Frequency of the metabolic syndrome in obese Spanish pediatric population

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Abstract

Objective: Obesity is associated with insulin-resistance (IR), type 2 diabetes (T2D) and a constellation of cardiovascular risk factors at the early years of life. These features define the so-called metabolic syndrome (MS).

Aims: To assess the frequency of the MS among obese pediatric Spanish population and analyse the individual contribution and the predictive potential of individual components to the development of the syndrome.

Patients and methods: A total of 429 patients, 220 boys and 209 girls, aged 4–18 years, with a body mass index of > 2 standard deviation scores for Spanish normative charts, were included in the study. Forty-seven percent were prepubertal and ten percent had Hispanic ethnicity. HbA1c, lipids, liver enzymes and uric acid levels were determined from blood and a standard 2-h oral glucose tolerance test was performed. MS was defined by the National Cholesterol Education Program’s Adult Treatment Panel III criteria modified by Cook as having at least three features among: obesity, low high-density lipoprotein (HDL), hypertriglyceridemia, hypertension (HTA) or impaired glucose metabolism (IGM). We defined IR as homeostatic model assessment of IR index and/or fasting insulin levels > 95th centile of the control population.

Results: Almost 18% of the patients had MS, with significantly higher frequency in Hispanic (32%) than in Caucasian (16%) population. There were no differences by sex or pubertal status. Prevalence of low HDL, HTA, hypertriglyceridemia and IGM were 27, 23, 16 and 7% respectively. No silent T2D was identified. According to International Obesity Task Force charts, 22% of the patients were overweight and not obese, but no differences in the frequency of individual features of MS between these two groups were observed. Among IR patients (35% of our population), the frequency of MS reached 28%. IR predicted the presence of MS independently from age and race.

Conclusion: MS is present in 18% of our obese pediatric population. IR is closely associated with the components of MS and strongly predicts its development.

Introduction

Obesity is the sixth most important risk factor contributing to the overall burden of disease worldwide (1) and is associated with a constellation of metabolic derangements during the pediatric age (2). The prevalence of overweight and obesity is increasing rapidly worldwide in all age groups (3, 4). During 2001–2002, 16.5% of children aged 6–19 years in the US were overweight (3). In Europe, the number of children affected by overweight and obesity is now rising to at least 400 000 cases per year, and already affecting almost one in four children across the European Union (5). The highest prevalence is shown in southern European countries (20–35%). In Spain, prevalence of pediatric obesity increased from 13 to 35% in males and from 16 to 32% in females during 1985–2002 (6).

Childhood obesity has significant adverse health consequences (7–10); it is associated with dyslipidemia, hypertension (HTA) and glucose intolerance and predisposes to early cardiovascular disease. This constellation of metabolic disturbances has been defined as metabolic syndrome (MS). Insulin resistance (IR) has been implicated in the pathogenesis of this syndrome and obesity is, also in children, the most common feature associated with IR.

Although the term MS is widely used both in research and clinical practice, it has been defined imprecisely (11). While the concept of MS exists for at least 80 years, it was not until 1988 (12) that initiatives developed toward an internationally recognised definition for MS. Definitions by the World Health Organization (WHO), The National Cholesterol Education Program’s Adult Treatment Panel III (NCEP-ATP III), The European Group for the Study of
Insulin Resistance. The American College of Endocrinology and The International Diabetes Federation agree on the essential components of the syndrome but differ in some diagnostic criteria (13). There is no standard pediatric definition of MS, since it has not been well characterized in children in terms of diagnostic criteria and prevalence. Cook et al. (14) and de Ferranti et al. (15) modified the adult NCEP-ATP III criteria for adolescents. However, Viner et al. (16) define MS following WHO criteria adapted for children and, consequently, used hyperinsulinism as an additional component of MS.

The purpose of our study was to establish the frequency of the MS and its individual components in obese Spanish pediatric and adolescent population and to identify clinical or biochemical factors related with MS.

Patients and methods

We studied 429 children and adolescents (220 boys, 209 girls) with a mean age of 11.2 ± 2.8 years, who were referred to our Pediatric Endocrine Unit for the evaluation of obesity. Inclusion criteria were the existence of obesity as defined by body mass index (BMI) greater than 2 standard deviation scores (SDS) for age and sex upon Spanish normative charts (17) and age between 4 and 18 years, in the absence of previously diagnosed diabetes or medical treatment for hyperglycemia.

Detailed medical, personal and family histories of MS were obtained from all subjects, including birth weight for gestational age. A complete physical examination was performed with special attention to the existence of acanthosis nigricans. The height was measured using a Harpenden stadiometer. The weight status was evaluated as BMI (calculated as the weight in kilograms divided by the square of the height in meters) and the BMI SDS. Obesity in our study was defined by BMI SDS exceeding 2SDS according to Spanish charts. To explore the impact of the definition of obesity used by other international studies on the frequency of MS features, we also applied the obesity criteria by Cole (International Obesity Task Force) (18) to our BMI data. Pubertal development was assessed by physical examination according to Tanner staging (I–V). Sitting blood pressure (BP) was measured with the monitor Critikon Dinamap 8100 (Vital Signs), three times after the subject had rested at least 5 min. The lowest BP was chosen and was evaluated using the percentiles of International Task Force for BP (19).

All participants and their parents gave their written informed consent. The study was approved by the Ethical Committee of our Institution.

Metabolic evaluation

Before the implementation of weight-maintenance diets and personally adapted exercise programs in our patients, and after at least 3 days under 50% calorie intake of carbohydrates per day and 12-h overnight fast, lipids, liver enzymes, uric acid, HbA1c, glucose and insulin levels were obtained from blood and a standard 2-h oral glucose tolerance test (OGTT) was performed. Blood samples were obtained every 30 min for 120 min for the measurement of plasma glucose and insulin levels after the oral administration of 1.75 g of glucose per kilogram of body weight (maximal dose, 75 g). Plasma glucose concentrations were measured by the AEROSET c8000 analyzer using the glucose oxidase method. Insulin was measured by immunoassay, which does not importantly cross-react with proinsulin, using the Immulite 2000 Analyzer. The intraassay coefficient of variation (CV) values for controls at 7.67 and 12.5 μU/ml were 5.5 and 4.0% respectively, whereas the interassay values were 7.3 and 4.9% respectively.

The IR was determined by the plasma insulin levels and the use of a homeostatic model assessment of IR (HOMAIR = G (mmol/l) × I (μU/ml)/22.5) (20). The HOMAIR index was also evaluated in 69 healthy, non-obese children and adolescents with familiar short stature and without personal or familiar history of MS with a mean age of 12 ± 3 years.

The 95th percentile of HOMAIR index in these prepubertal and pubertal patients was 2.4 and 3 respectively. The fasting level of insulin >10.5 in prepubertal and >15 μU/ml in pubertal patients (>95th percentile of control group) were considered hyperinsulinemic levels. We defined IR when HOMAIR was ≥95th percentile and/or when hyperinsulinemic levels were observed.

Insulin sensitivity was calculated as quantitative insulin-sensitivity check index (QUICKI) (21, 22).

The insulinoenic index (IGI) (23) was estimated as a marker of early β-cell insulin response.

Plasma lipids levels were measured by enzymatic method with the use of AEROSET/ARCHITECT c8000 System (Abbott). Fasting levels of high-density lipoprotein (HDL) cholesterol and triglycerides were expressed in SDS and adjusted for age and sex according to Lopez’ study in Spanish pediatric population (24).

HbA1c was measured by HPLC Menarini technique standardized to the Diabetes Control and Complication Trial (normal range 4.05–6.05%). Plasma liver enzyme levels were measured with the use of AEROSET/ARCHITECT c8000 System (Abbott). Serum alanine amino transferase (ALAT) levels ≥40 U/l, were defined as increased. The existence of fatty liver was diagnosed by ultrasound scan, the study being performed by the same pediatric radiologist. Primary non-alcoholic fatty liver disease was diagnosed when other hepatic diseases like B, C and autoimmune hepatitis, al-anti-trypsin defect, Wilson’s disease and alcohol consumption were excluded.

The MS was defined by modified Cook’s criteria for adolescents (14) as having at least three of the following features: low HDL-cholesterol (<40 mg/dl),
hypertriglyceridemia (TG 110 mg/dl), obesity (BMI ≥ 2SDS for age and sex for Spanish normative charts (17)), HTA as diastolic and/or systolic BP > 95th percentile for age, sex and height according to the Task Force (19) and impaired glucose metabolism (IGM) according to the American Diabetes Association (ADA) criteria for children and adolescents (25). Impaired fasting glucose (IFG) was defined by levels, ≥ 100 mg/dl (5.6 mmol/l) but < 126 mg/dl (7 mmol/l), impaired glucose tolerance (IGT) as glucose levels between 140 and 199 mg/dl (7.8–11 mmol/l) 2 h after oral glucose load and diabetes (T2D) as fasting glucose ≥ 126 mg/dl (7 mmol/l) or ≥ 200 mg/dl (11.1 mmol/l) after oral glucose.

Statistical analysis

The values are presented either as mean ± S.D. or as frequencies. BMI, lipids and lipoprotein values are adjusted for age and sex by using the SDS (2), calculated according to the formula $z = x - \overline{x}/S.D$. The following statistical tests were used: the unpaired Student’s t-test, the $\chi^2$-test for categorical variables, non-parametric test (U Mann–Whitney) for variables that were not normally distributed. Multivariable logistic regression analysis was performed using statistically significant variables. Maximum model was performed for age, race, BMI SDS, HOMA, existence of acanthosis nigricans, HbA1c, γ-glutamyl transferase (GGT) and uric acid to identify their independent contributions to the MS. Co-linearity was assessed by Belsley criteria (26). The odds ratios (OR) are presented together with 95% confidence intervals (CI). Statistical significance was set at $P < 0.05$. The analyses were performed using SPSS statistical package version 12.0 (SPSS, Inc., Chicago, IL, USA).

Results

The average age of the 429 children and adolescents included in our study was 11 ± 3 years with a mean BMI of 27.3 ± 3.5 kg/m². Forty-seven percent of them were prepubertal. Patients were mainly Caucasian with the exception of 10%, who were from Hispanic origin. The baseline clinical and biochemical characteristics of the total population grouped according to the presence or absence of MS are shown in Table 1.

Seventy-six patients (18%) had diagnostic criteria for MS. Nearly 50% of our obese pediatric population had at least one additional cardiovascular risk factor. Abnormal glucose homeostasis was identified in 29 patients (7%). Twenty (4.6%) had IFG and 11 (2.4%) IGT. Two patients had both glucose metabolism abnormalities and no subjects had silent T2D. HTA was detected in 23% of our population (22.8% systolic and 0.6% diastolic HTA). Frequency of low-HDL cholesterol and hypertriglyceridemia was 27 and 16% respectively (Fig. 1).

Patients with MS were significantly older than patients without MS (Table 1). Percentage of prepubertal patients in the MS group was lower (38 vs 49%) but the difference was not statistically significant. In addition, no significant differences between boys and girls were found. There was a significantly higher frequency of MS in the Hispanic population of our cohort with respect to Caucasian patients (32 vs 16%). We did not find increased risk of MS among patients with parental obesity or familiar history of MS (data not shown). Subjects with MS had markedly higher IR and lower insulin sensitivity parameters than those without MS; the former also had significantly higher GGT, uric acid and HbA1c levels (Table 1).

In multivariable logistic regression analysis with MS as the dependent variable, IR (HOMA), HbA1C, GGT and uric acid significantly predicted the presence of MS independently from confounding variables (age or race). The estimated OR values for the presence of MS are shown in Table 2.

IR was found in 35% of the total population (150 patients). The presence of IR significantly influenced the frequency of MS; 29% of IR patients had MS compared with 8% in patients without IR ($P < 0.005$). All individual components of MS were significantly higher in IR patients than non-IR subjects, except low HDL (see Fig. 1); HTA: 29 vs 19% ($P < 0.005$), low HDL: 31 vs 24% (ns), hypertriglyceridemia: 23 vs 11% ($P < 0.005$), IFG: 10 vs 2% ($P < 0.005$) and IGT: 5 vs 1% ($P < 0.005$). Patients with IR also had higher frequency of hepatic steatosis by ultrasound scan (35 vs 6%, $P < 0.005$) and higher frequency of increased serum ALAT levels (11 vs 3%, $P = 0.05$) compared to non-IR obese children.

According to Cole charts (International Obesity Taskforce) (18), 22% of our patients should be classified as overweight and not obese. When we compared the frequency of the different components of MS in overweight vs obese patients, according to the IOTF criteria, we did not find significant differences in these two subgroups with respect to HTA (21 vs 23%), low HDL (25 vs 27%), hypertriglyceridemia (15 vs 16%) or IGM rates (10 vs 6%).

Discussion

In the last few decades, the prevalence of obesity has rapidly increased to epidemic proportions around the world (27), having worrying consequences on the health status of the populations and economies of developed and developing countries (28). The MS associated with obesity is an important risk factor for the development of cardiovascular disease, also among children. While an increasing number of studies are available on the prevalence and impact of MS in the adult population, there is a paucity of information on the epidemiology of MS at the pediatric age.

Our study, with a hospital-based study design, represents the first report on the frequency of MS in
Table 1 Clinical and biochemical characteristics of our population cohort. Values are presented as mean ± s.d. or percentage.

<table>
<thead>
<tr>
<th></th>
<th>Global (n = 429)</th>
<th>MS (n = 76)</th>
<th>No MS (n = 353)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (year)</td>
<td>11.2 ± 2.8</td>
<td>11.9 ± 2.8</td>
<td>11.1 ± 2.8</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Prepubertal</td>
<td>204/225</td>
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<td>175/178</td>
<td>n.s.</td>
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<td>Race hispanic (%)</td>
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<tr>
<td>SGA (%)</td>
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</tr>
<tr>
<td>BMI (kg/m²)</td>
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<td>29 ± 4.2</td>
<td>27 ± 3.2</td>
<td>&lt;0.005</td>
</tr>
<tr>
<td>BMI z-score</td>
<td>3.7 ± 1.3</td>
<td>4.1 ± 1.5</td>
<td>3.7 ± 1.2</td>
<td>n.s.</td>
</tr>
<tr>
<td>BMI &gt; 30 kg/m² (IOTF) (%)</td>
<td>78</td>
<td>82</td>
<td>78</td>
<td>n.s.</td>
</tr>
<tr>
<td>Acanthosis nigricans (%)</td>
<td>28</td>
<td>45</td>
<td>24</td>
<td>&lt;0.005</td>
</tr>
<tr>
<td>HOMAIR (G30)</td>
<td>1.3 ± 2.1</td>
<td>1.5 ± 1.8</td>
<td>1.5 ± 3.7</td>
<td>n.s.</td>
</tr>
<tr>
<td>Gender (female)</td>
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<td>36/37</td>
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<td>n.s.</td>
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MS, metabolic syndrome; SGA, small for gestational age; BMI, body mass index; HTA, hypertension; HDL, high density lipoprotein; LDL, low density lipoprotein; GGT, oral glucose tolerance test; HOMAIR, homeostatic model assessment of insulin resistance; QUICKI, quantitative insulin-sensitivity check index; IGI, insulinogenic index; AST, aspartate aminotransferase; ALT, alanine aminotransferase; GGT, g-glutamyl transferase; IR, insulin resistance (HOMA and/or fasting insulinemia > 95th centile). Differences were tested by the unpaired t-test and Mann-Whitney test (for continuous variables) and by the χ²-test (for categorical variables). P refers to differences between MS and non-MS groups. To convert the values for glucose to millimole per liter, multiply by 0.0551; to convert the values for triglycerides to millimole per liter, multiply by 0.01 129; to convert the values for cholesterol to millimole per liter, multiply by 0.02 586. The population has been divided according to the presence or absence of metabolic syndrome (MS).

Obese children and adolescents in Spain, as conducted in a large cohort. We found the presence of MS in 18% of children and adolescents in our series. MS frequency was significantly higher among the Hispanic population (32%) than in Caucasians (16%). The overall MS frequency appears to be lower but within the range of MS prevalence identified in other European countries (16, 29), and also lower than that found among North American children and adolescents (14, 15).

In European countries, a few studies using the modified WHO criteria for MS adapted for children, have shown MS prevalence of 33% in UK and 27.2% in a recent study of obese Turkish children and adolescents (30). In contrast, Csabi et al. (29) identified MS only in 8.9% of Hungarian obese children.

In US, the Third National Health and Nutrition Examination Survey study reported the prevalence of MS in 30% of overweight adolescents (14, 15) using the ATP III criteria for the definition of the syndrome. Similarly, Cruz et al. (31) reported a prevalence of 30% MS in 126 overweight Hispanic children and adolescents. However, Butte et al. (32) recently found a lower 20% MS frequency in an American pediatric cohort with the same Hispanic background.

However, the straightforward comparison of pediatric and adolescent MS frequencies found in different countries is not without difficulty. The main reason is the current lack of a standardized and internationally accepted definition for pediatric MS. In a recent article on obese French children, the frequency of MS was found to be 15.9% using the ATP III criteria; however, the accepted definition for pediatric MS. In a recent article on obese French children, the frequency of MS was found to be 15.9% using the ATP III criteria; however, the frequency reached 42.5% using the WHO definition (33). Discrepancies in the definition of individual components of the syndrome as well as slightly different normality thresholds used in different studies can have an impact on the overall MS prevalence identified (34). Other factors to consider are the specific characteristics of the populations studied, including ethnic background, age range and pubertal status of population samples. Finally, the global severity of obesity within each cohort might influence the prevalence of MS, as suggested by the work of Weiss et al. (35), who report MS prevalence reaching 50% in heavily obese children. Thus, an international definition for pediatric and...
adolescent MS seems necessary for its uniform application worldwide.

In our study, we used the NCEP-ATP III criteria for the definition of MS (14) with modifications representing the most recent updates on recommendations to diagnose pediatric HTA (ITF, 2004) (19) and alterations in glucose metabolism (ADA, 2004) (25). To define obesity, we used the threshold of >2SDS of BMI z-score on the national normative charts for growth, available in Spain since 1988 (17). To explore the possible implications of the use of international weight reference values on MS frequency, we also applied the IOTF criteria for obesity (18) to the BMI data from our obese patients. Following IOTF, 22% of our obese patients upon Spanish normative charts would be considered overweight. We compared the frequency of MS (and its individual components) in IOTF-overweight vs IOTF-obese patients and did not find any significant difference (data not shown). This is in agreement with the recent publications showing that discrimination between obesity and overweight using BMI in young children is not a good marker for the prediction of IR and, consequently, for the prediction of metabolic risk (36).

Furthermore, the mean BMI z-score of our group of patients with MS and the ones without MS is not significantly different, suggesting that severity of obesity did not play a major role in the development of MS in our cohort. This underlines the significance of factors additional to adiposity (e.g. genetic factors) in the development of MS (37, 38).

IGM is an important feature among the metabolic disturbances of MS and it has been studied in the obese pediatric population (39). In our cohort, we found IGM in 7% of children, either having IGT (2.4%) or IFG (4.6%). No individuals were identified with clinically silent type 2 diabetes (T2D).

The prevalence of IGT found in our cohort seems lower than that in other studies (31, 37, 39). Only the recent reports from Germany (40) and France (33) show a similar IGT frequency among obese patients (2.1 and 3.6% respectively). Other European studies show significantly higher rates of IGT ranging between 19 and 21% (30, 41), but also intermediate IGT frequencies ranging from 11% in British (16) and 7.5% in German (42) and Spanish (43) children to 4.5% in Italian obese children and adolescents (44). These variable IGT rates between studies can be influenced by the particular characteristics of cohorts and probably reflect the different IR indices found in these sample populations.

In contrast to the previous studies suggesting that IFG is rare in children (35), the IFG frequency we found doubles the one found for IGT in our cohort. This could be due to the more strict definition of IFG we applied following the latest recommendations of the ADA (2004) (25), probably allowing a better identification of these initial alterations of glucose metabolism.

IR is the defining pathophysiological defect in MS (45). Obesity leads to fat accumulation not only in adipocytes but also in muscle and liver cells, resulting in IR in these organs (46). Cruz et al. hypothesized that IR would be more closely associated with MS than overall adiposity (47). We found that 35% of our children and adolescents have IR.

The mean HOMAIR index in our obese patients was 2.5 (4.5 in those with IGM), whereas in the Yeste (41) and Sinha (39) cohorts, they were 3.95 (5.85 in those with IGT) and 5 (7.2 in those with IGT) respectively. These data emphasize the importance of IR as a contributing factor in the expression of IGM.

In different studies, IR has been shown to cluster with all the features of MS. We found that the prevalence of MS is significantly higher among our group of IR patients. Prevalence of other factors related to IR like HTA, low HDL, hypertriglyceridemia and IGM were also individually higher among our IR patients. Furthermore, in multivariable regression analysis, IR significantly predicted the presence of MS, independently of several confounding variables (Table 2). These findings stress the importance of IR in the development of MS.

### Table 2 Factors influencing the presence of MS.

<table>
<thead>
<tr>
<th>OR (OR CI 95%)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>HOMA</td>
<td>1.346 (1.04–1.73)</td>
</tr>
<tr>
<td>HbA1C</td>
<td>3.254 (1.35–7.79)</td>
</tr>
<tr>
<td>GGT</td>
<td>1.044 (1.0–1.08)</td>
</tr>
<tr>
<td>Uric acid</td>
<td>1.573 (1.17–2.1)</td>
</tr>
</tbody>
</table>

Multivariable logistic regression analysis with metabolic syndrome as the dependent variable and IR (HOMA), HbA1C, γ-glutamyl transferase (GGT) and uric acid as independent variables. OR, odds ratio.
and underline the interest of evaluating IR in obese children.

Interestingly, abnormalities in serum uric acid levels are often found in association with the presence of IR. In agreement with other studies (48), we found that uric acid is a reliable indicator for MS in obese children (Table 2). Elevation in serum GGT in obese children compared with normal weight children has also been described (49). The estimated OR values for the presence of MS were significant for HbA1c and GGT levels, suggesting these biochemical parameters could as well be useful predictors for MS.

In conclusion, we report a frequency of 18% of MS in Spanish children and adolescents with moderate obesity. Our findings suggest that IR is a good predictor for the development of MS in obese children and adolescents, with independence of age, ethnicity and the severity of obesity. These results provide evidence that, early in life, alterations in glucose metabolism and insulin sensitivity start to develop in obese children, and should be monitored in this segment of population at high cardiovascular risk.

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