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Original Article

Association of serum uric acid levels to inflammation biomarkers and endothelial dysfunction in obese prepubertal children

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Background: High serum uric acid (SUA) levels are present in patients with metabolic syndrome (MetS), when the latter is associated with endothelial dysfunction, inflammation, and hypertension. This increase in SUA levels may have a key role in cardiovascular diseases.
Objective: We aim to quantify the differences in inflammation biomarkers, endothelial dysfunction, and parameters associated with MetS in obese prepubertal children compared to non-obese children, and determine if there is a relationship between uric acid levels and these variables.
Methods: A cross-sectional study was carried out on obese children (6–9 yr old). The study included 43 obese children and the same number of non-obese children (control group), matched by age and sex. SUA, C-reactive protein (CRP), interleukin-6 (IL-6), soluble intercellular adhesion molecule-1 (sICAM-1), glucose, insulin, lipid profile, and blood pressure were all measured.
Results: SUA levels, CRP, and sICAM-1 were significantly higher in obese children. In the obese group, SUA levels showed a positive correlation with body mass index (BMI), insulin, homeostasis model assessment for insulin resistance (HOMA-IR), CRP, IL-6, sICAM-1, and triglycerides (TGs), and correlated negatively with high-density lipoprotein cholesterol (HDL-C) and Apo-AI, but not with Apo-B. When adjusted for age, sex, and creatinine, it was noted that SUA levels are independent predictive factors for sICAM-1, CRP, and IL-6.
Conclusions: Inflammation biomarkers, endothelial dysfunction, and parameters associated with MetS are elevated in obese prepubertal children and correlate to uric acid levels.

Miguel Valle[a], Rosario Martos[b], María Dolores Cañete[c], Rosario Valle[d], Eva L van Donkelaar[e], Francisco Bermudo[a] and Ramón Cañete[f,g]

[a]Clinical Laboratory Department, Valle de los Pedroches Hospital, Pozoblanco, Córdoba, Spain; [b]Health Center of Pozoblanco, IMIBIC Córdoba, Spain; [c]PAIDI Group TSH-329 (IMIBIC), University of Cordoba, Córdoba, Spain; [d]Faculty of Medicine, Medical Surgical Specialties Department, Córdoba, Spain; [e]Faculty of Health, Medicine and Life Sciences, Maastricht University, Maastricht, the Netherlands; [f]Pediatric Department, Reina Sofía Hospital, School of Medicine Córdoba, Córdoba, Spain; and [g]School of Medicine Córdoba, Córdoba, Spain

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Corresponding author: Dr Miguel Valle Jiménez,
Clinical Laboratory Department,
Valle de los Pedroches Hospital,
C/ Juan del Rey Calero s/n,
Pozoblanco 14400,
Córdoba,
Spain.
Tel: (34) 957026309;
fax: (34) 957026309;
(34) 957026310;
e-mail: miguelvalle90@yahoo.es

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The last few years have seen a progressive increase in childhood obesity (1), and it is the most prevalent nutritional condition in developed countries (2). It is frequently associated to a series of metabolic disorders that comprise the so-called metabolic syndrome (MetS) (3, 4). Together with this syndrome, the following are

described in the obese adult: endothelial dysfunction, insulin resistance (IR), low degree of systemic inflammation, and inadequate fibrinolysis (5–8).

Increased serum uric acid (SUA) levels are present in patients with MetS, and obesity is the main determining factor of SUA level variation (9). In adults, the prevalence of this syndrome increases with increasing SUA levels (9–11). Uric acid may be a determining factor in this syndrome (9).

Therefore, high levels of SUA are associated with MetS, when this is associated to endothelial dysfunction, inflammation, and hypertension, and all this may contribute to the development of atherosclerosis (12, 13).

A positive and significant association has been described between SUA and several inflammation markers, such as C-reactive protein (CRP) and interleukin (IL)-6 (13).

Elevated levels of soluble intercellular adhesion molecule-1 (sICAM) are indicative of endothelial dysfunction, and this molecule plays an important role in the initiation of the inflammatory process (14).

Increased SUA levels may be an expression of an insulin-resistant state. Recent data have found that SUA is significantly associated with the homeostasis model assessment of IR in obese children (15). IR has a central role in the relationship between uric acid and MetS (9, 10, 16) and it is believed to cause a reduced excretion of SUA.

Different studies have described SUA as an independent risk factor for cardiovascular disease (CVD) (17, 18). Uric acid may mediate these effects by inducing oxidative stress, inflammation, and endothelial dysfunction (19, 20). Different evidence suggests that SUA stimulates vascular smooth muscle proliferation and induces endothelial dysfunction. This direct action of SUA has been suggested as a possible mechanism for its deleterious effects (21, 22).

In children and adolescents, the association between SUA and MetS has been described, as well as the different factors of cardiovascular risk in MetS (15, 23, 24).

Together with the disorders that define MetS, an increase in markers associated to endothelial dysfunction and inflammation, as well as elevated levels of SUA have been described in obese children compared to children with normal weight (25–28).

The association between the increase in uric acid and these variables may be initiated, in the obese child, at very early ages. The studies that analyze this possible association in obese children are scarce, and even more so the studies that analyze prepubescent children.

The aim of this study is to quantify the differences in inflammation biomarkers, endothelial dysfunction, and parameters associated with MetS in obese prepubertal children vs. non-obese children, and determine if there is a relationship between uric acid levels and these variables.

Materials and methods

Subjects

A cross-sectional study was carried out in obese children of both genders. One group included 43 obese children [body mass index (BMI) that surpassed the percentile 95 in the reference tables for the Spanish population] (29), and the other group (control) included an equal number of non-obese children (percentile <85) matched by age and sex (6–9 yr old). The study only included prepubertal children (Tanner stage 1).

Taking the homeostasis model assessment for insulin resistance (HOMA-IR) as the main variable, and given that the standard deviations for the two groups were 0.059 and 0.106, respectively, and that the expected mean difference was 0.052, with a power of 80% and a confidence level of 95%, 43 patients were required in the obese group and 43 in the control group.

Children with primary hyperlipidemia, hypertension, diabetes (fasting glucose ≥7.0 mmol/L), and impaired fasting glucose (fasting glucose ≥6.1 mmol/L and <7.0 mmol/L) (30) were excluded from both the test group and the control group, as were children with secondary obesity. None of the subjects were receiving regular drug treatment.

The study groups were formed of children from several schools. First, their corresponding pediatricians in the different schools were informed about the realization of the study. Child was included in one or another group according to his BMI. All the children are of Spanish origin. All parents gave their written consent, and the study was authorized by the hospital ethics committee.

Blood sampling and analysis

After a fasting period of 12 h, blood samples were collected from a vein in the antecubital fossa, without venous occlusion. Entire collections were made between 08:00 and 09:00 hours.

The samples were separated into aliquots and frozen immediately at −45°C until analysis. The following were measured in all the children: sICAM, CRP, and IL-6 levels, together with a range of MetS-related variables (insulin, lipids, blood pressure, carbohydrate metabolism, and uric acid). Glucose, uric acid, cholesterol, and triglyceride (TG) concentrations were measured using a random access analyzer (Axon, Bayer Diagnostics) with reagents from Bayer Diagnostics. The homeostasis model assessment for IR (HOMA-IR) was used to detect the degree of IR.

Resistance was assessed from fasting glucose and insulin concentrations using the formula: resistance (HOMA-IR) = [insulin (mU/L) × glucose (mmol/L)]/22:5. High-density lipoprotein cholesterol (HDL-C) was measured after precipitation of chylomicrons, very low-density lipoproteins, and low-density lipoproteins with phosphotungstic acid and magnesium ions. Insulin was quantified using an Access2-Immunoassay System (Beckman Coulter, Brea, CA, USA). Apolipoprotein A-I (Apo A-I), apolipoprotein B, and CRP were measured by nephelometry [N Antisera to Human Apo A-I, Apolipoprotein B (Apo-B), and N High Sensitivity CRP reagent, Behringwerke AG, Marburg, Germany] in a Dade Behring Analyzer II Nephelometer (Dade Behring, Inc., Deerfield, IL, USA). Antigenic immunoassay methods were used for the quantification of IL-6 (Quantikine human IL-6, RD systems, Wiesbaden-Nordenstadt, Germany) and sICAM-1 was measured by ELISA (IBL Immuno-Biological Laboratories, Hamburg, Germany) using a microtiter plate analyzer (Personal LAB, Phadia Spain S.L. Barcelona. Spain).

Anthropometric measurements and blood pressure: weight was measured to the nearest 0.1 kg and height to the nearest 0.1 cm. BMI was calculated as weight (kg)/height $(m)^2$. Blood pressure was measured with a mercury sphygmomanometer (Pymah Corporation, Sommerville, NJ, USA) after a 20-min rest, in a supine position. Three cuff sizes were used (9 × 32, 11 × 36, and 12 × 41 cm); the cuff width was required to cover 2/3 of the length of the child's arm. Three measurements were made, one every day, and the mean of the three was used.

Statistical analysis

Statistical assessment was performed using Microstat (Ecosoft, Indianapolis, IN, USA) or GraphPAD InStat (GraphPAD Software, San Diego, CA, USA). Abnormal values (outliers) were excluded. Results were expressed as a mean ± standard error mean (SEM), with a 95% confidence interval (95% CI).

The distribution of each variable was tested for departure from Gaussian distribution, and variance equality was controlled by Snedecor's F-test. The mean values of the groups were compared using Student's unpaired *t*-test. Statistical significance was set at $p < 0.05$. Correlation between variables was evaluated using Pearson's correlation coefficient and regression analysis. Multivariate regression analysis was performed using the stepwise method. For each variable, potential confounders ($0.05 < p < 0.2$) were evaluated by an analysis of raw and adjusted regression coefficients.

Table 1. Comparison between obese and non-obese chidren. Anthropometric measurements, insulin resistance, and blood pressure

	Non-obese children (n = 43)	Obese children (n = 43)	p
Male/female	18/25	18/25	
Age (yr)	7.91 ± 0.15	8.03 ± 0.17	0.601
Weight (kg)	27.37 ± 0.67	41.45 ± 0.98	<0.001
Height (cm)	127.46 ± 1.08	132.03 ± 1.09	0.004
BMI (kg/m^2)	16.83 ± 0.21	23.68 ± 0.34	<0.001
BMI z-score	0.05 ± 0.01	3.39 ± 0.17	<0.001
Waist circumference (cm)	57.72 ± 1.97	73.04 ± 2.19	<0.001
Glucose (mmol/L)	4.72 ± 0.04	4.75 ± 0.06	0.677
Insulin (μU/mL)	5.40 ± 0.34	6.88 ± 0.46	0.013
HOMA-IR	1.13 ± 0.06	1.48 ± 0.11	0.006
SBP (mm Hg)	88.87 ± 1.20	99.08 ± 1.46	<0.001
DBP (mm Hg)	52.25 ± 1.07	60.81 ± 1.22	<0.001

BMI, body mass index; DBP, diastolic blood pressure; HOMA-IR, homeostasis model assessment for insulin resistance; SBP, systolic blood pressure.
Values are means ± SEM.

Table 2. Comparison between obese and non-obese chidren. Uric acid, lipids levels, inflammation, and endothelial biomarkers

	Non-obese children (n = 43)	Obese children (n = 43)	p
Uric acid (mmol/L)	0.21 ± 0.004	0.24 ± 0.007	0.006
sICAM-1 (ng/mL)	247.73 ± 6.43	278.30 ± 9.93	0.011
C-reactive protein (mg/L)	0.92 ± 0.23	2.48 ± 0.31	<0.001
IL-6 (pg/mL)	1.60 ± 0.22	1.81 ± 0.16	0.441
Cholesterol (mmol/L)	4.32 ± 0.10	4.51 ± 0.09	0.174
Triglycerides (mmol/L)	0.585 ± 0.02	0.804 ± 0.05	<0.001
Apolipoprotein A-I (g/L)	1.61 ± 0.03	1.47 ± 0.03	0.001
Apolipoprotein B (g/L)	0.67 ± 0.02	0.72 ± 0.02	0.099
HDL-C (mmol/L)	1.44 ± 0.05	1.31 ± 0.04	0.027
LDL-C (mmol/L)	2.62 ± 0.08	2.844 ± 0.09	0.056

Values are means ± SEM. HDL-C, high-density lipoprotein-cholesterol; IL-6, interleukin-6; LDL-C, low-density lipoprotein-cholesterol; SEM, standard error mean; sICAM-1, soluble intercellular adhesion molecule-1.

Results

Clinical, anthropometric, and biochemical parameters were measured in the obese and control groups (Table 1). The mean age was 8.03 (obese) and 7.91 yr (control), with a range of 6–9 yr.

Mean SUA levels were significantly higher in obese children, at 3.96 mg/dL (95% CI 3.73–4.19) compared to 3.59 mg/dL in the control group (95% CI 3.44–3.74) (Table 2).

Although glucose concentration was slightly higher in the obese group, the differences were not significant (Table 1).

Relationship between uric acid and biomarkers of inflammation and endothelial dysfunction

Obese children displayed higher plasma sICAM-1 and CRP concentrations than non-obese subjects (Table 2). No significant differences were found in IL-6 levels between the obese group and the control group.

In the single linear correlation, for the obese group, SUA concentration was positively correlated with sICAM-1, CRP, and IL-6 (Fig. 1).

In the obese group, a multivariate regression analysis was carried out. Adjusting for age, sex, and creatinine, it was noted that SUA is an independent predictive factor for sICAM-1 (partial $p = 0.0014$), CRP (partial $p = 0.020$), and IL-6 (partial $p = 0.023$).

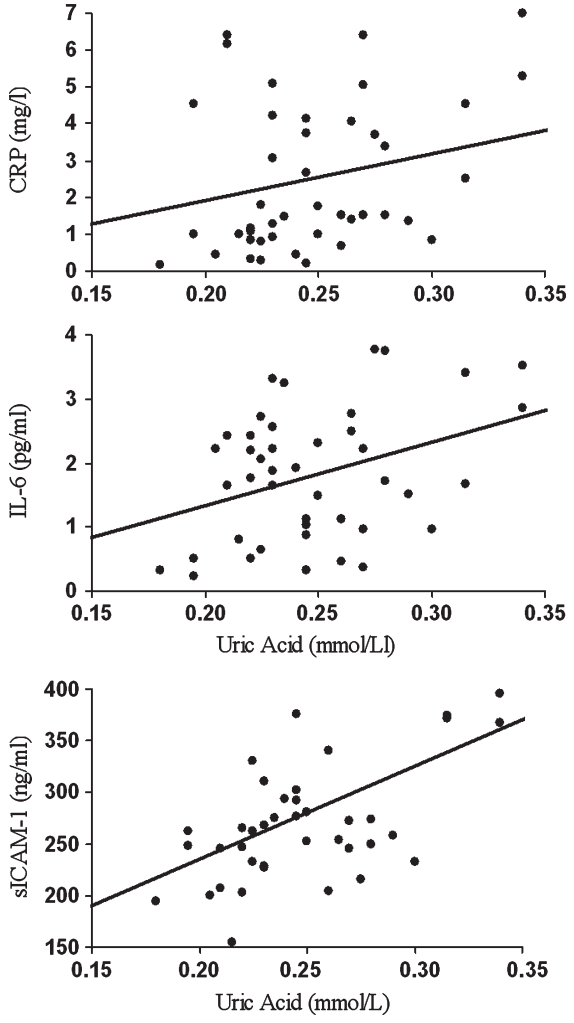

Fig. 1. Serum uric acid (SUA) concentrations as a function of C-reactive protein (CRP) ($r = 0.3375$; $p = 0.027$), interleukin (IL)-6 ($r = 0.3614$; $p = 0.017$), and soluble intercellular adhesion molecule-1 (sICAM-1) ($r = 0.5152$; $p < 0.001$) in obese children.

Table 3. Simple correlation coefficients (r) between uric acid and different variables of the obese group (n = 43) and the total group (obese and non-obese together) (n = 86)

	Uric acid	
	Obese	Obese and non-obese (together)
BMI	0.3943*	0.4275***
Insulin	0.3601**	0.4025***
HOMA-IR	0.3513**	0.3956***
C-reactive protein	0.3375**	0.3896***
IL-6	0.3614**	0.3145**
sICAM-1	0.5152***	0.4653***
Cholesterol	−0.0503	0.0340
Triglycerides	0.3631**	0.4454***
Apolipoprotein A-I	−0.3018	−0.2923**
Apolipoprotein B	0.0355	0.0710
HDL-C	−0.3850**	−0.2956**
SBP	−0.2187	−0.0750
DBP	−0.2069	−0.0808

BMI, body mass index; DBP, diastolic blood pressure; HDL-C, high-density lipoprotein-cholesterol; HOMA-IR, homeostasis model assessment for insulin resistance; IL-6, interleukin-6; SBP, systolic blood pressure; sICAM-1, soluble intercellular adhesion molecule-1.
*$p < 0.01$; **$p < 0.05$; ***$p < 0.001$.

In the combined group (obese and non-obese together), SUA correlates positively with sICAM-1, CRP, and IL-6 (Table 3). Adjusted for age and gender, in the entire group, the level of uric acid is an independent predictive factor for sICAM-1 (P partial < 0.001), CRP (P partial $= 0.028$), and IL-6 (P partial $= 0.023$).

Relationship between uric acid, IR, and parameters related to MetS

Tables 1 and 2 show MetS-related parameters for obese and non-obese children. Mean values for insulin, HOMA-IR, systolic blood pressure (SBP), diastolic blood pressure (DBP), and TGs were significantly higher in the obese group.

HDL-cholesterol and apolipoprotein A-I levels were significantly lower in obese children (Table 2).

The univariate correlation analysis for MetS-related parameters for obese and total group (obese and non-obese together) is summarized in Table 3. In the single linear correlation, in both the obese group and the whole group, SUA levels correlated positively with BMI, insulin, HOMA-IR, and TGs, and negatively with apolipoprotein A-I and HDL-C.

Discussion

Relationship between uric acid, IR, and parameters related to MetS

Obesity is a chronic condition that is frequently associated with various metabolic disorders that are grouped under the heading of MetS (3). This

syndrome is associated with high risk for diabetes and atherosclerotic CVD (31).

In adults, MetS may be accompanied by alterations of the endothelial function, resistance to insulin, and a low degree of systemic inflammation and inadequate fibrinolysis.

In this study, together with the disorders that are characteristic of MetS an increased SUA and increased biomarkers for IR are noted in obese compared to non-obese prepubescent children. These biomarkers correlate significantly with SUA levels.

There are high levels of SUA in MetS patients. The prevalence of this syndrome increases with increasing SUA levels (9, 10, 32). Obesity is the main determining factor for the variation of uric acid. An increase of one standard deviation in uric acid levels is associated in both genders to a 35% higher probability of MetS, which suggests that uric acid is a determining factor for this syndrome (9). Reduction in Standard Deviation Score (SDS)-BMI significantly correlates with changes in SUA in obese adolescents (33). In the results described in this study, SUA levels are significantly associated with the BMI, both in obese children and in the total group (obese and non-obese children jointly).

In obese prepubertal children, high levels of SUA have been described compared to non-obese children, as well as a significant association with features of IR syndrome (23). SUA was significantly associated with the homeostasis model assessment of IR in obese children (15). The association between SUA and MetS can be measured by the resistance to insulin (9, 10, 16). IR could be implicated in the lower uric acid excretion. Consistently with these statements, the current study found high levels of SUA and HOMA-IR in obese children compared to the levels in non-obese children. Furthermore, SUA levels correlate significantly with baseline insulin levels and HOMA-IR index.

The relationship between SUA level and CVDs has long been controversial (34). Some studies describe uric acid as an independent risk factor for CVD (17, 18). A significant correlation has been described between various indexes of coronary heart disease and SUA levels (5). In healthy adults, SUA levels are associated with different cardiovascular risk factors associated with MetS, such as obesity, hypertension (35, 36), low- and high-density lipoprotein-cholesterol, hypertriglyceridemia, and impaired glucose tolerance (11, 32, 34).

In this study, although SBP and DBP values were higher in obese children, there was no correlation between them and SUA values. Although other authors have reported a correlation between blood pressure and SUA (37), the children in this study were younger, and were all prepubertal. A future correlation between these two variables in the same subjects correlation at later ages cannot be ruled out.

Just as with adult subjects, SUA levels are inversely associated to the HDL-C concentration (33, 38).

Relationship between uric acid and biomarkers of inflammation and endothelial dysfunction

Therefore, high concentrations of SUA are associated with MetS, which in turn is associated with endothelial dysfunction, inflammation, and hypertension, and all this may contribute to the development of early atherosclerosis (12, 13, 20, 39). IR and a range of metabolic disorders grouped under the label 'MetS' are reported in obese children (24, 40); a number of authors – including the present team – have detected a low-grade systemic inflammation, alterations indicative of endothelial dysfunction (14, 25, 5, 41, 42), and findings consistent with inappropriate fibrinolysis (43) in these children. Hyperuricemia is associated with endothelial dysfunction in humans and lowering uric acid with xanthine oxidase inhibitors is associated with improvement in endothelial function (44–46).

sICAM plays an important role in the initiation of the inflammatory process (14) and is a biochemical marker associated to atherosclerotic progression and to other inflammatory disease processes (47). Elevated levels of this molecule are indicative of endothelial dysfunction and entail an enhanced leukocyte adhesion to the endothelium (48), a physiopathologically decisive stage in atherogenesis. Vascular endothelial dysfunction is considered to be the earliest stage in the atherogenic process.

Uric acid may mediate these effects by inducing oxidative stress, inflammation, and endothelial dysfunction (19). Significant association has been described between SUA and CRP and interleukin-6 (IL-6) (13).

This study not only shows an increase in inflammation biomarkers and endothelial dysfunction in obese prepubertal children, but also, that these biomarkers are associated very significantly to SUA levels. This association persists when obese and non-obese prepubertal children are jointly analyzed. This suggests that the increase in SUA levels entails a progressive increase in the values of markers for inflammation, endothelial dysfunction, and IR, both in healthy and obese children.

The study design did not permit sex-related differences to be established. The study focused only on prepubertal children, and therefore it was not possible to determine the influence on hormonal changes taking place in puberty on the variables studied.

Hyperuricemia is closely associated with obesity and MetS, and it may be involved in the development of the group of cardiovascular risk factors that accompany MetS. Although more studies are necessary

to determine the true importance of SUA levels, their quantification should be considered in the early evaluation of obesity and MetS.

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Conflict of interest

The authors declare no conflict of interest.

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