Association of Arterial Stiffness and Endothelial Dysfunction with Metabolic Syndrome in Obese Children

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Objective We investigated whether metabolic syndrome, defined in 3 different ways (2 commonly used and 1 novel) is associated with arterial alterations in obese children.

Study design The study group comprised 384 obese children age 2.5 to 18 years. Blood pressure, fasting blood glucose, blood insulin, plasma lipids, and body composition were measured. Noninvasive ultrasound measurements were obtained in 161 patients to investigate arterial mechanical properties and endothelial function.

Results The prevalence of metabolic syndrome was 10.4%. Intima-media thickness correlated positively with low-density lipoprotein cholesterol ($r = .21$; $P < .01$) and negatively with high-density lipoprotein cholesterol ($r = -.17$; $P < .05$). In adolescents (11 to 18 years), cross-sectional vascular compliance correlated negatively with abdominal fat ($r = -.22$; $P = .02$). The only synergistic effects among individual metabolic syndrome components was an effect of insulinemia and systolic blood pressure on cross-sectional compliance (4.05; $P < .05$). No significant difference in vascular variables was found between the patients with and without metabolic syndrome using any of the 3 definitions.

Conclusion Metabolic syndrome in obese children is not related to arterial variables, whereas several of its individual components are associated with vascular alterations. These data suggest that the value of the metabolic syndrome as a predictor of future cardiovascular events in children remains to be prospectively evaluated. In the meantime, individual cardiovascular risk factors should be evaluated and controlled. *(J Pediatr 2008;153:65-70)*

In adults, the cluster of metabolic risk factors known as *metabolic syndrome* is associated with an increased risk of cardiovascular events.[1] The presence of these metabolic cardiovascular risk factors in obese children has been widely reported.[2-7] In an earlier study, we documented a link between early vascular alterations in obese children and several of these risk factors.[2] Whether metabolic syndrome in children and adolescents is directly linked to arterial function remains unknown, however.

The definition of metabolic syndrome is controversial in adults and children.[8-10] Variations in the definitions used probably explain some of the variability in reported prevalence of metabolic syndrome in obese children, which ranges from 19.5% to 50%.[11-14] Based on a literature review in 2005, Kahn et al[8] concluded that the definition of metabolic syndrome is imprecise and its relevance in predicting cardiovascular disease uncertain. Important issues include whether the individual components of metabolic syndrome may affect cardiovascular risk differently from the full-blown syndrome and whether clustering of these individual components in a given patient results from a common underlying pathological process. The distinction between causal and descriptive definitions of metabolic syndrome[10] underscores the need to evaluate whether a cluster of metabolic abnormalities indicates an increased cardiovascular risk in obese children.

Echotracking techniques can be used to detect alterations in mechanical properties of the common carotid artery and endothelial function of the brachial artery, which are

AF	Abdominal fat	HOMA-IR	Homeostasis model of assessment of insulin resistance
ApoA1	Apolipoprotein A1	IMT	Intima-media thickness
ApoB	Apolipoprotein B	LCSA	Lumen cross-sectional area
BMI	Body mass index	LDL	Low-density lipoprotein
CSC	Cross-sectional compliance	LLF	Lower-limb fat
CSD	Cross-sectional distensibility	OGTT	Oral glucose tolerance test
DWS	Diastolic circumferential wall stress	TC	Total cholesterol
FMD	Flow-mediated dilation	TG	Triglyceride
GTNMD	Glyceryltrinitrate-mediated dilation	WCSA	Intima-media cross-sectional area
HDL	High-density lipoprotein		

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Table I. Main characteristics of the study population

	Girls (n = 233)	Boys (n = 151)	Total (n = 384)
BMI z-score, mean (95% CI)	4.0 (3.8 to 4.1)	4.3 (4.1 to 4.5)	4.1 (4 to 4.2)
Insulin resistance, n (%)	142 (60.9%)	90 (59.6%)	232 (60.4%)
Glucose intolerance, n (%)	19/118 (16.1%)	6/74 (8.1%)	25/192 (13.0%)
Diabetes, n (%)	0	2 (1.3%)	2 (0.5%)
Systolic or diastolic blood pressure > 95th percentile, n (%)	34 (14.6%)	16 (10.6%)	50 (13.0%)
TG > 95th percentile, n (%)	11 (4.7%)	18 (11.9%)	29 (7.5%)
HDL < 5th percentile, n (%)	14 (6.0%)	36 (23.8%)	50 (13.0%)

CI, Confidence interval.

established markers for coronary artery atherosclerosis in adults. In the present study, we evaluated the relationship between arterial alterations identified using echotracking techniques and various definitions of metabolic syndrome, with the goal of determining whether the metabolic syndrome concept is relevant to the management of obese children.

METHODS

Study Population

We studied 384 obese children and adolescents, ranging in age from 2.5 to 18 years, recruited in 3 different teaching hospitals. In the study patients, the body mass index (BMI, computed as the weight in kilograms divided by the square of the height in meters) *z*-score was at least 2.5 standard deviations above the age- and sex-specific mean in normal French children.[15] We divided the patients into 2 age groups: 2.5 to 10.9 years (128 children; 84 [65.6%] girls; mean age, 8.5 years) and 11 to 18 years (256 adolescents; 149 [58.2%] girls; mean age, 13.9 years). Age at onset of obesity was defined as the age at which the BMI exceeded the 97th percentile of reference BMI curves established in France.[15] Pubertal stage was determined in each patient according to Tanner's criteria.[16]

Our Institutional Review Board approved the study. Written informed consent was obtained from the oldest children and from both parents of all children before study enrollment.

Procedure

Each patient underwent a thorough physical examination, including weight, height, and blood pressure measurements. Blood samples obtained after an overnight fast were used to determine plasma glucose, insulin, and lipid (total cholesterol, high-density lipoprotein [HDL], low-density lipoprotein [LDL], apolipoprotein A1 [apoA1] and B [ApoB], and triglycerides [TGs]) levels. An oral glucose tolerance test (OGTT) was performed in a subgroup of 192 patients. involving administration of an oral glucose load of 1.75 g/kg body weight (maximum, 75 g) after an overnight fast and measuring plasma glucose and insulin concentrations immediately before and 120 minutes after the load. Plasma glucose was measured using the glucose oxidase method, and plasma insulin was assessed using a radioimmunoassay with polyclonal antibodies (INSI-PR; CIS Bio International, Gif-Sur-Yvette, France). Total cholesterol, TG, and ApoA1 and ApoB were measured by enzymatic assay (Boehringer, Mannheim, Germany). HDL cholesterol was assayed after precipitation of very-low-density lipoprotein (VLDL) and LDL with phosphotungstic acid. LDL cholesterol concentration was estimated using Friedewald's formula. High total cholesterol, LDL cholesterol, ApoA and Apo B, and TG concentrations were defined as values above the 95th percentile,[17-19] and low HDL cholesterol concentrations were defined as values below the 5th percentile.[17] Insulin resistance was defined as a value of the homeostasis model of assessment of insulin resistance (HOMA-IR, the product of fasting glucose concentration times fasting insulin concentration divided by 22.5) > 2.[20] Body fat was measured by dual-energy X-ray absorptiometry (Hologic Discovery, Waltham, MA).

Our definition of pediatric metabolic syndrome was based on the World Health Organization and National Cholesterol Education Program reference definitions[11,21] (Table I and II; available at www.jpeds.com) and was similar to the definition used by Weiss et al.[12] We considered metabolic syndrome to be present in all patients with at least 3 of the following 5 criteria: abdominal obesity, high TG (above the 95th percentile[18]), low HDL cholesterol (below the 5th percentile[17]), high systolic or diastolic blood pressure (above the 95th percentile[22]), and diabetes or glucose intolerance as detected by the OGTT. Abdominal obesity was defined as an abdominal fat to lower-limb fat ratio (AF/LLF) > 0.85. The choice of this threshold was based on the World Health Organization definition for adult metabolic syndrome, which includes a waist-to-hip ratio > 0.90 for men and > 0.85 for women.[21] According to American Diabetes Association criteria,[23] we defined diabetes as fasting glucose level > 7 mmol/L (1.26 g/dL) or glucose level > 11.1 mmol/L 120 minutes after the glucose load during the OGTT, and defined glucose intolerance as glucose level of 7.8 to 11.1 mmol/L at the same OGTT time point. This definition of the metabolic syndrome is very close to that of Weiss et al;[12] their definition differs only by a criterion of BMI above the 97th percentile instead of our abdominal obesity criterion.

In contrast, the definition of Viner et al,[13] the third definition that we used to study our population, differs greatly. They base the definition of metabolic syndrome on the presence of 4 of the following 5 criteria: BMI above the 95th percentile for age and sex; TG concentration > 150 mg/dL, HDL cholesterol concentration < 35 mg/dL, or total