CLINICAL STUDY

Serum uric acid and its association with metabolic syndrome and carotid atherosclerosis in obese children

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Abstract

Objective: The association between hyperuricemia, metabolic syndrome (MS), and atherosclerotic vascular disease has been reported in adults, but very little is known about this association in children. The aims of our study were to ascertain the correlates of uric acid (UA) in a sample of obese children, and to investigate whether UA is associated with carotid intima-media thickness (IMT) independently from classical risk factors including MS.

Methods: We analyzed carotid IMT along with serum triglycerides, total and high-density lipoprotein cholesterol, glucose, insulin, insulin resistance index (as homeostasis model assessment of insulin resistance), alanine aminotransferase, γ-glutamyltransferase, creatinine, and UA in 120 obese children and 50 healthy control children.

Results: UA concentrations were significantly higher in obese children compared with controls; moreover, they correlated with the most established cardiovascular risk factors. In the group of obese children, after adjustment for age, sex, pubertal stage, and creatinine, an independent association between UA levels and the presence of MS syndrome was observed (unstandardized coefficient, 0.044 (95% confidence intervals (CI) 0.015–0.072); P<0.01). Carotid IMT significantly increased in the fourth quartile of UA compared with that in the first, second, and third quartile (0.49 (0.46–0.53), 0.53 (0.49–0.56), and 0.55 (0.52–0.59) vs 0.61 (95% CI, 0.58–0.64); P<0.01). When multivariate analysis was performed after adjusting for age, gender, pubertal stage, creatinine, and MS (considered as a single clinical entity), or the individual components of MS simultaneously included, the association between UA and carotid IMT was significant (P<0.01).

Conclusions: In obese children and adolescents, increased UA levels are associated with carotid atherosclerosis.

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Introduction

Several epidemiological studies have shown that hyperuricemia is a risk factor for cardiovascular diseases (CVDs) in the general population (1–3). The contribution of serum uric acid (UA) to atherosclerotic vascular disease, however, remains controversial (4). Some studies argue that the observed association between UA and atherosclerotic vascular disease is attributable to an indirect association of hyperuricemia with cardiovascular risk factors or clustering of these metabolic and hemodynamic risk factors, designated 'metabolic syndrome' (MS) (5, 6). Recent evidence suggests that UA stimulates vascular smooth muscle proliferation and induces endothelial dysfunction. UA has been shown to decrease endothelial nitric oxide production and to lead to endothelial dysfunction and insulin resistance (7, 8). Consequently, UA induces vascular inflammation and artery damage, which in turn leads to an increased risk of atherosclerosis. Although many studies in adults have focused on the relationship between UA, MS, and carotid atherosclerosis (9–12), very little is known about this association in children and adolescents. Because atherosclerosis often begins in childhood or young adulthood (13), studies in this age group are important. One additional advantage of examining children is that a diminished potential confusion exists with adult-onset complications. Previous cross-sectional data have shown a close relationship between UA concentrations and cardiovascular risk factors in obese children and adolescents (14–17); however, the role of UA as an independent risk factor for CVD remains to be clarified in children.

Carotid intima-media thickness (IMT) measured noninvasively by ultrasonography is a well-established index of atherosclerosis and directly associated with increased risk of CVD (18, 19). This study aimed first to ascertain the correlates of UA in a sample of obese children.
children and adolescents, and then to investigate whether UA is associated with carotid IMT independently of classical risk factors including MS.

Methods

Study subjects

Between May 2007 and April 2008, 120 children and adolescents with primary obesity (body mass index (BMI) equal to or higher than the age- and sex-specific 97th percentile, which defines obesity according to the Italian BMI charts (20, 21)) were consecutively enrolled at the Department of Pediatrics, La Sapienza University of Rome, Italy. Exclusion criteria included the presence of renal disease; type 1 or 2 diabetes; any condition known to influence body composition, insulin action, or insulin secretion (e.g. glucocorticoid therapy, hypothyroidism, Cushing’s disease); a history of preexisting heart disease; history of use of medications that would affect carotid IMT or lipid profile; and history of alcohol consumption and smoking (where appropriate). All patients underwent physical examination (including measurements of weight, standing height, BMI, and determination of the stage of puberty according to the criteria of Tanner, laboratory tests, and carotid ultrasound (22)). The degree of obesity was quantified using Cole’s least mean-square method, which normalizes the skewed distribution of BMI and expresses BMI as a SDS. This measure gives age- and sex-specific estimates of the distribution median, the variation coefficient, and the degree of skew by a maximum-likelihood fitting technique (23). Systolic and diastolic blood pressures (BP) were measured twice at the right arm after a 10-min rest in the supine position by using an automated oscillatory system (Dinamap Vital Signs Monitor, Model 1846 SX; Criticon Incorporated, Tampa, FL, USA).

Over the same study period, 50 healthy children with BMI appropriate for gender and age were recruited to the study if parents consented to participate in the study, which included anthropometric measurements, laboratory investigations, and carotid ultrasound. No control child had a history of alcohol consumption and smoking (where appropriate). Yet, none of the healthy children had family risk factors for premature atherosclerosis, including hyperlipidaemia, hypertension, diabetes mellitus, and CVDs. The study was approved by the Hospital Ethics Committee, and informed consent was obtained from subjects’ parents prior to assessment.

Laboratory data

Blood samples were taken from each subject after an overnight fast, for estimation of serum concentrations of glucose, insulin, alanine aminotransferase (ALT), y-glutamyltransferase (GGT), total and high-density lipoprotein (HDL) cholesterol, creatinine, and UA. Insulin concentrations were determined using a RIA with polyclonal antibodies (CIS Bio International, Schering S.A., Gif-Sur-Yvette Cedex, France: detection limit, 2.0 mU/l; inter- and intra-assay CVs, 6.4–8.8 and 4.2–8.2% respectively) (22). We measured the remaining analytes on a COBAS INTEGRA 800 analyzer (Roche Diagnostics). UA, total cholesterol, HDL cholesterol, triglyceride, and GGT concentrations were assessed with the cassettes COBAS INTEGRA UA ver.2 (detection limit, 0.012 mmol/l; inter- and intra-assay CVs, 1.8–1.9 and 1.0–1.1% respectively), total cholesterol ver.2, HDL cholesterol ver.3, triglyceride according to IFCC, and GGT ver.2 respectively (Roche Diagnostics), by enzymatic colorimetric methods; ALT concentration with the cassette ALT according to IFCC by enzymatic u.v. method; glucose concentration with the cassette ver.3 by a hexokinase method; and creatinine concentration with the cassette creatinine Jaffé by a colorimetric method.

Carotid ultrasound

High-resolution B-mode ultrasonography of the common carotid arteries was performed with an Apio XV (Toshiba America Medical Systems, Tustin, CA, USA) with a linear 14 MHz linear transducer, following a standardized protocol (22). In brief, on a longitudinal, two-dimensional ultrasound image of the carotid artery, the posterior (far) wall of the carotid artery was displayed as two bright white lines separated by a hypoechogenic space. The distance between the leading edge of the first bright line of the far wall and the leading edge of the second bright line indicated the carotid artery IMT. The measurement was performed at the common carotid artery near the bifurcation during end diastole. We measured four values on each side, and maximum and mean IMT were calculated separately for each side.

The intraobserver variability of ultrasonographic measurements was <3% and all examinations were performed by a single experienced examiner who was blinded to the clinical and biochemical data.

Definitions

Identification of MS among children is often based on the adult criteria defined by the National Cholesterol Education Program’s Adult Treatment Panel (24) and the World Health Organization (25). In the adult definition, a minimum of three of five major criteria (obesity determined by waist circumference, hypertension, low HDL levels, elevated triglyceride levels, and glucose intolerance) should be fulfilled. These criteria have been modified for children (14, 21, 26). Obesity was defined as a BMI ≥ 97th percentile adjusted for age and sex (20, 21); hypertriglyceridaemia as triglycerides >95th percentile for age and gender (27); low HDL
cholesterol as concentrations <5th percentile for age and sex (27); elevated BP as systolic or diastolic BP > 95th percentile for age and sex (28). Impaired fasting glucose was defined according to the criteria of the American Diabetes Association (29). Insulin resistance was determined by a homeostasis model assessment of insulin resistance (HOMA-IR). Scores were calculated as the product of the fasting serum insulin level (mU/l) and the fasting serum glucose level (mmol/l), divided by 22.5. HOMA-IR changes during childhood depending on the age, gender, and pubertal stage (30). We have, therefore, considered HOMA-IR values above the 95th percentile as an indicator of insulin resistance. Thus, we defined MS in the presence of ≥3 of the following criteria: obesity, hypertension, low HDL cholesterol, elevated triglycerides, and impaired fasting glucose and/or insulin resistance.

Statistical analysis

Statistical analyses were performed using the SPSS package. Data are expressed either as frequencies or as means with 95% confidence intervals (CI). Distributions of continuous variables were examined for skewness and kurtosis and were logarithmically transformed, when appropriate. Geometric means are reported for log-transformed variables. Pearson’s correlation and linear regression coefficients were used to examine the relationship between variables, both in the whole population and, separately in controls and in obese children. The association between UA concentrations and the components of the MS were examined by multiple linear regression analysis. The fully adjusted regression model included age, gender, puberty stage, creatinine, and the individual components of MS entered as continuous variables. The independence of the association of UA with carotid IMT was assessed by multiple linear regression analysis. The fully adjusted regression model, together with UA, age, gender, puberty stage, creatinine, and MS (considered as a single clinical entity) were included as covariates. Separate regression models were also tested with the individual components of MS that were simultaneously included as either continuous or categorical variables in the same equation.

We took the maximum value of carotid IMT as the dependent variable in the regression models because the strongest association between the different measurements of IMT and coronary risk factors in otherwise healthy individuals is achieved by applying the maximum value of IMT and not the mean value of IMT (22). P<0.05 was considered to be statistically significant.

Results

Characteristics of the study population

The baseline clinical and metabolic characteristics for the 120 obese children and 50 healthy controls are shown in Table 1. Within the entire study population, there was no family history of symptomatic hyperuricemia. Values for glucose, insulin, HOMA-IR, triglycerides, ALT, GGT, creatinine, UA, and BP were significantly higher in the obese children, whereas HDL cholesterol levels were lower. The prevalence of MS in obese subjects was 27.5% (27.2% among males and 27.7% among females).

<table>
<thead>
<tr>
<th>Table 1 Baseline anthropometric and metabolic characteristics of the study cohort.</th>
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<tbody>
<tr>
<td><strong>Obese children</strong></td>
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<tr>
<td>(n=120)</td>
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<tr>
<td>Age (years)</td>
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<tr>
<td>Sex no. (%)</td>
</tr>
<tr>
<td>Male</td>
</tr>
<tr>
<td>Tanner stage no. (%)</td>
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<tr>
<td>I</td>
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<tr>
<td>II–III</td>
</tr>
<tr>
<td>IV</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
</tr>
<tr>
<td>BMI-SDS</td>
</tr>
<tr>
<td>Systolic BP (mmHg)</td>
</tr>
<tr>
<td>Diastolic BP (mmHg)</td>
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<tr>
<td>Alanine aminotransferase (U/l)</td>
</tr>
<tr>
<td>γ-Glutamyltransferase (U/l)</td>
</tr>
<tr>
<td>Total cholesterol (mg/dl)</td>
</tr>
<tr>
<td>HDL cholesterol (mg/dl)</td>
</tr>
<tr>
<td>Triglycerides (mg/dl)</td>
</tr>
<tr>
<td>Fasting glucose (mmol/l)</td>
</tr>
<tr>
<td>Uric acid (mmol/l)</td>
</tr>
<tr>
<td>Creatinine (mmol/l)</td>
</tr>
<tr>
<td>Insulin (mU/l)</td>
</tr>
<tr>
<td>HOMA-IR values</td>
</tr>
</tbody>
</table>

Results are expressed as n(%), mean (95% CI), or geometric mean (95% CI) for log-transformed variables.

**Notes:** UA values are within the recently established age- and sex-specific pediatric reference intervals for UA (31).
UA levels in relation to clinical, anthropometric, biochemical parameters, and MS

Within the entire study population, UA concentrations were significantly correlated with the most established cardiovascular risk factors (Table 2). When the association was restricted to the group of obese subjects, UA levels were significantly associated with BMI-SDS, systolic BP, triglycerides, HDL cholesterol, ALT, GGT, creatinine, insulin, and HOMA-IR, after adjustment for age, gender, and pubertal stage. No correlation was found between UA and total cholesterol. By contrast, when the association was restricted to the control group, UA levels were significantly correlated with BMI-SDS only (Table 2).

The mean concentrations of UA were significantly higher in the obese patients with MS compared with those without (0.32 (95% CI, 0.30–0.34) vs. 0.27 (0.26–0.29); P<0.0001), and they increased with the number of the components of MS (0.26 (95% CI, 0.24–0.28) vs. 0.28 (0.26–0.30) vs. 0.31 (0.28–0.33) vs. 0.36 (0.29–0.43)) in subjects with 1, 2, 3, and ≥4 components of the MS, P<0.0001 for trend (Fig. 1). In the group of obese children, an independent association between the concentrations of UA and the presence of MS syndrome (considered as a single clinical entity) was observed (unstandardized regression coefficient, 0.044 (95% CI, 0.015–0.072); P<0.01), after adjustment for age, sex, Tanner stage, and creatinine.

Table 2 Age-, sex-, and Tanner stage-adjusted correlation coefficients between serum uric acid concentration and variables measured in the study participants.

<table>
<thead>
<tr>
<th></th>
<th>All cases (n=170)</th>
<th>Controls (n=50)</th>
<th>Obese (n=120)</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMI-SDS (kg/m²)</td>
<td>0.597*</td>
<td>0.491*</td>
<td>0.341*</td>
</tr>
<tr>
<td>Systolic BP (mmHg)</td>
<td>0.394*</td>
<td>0.140</td>
<td>0.354*</td>
</tr>
<tr>
<td>Diastolic BP (mmHg)</td>
<td>0.218†</td>
<td>0.103</td>
<td>0.086</td>
</tr>
<tr>
<td>Triglycerides (mg/dl)</td>
<td>0.292*</td>
<td>0.127</td>
<td>0.211*</td>
</tr>
<tr>
<td>Total cholesterol (mg/dl)</td>
<td>0.169*</td>
<td>0.146</td>
<td>0.158</td>
</tr>
<tr>
<td>HDL (mg/dl)</td>
<td>−0.199*</td>
<td>−0.012</td>
<td>−0.194*</td>
</tr>
<tr>
<td>Fasting glucose (mmol/l)</td>
<td>0.113</td>
<td>0.134</td>
<td>0.028</td>
</tr>
<tr>
<td>Insulin (mU/l)</td>
<td>0.400*</td>
<td>0.068</td>
<td>0.383*</td>
</tr>
<tr>
<td>HOMA-IR values</td>
<td>0.430*</td>
<td>0.098</td>
<td>0.409*</td>
</tr>
<tr>
<td>ALT (UI/l)</td>
<td>0.427*</td>
<td>0.039</td>
<td>0.301*</td>
</tr>
<tr>
<td>GGT (UI/l)</td>
<td>0.325*</td>
<td>0.172</td>
<td>0.265*</td>
</tr>
<tr>
<td>Creatinine (mmol/l)</td>
<td>0.485*</td>
<td>0.196</td>
<td>0.240*</td>
</tr>
</tbody>
</table>

*P<0.05; †P<0.01; §P<0.001; ¶P<0.0001.

prevalence of the MS rose from 4.6% among obese subjects with concentrations of UA in the first quartile to 17.6, 37.9, and 41.6% among those with UA levels in the second, third, and fourth quartile respectively (P<0.01).

Carotid IMT in relation to clinical, anthropometric, biochemical parameters, and MS

Compared with controls, obese children showed increased mean carotid IMT (0.49 (95% CI, 0.47–0.51) vs. 0.40 (95% CI, 0.38–0.42) mm; P<0.0001) and maximum (0.55 (95% CI, 0.53–0.57) vs. 0.42 (95% CI, 0.39–0.44) mm; P<0.0001). Within the entire study population, carotid IMT were significantly correlated with BMI-SDS, systolic BP, triglycerides, ALT, GGT, glucose, insulin, HOMA-IR, and UA (r=0.562, P<0.0001), after adjustment for age, gender, and pubertal stage (Table 3). In the obese children, a significant correlation remained between carotid IMT values and systolic BP, ALT, insulin, HOMA-IR, and UA. By contrast, in the control group no associations were observed between carotid IMT values and systolic BP, ALT, insulin, and HOMA-IR, although a trend was observed between carotid IMT values and HOMA-IR, and UA (r=0.268, P=0.069; Table 3).

Maximum carotid IMT was significantly higher in the obese patients with MS compared with those without (mean, 0.60 (95% CI, 0.57–0.63) vs. 0.53 (0.50–0.55); P<0.0001); in particular, it was 0.53 (95% CI, 0.50–0.55), 0.53 (0.50–0.55), 0.59 (0.55–0.62), and 0.64 (0.58–0.71) in subjects with 1, 2, 3, and ≥4 components of the MS.
components of the MS, $P<0.05$ for trend (Fig. 1). In the group of obese subjects, an independent association between carotid IMT and the presence of MS was observed (unstandardized regression coefficient, 0.064 (95% CI, 0.026–0.102); $P<0.01$), after adjustment for age, sex, and pubertal stage. When the obese children were classified into four groups by UA quartiles, carotid IMT significantly increased in the fourth quartile of UA compared with that in the first, second, and third quartile (0.49 (0.46–0.53), 0.53 (0.49–0.56), and 0.55 (0.52–0.59) vs 0.61 (95% CI, 0.58–0.64); $P<0.01$ for trend); moreover, if patients with and without MS were analyzed separately, carotid IMT was still significantly increased in the fourth quartile of UA (Table 4).

### Discussion

In this study, we have shown that UA concentrations are associated with MS, independent of age, sex, Tanner stage, and degree of obesity in obese children and adolescents. We have also demonstrated for the first time that uric acid and carotid intima-media thickness (IMT) are significantly associated with metabolic syndrome after adjusting for age, gender, pubertal stage, creatinine, and MS (considered as a single clinical entity) or the individual components of MS simultaneously included (Table 5).
time that UA values are associated with carotid atherosclerosis independent of other atherogenic risk factors in this population.

Previous studies have shown a close relation between hyperuricemia and the MS both in adults and children (9, 11, 14, 16, 21, 32, 33). The prevalence of the MS among our obese children in the lowest quartile of concentrations of UA was very low (4.6%), while a high percentage (41.6%) of the children in the highest quartile of concentrations of UA had the MS. Therefore, our results are consistent with those of Ford et al. who previously demonstrated the association of the prevalence of MS in obese adolescents with quartiles of serum UA concentrations in a nationally representative sample of 1370 males and females aged 12–17 years (14). In addition, the UA concentration increased monotonically with the number of MS components. Similar findings have also been previously reported by Ford et al. (14).

In children, hyperuricemia has been associated with many of the established risk factors for CVD, including underlying abnormalities of insulin metabolism (i.e. impaired glucose tolerance, insulin resistance, or multiple MS, hypertension, dyslipidemia, obesity, and central adiposity (16, 21, 33)). In the study by Ford et al. abdominal obesity, hypertriglyceridemia, and hyperglycemia remained significantly associated with concentrations of UA even after adjustment for age, sex, race or ethnicity, concentrations of C-reactive protein, and other components of the MS (14). In addition, the association between high BP and concentrations of UA was of borderline significance (14). In a recent study involving the enrollment of 125 consecutive children for the evaluation of hypertension, Feig & Johnson have shown a continuous and strong correlation of UA with systolic BP in control subjects and in subjects with primary hypertension that was not explained by obesity or decreased renal function (34). Furthermore, the recent observation that allopurinol lowers UA and BP values in adolescents with essential hypertension (35). In the present study, we showed that the association of UA with IMT (17). These authors writing, only Schiel et al. have previously investigated the association between UA and carotid atherosclerosis and reported that this may not be independent of other cardiovascular risk factors (9–12). A number of studies have also shown that UA concentrations are influenced by conditions more commonly found in adults, such as impaired renal function, use of diuretics, alcohol consumption, smoking habits, diabetes mellitus, and CVD (9, 11, 43, 44).

In children, to our knowledge, at the time of this writing, only Schiel et al. have previously investigated the association of UA with IMT (17). These authors evaluated 81 overweight or obese children and adolescents (but no controls), and found an association between UA and IMT that was no longer significant when included in a very large regression model (21 variables for 81 participants) with multicollinearity problems. Differences in the compositions of the populations studied, sample size, and statistical adjustment for confounding variables may all have contributed to the conflicting conclusions between that study.
and ours. Thus, our finding of an independent and strong association between UA and carotid IMT among obese children and adolescents, even after adjustment for the MS (considered as a single clinical entity) or its individual components is novel, and because of the absence of chronic factors that confound studies among adults, it may contribute to a better understanding of the link between childhood obesity and adult CVD and have implications for lifestyle and health risks in a juvenile group. As for the adults, obesity in children is in rapid expansion across the world with the potential of adding considerably to the future health burden of cardiovascular and metabolic diseases. Coronary risk factors measured in children are associated with the early development of coronary artery calcifications, and obesity in adolescence is related with a significantly increased risk of early death from coronary heart disease during adulthood (45). For these reasons, the recognition of high-risk subjects is of great importance from a clinical and public health perspective. Measurement of UA is easy in terms of preanalytics, can be performed with simple methods in routine laboratories, and is inexpensive. Thus, a preventive, cost-effective approach may be available with potential implications for public health.

In conclusion, the strong association in obese children between UA and carotid atherosclerosis, independent of classical risk factors, insulin resistance, and components of the MS, supports the notion of a possible role for UA as a risk factor for early signs of atherosclerosis.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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