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The possible role of liver steatosis in defining metabolic syndrome in prepubertal children

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Abstract

Insulin resistance is a key component of the metabolic syndrome (MS) and is strongly associated with liver steatosis. Our aim was to evaluate whether MS should be diagnosed already in obese prepubertal children and whether its prevalence is influenced by the inclusion of hepatic steatosis as a diagnostic criterion. Eighty-nine obese children (43 boys; age median [range], 8.5 [6-10] years) were enrolled. Metabolic syndrome was diagnosed according to a classic definition: presence of 3 or more of the following criteria—body mass index greater than 2 standard deviation score, triglycerides greater than the 95th percentile, high-density lipoprotein cholesterol less than the fifth percentile, blood pressure greater than the 95th percentile, and impaired glucose tolerance. Afterward, liver steatosis was included as an additional criterion to this definition. Metabolic syndrome was diagnosed in 12 children (13.5%) according to the first definition and in 18 children (20.2%) when liver steatosis was included. The prevalence of MS increased across homeostasis model assessment of insulin resistance tertiles (P for trend = .01). The prevalence of the single components of the MS was as follows: obesity, 100%; hypertriglyceridemia, 27%; low high-density lipoprotein cholesterol, 2.2%; hypertension, 34.8%; impaired glucose tolerance, 4.5%; and nonalcoholic fatty liver disease, 21.3%. In conclusion, MS is common already among prepubertal obese children, particularly when liver steatosis is included among the diagnostic criteria. Therefore, screening for the MS should be performed in this age group; and hepatic steatosis should be considered as an additional diagnostic criterion.

1. Introduction

Metabolic syndrome (MS) is a cluster of metabolic abnormalities, including insulin resistance (IR)/hyperinsulinemia, hypertension, dyslipidemia, central obesity, and impaired glucose tolerance (IGT), and represents an important risk factor for the development of cardiovascular diseases and type 2 diabetes mellitus [1].

Concomitant with the increasing prevalence of childhood obesity, the prevalence of MS is rising among children and adolescents [2,3]. However, as different criteria for the diagnosis of MS have been applied among several studies, discordant results have emerged; and these have generated some confusion on which definition should be applied to the pediatric population [4-6]. For this purpose, recently, the International Diabetes Federation (IDF) has proposed a new unifying definition for MS in children, including central obesity plus the presence of 2 additional criteria among hypertriglyceridemia, low high-density lipoprotein cholesterol (HDL-C), hypertension, and hyperglycemia [7]. The IDF specifically recommends applying this definition to children older than 10 years, whereas it suggests using the adult IDF definition for those 16 years or older. In contrast, the IDF states that, below the age of 10 years, MS as an entity is not diagnosed [7].

This last statement is arguable, given that there is clear evidence that obesity and other associated metabolic abnormalities are already present in prepubertal children [8-10]. Therefore, it seems plausible that also the

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constellation of these metabolic alterations is already detectable in this age group; and its prompt diagnosis is of particular relevance for the early implementation of preventive and therapeutic strategies.

In addition, recently, liver steatosis has been recognized as a relevant hepatic manifestation of the MS in obese adult [11,12] and pediatric populations [13,14], leading to the proposal of including liver steatosis among the criteria for the definition of the MS [12,13,15].

The aim of the present study was to assess the prevalence of the MS among a group of prepubertal children, aged 6 to 10 years, by using a classic definition [4] and then to evaluate a potential variation in its prevalence by considering liver steatosis as an additional criterion for the definition of MS in the same group of children.

2. Methods

2.1. Study population

Eighty-nine white prepubertal children (43 boys and 46 girls) aged between 6 and 10 years (mean age [±SD], 8.5 ± 1.1 years) who had been referred to the Obesity Clinic of the Department of Pediatrics, University of Chieti, Italy, between November 2006 and January 2008 were included in the present study. All subjects were affected by obesity (standard deviation score for body mass index [SDS-BMI] >2 SD for age and sex) [16], were otherwise in good health, and were not affected by any chronic disease. Autoimmune hepatitis, Wilson disease, antitrypsin deficiency, hepatitis B and C, and iron overload were excluded with appropriate tests in subjects with elevation in alanine aminotransferase (ALT). None was taking any medication known to affect liver function, and none had a history of consumption of alcohol.

A detailed medical and family history was obtained from all subjects; and a complete physical examination was performed, including anthropometric parameters (height and weight) and staging of puberty on the basis of breast development in girls and genital development in boys according to the Tanner criteria (all patients had preadolescent characteristics corresponding to stage 1).

After an overnight fast, all subjects had blood samples taken in the morning for the evaluation of ALT, lipid profile (total cholesterol, triglycerides, HDL-C and low-density lipoprotein cholesterol [LDL-C]). An oral glucose tolerance test (OGTT) was also performed in all study participants.

A liver ultrasound scan was performed in all subjects to assess the presence of steatosis. All liver ultrasound scans were performed by the same operator to reduce inter-operator variability. *Liver steatosis* was defined as the coexistence of elevated ALT (>40 U/L) and hepatic steatosis at ultrasound.

The study was approved by the Ethical Committee of the University of Chieti. Written informed consent was obtained from all parents; and oral consent, from all children.

2.2. Anthropometric measurements

Body weight was determined to the nearest 0.1 kg, and height was measured with Harpenden stadiometer to the nearest 0.1 cm. As fatness indexes, we used the SDS-BMI for age and sex and waist circumference (WC). The SDS-BMI was calculated using the following formula: SDS = (individual's measurement − population mean)/population SD [17], and WC was measured at its smallest point between iliac crest and rib cage.

2.3. Laboratory procedures

2.3.1. Alanine aminotransferase

ALT levels were measured using a standard automated kinetic enzymatic assay. We defined *elevated levels of ALT* as values greater than 40 U/L.

2.3.2. Lipid profile

Total cholesterol, HDL-C, and triglycerides were measured with an enzymatic-calorimetric test. LDL-C was derived according to the Friedewald equation.

2.3.3. Glucose and insulin

Plasma glucose levels were determined by using the glucose oxidase method, and plasmatic insulin levels were measured with 2-site immunoenzymometric assay (AIA-PACK IRI; Tosoh, Tokyo, Japan).

2.3.4. Oral glucose tolerance test

Subjects were seated for the test between 8:00 and 9:00 AM, after an overnight fasting of at least 12 hours. Baseline plasma glucose and insulin levels were measured. Thereafter, a flavored glucose in a dose of 1.75 g/kg body weight (up to a maximum of 75 g) was given orally; and blood samples were obtained every 30 minutes for the measurement of plasma glucose and insulin.

According to the American Diabetes Association criteria, subjects were diagnosed with IGT if their 2-hour glucose levels were between 140 and 200 mg/dL and as having diabetes if their 2-hour glucose levels were greater than 200 mg/dL [18].

2.3.5. IR index

Homeostasis model assessment of insulin resistance (HOMA-IR) was used as an index of IR and was calculated as follows: [fasting insulin (in milliunits per liter) × fasting glucose (in millimoles per liter)/22.5] [19].

2.4. Blood pressure

Blood pressure (BP) was measured in children by one investigator using a validation protocol. Systolic blood pressure (SBP) and diastolic blood pressure (DBP) were measured twice at the right arm after 10-minute rest in supine position using a calibrated sphygmomanometer and averaged. The cuff size, which was based on the length and circumference of the upper arm, was chosen to be as large

as possible without having the elbow skin crease, obstructing the stethoscope. An inflatable bladder width that was at least 40% of the arm circumference at a point midway between the olecranon and the acromion and whose length covered 80% to 100% of the circumference of the arm was used. *Hypertension* was defined as BP values greater than the 95th percentile for height, age, and sex [20].

2.5. Ultrasound examination

The diagnosis of hepatic steatosis was based on liver ultrasonography scanning that was performed in all participants by a single trained and experienced operator using a scanner LOGIQ 400 CL PRO (GE Healthcare, CA) with a 3.5-MHz transducer. The operator was unaware of the clinical course and laboratory details of the patients. Liver echotexture, liver-kidney differentiation in echo amplitude, hepatic echo penetration, and clarity of blood vessels were used to determine the presence of steatosis, as previously reported [21]. For quality control assessment, 10% of the subjects were reexamined; and these repeated measurements gave a coefficient of variation within 1%.

2.6. Definitions of MS

The following 2 definitions of MS were applied:

- Definition 1 (MS1) [4]: presence of 3 or more of the following criteria—BMI greater than 2 SDS; triglycerides greater than the 95th percentile for age, sex, and ethnic group; HDL-C less than the fifth percentile for age, sex, and ethnic group; BP greater than the 95th percentile for age and sex; and IGT: 2-hour plasma glucose during OGTT between 140 and 200 mg/dL.
- Definition 2 (MS2): presence of 3 or more of the following criteria—BMI greater than 2 SDS; triglycerides greater than the 95th percentile for age, sex, and ethnic group; HDL-C less than the fifth percentile for age, sex, and ethnic group; BP greater than the 95th percentile for age and sex; IGT: 2-hour plasma glucose during OGTT between 140 and 200 mg/dL; and nonalcoholic fatty liver disease (NAFLD): hepatic steatosis plus ALT greater than 40 U/L.

2.7. Statistical analysis

Analysis was performed using SPSS version 14.0 software for Windows (SPSS, Chicago, IL). P values < .05 were considered statistically significant. All data were expressed as mean ± SD unless otherwise stated. χ^2 for trend was used to assess changes in the prevalence of the MS across tertiles of HOMA-IR. Spearman correlation analysis was used to assess potential associations between HOMA-IR and components of the MS.

3. Results

Baseline clinical characteristics, anthropometric measurements, and laboratory investigations for the whole study population are reported in Table 1.

The study population included 43 boys and 46 girls. Out of the 89 obese prepubertal children, MS was diagnosed in 12 children (13.5%) according to the criteria of Weiss et al [4] (MS1 definition) and in 18 children (20.2%) when liver steatosis was also considered (MS2 definition). The prevalence of MS was equally distributed between the 2 sexes using both definitions ($P > .05$), but increased across tertiles of HOMA-IR (first, <1.97; second, 1.97-3.39; third, >3.39) based on both definitions (MS1—first tertile, 3.6%; second tertile, 10.6%; third tertile, 24.1%; P for trend = .02; MS2—first tertile, 3.6%; second tertile, 27.6%; third tertile, 27.6%; P for trend = .02) (Fig. 1).

The prevalence of the single components of the MS was as follows: obesity, 100% (by definition); hypertriglyceridemia, 27%; low HDL-C, 2.2%; hypertension, 34.8%; IGT, 4.5%; and NAFLD, 21.3% (Fig. 2). Significant correlations were found between HOMA-IR and triglycerides as well as between HOMA-IR and SDS-BMI and 2-hour plasma glucose (Table 2). In contrast, no significant correlation was found between HOMA-IR and the other components of the MS.

4. Discussion

The prevalence of childhood obesity and its metabolic comorbidities, which can all cluster together in the MS, is increasing at an alarming rate in both developed and developing countries [2,3]. In the present study, we assessed the prevalence of the MS in a group of prepubertal obese children and found a prevalence of around 14%, which increased to 20% when liver steatosis was included as an additional diagnostic criterion for the syndrome, therefore underlying the relevance of the MS even among prepubertal children.

Although in the literature there is a general agreement that MS is a common finding already in the pediatric age

Table 1
Clinical and biochemical characteristics of the study population

	Obese prepubertal children
Age	8.5 ± 1.1
Sex (M/F)	43/46
BMI (kg/m^2)	28.2 ± 5.70
SDS-BMI	7.7 ± 2.8
SBP (mm Hg)	114.2 ± 12.0
DBP (mm Hg)	69.7 ± 8.8
HDL-C (mg/dL)	49.1 ± 11.9
Triglycerides (mg/dL)	90.2 ± 42.0
HOMA-IR	3.03 ± 2.52
2-h plasma glucose (mg/dL)	104.6 ± 16.4

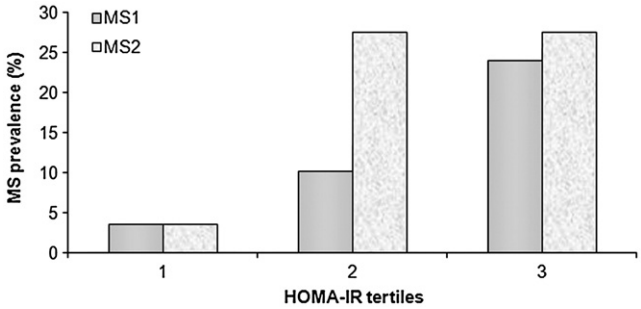

Fig. 1. Prevalence of the MS according to tertiles of HOMA-IR. The HOMA-IR tertiles are as follows: first, less than 1.97; second, 1.97 to 3.39; third, greater than 3.39. MS1: *P* for trend = .02; MS2: *P* for trend = .02.

group, there is no general consensus on how to define MS in children and adolescents. The application of the adult criteria is complicated by the coexistence of several definitions [1,22] and by the fact that many of the diagnostic parameters, such as BMI, WC, BP, and lipids, vary with age. Therefore, different authors have tried to modify the adult criteria, mainly by replacing specific numerical cutoffs with age-specific percentiles [4,23]. However, this has generated confusion and difficulties when comparing results across different studies. In fact, Goodman et al [24] have clearly shown that the prevalence of the MS varied from 4.2% to 8.4% by applying 2 different definitions to the same pediatric population. The IDF recently published a new definition of MS for the pediatric population [7], which, although it represents a valuable attempt of unifying the diagnosis of this condition in children, might be affected by some limitations, particularly related to the statement that, below the age of 10 years, MS should not be diagnosed as not being definable. This is in contrast with a large body of evidence showing that many of the metabolic and cardiovascular complications of obesity are already present in prepubertal children and are closely related to the presence of IR [9,25,26], the most common metabolic abnormality seen in obesity and the most important underlying factor of obesity-related complications [27].

Although IR represents the first complication of obesity, several recent studies have demonstrated that liver

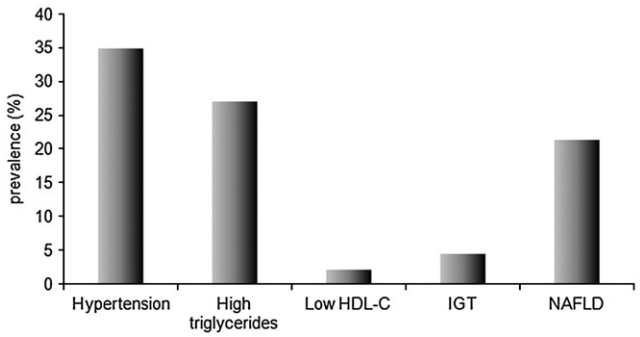

Fig. 2. Prevalence of components of the MS among obese prepubertal children.

Table 2
Correlation between HOMA-IR and components of MS

	r	*P*
SDS-BMI	0.277	.01
SBP (mm Hg)	0.198	.1
DBP (mm Hg)	0.59	.06
Triglyceride (mg/dL)	0.254	.019
HDL-C (mg/dL)	−0.07	.6
2-h glucose (mg/dL)	0.4	<.0001

steatosis is another frequent obesity-related comorbidity diagnosed early on during childhood [27], the prevalence of which can rise up to 52%, as recently documented in a cross-sectional study conducted on a sole prepubertal obese population [9]. In addition, each single component of the MS has been associated with obesity in young children. The strong relationship between hypertension and childhood overweight and obesity has been documented in several studies [8,25,28]. Furthermore, obese children and adolescents have consistently been observed to have an unfavorable lipid and lipoprotein profile [29,30]; and a clear predisposition to IGT [26] has also been demonstrated. Therefore, childhood obesity, even in the prepubertal age group, is linked to the whole spectrum of metabolic complications, raising the issue of why children younger than 10 years should not have the possibility of an accurate diagnosis of MS. This important issue has been clearly demonstrated by the present study, where we specifically aimed to assess the presence and cluster of metabolic abnormalities among prepubertal children and where we found a prevalence of MS as high as 13.5%. These data are in agreement with a previous study conducted by Ferreira et al [31], reporting a prevalence of 17.3% in a similar study population. In contrast, the study of Weiss et al [4] showed an alarmingly higher rate of MS among obese youths, equal to 38.7% in moderately obese children and to 49.7% in severely obese children. However, these prevalence data are not completely comparable to ours, as they are related to a mixed ethnic population, including also adolescents.

It needs to be acknowledged that the results of the present study might have been biased by the specific definitions we applied to define MS. However, at the moment, the choice to apply the criteria of Weiss et al [4] for the definition of MS is the most reasonable within common pediatric procedures. In fact, age- and sex-specific percentiles are used for the definition of abnormalities within the whole spectrum of pediatric diseases. A potential limitation in our study is the fact that a BMI *z* score greater than 2 was an inclusion criterion; and therefore, all our children had, by definition, already one of the criteria for the diagnosis of MS. However, similarly to the IDF definition, 2 other criteria—among hypertriglyceridemia, low HDL-C, hyperglycemia, and hypertension—were further required to define the syndrome.

In addition, as earlier shown, given the increasing prevalence and the early onset of obesity-related hepatic complications, particularly liver steatosis, we decided to add

this condition to the diagnostic criteria of MS. This is in agreement with the suggestion of Engelmann et al [13] and Weiss et al [32] of emphasizing the potential importance of testing for fatty liver as a component of the MS in obese children and adolescents. By considering liver steatosis as a diagnostic criterion, the prevalence was raised to 20.2%, although the limit of this study is that liver steatosis was defined by detectable ultrasound alterations in association with increased ALT instead of the criterion standard, invasive liver biopsy [33].

Although radiological modalities are unable to distinguish between nonalcoholic steatohepatitis and other forms of NAFLD [34], liver ultrasonography and other noninvasive methods (eg, computer tomography, magnetic resonance imaging) have an acceptable sensitivity and specificity for the diagnosis of increased fat accumulation (steatosis) in the liver. [34,35]. Nevertheless, ultrasound represents a good tool for the detection of fatty liver only when there is moderate or severe (>33%) fatty infiltration of the liver parenchyma [34]. Therefore, it might be argued that, in our study, hepatic steatosis has been slightly underestimated, indicating that a certain percentage of our patients would be affected without the disease being detected.

As expected and in accordance with previous studies [1,4,23], in this population, we confirmed the central role of IR in the MS, given that its prevalence significantly increased with worsening of insulin sensitivity, as assessed by HOMA-IR. As IR and the cluster of metabolic abnormalities characterizing MS can be further exacerbated by the hormonal and metabolic changes occurring during puberty, the high prevalence of MS within the prepubertal age group is alarming because, during puberty, it can only increase, not excluding the possibility of reaching the prevalence data of the study of Weiss et al [4]. Therefore, obese prepubertal children, particularly those with impaired insulin sensitivity, need to be screened for the whole spectrum of obesity-related metabolic complications and should be targeted as being affected by MS, as only a prompt diagnosis and a consequent implementation of preventive and therapeutic strategies can prevent cardiovascular morbidity and mortality later in life.

In conclusion, our study demonstrates the importance of screening for metabolic complications of obesity, including MS, already in very young children. There is an urgent need to establish universally accepted criteria for the MS for this age group to identify affected children. A misdiagnosis of MS represents a serious risk factor for the development of further consequences related to the persistent and exacerbated metabolic abnormalities later in life and especially during adolescence.

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