Research Paper:

The Relationship Between Serum Uric Acid and Cardio-metabolic Risk Factors in Iranian Children and Adolescents

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ABSTRACT

Context: There has been an increasing interest in epidemiological and clinical studies concerning the role of uric acid in cardiometabolic diseases, especially in children and adolescents. However, these potential relationships remain undiscovered; accordingly, its pathophysiological mechanisms remain unrecognized. This study aimed to assess the potential association between Serum Uric Acid (SUA) levels and cardiometabolic risk factors in a population-based sample of Iranian children and adolescents.

Objectives: This study aimed to assess the potential association between Serum Uric Acid (SUA) levels and cardiometabolic risk factors in a population-based sample of Iranian children and adolescents.

Methods: The data of 595 individuals aged 7-18 years were assessed in this research. Anthropometric measurements and laboratory tests were performed according to standardized protocols.

Results: The Mean±SD age of the 595 explored students was 12.39±3.07 years. The overall Mean±SD SUA level of the study participants was measured as 4.22±1.13 mg/dL, with significant gender-wise differences (4.04±0.97 mg/dL vs 4.38±1.24 mg/dL, respectively; P<0.05). The prevalence of hyperuricemia based on the 90th percentile of SUA levels was equal to 10.6%. There was a positive association between SUA levels and abdominal obesity (waist circumference: ≥90th percentile) [Odds Ratio (OR): 1.54; 95% Confidence Interval (CI): 1.26 to 1.86] and general obesity [gender-specific Body Mass Index (BMI) for >95th percentile] (OR: 2.32; 95% CI: 1.74 to 3.11).

Conclusions: This study suggested BMI and waist circumference as cardiometabolic risk factors, i.e. significantly associated with SUA levels in children and adolescents.

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1. Context

Serum Uric Acid (SUA) as the end product of purine catabolism is produced in the liver and excreted by the kidneys. According to studies, SUA levels are correlated with cardiometabolic risk factors, including aging, dyslipidemia, impaired glucose tolerance, hypertension, and obesity in adults (1, 2). SUA has been considered as a risk factor for atherosclerosis and Cardiovascular Diseases (CVDs) in adults (1). Elevated levels of SUA can increase morbidity and mortality in individuals (2). According to evidence, an important risk factor in the health status of children and adolescents is hyperuricemia, especially concerning Non-Communicable Diseases (NCDs). However, these potential relationships remain undiscovered and its pathophysiological mechanisms remain unrecognized (3).

The SUA, as a cardiometabolic risk factor, can be used in clinical practice. This is because of its low-cost and feasible testing, particularly for patients with metabolic syndrome (4). Some studies have assessed the relationship between SUA and cardiometabolic risk factors; they also addressed the predictive role of SUA levels in the pediatric population (5, 6). A national study on children and adolescents demonstrated higher uric acid levels were correlated with metabolic abnormalities (1). However, studies on pediatric hyperuricemia are rare; thus, the specific relationship between uric acid levels and cardiometabolic risk factors remains undefined in children and adolescents (7).

Recent studies focused on the association between SUA and cardiometabolic risks in young subjects using various age groups, including pre-pubertal children (8, 9). Therefore, the present study aimed to investigate the potential association between SUA levels and cardiometabolic risk factors in children and adolescents.

2. Participants and Methods

This cross-sectional survey was performed among Iranian children and adolescents as a part of the fifth phase of a national school-based surveillance survey entitled "Childhood and Adolescence Surveillance and Prevention of Adult Non-Communicable Disease" (CASPIAN V). The study population consisted of students aged 7-18 years (males & females) in primary and secondary schools in the urban and rural areas of 31 provinces in Iran. The study subjects were selected using a multistage, stratified cluster sampling method. The protocol and details of the main study were reported elsewhere (10). Students with Iranian nationality, without any history of chronic diseases or surgery, were eligible to be recruited in the main survey.

In total, 600 blood samples were referred to the laboratory. All individuals with valid biochemical and anthropometric examination data were included in the final analysis. Finally, 595 samples with complete information were analyzed in the current study.

For assessing physical activity, performing ≥30 minutes/day exercises, that lead to an increase in breathing or heavy sweating or heart rate was considered as the physical activity. For statistical analysis, the obtained responses were categorized into two classes, as follows: up to 3 days per week was considered as low and 4 to 7 days/week was set as high. Blood Pressure (BP) was measured on the right arm in the sitting position by a mercury sphygmomanometer. BP was measured two times (5-min intervals) and the average level was considered for the analysis.

A team of healthcare specialists conducted the physical examinations using calibrated tools under the standardized protocol. Height (without shoes) and weight (with light clothes, on flat ground) were measured to the nearest 200 g and 0.1 cm, respectively. Then, Body Mass Index (BMI) was determined by the weight (kg) divided by height squared (m^2). BMI categories were defined according to the World Health Organization's (WHO) growth curves (11). Additionally, Waist Circumference (WC) was measured using a non-elastic tape in a standing position from a midpoint between the top of the iliac crest and the lowest rib at the end of expiration (the nearest 0.2 cm).

For biochemical measurements, the eligible subjects were referred to the laboratory with one of the parents. In total, a 6 mL venous blood sample was collected after 12 h overnight fasting. All collection tubes were centrifuged at 2500-3000×g for 10 minutes. Serum samples were aliquot into 200 µL tubes and stored at −70°C immediately after centrifugation. The cold chain method was used for transferring samples to the medical laboratory. Hitachi Auto Analyzer was used for determining the levels of Fasting Blood Glucose (FBS), Triglycerides (TGs), Total Cholesterol (TC), High-Density Lipoprotein-Cholesterol (HDL-C), alanine aminotransferase, and creatinine. The SUA was determined on a standard autoanalyzer with a Uri case and reagent. Uric acid values of >90th percentile were considered high (12).

Metabolic syndrome was defined to the presence of ≥3 of the following indexes: WC: ≥90th percentile based on gender and age; BP: ≥90th percentile based on gen-

der, age, and height; fasting triglycerides: ≥110 mg/dL; HDL-C: <40 mg/dL, and FBS level: ≥110 mg/dL (13).

The continuous variables were represented as Mean±SD and the categorical variables as frequency (percentage). The t-test and Mann–Whitney U tests were used to compare cardiometabolic risk factors based on the hyperuricemia status. Multiple logistic regression models were employed to examine the relationship between SUA level (mg/dL) and cardiometabolic risk factors. In the multiple logistic models, the potential confounding factors, including age, gender, physical activity, and sedentary behaviors were adjusted. The results of logistic regression are presented as OR with 95%CI. STATA was used for data analysis. The significance level was considered as P<0.05.

3. Results

The Mean±SD age of the investigated 595 students was 12.39±3.07 years. The majority of the children and adolescents (69.6%) were from urban areas. The overall Mean±SD SUA level of the study subjects was measured as 4.22±1.13 mg/dL, with significant gender-wise differences between (4.04±0.97 mg/dL vs 4.38±1.24 mg/dL, respectively; P<0.05) (Figure 1). The prevalence of hyperuricemia in children and adolescents based on the 90th percentile of SUA value (5.7 mg/dL) was calculated as 10.6%.

The prevalence of hyperuricemia based on the 90th percentile of each age group and gender was as follows: for boys: 10% for 6-9 year-olds (SUA ≥5.08 mg/dL), 10.4% for 10-13 year-olds (SUA ≥5.7 mg/dL), and 10.1% for 14-18 year-olds (SUA ≥6.8 mg/dL); for girls: 10.5% for 6-9 year-olds (SUA ≥4.7 mg/dL), 10.95 for 10-13 year-olds (SUA ≥5.2 mg/dL), and 13.5% for 14-18 year-olds (SUA ≥5.5 mg/dL). Table 1 presents the characteristics and cardiometabolic risk factors of the study participants according to SUA levels. The Mean±SD values of BMI (kg/m^2) (20.35±4.23 vs 18.13±5.39; P=0.001), WC (cm) (71.99±13.21 vs 65.92±12.6; P=0.002), and TG levels (mg/dL) (75.52±32.49 vs 88±47.91; P=0.003) were significantly higher among the participants with hyperuricemia, compared to the their healthy counterparts (Table 1).

The prevalence of cardiometabolic risk factors according to SUA level is represented in Table 2. The prevalence of abdominal obesity (39.1% vs 17.5%; P<0.001) and general obesity (26.6% vs 7.4%; P<0.001) were significantly higher among the research participants with hyperuricemia, compared to their healthy counterparts (Table 2).

The association between SUA and cardiometabolic risk factors (using multiple logistic regression) is listed in Table 3. There was a positive association between SUA level and the odds of abdominal obesity and general obesity; a 1 mg/dL increase in SUA was correlated with

Table 1. The characteristics and cardiometabolic risk factors of the study participants according to hyperuricemia status

Variables	Mean±SD		
	Uric Acid Level		
	Normal (n=530)	Hyperuricemia (n=65)	Total (n=595)
Age (y)	12.34±3.04	12.80±3.25	12.39±3.07
BMI (kg/m^2)	18.13±5.39	20.35±4.23*	18.37±5.32
WC (cm)	65.92±12.6	71.99±13.21*	66.59±12.80
SBP (mmHg)	96.68±12.97	100.62±13.79	97.11±13.11
DBP (mmHg)	63.02±9.81	64.23±10.76	63.15±9.91
FBS (mg/dL)	90.95±10.46	91.84±10.72	91.05±10.48
TG (mg/dL)	88±47.91	75.52±32.49[a]*	86.63±46.62
TC (mg/dL)	155.63±20.06	148.80±29.97[a]	154.88±28.33
HDL-c (mg/dL)	46.38±12.01	43.63±9.71	46.09±11.81

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SBP: Systolic Blood Pressure; DBP: Diastolic Blood Pressure; TC: Total Cholesterol; HDL: High-Density Lipoprotein; TG: Triglycerides; FBG: Fasting Blood Glucose. [a]P-values have resulted from Mann–Whitney U test; *P<0.05. The analyses were conducted based on the cutoff points of high SUA for each gender and age group (90th percentiles).

Table 2. The prevalence of cardiometabolic risk factors according to the hyperuricemia status in the explored children and adolescents

Variables	No. (%)			P
	Uric Acid			
	Total (n=595)	Normal (n=530)	Hyperuricemia (n=65)	
Abdominal obesity (WC ≥90th percentile)	117 (19.8)	92 (17.5)	25 (39.1)	<0.001*
Obesity (sex-specific BMI for >95th)	56 (9.5)	39 (7.4)	17 (26.6)	<0.001*
High BP (≥90th percentile for age/gender)	48 (8.1)	41 (7.7)	7 (10.8)	0.397
High FBS (≥110 mg/dL)	25 (4.7)	21 (4.4)	4 (7.1)	0.321a
High TC (≥200 mg/dL)	35 (6.6)	33 (6.9)	2 (3.6)	0.566a
High TG (≥110 mg/dL)	147 (27.6)	136 (28.6)	11 (19.6)	0.158
Low HDL-c (<40 mg/dL)	166 (31.2)	148 (31.1)	18 (32.1)	0.873

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WC: Waist Circumference; BMI: Body Mass Index; SBP: Systolic Blood Pressure; DBP: Diastolic Blood Pressure; TC: Total Cholesterol; HDL: High-Density Lipoprotein; TG: Triglycerides; FBG: Fasting Blood Glucose. [a]P-values were resulted from Fisher's Exact test. * P<0.05.

a 54% increase in the odds of abdominal obesity (OR: 1.54; 95%CI: 1.26-1.86). Furthermore, a 1 mg/dL increase in SUA level was associated with a 32% increase in general obesity (OR: 2.32; 95%CI: 1.74-3.11).

4. Discussion

The main findings of the present study were the significant association between SUA levels and BMI and WC in the explored children and adolescents. The levels of uric acid in boys were higher than that in girls.

Studies have shifted to NCDs and associated risk factors (14). The incidence of cardiovascular risk factors are on the rise in children and adolescents; thus, it is critical to explore this topic. A relevant risk factor is higher SUA levels. Uric acid, as an organic compound and a metabolite of purine, is endogenously produced by the liver in humans. Adenosine, inosine, hypoxanthine, adenine, and guanine generate uric acid. Increased levels of uric acid are associated with the risk of NCDs, including metabolic syndrome, obesity, hypertension, diabetes, kidney disease, and CVDs in adults (15, 16). The correlation between uric acid and metabolic syndrome

Table 3. The association between cardiometabolic risk factors and serum uric acid by multiple logistic regression analysis

Variables	OR	95%CI		P
		Lower Bound	Upper Bound	
High BP (≥90th percentile for age/sex)	1.09	0.82	1.45	0.56
High FBS (≥110 mg/dL)	1.14	0.78	1.68	0.50
High TG (≥110 mg/dL)	1.09	0.91	1.31	0.36
High TC (≥200 mg/dL)	1.07	0.40	2.86	0.90
Low HDL-c (<40 mg/dL)	0.98	0.82	1.17	0.85
Abdominal obesity (WC ≥90th percentile)	1.54	1.26	1.86	<0.001*
Obesity (sex-specific BMI for >95th)	2.32	1.74	3.11	<0.001*

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WC: Waist Circumference; SBP: Systolic Blood Pressure; DBP: Diastolic Blood Pressure; TC: Total Cholesterol; HDL: High-Density Lipoprotein; TG: Triglycerides; FBG: Fasting Blood Glucose

Model adjusted for age, sex, physical activity, and sedentary behaviors; * P<0.05.

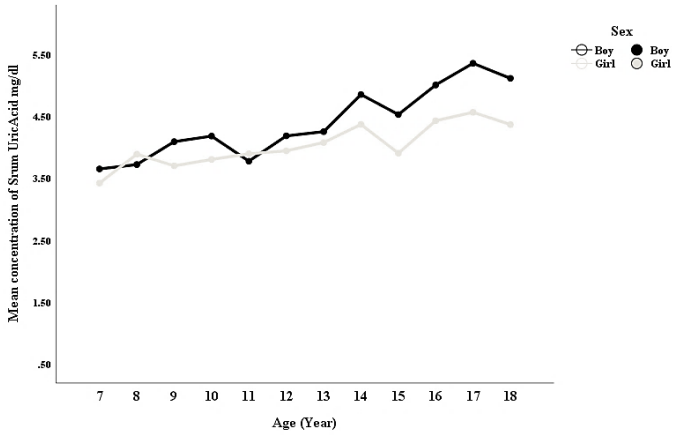

Figure1. Serum uric acid levels in Iranian children and adolescents according to gender and age *Journal of Pediatrics Review*

components has been widely assessed in adults. However, there is less data regarding such relationships in children and adolescents (12).

Uric acid is not considered in the definition of metabolic syndrome; however, several epidemiologic studies have reported that higher uric acid levels were correlated with metabolic syndrome in different ethnic populations (17, 18).

The potential mechanisms of the association between SUA and NCDs are related to endothelial dysfunction, insulin resistance, impaired endothelial nitric oxide productions, and vascular smooth muscle cell proliferation (19).

Investigating Brazilian children suggested that higher SUA values were correlated with overweight/obesity, high waist circumference, dyslipidemia, high body fat percentage, insulin resistance, and metabolic syndrome (12).

A large cohort on 4706 Chinese community-dwelling population indicated that age, gender, BMI, BP, TG, HDL-c, LDL-c, and FBG levels were significantly correlated with SUA levels (3). Exploring pre-pubertal children specified an association between higher SUA levels and carotid intima-media thickness. These findings highlight the effect of uric acid levels in the development of CVD in early childhood; hyperuricemia can be considered as a CVD risk factor (5). A cross-sectional study on 1364 Caucasian overweight/obese children revealed that high uric acid levels were associated with metabolic abnormalities, including worst lipid and insulin metabolism and particularly with WC (1). A national study on 1370 adolescents aged 12-17 years indicated that patients with metabolic syndrome presented higher uric acid levels. The strongest association was reported between uric acid and WC, in this respect (20). Investigating 4073 Chinese preschool children (3-6-year-olds) demonstrated that higher SUA level was correlated with greater levels of serum TG and DBP (21). Studying 129 Brazilian children and adolescents aged 2 to 18 years demonstrated a correlation between high levels of uric acid and BMI, WC, and BP, i.e. similar to our findings (22). These findings might provide a novel target or a potential novel treatment for NCDs by decreasing the SUA levels (23). A meta-analysis of prospective cohort studies revealed a pooled risk ratio of 1.13 for the incidence of hypertension per 1 mg/dL enhance in uric acid (95% CI 1.06-1.20) (24).

In concordance with the previous findings (25, 26), our study demonstrated a positive association between BMI (general obesity) and WC (central obesity) and uric acid levels in the pediatric age group. Increased adiposity leads to enhanced leptin levels. It induces oxidative stress in endothelial cells and increases uric acid levels. Moreover, the renal excretion of uric acid can decrease by increasing the release of leptin and insulin resistance (27).

Studies reported that higher SUA levels could increase the progress of hypertension. Higher SUA levels can be used as a beneficial biomarker of hypertension in children and adolescents (28, 29). The mechanisms of the effect of hyperuricemia on hypertension include the activation of the renin-angiotensin-aldosterone system, decreased nitric oxide synthase activity, the dysregulation of sodium homeostasis, and endothelium dysfunction (1, 21).

Hyperuricemia leads to insulin resistance, impaired glucose metabolism, and decreased insulin sensitivity. Higher uric acid levels reduce endothelial nitric oxide production, increase oxidative stress, systemic inflammation, and endothelial dysfunction, and impair insulin sensitivity (30, 31).

However, some studies reported that SUA was not a precise independent risk factor for NCDs (32, 33). The relationship between SUA levels and cardiometabolic risk factors in children and adolescents depends on racial/ethnic and genetic background, diet differences, and gender differences (28). Lifestyle modification and pharmacotherapy can be used as practical methods for the management and treatment of hyperuricemia. Healthy lifestyle interventions can be beneficial not only for hyperuricemia but also for the prevention of NCDs (34).

The limitations of the present study were as follows: a causal association between the variables cannot be found by cross-sectional studies and we overlooked assessing pubertal status. Despite these limitations, we evaluated a large sample size and investigated the association between SUA levels and cardiometabolic risk factors in children and adolescents, although studies in pediatric age groups are rare.

5. Conclusion

The main cardiovascular risk factors associated with hyperuricemia in the explored population were obesity and high waist circumference. Our results highlighted the importance of uric acid as a useful biomarker for assessing cardiometabolic risk factors. Future studies are required for finding how hyperuricemia in childhood or adolescence impacts health in adulthood, particularly regarding NCDs. Large cohort, long-term follow-up studies are needed to answer this question.

Ethical Considerations

Compliance with ethical guidelines

The study protocol was approved by the Ethics Committee of the Isfahan University of Medical Sciences (Code: IR.MUI.MED.REC.1398.284).

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Authors' contributions

Conceptualization, investigation, writing – original draft, writing – review & editing, and supervision: Motahar Heidari-Beni, Roya Kelishadi; Methodology: Roya Kelishadi, Majid Khademian; Data collection: Fatemeh Mohebpour; Data analysis: Roya Riahi.

Conflicts of interest

The authors declared no conflict of interest.

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