Metabolic Syndrome in Children and Adolescents: Prevalence, Public Health Issue, and Time for Initiative

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Screening for features of the metabolic syndrome is being recommended by many learned societies and scientists in the field. Guidelines and recommendations as to how and whom to screen still vary from country to country and are not solely based on evidence from large, longitudinal studies. Whether the term “metabolic syndrome” is of clinical relevance in children and adolescents and more meaningful than individual components such as hypertension, insulin resistance, and type 2 diabetes mellitus or dyslipidemia is still open for debate. In addition, comorbidities of obesity such as sleep-disordered breathing and sleep apnea even at a young age have been recognized more recently. Nevertheless, along with the increasing prevalence of obesity in childhood and adolescence, the existence of the metabolic syndrome in obese children and adolescents is being recognized. The prevalence of any feature of the metabolic syndrome is being reported to be up to 30%, irrespective of the definition that is applied. Signaling molecules, termed adipokines, secreted from the adipose tissue, are thought to play a major role in the pathophysiology of the metabolic syndrome. Leptin and its soluble receptor may be more important in states of energy deficiency rather than as a predictor of the metabolic syndrome in humans. Adiponectin is not only related to obesity and insulin resistance but also appears to be the strongest predictor for the metabolic syndrome, even in children. In addition, adiponectin is thought to play a role in protecting against cardiovascular events. Finally, low-grade systemic inflammation may underlie the clustering of metabolic risk factors. In this issue of the Journal of Pediatric Gastroenterology and Nutrition, Viggiano et al (1) report on the prevalence of the metabolic syndrome in a primary care setting in Europe. They have collected clinical and biochemical data to characterize comorbidities in obese children and adolescents in a pediatric cohort followed within the Italian National Health Service. The overall prevalence of the metabolic syndrome in this unselected pediatric population was more than 30%. Screening for metabolic syndrome and individual features thereof is warranted and should be included in the healthy children clinics in Europe.

DEFINITION OF METABOLIC SYNDROME

The concept of and the term metabolic syndrome were introduced by Reaven (2) in 1988 in adults, when he noticed from the analysis of experimental, clinical, and epidemiological studies the simultaneous occurrence of hyperinsulinemia with several other cardiovascular risk factors in the same patient, and that this clustering resulted in a markedly higher cardiovascular morbidity. He had already recognized obesity and insulin resistance to be the common underlying pathogenetic mechanisms. The concept of the metabolic syndrome was subsequently refined and developed further (3–5). In a joint statement of the American Diabetes Association and the European Association of the Study of Diabetes, the clarity and accuracy of the existing definition was questioned (6). Some criteria used are ambiguous or incomplete, and it has not been proven that the predictive value of the “syndrome” over the predictive value of single components themselves is actually higher. In addition, ongoing research has identified more components worth considering, including cytokines and adipokines. Nevertheless, there is no doubt that there is a clustering of risk factors that correlate with each other and are

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associated with cardiovascular disease, increased sympathetic activity, and obstructive sleep apnea (OSA), and certainly, obesity and insulin resistance constitute major risk factors.

METABOLIC SYNDROME IN CHILDREN AND ADOLESCENTS

Until recently, the metabolic syndrome has been regarded as a syndrome of multimorbid adults. However, in recent years, pediatricians around the world increasingly see obese children and adolescents with impaired glucose tolerance, hypertensive blood pressure (BP) levels, dyslipidemia, and hyperuricemia. Hence, no matter what definition is applied, there are obese children at high risk for cardiovascular disease and sleep apnea. The increase in the prevalence of obesity in children is well known (7,8). This phenomenon is demonstrated by the dynamic long-term alterations in body mass index (BMI) percentiles. Comparing BMI percentiles 15 years apart, there is a clear rise in the 97th percentile over time, whereas the 3rd and 50th percentile remained stable during the same period of time. This indicates not only that more children become obese but also that the degree of obesity increases (9,10). The 97th percentile crosses the adult cutoff of 25 kg/m² at an age range of about 10 years, and by 14 years the 97th percentile exceeds 30 kg/m².

With the increasing prevalence of obesity, we will have to and already do face the consequences of obesity at a much younger age. In our cohort of obese children, we saw a high prevalence of metabolic pathology. One third had signs of insulin resistance that correlated with BMI and many had dyslipidemia (11). This is in agreement with many other studies such as that by Sinha (12) and is also seen in German white cohorts (13,14). Another important component is BP and hypertension that is not as well investigated in children so far. In a large cross-sectional study of about 2500 children, we identified a mild but continuous increase in the prevalence of hypertensive BP levels that sharply raised when children became overweight (15). It also appears that cardiovascular risk factors cluster in children as shown in other studies, and similarly observed that about one third of overweight and obese children had classical cardiovascular risk factors, such as dyslipidemia and particularly BMI-dependent hypertension (16). There are few studies that aimed to define the metabolic syndrome in children, which is probably even more difficult than in adults because the selection and the cutoffs of the parameters are even more arbitrary. These studies uniformly show that the metabolic syndrome is a disorder that is highly prevalent in the pediatric population (17–20) (Table 1).

NONALCOHOLIC STEATOHEPATITIS

In addition to these classical components of the metabolic syndrome, there is increasing concern about the emergence of nonalcoholic steatohepatitis (NASH) in obese children. Nonalcoholic fatty liver disease was found in 55% (21) to 77% of obese children, with about 24% already suffering from NASH (22). Recent studies suggest that insulin resistance and oxidative stress are important in the pathogenesis of NASH and that NASH may hence be considered the hepatic manifestation of the metabolic syndrome (23). As in adults, NASH in children may progress to cirrhosis in later life in about 20% and 30% to 40% of patients with NASH cirrhosis will experience liver-related death (24,25).

TABLE 1. Overview of the incidence of metabolic syndrome in children in representative studies (29–31)

<table>
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<tr>
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</tr>
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<tbody>
<tr>
<td>Obesity</td>
<td>BMI &gt;97th percentile</td>
<td>Waist &gt;75th percentile</td>
<td>BMI &gt;85th percentile</td>
<td>Waist &gt;90th percentile</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>&gt;95th percentile</td>
<td>&gt;1.1 mmol/L</td>
<td>&gt;75th percentile</td>
<td>&gt;90th percentile</td>
</tr>
<tr>
<td>HDL cholesterol</td>
<td>&lt;5th percentile</td>
<td>&lt;1.3 mmol/L</td>
<td>&lt;25th percentile</td>
<td>&lt;10th percentile</td>
</tr>
<tr>
<td>Blood pressure</td>
<td>&gt;95th percentile</td>
<td>&gt;90th percentile</td>
<td>&gt;75th percentile</td>
<td>&gt;90th percentile</td>
</tr>
<tr>
<td>Glucose metabolism</td>
<td></td>
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<tr>
<td>Fasting glucose</td>
<td>≥6.1 mmol/L</td>
<td></td>
<td>≥6.1 mmol/L</td>
<td>&gt;100 mg/dL</td>
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<tr>
<td>IGT</td>
<td>≥7.8 mmol/L</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prevalence of metabolic syndrome in the study population</td>
<td>38.7 (moderate)</td>
<td>31.2</td>
<td>11.5</td>
<td>20 (overweight)</td>
</tr>
<tr>
<td>Prevalence (degree of obesity), %</td>
<td>49.7% (morbid)</td>
<td></td>
<td></td>
<td>30% (BMI &gt;99th percentile)</td>
</tr>
<tr>
<td>n (ethnic population)</td>
<td>439 obese (mixed)</td>
<td>1960 obese (mixed)</td>
<td>2244 normal (normal)</td>
<td>1030 (319 families) (Hispanic); 34% overweight, 57% obese</td>
</tr>
</tbody>
</table>

IGT = impaired glucose tolerance.

Definition criteria for metabolic syndrome are shown in the upper part of the table. Metabolic syndrome was defined as having 3 or more of the components. Cutoff levels for the respective studies are given.

MOLECULAR PREDICTORS FOR THE METABOLIC SYNDROME IN CHILDREN

Research into the mechanisms and mediators of obesity-related sequelae has greatly expanded during the last several years. In particular, factors released from adipose tissue appear to play a key role in pathogenetic mechanisms. These compounds, such as inflammatory molecules (eg, tumor necrosis factor-α, interleukin-6, and C-reactive protein [CRP]), cytokines (eg, leptin, adiponectin, visfatin, and others), and fatty acids, exert biological actions beyond the adipose tissue, and many directly influence peripheral metabolic, vascular, and endocrine processes (11,26–28).

OSA SYNDROME/SLEEP-DISORDERED BREATHING

In a recent study of obese children 53% were normal, 11% had primary snoring, 11% had mild OSA, 8% had moderate-to-severe OSA and 17% had central sleep apnea. Half of the patients with central sleep apnea had desaturation <85% SO₂. Only enlarged tonsils were predictive of moderate-to-severe OSA. On the contrary, higher levels of abdominal obesity and fat mass were associated with central sleep apnea. A number of additional studies also show that sleep-disordered breathing is common in clinical samples of obese and overweight children. Obstructive sleep apnea is not associated with abdominal obesity; on the contrary, higher levels of abdominal obesity and fat mass are associated with central sleep apnea. Importantly, significant positive correlations were found between log-CRP levels and arousal index, whereas an inverse correlation was found between the lowest nocturnal arterial oxygen saturation and log-CRP levels. Moreover, 94% of the children with elevated log-CRP levels reported excessive daytime sleepiness and/or learning problems, compared with 62% of the children with normal log-CRP levels. Therefore, plasma CRP levels were increased among some children with sleep-disordered breathing and were correlated with arterial oxygen saturation nadir and arousal index measures. These changes were particularly prominent among children who were sleepy or presented with neurobehavioral complaints. The intermittent hypoxemia and sleep fragmentation of sleep-disordered breathing may underlie inflammatory responses, the magnitude of which may ultimately lead to cardiovascular, cognitive, and behavioral morbidities of obese children (29,30).

In summary, there is an alarming increase of obesity-related comorbidities in children and adolescents beginning from a relatively young age, even leading to the full complex of “metabolic syndrome,” including features of insulin resistance, hypertension, and sleep-disordered breathing. Factors from the adipose tissue may constitute not only markers but also mediators of metabolic seque-lae of obesity already at a young age. On the basis of these considerations and epidemiologic evidence such as the one reported on by Viggiano et al (1), action is warranted; obesity screening programs within all national health services indeed need to be implemented. Key parameters to be monitored include weight and height measurements, BP data, waist-to-hip ratio, preferably waist circumference, and in high-risk populations, laboratory parameters such as fasting blood glucose, triglycerides, and cholesterol measurements. However, such screening advice is only prudent if preventive and/or treatment measures are defined and followed systematically and in all individuals identified with the metabolic syndrome. Such measures will aim toward lifestyle interventions rather than drug treatments.

REFERENCES