Metabolic syndrome (consisting of increased waist circumference, hypertension, hypertriglyceridemia, low high-density lipoprotein cholesterol [HDL-C], and hyperglycemia) became a medical diagnosis in adults in the late 1980s after publication of the concept that these cardiovascular (CV) risk factors may be linked together through a relation with insulin resistance. The syndrome later became formally defined as the presence of any three of the above five components, and it is widely accepted as an important predictor of CV disease and type 2 diabetes.

It is no secret that obesity has become a major universal health issue in children, that it is associated with significant metabolic dysfunction, and that it tracks into adulthood. Thus, it is not surprising that attempts have been made to develop a metabolic syndrome for children patterned on the adult syndrome. While the adult diagnosis is based on well-defined definitions for the five components comprising the syndrome, similar definitions are not available in children. As a consequence, arbitrary cutoff points, adapted from childhood standards, have been substituted. Using these criteria, it was estimated that the prevalence of the metabolic syndrome in adolescents was approximately 4%, with an increase to 29% in overweight adolescents. However, the use of arbitrary definitions has led to controversy in pediatrics. The result is clearly shown in the paper by Costa et al. published this month in the Journal, comparing three prevalence studies, each with its own separate independent definitions for diagnosing the metabolic syndrome. It is not clear why the different definitions were chosen, but the outcome is clear, i.e., three different definitions lead to three substantially different levels of prevalence for the childhood metabolic syndrome. It is understandable, as Costa et al. conclude, “disagreements regarding the prevalence of the disease in the pediatric population will be frequent”.

There is general agreement that the risk factors comprising the metabolic syndrome tend to cluster together. However, there are differences between adults and children. A variety of combinations of all five components may be found in adults with the syndrome, but in children obesity predominates, associated in most cases with elevated triglycerides and low HDL-C. Despite the high correlation with body mass index (BMI), hypertension is infrequent; and fasting hyperglycemia, common in adult obesity, is least common. Although fasting glucose levels may be higher in obese than non-obese children, the levels are usually within the normal range, requiring an oral glucose tolerance test to diagnose disordered glucose metabolism. The lower frequency of hypertension and hyperglycemia may explain, in part, the lower prevalence of the syndrome in children than adults. As seen in Costa et al.’s Table 4, prevalence can be easily influenced by altering the definition of any of the five components, noted in this case by the major effect of lowering the threshold for HDL-C and waist circumference by de Ferranti.

Emphasis on elevated CV risk factors in children is logical for pediatricians, who have always been at the forefront of preventive medicine. However, it is important to recognize that a focus on the metabolic syndrome rather than the individual risk factors may detract from the most effective approach to preventive care or therapy. First, the metabolic syndrome tracks poorly during childhood, from childhood to young adulthood, and to a greater degree in children in the higher risk categories. As a consequence, major advisory bodies have raised questions about its usefulness in children. The lack of tracking may be explained by longitudinal studies showing significant changes in levels of blood pressure, triglycerides and HDL-C during the transition from childhood to young adulthood. These changes and the resultant variability in levels are likely to have a major impact on the usefulness of the metabolic syndrome in children.
impact on diagnosis of the metabolic syndrome, which depends on rigid dichotomization of risk factor levels. Second, obesity is the strongest determinant of elevated CV risk. Although diagnosis of the metabolic syndrome requires abnormal levels of three of the five components, as shown in the study by Costa, a significant percentage of obese children have adverse levels in only one or two, as opposed to three. Other studies in children have shown that obesity is the single factor routinely associated, either cross-sectionally or longitudinally with clustering of the risk factors, and it is equal to the metabolic syndrome in predicting adult risk. Moreover, many studies have reported the exceptionally strong tracking effect of obesity from childhood to adulthood. It appears that placing greater emphasis on early recognition of obesity and elevated individual risk factors, rather than searching for a syndrome of factors, would be more productive in pediatric care.

Despite the failure of the metabolic syndrome to track significantly during childhood or from childhood to adulthood, there is an association between clustering of elevated risk factors in childhood with risk factor levels later in life. Our studies have shown that while only 16% of children with the metabolic syndrome at mean age 13 had the syndrome at mean age 22, they had significantly higher levels of BMI, waist circumference, percent body fat, and triglycerides and significantly lower levels of HDL-C, compared to individuals without the syndrome at age 13. In an attempt to design a more reliable method than the metabolic syndrome for evaluating degrees of CV risk in children, we developed a metabolic factor cluster score by taking the average of the standardized deviates of the five metabolic syndrome criteria. The results were striking, with the cluster score at age 22 approximately eight times higher in the individuals with metabolic syndrome at age 13 than the non-metabolic syndrome group. In addition, there was a strong tracking effect for the cluster score \( r = 0.51, p < 0.0001 \), indicating that relative rank of the cluster score at age 13 predicted its rank at age 22. These findings are consistent with the risk factor components of the metabolic syndrome being continuous variables with graded risk, rather than having threshold levels of risk that are compatible with dichotomization into normal and abnormal values.

Substituting homeostatic model assessment (HOMA) for fasting plasma glucose significantly increased the percentage of children with metabolic syndrome in each of the three prevalence studies. The HOMA measurement was developed in an attempt to provide a less burdensome surrogate measure of insulin resistance than the more involved direct measures, such as the euglycemic, hyperinsulinemic clamp. However, despite the combination of fasting glucose and insulin, HOMA is not an improvement over fasting insulin alone, with a correlation of \( r = 0.99 \) in children and an equally high correlation in adults. Moreover, it is a poor estimate of insulin resistance in children, particularly in thin children. It is not surprising that including HOMA instead of fasting glucose in the metabolic syndrome would significantly increase prevalence. This is most likely related to the confounding effect of fatness on insulin levels, as evidenced by the high correlation between fasting insulin and BMI in children and the influence of obesity on insulin hypersecretion independent from obesity-related insulin resistance.

The relation between insulin resistance and the metabolic syndrome (or clustering of CV risk factors) has long been attractive as an etiologic unifying concept. However, despite the significant relation between BMI and insulin resistance, studies in adults and children have shown that not all obese individuals are insulin resistant. Using data from a cohort of obese adults, the highest levels of insulin resistance were associated with the highest levels of blood pressure, plasma glucose and lipids. Our studies have shown 1) in a cohort of 300 15 year old's significantly higher levels of CV risk factors are found in heavy-insulin resistant adolescents than heavy-insulin sensitive adolescents; and 2) levels of insulin resistance at age 13 predict levels of blood pressure, triglycerides and a cluster score at age 19. Thus, it appears that insulin resistance has a relevant, but undefined, role in early CV risk development.

The paper by Costa et al. points out the complex nature of the metabolic syndrome. How then, should CV risk be addressed in children? Based on available information, the following can be concluded: 1) thin children, without strong genetic history, rarely have elevated CV risk factors; 2) elevated CV risk has a significant relation to insulin resistance, but currently there are no simple and effective methods for measuring it; 3) obese children should be screened for elevated CV risk factors, with an emphasis on identifying abnormal factors as opposed to relying on the metabolic syndrome to determine degree of risk.

References

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