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Metabolic syndrome, hepatic steatosis, and cardiovascular risk in children

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ABSTRACT

Objectives: Pediatric metabolic syndrome (MetS) is a well-recognized entity; however, there is no consensus on its exact value in predicting long-term cardiovascular (CV) risk. Hepatic steatosis (HS) is another emerging condition associated with pediatric obesity, and data have been reported suggesting a possible role of HS in CV risk linked to MetS. The aim of the present study was to evaluate the usefulness of HS and MetS cluster in predicting CV risk linked to pediatric obesity.
Methods: We studied 803 overweight and obese children (395 girls and 408 boys, mean age 9.4 ± 2.5 y, body mass index *z*-score 2.2 ± 0.53) with complete clinical and biological assessment. MetS was defined using the modified criteria of the American Heart Association. The diagnosis and severity of the HS was based on ultrasound. To assess CV risk, all patients underwent ultrasonography to measure carotid intima-media thickness (cIMT)—a validated marker of subclinical vascular disease.
Results: The overall prevalence of MetS was 13.07%; HS was significantly higher in patients with MetS (40.9 versus 18.5%; $P < 0.001$; odds ratio, 3.059; 95% confidence interval, 1.98–4.7). Spearman's correlation between HS grade and the number of MetS criteria met by each patient was significant ($r = 0.285$; $P < 0.001$). No statistical difference was recorded in cIMT and cIMT *z*-scores between patients with or without MetS, until inclusion of HS as an additional criterion for the diagnosis of MetS. In this case, there was a significant difference in cIMT *z*-scores between the two groups. In multiple linear regression analysis, the cIMT *z*-score value was better predicted with HS grade and the MetS cluster (adjusted $R^2 = 2.6\%$; $P = 0.002$) than when using the MetS cluster only.
Conclusions: HS could be used as additional criterion in detecting pediatric MetS phenotype at higher risk for long-term CV morbidity.

Introduction

Metabolic syndrome (MetS) is characterized by metabolic and clinical abnormalities such as obesity, impaired glucose metabolism, dyslipidemia, and hypertension. It plays an important role in the development of cardiovascular diseases (CVDs) and type 2 diabetes [1,2]. Once considered to be typical of adulthood, MetS is currently a serious, social, health-related problem and may be present at any age, although in varying degrees [3,4].

IR, AC, GDF, and RV conceptualized and designed the study, coordinated and supervised data collection, carried out analysis and interpretation of data, drafted the initial manuscript, and approved the final manuscript as submitted. MM and LS collected data, critically reviewed the manuscript, and approved the final manuscript as submitted. MDA, IG, LM, and MPM designed data collection instruments, critically reviewed and revised the manuscript, and approved the final manuscript as submitted. The authors have no conflicts of interest to disclose.

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Metabolic abnormalities typical of MetS—even considered singularly (and not necessarily in the context of MetS)—are a significant risk for CVDs and premature death [5]. Obesity is an independent predictor for the onset of MetS, and its prevalence increases with the degree of obesity. An obese child is at higher risk for developing MetS and, consequently, at a higher risk for CV accidents later in life [6]. Indeed, the appearance of MetS would result in early structural and functional modifications of the arteries leading to atherosclerosis [7].

A validated method for the diagnosis of early subclinical vascular disease is the evaluation of carotid intima-media thickness (cIMT), which is the thickening of the carotid vessel wall as measured by ultrasound. This was reported to be directly related to higher CV risk [8]. The effects of the proinflammatory state lead to an increased arterial wall thickness and are amplified in young adulthood, 20 to 30 years before coronary artery disease is clinically manifest [7]. Therefore, early screening for MetS in children corresponds to an early identification of individuals at increased CV risk during adulthood [9].

To our knowledge, there currently is no consensus on the diagnosis of MetS in pediatric patients. Various definitions in the literature have interesting suggestion to homogenize the definition [10,11]. One side of the debate claims that the risk is better represented by the MetS cluster than the isolated well-known items [12]. In this respect, some authors have suggested that hepatic steatosis (HS) should be considered an organ manifestation of MetS in adults as well as in children and adolescents; therefore, it should have a place in the exact definition of CV risk belonging to MetS or even independently [13,14].

The aim of the present study was to evaluate the usefulness of HS and MetS cluster in predicting CV risk linked to pediatric obesity.

Methods

Study sample and anthropometric measurements

We analyzed white children aged >2 y and adolescents referred for overweight or obesity to the Unit of Pediatrics at the University Hospital of Foggia, Italy, from October 2007 to April 2013, by retrospective analysis of medical records. Obesity was defined as a body mass index (BMI) ≥95% according to Centers for Disease Control and Prevention growth charts [15,16].

Exclusion criteria were the presence of secondary or syndromic obesity, other chronic diseases, acute illness, acute or chronic viral hepatitis, use of alcohol or any other toxic substance, or use of medication known to have an effect on liver function.

We recruited 1300 participants ages 2 to 16 y; 497 were excluded. Of these, 180 had no informed consent signed by their parents or caregivers, 250 patients presented one or more exclusion criteria and 67 children did not accept or undergo carotid or liver ultrasonography.

The control group was recruited from children with functional bowel disorders, with a normal nutritional status, and without any history of chronic disease or drug treatment. All patients and controls underwent an identical 1-d screening program.

A complete medical history was recorded including auxologic data that allowed definition of evolution of height and weight parameters. All clinical examinations were conducted by trained medical staff, according to standardized procedures: Body weight was measured by the same physician scale to the nearest 0.1 kg in light underwear, before breakfast and after voiding. The standing height was measured barefoot to the nearest 0.1 cm on a standardized wall-mounted height board. BMI was calculated for each participant and BMI *z*-score was assessed.

Each patient underwent a pubertal evaluation according to Tanner's criteria [17,18]. Blood pressure (BP) was measured at the right arm, with appropriate sized cuff after 10 min of resting in a comfortable supine position. Systolic BP (SBP) and diastolic BP (DBP) were assessed by standardized protocols. The mean value of three measurements was registered and BP *z*-scores were calculated [19].

Laboratory analyses

Blood samples were obtained for each patient after an overnight fast for determination of metabolic parameters including glucose, insulin, serum triacylglycerols (TG), total cholesterol (TC), low-density lipoprotein (LDL) and high-density lipoprotein (HDL) cholesterol, and hepatic profile (aspartate transaminase [AST], alanine aminotransferase [ALT], and gamma-glutamyl transferase [γGT]). Plasma glucose was measured by using Beckman glucose analyzer (Beckman, Fullerton, CA, USA).

TG, TC, LDL, and HDL levels were determined by using an automated analyzer (Unicle DxC800 Synchron System, Beckman Coolter, Fullerton, CA, USA). The relative percentile for TG, TC, LDL, and HDL was calculated according to data by Daniels et al. [20].

Carotid ultrasonography

Right and left cIMT were determined by the same trained radiologist who was blinded to the clinical and laboratory data of patients and controls. The carotid arteries were evaluated with high resolution B-mode ultrasonography with a 7.5 MHz transducers (LOGIQ 7, GE Medical Systems, Milwaukee, WI, USA).

Patients were in the supine position with the head rotated to the other side of examination during ultrasonography. cIMT was measured in three main segments of extracranial carotid arteries: carotid bulb, common carotid artery (1–2 cm proximal segment of carotid bulb), and internal carotid artery [21]. The wall thickness was calculated on both sides as the distance between the leading edges of the lumen-intima interface and the media-adventitia interface [22]. The average cIMT value was used for analyses, and the cIMT *z*-score was then calculated using reference data according to the ESCAPE (The Effect of Strict Blood Pressure Control and ACE Inhibition on the Progression of CRF in Pediatric Patients) study [23].

Liver ultrasonography

Liver ultrasonography was performed by the same experienced radiologist, who was blinded to the clinical and laboratory data of patients and controls, with linear and convex transducers 7.5 MHz (LOGIQ 7, GE Medical Systems).

The Ultrasonographic Steatosis Score (US-Score) was used to evaluate the degree of HS [24]:

Score 0: Normal liver echotexture, absence of steatosis;

Score 1 (mild hepatic steatosis): Increase in fine parenchymal echoes and preservation of echoes from portal vein walls and diaphragm;

Score 2 (moderate steatosis): Moderate and diffuse increase in parenchymal echoes and slightly impaired visualization of portal vein walls and diaphragm;

Score 3 (severe hepatic steatosis): Fine diffuse parenchymal echoes with reduction in beam penetration, vascular blurring, and poor or no visualization of the diaphragm.

Definition of metabolic syndrome

The diagnosis of MetS was made when at least three of the following clinical and laboratory criteria were fulfilled: BMI ≥ +2 SD; hypertension: SBP and/or DBP >90th percentile; HDL-C <10th percentile; TGs ≥110 mg/dL; or fasting blood glucose ≥100 mg/dL [4,10]. Thereafter, each patient was evaluated considering HS as an additional CV risk marker and defined as having a higher metabolic risk (HMR) when harboring at least three of these criteria: BMI ≥ +2 SD; hypertension: SBP and/or DBP >90th percentile; HDL-C <10th percentile; TGs ≥110 mg/dL; fasting blood glucose ≥100 mg/dL; hepatic steatosis.

Statistical analysis

All data were entered and analyzed in SPSS Statistics for Windows, version 22.0 (IBM, Armonk, NY). Results are expressed as means ± SD for continuous variables and as frequencies for categorical and qualitative variables. The Kolmogorov–Smirnov goodness of fit test was used for assessing the hypothesis of normal distribution of data. Mean values were compared by the *t* test and one-way analysis of variance for normally distributed variables, by the Mann–Whitney U test and Kruskal–Wallis analysis for nonparametric data. Bonferroni post hoc test was applied when appropriated. Spearman's rank correlation coefficient was used to evaluate significant association among variables, including the χ^2 test. Data were analyzed by sensitivity and specificity derived from the receiver operating characteristic (ROC) curve and the area under the ROC curve (AUC). Trend test was designed based on the Jonckheere–Terpstra test.

Multiple linear regression models were used to assess the effect of diagnostic criteria of MetS and ultrasound grading of HS on the cIMT *z*-score; the linear regression equation was calculated according to:

$$Yi = (\beta 0 + \beta 1Xi + \beta nXn) + \varepsilon i$$

where β0, β1, and βn are the regression coefficients, and Ɛ is the possible error associated with prediction. The level of significance was set at $\alpha = 0.05$.