in 52 obese children aged 7-10 years, defined by body mass index (BMI) > 95th percentile. In these children, they found a prevalence of metabolic syndrome (17.3%) defined by a clustering of central obesity, hypertriglyceridemia, low HDL cholesterol, hyperglycemia and elevated blood pressure. They also recognized that the clustering of these risk factors is strongly associated with insulin resistance measured as the homeostasis model assessment (HOMA) of insulin resistance. The important issue addressed by the authors is the role of obesity and insulin resistance in the development of metabolic syndrome in children. We and others have shown that obesity is more important than hyperinsulinemia as the primary etiologic process.[5] Distressingly, overweight and obesity prevalence among both adults and children is rising throughout the world. Overweight prevalence tripled in U.S. children and adolescents in the past two decades. According to recent estimates, 17.1% of 2-19 year-old children are overweight.[6] Consequently, the metabolic syndrome in children becomes a global public health problem. The research focus of the metabolic syndrome has shifted to its prevention in early life.

Significant clustering of the metabolic syndrome components has been consistently demonstrated in various ethnic groups and populations; however, there are still some concerns and debates regarding the definition of metabolic syndrome.[7] Several organizations (World Health Organization, National Cholesterol Education Program, International Diabetes Federation, American College of Endocrinology, and European Group for the Study of Insulin Resistance) have proposed definitions of the metabolic syndrome for adults using different components and cutoff points. One consequence of the nonuniform definition is that currently available data on the frequency of the syndrome in various populations vary widely. A detailed review on the prevalence of metabolic syndrome using different criteria has been published recently.[8] In spite of attempts in recent years to reach agreement on the definition of the syndrome, comparisons of published prevalence rates for different populations worldwide are difficult.

Although the prevalence of the metabolic syndrome is rising in children, there have been no consistent criteria available to diagnose the metabolic syndrome in pediatric populations in terms of the components and cutoff points.

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Percentiles and adjusted values have been commonly used as cutoff points for the metabolic syndrome components in children and adolescents.[4,9] As in adults, the comparison of the prevalence among pediatric populations is problematic. An alternative method is to analyze the clustering of the components as continuous variables. We applied intraclass correlation[2] and path analysis in our studies on the metabolic syndrome in children, adolescents and adults from the Bogalusa Heart Study. Although the degree of clustering of the risk variables can be determined by using this approach, it does not provide prevalence data. In Ferreira's study, the authors used both percentiles and age- and sex-specific cutoff values of the components to define the metabolic syndrome in children. A recent report by Weiss et al. showed alarming high rates of metabolic syndrome among obese youths: 38.7% in moderately obese children and 49.7% in severely obese children.[10] The definition used in Weiss' study is BMI > 97th percentile, triglyceride > 95th percentile, HDL cholesterol < 5th percentile and glucose between 140-200 mg/dL. Obviously, the huge variations in the prevalence rates are in large part because of the different components and cutoff points used in the two studies. In fact, according to Weiss' criteria, the prevalence of the metabolic syndrome would be much higher in Ferreira's study sample of obese children if the two-factor clustering is taken into account. Cook et al. analyzed a sample of adolescents aged 12-19 years from the Third National Health and Nutrition Examination Survey (NHANES III) (1988-1994) using the same components as Ferreira's study, but different cutoff points. They found that the prevalence of the metabolic syndrome is 6.8% among overweight adolescents and 28.7% among obese adolescents.[9]

In these previous studies, another problem resulted from the inconsistent criteria used in children is that BMI is used as both a stratifying indicator and a component of the syndrome.[10,11] Although obesity is an important determinant of the metabolic syndrome, it is far from being a necessary and sufficient etiologic factor of the syndrome. Therefore, the observations such as "No nonobese subjects met the criteria for the metabolic syndrome",[10] "the metabolic syndrome was found almost exclusively among obese teens"[11] or "The syndrome was present in 0.1% of adolescents with a BMI below the 85th percentile"[9] are in large part due to the definition of obese and nonobese children. In these studies, very few or no nonobese children had the obesity component by the authors' definition. In Ferreira's and Cook's studies, they used the BMI percentile to define obesity and used a central obesity measure as a component of the metabolic syndrome. The concern is that the prevalence may be overestimated because central obesity measured by waist circumference is expected to be strongly correlated with overall obesity measured by BMI. The high prevalence is, to some extent, due to the sample selection of obese children. Another concern is that fasting glucose was repeatedly included in both clustering analysis as a component and the calculation of HOMA index, which in part accounted for a strong correlation between insulin resistance and the metabolic syndrome.[4,10]

Such discrepancies in the prevalence and inconsistent definition criteria highlight a need of universal definition of the metabolic syndrome for children. While a global definition of the metabolic syndrome for adults is being attempted, it is suggested that the metabolic syndrome should be considered a "loose" concept instead of a strict definition.[12] This argument is especially true for children.

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Obesity, insulin resistance and the metabolic syndrome

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There has been a remarkable increase in interest during the past two decades in the relation between cardiovascular risk factors in children and the development of arteriosclerotic cardiovascular disease (ASCVD) and type 2 diabetes in adulthood. Initial studies concentrated on individual factors such as lipids and blood pressure. However, as research in this area has evolved and pediatricians have followed the lead of their colleagues in internal medicine, attention has turned to broader considerations of risk and, in particular, to obesity, insulin resistance and the metabolic syndrome. It is not surprising that these studies are affirming the concept that the roots of ASCVD and type 2 diabetes extend back into childhood.

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The relation of obesity to ASCVD in adults is well known. Although children and adolescents do not have overt ASCVD, obese children have a cardiovascular risk profile consistent with its early development, i.e., significantly higher blood pressure, triglycerides and fasting insulin and significantly lower HDL-C.[1] Moreover, the degree of risk increases with increasing obesity.[2] The result is early deposition of fatty streaks and plaque in adolescent coronary arteries,[3] and the outcome in adulthood is an increased incidence of premature cardiovascular and all-cause mortality in individuals who were obese adolescents.[4] Despite a perception in the general population that overweight children tend to become thinner as they go through adolescence and maintain the thinness as they become young adults, longitudinal growth studies have shown a highly significant (r = 0.61) correlation in body mass index (BMI) between ages 7 and 24, and have further shown that BMI at age 7 predicts the ASCVD risk factors at age 24.[5] The relevance of these findings is of increasing importance to pediatricians, since the prevalence of obesity in children is steadily increasing in all ethnic groups.[6]

The relation of obesity to insulin resistance is also well known, and while insulin resistance is related to the development of ASCVD, its role independent from obesity is not clearly defined. Nevertheless, it has become evident that obesity cannot completely explain the development of insulin resistance. Insulin resistance is not present in all obese individuals; nonobese, nondiabetic individuals can be insulin-resistant; and type 2 diabetes occurs in nonobese individuals. In an attempt to clarify the independent influence of BMI and insulin resistance on the development of cardiovascular risk and type 2 diabetes, we have been conducting a longitudinal study, including euglycemic hyperinsulinemic clamps, in children who were randomly recruited from a public school population of 11-14 year olds. Results from this study are showing that insulin resistance, of itself, is associated with increased levels of cardiovascular risk factors.[1] When the cohort was divided into two groups according to insulin sensitivity and resistance, the insulin resistant group was found to have significantly higher fasting insulin, triglycerides and lower HDL-C, independent of BMI. And, when the cohort was further divided according to levels of both BMI and insulin resistance, an interaction was uncovered in the obese, insulin resistance group, leading to higher levels of risk factors than would be expected by simply adding together the individual effects of BMI and insulin resistance. This cohort has now been followed to early young adulthood (age range 18-21). Recent studies[7] have shown that insulin resistance measured at age 13 predicts, independent from BMI, blood pressure and lipids at age 19. Thus, it

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