Association Between Serum Uric Acid and Metabolic Syndrome Components in Prep Ubertal Obese Children (Tanner Stage I) At Zagazig University Hospital

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ABSTRACT
Background: Biomarkers are useful in the early detection and risk stratification of metabolic syndrome (MetS) patients. Serum uric acid (SUA) is the end metabolite product of purine degradation and is the most abundant antioxidant in human plasma, as it protects against free radical oxidative damage.
Objective: To investigate the potential association between serum uric acid (sUA) and MetS.
Patients and Methods: A prospective case-control study was conducted in Cardiac Unit, Zagazig University Children's Hospital, during the period from February 2019 until August 2019. Our Study included 26 patients with metabolic syndrome who were randomly selected from 129 random obese pediatric patients according to waist circumference and BMI with percentage of 20.1%. We enrolled matched control with same number.
Results: Cases were significantly higher concerning uric acid. We found significantly positive correlation between body mass index (BMI), waist circumference (WC), systolic blood pressure (SBP), diastolic blood pressure (DBP), fasting blood glucose (FBG), triglycerides (TG), total cholesterol, low-density lipoproteins (LDL) and serum uric acid (SUA), while significant negative correlation of serum uric acid and high density lipoprotein (HDL-C). According to ROC curve analysis, the AUC of SUA for detection of metabolic patient with best cutoff value > 4.3 with sensitivity 70% and specificity 96.3%, and this was maximizing sensitivity and specificity to predict future metabolic syndrome and their area under the curve was 0.79.
Conclusion: Serum uric acid showed a significant correlation with components of metabolic syndrome making it a potent biomarker for diagnosing of metabolic syndrome patients in coming years.
Keywords: Serum uric acid - metabolic syndrome- obese Tanner Stage I.

INTRODUCTION

Hypertension, central obesity, increased triglycerides, decreased high-density lipoprotein cholesterol (HDL-C), increased blood glucose and insulin resistance are collectively defined as risk factors for cardiovascular disease triggered by metabolic syndrome [1]. The pathogenesis of MetS is very complex and not yet clear. Several studies support the concept that oxidant/antioxidant imbalance may play an important role in its manifestations [2]. In the last few years, in addition to the clinical factors, new factors in the pathogenesis of MetS have also been taken into consideration. These factors can be classified based on their function (e.g., marker of exposition, markers of effects, etc.) or in their biochemical or biologic properties (e.g., proteins metabolites, hormones, cytokines, etc.) [3].

For many pathological states, medicine relies on biomarkers to aid in diagnosis and management when overt clinical signs or gross anatomic abnormalities are absent or are not obvious. In addition to this, biomarkers can identify individuals within a population susceptible to disease on the basis of a "genotype" rather than on a reported history. Biomarkers also afford the ability to quantify this susceptibility, allowing for an estimation of disease risk for a population. A panel of metabolic syndrome biomarkers could provide a relatively easy, minimally invasive means of identifying those who are at risk for developing metabolic syndrome and subsequent complications [4]. Nowadays, biomarkers are useful in the early detection and risk stratification of MetS patients. Studies confirmed the implication of adipokines, neuropeptides, inflammatory cytokines, prothrombotic factors, and others in MetS pathogenesis [5]. Increased biomarkers of oxidative stress (OS) and decreased antioxidant defenses have been measured in blood of patients with MetS suggesting an *in vivo* overproduction of oxidizing species. In particular, it has been reported that patients with MetS have decreased antioxidant protection, in the form of depressed serum vitamin C and α-tocopherol concentrations, decreased superoxide dismutase (SOD) activity and increased protein and lipid oxidation levels [6].

Serum uric acid (SUA) is the end metabolite product of purine degradation and is the most abundant antioxidant in human plasma, as it protects against free radical oxidative damage [7]. Apart from the antioxidant property of uric acid, its abnormal raised levels crystallize in joints resulting in gouty arthritis. Moreover, gout is also associated with various cardiometabolic diseases like hypertension, diabetes, CV diseases and metabolic syndrome.

Increased prevalence of metabolic syndrome have been found in patients of hyperuricemia as compared to healthy population [8].

Previous studies based on the serum antioxidant capacity of uric acid, suggested that the raised uric acid in metabolic syndrome might be the defensive reaction of body to protect the RBC membranes against the increased oxidative stress [9, 10]. Hyperuricemia not only act as a separate determinant of MetS but also act as a risk factor for atherosclerosis and CV events [11].

Studies have established an association between hyperuricemia with metabolic syndrome and found 30% to 41% prevalence of metabolic syndrome in patients suffering from gout [8].

In fact, even though the exact biological mechanism is not yet known, uric acid seems to irreversibly react with nitric oxide (NO), disabling it and leading to endothelial dysfunction and, consequently, promoting the development of hypertension and MetS. At the same time, NO has a well-known role in the insulin resistance and its shortage reduces the blood flow to the tissues sensitive to insulin, resulting in blocking of the insulin action [12].

The study aimed to investigate the potential association between serum uric acid and MetS.

PATIENTS AND METHODS

A prospective case-control study that was conducted in Cardiac Unit, Zagazig University Children's Hospital during the period from February 2019 till August 2019. Our Study included 26 patients with metabolic syndrome who were randomly selected from 129 random obese pediatric patients according to waist circumference and BMI with percentage of 20.1%. We enrolled matched control with same number.

1) Patients' group: (*Group A):* Twenty-six obese prepubertal children (6-9 years old) patients with metabolic syndrome was diagnosed according to the criteria of International Diabetes Federation.
2) Control group *(Group B):* Twenty-six age and sex-matched healthy children are considered as control group.

Ethical and patients' approval: A written consent was taken from parents of the children. **The study was approved by our Ethical Committee.**

Inclusion criteria:
➕ All pre-pubertal obese with metabolic syndrome according to the International Obesity Task Force (IOTF) criteria and International Diabetes Federation (IDF) criteria. 6-9 years old children attending Pediatric Department and not on weight loss diet.
➕ The International Obesity Task Force (IOTF) developed a definition for overweight and obesity in children, which was based on gender and age specific body mass indices to classify children as:

❖ Overweight: BMI (25-29 kg/m^2)
❖ Obese: BMI of ≥30 kg/m^2 respectively.

According to the IDF definition, someone has the metabolic syndrome if he or she has central adiposity (waist circumference (WC) ≥ 90th percentile) plus two or more of the following four factors:

a) Blood pressure ≥ 95th percentile.
b) Fasting triglycerides (TG) ≥150 mg/dL.
c) High density lipoprotein (HDLc) < 40 mg/dL.
d) Fasting glucose ≥100 mg/dL) [13].

Exclusion criteria:
1) Specific causes of endocrine or genetic obesity.
2) Patients with type 1 or type 2 diabetes.
3) Patients with any disease that may affect level of serum uric acid e.g. previous heart, respiratory, liver and kidney diseases,
4) Current or past use of hormonal or interfering therapies (lipid-lowering, hypoglycemic, or antihypertensive treatments).
5) Child under the age of 6 years old, or above the age of 9 years old.
6) Child with sexual maturity more than Tanner stage 1.

OPERATIONL DESIGN
Type of the study:
A case-control study.
All patients were subjected to
A) **Full history taking:**
• Detailed history taking including name, age, sex, order in family, pregnancy and perinatal history of diseases, drugs or operation
• Birth history: gestational age, birth weight and NICU admission
• Nutritional history: Weaning food, routine diet and special dietary habits.
• Family history: similar condition and consanguinity:
  - Mother age, drug, disease, obesity, operation
  - Father age, smoking, obesity, diseases.
B) **Through clinical examination including:**
1) **General examination** including abnormal facies and obesity.
2) **Vital signs:** Respiratory rate, heart rate and core body temperature.
3) **Assessment of blood pressure:** Using a mercury sphygmomanometer, the cuff length for blood pressure measurement was chosen according to the arm circumference value. Children were asked to sit for at least 5 minutes before measurement. Two records were taken, with 2-min interval in between, plus a further one in case of difference > 5% in blood pressure between the two previous readings. The average of the two (or three) measurements was used for statistical analysis [14]. The patient should be as relaxed as possible and measurement done for all subjects on their right arm [15].

4) Anthropometric measurement:
i. Weight was measured using digital scales.
ii. Height was measured to the nearest 1 cm using a non-elastic tape meter while subjects were in a barefoot standing position, with their shoulders in a normal position.
iii. BMI was calculated as weight in kilograms divided by the square of height in meters (kg/m²) [16].
iv. Waist circumference (WC) is measured in the horizontal plane midway between the lowest rib and the iliac crest [17].

Biochemical measurements:
Blood was collected from the antecubital vein after an 8–12 h overnight fasting, centrifuged within 2 h for separation of serum. Aliquoted samples were stored at −20 °C until analyses:
1. Serum Total cholesterol and TG were determined enzymatically by an autoanalyzer using commercial kits available (Beckman Coulter, Inc., CA, USA).
2. Serum HDLc was measured similarly after precipitation with magnesium phosphotungstate.
3. Serum low density lipoprotein cholesterol was calculated using Friedwald's formula:
LDL−chol ½ ¼ Total chol ½− HDL−chol ½− TG ½=5 ðÞ where all concentrations are given in mg=dL [18].
4. Fasting plasma glucose was measured via colorimetric assay.
5. Serum uric acid levels were determined colorimetrically using Uricase [19].

Statistical analysis
A collected throughout history, basic clinical examination, laboratory investigations and outcome measures were coded, entered and analyzed using Microsoft Excel software. Data were then imported into Statistical Package for the Social Sciences (SPSS version 20.0) (Statistical Package for the Social Sciences) software for analysis. According to the type of data, qualitative data were represented as number and percentage, quantitative data were represented by mean ± SD. The following tests were used to test differences for significance: difference and association of qualitative variable by Chi square test (X^2). Differences between quantitative independent groups by t test. Correlation by Pearson's correlation or Spearman's. P value was set at ≤ 0.05 for significant results & < 0.001 for high significant results.

RESULTS
Figure (1) showed percentage of metabolic syndrome patients among 129 random obese pediatric patients. There was no significant difference or association regarding sex and age between groups. (Table 1).
All Anthropometric measures were significantly higher among cases than control (Table 2).
Cases were significantly higher regarding uric acid (Table 3).
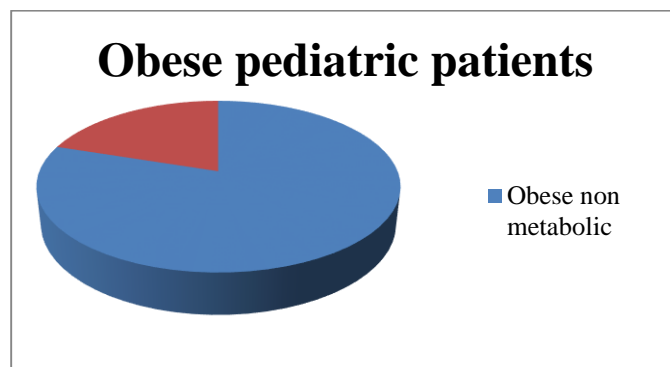Significant area under curve with cutoff > 4.3, with sensitivity 70% and specificity 96.3% (Table 4 and Figure 2).

Fig (1): Pie diagram showing percentage of metabolic syndrome patients among 129 random obese pediatric patients

Table (1): Age and sex distribution between studied groups

			Case (No=26)	Control (No=26)	t	P
Age (year)			7.52 ± 0.91	7.37 ± 0.84	0.613	0.543
Sex	**Male**	N	13	14		
		%	50.0%	53.8%		
	Female	N	13	12	0.077	0.78
		%	50.0%	46.2%		
Total		N	26	26		
		%	100.0%	100.0%		

Table (2): Anthropometric measures distribution between groups

	Case (No= 26)	Control (No=26)	t	p
Weight (Kg)	51.51 ± 7.23	34.02 ± 3.51	11.085	0.00**
Height (cm)	126.8 ± 7.67	121.42 ± 5.6	2.889	0.006*
BMI (kg/m²)	31.92 ± 1.91	22.42 ± 1.41	20.312	0.00**
WC (cm)	68.4 ± 3.1	53.63 ± 2.0	20.397	0.00**

Table (3): Uric acid distribution between studied groups

	Case (No=26)	Control (No=26)	t	P
Uric acid (mg/dl)	4.59 ± 1.06	3.34 ± 0.73	4.942	0.00**

Table (4): SUA as a diagnostic marker for pediatric met S; ROC curve analysis

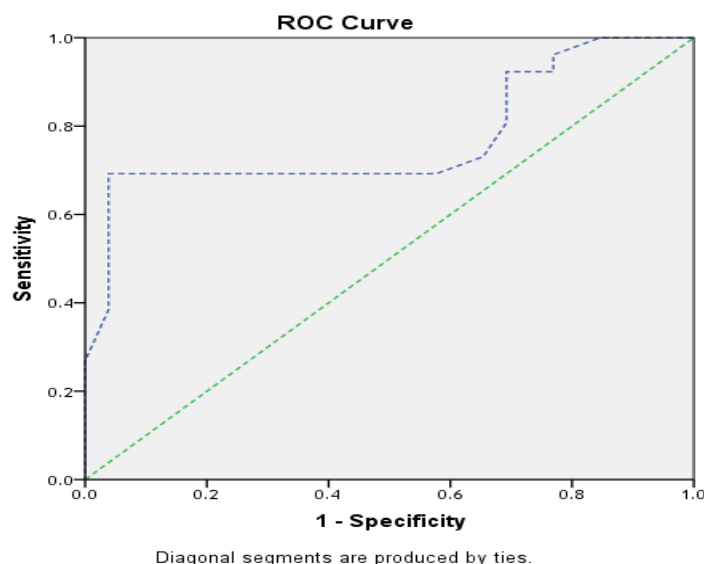| Uric acid cut off (mg/dl)	Sensitivity	Specificity	+Ve predictive value	-Ve Predictive value	Accuracy	Area under curve	P Value
>4.3	70.0%	96.3%	0.907	0.633	95%	0.79	0.001

Fig (2): Receiver operating characteristic (ROC) curve of uric acid for detection of metabolic syndrome

DISCUSSION

From 129 random obese pediatric patients we enrolled 26 patients with metabolic syndrome randomly with percentage of 20.1%, and matched control with same number. This is in agreement with **Fangfang et al.** [20] who noticed that the prevalence of MetS was much higher in obese subjects than in their normal weight counterparts (27.6% vs. 0.2%). Children with both general and central obesity had the highest prevalence of MetS. The association between metabolic disorders and obesity was strong.

As regards the demographic data of the studied groups, 26 obese children 13 of them were males (50%) and 13 were females (50%) with median age 7.52 ± 0.91years old. Control group 14 were males (53.8%) and 12 were females (46.2%) with median age 7.37 ± 0.84 year sold. There were no significant statistical difference between studied groups as regards age and sex distribution. Our result are supported by **Mahmoud et al.** [21] who showed that no significant difference between the two genders. Also, **Suhaimi et al.** [22] stated that there was no statistically significant difference in the proportion of obese children with metabolic syndrome by gender. However, other studies have reported a slightly higher prevalence of Met S in females compared to males [23].

According to most definitions, the prevalence of MetS is higher among girls than boys, But this difference seems to be slight [24].

Our study revealed a significant increase in all anthropometric measures in case group compared to control group. Where the mean height of cases was 126.8 ± 7.67 cm, while the mean height in control group was 121.42 ± 5.6 cm. The mean BMI in metabolic cases was 31.9 ± 1.91 kg/m², while mean BMI of control was 22.42 ± 1.41 kg/m². The mean waist circumference (WC) among metabolic cases was 68.4 ± 3.1 cm, while it was 53.63 ± 2 cm among control. Our results are in agreement with an Egyptian study done by **Moushira et al.** [25], which demonstrated that obese children had significantly higher values in waist circumference, waist-to-hip ratio compared to their lean controls. In addition, **Cook et al.** [26] demonstrated that close to 90% of obese children and adolescents have at least one feature of the metabolic syndrome. A study by **Wee et al.** [27] found that overweight/obese children had significantly worse clinical profiles and higher anthropometric parameters [height, weight, BMI, WC, hip circumference (HC), fat mass (FM) (%), waist hip ratio (WHR), waist to height ratio (WHtR).

Our study showed that obese metabolic children had significantly high uric acid compared to control where mean sUA was 4.59 ± 1.06 mg/dl among cases and 3.34 ± 0.73 mg/dl among control. Previous studies done by **Nejatinamini et al.** [28], reported higher serum uric acid level in MetS patients compared to non-MetS patients. In addition, **Nejatinamini et al.** [29] found strong correlation between serum uric acid and MetS components. These results are compatible with various epidemiologic cross sectional studies showing raised uric acid in metabolic syndrome patients [30].

ROC curve analysis showed that the AUC of sUA for detection of metabolic patients was with best cutoff value > 4.3 with sensitivity 70% and specificity 96.3%, and this maximizing sensitivity and specificity to predict future metabolic syndrome and their area under the curve was 0.79. **Modino et al.** [31] analyzed the relation between metabolic syndrome and hyperuricemia, among children with overweight and obesity, uric acid's level, from which a diagnosis of metabolic syndrome was most likely, corresponded to 5.4 mg/dl (area under the curve 0.66, sensitivity: 64% and specificity 62%).

CONCLUSION

Serum uric acid shows a significant correlation with components of metabolic syndrome making it a potent biomarker for diagnosis of metabolic syndrome patients in coming years.

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