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ASSOCIATION OF SERUM URIC ACID WITH METABOLIC SYNDROME COMPONENTS IN SYRIAN POPULATION

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The current study aimed to investigate the correlation between serum uric acid levels and metabolic syndrome and its components in adult patients from Homs, Syria. This study included 86 subjects divided into two groups; 20 healthy controls and 66 patients with metabolic syndrome. Physical examination and blood pressure (BP) information were recorded. Serum uric acid (SUA), fasting blood glucose (FBG), total cholesterol (TC), triglycerides (TG), high-density lipoprotein cholesterol (HDL-C), and low-density lipoprotein cholesterol (LDL-C) were tested. As a result, subjects with metabolic syndrome had significantly higher levels of SUA than controls ($P < 0.001$). Metabolic syndrome patients with hyperuricemia had higher BMI, WC, TC and LDL-C than those with normal uric acid levels ($P < 0.05$). Moreover, subjects with more metabolic syndrome components had higher SUA levels. On the other hand, SUA was positively correlated with WC, DBP, FBG, TG, TC and LDL-C and negatively with HDL-C ($P < 0.05$). Therefore, in general, elevated SUA levels appear to be positively associated with metabolic syndrome components in Syrian population and can be considered a therapeutic target in controlling metabolic syndrome disorders.

Keywords: *Metabolic syndrome components; Hyperuricemia; Serum uric acid*

INTRODUCTION

The term metabolic syndrome (MetS) is defined as a cluster of biochemical and physiological abnormalities that include central obesity, insulin resistance, hypertension, and dyslipidemia[1]. It has been shown that the simultaneous occurrence of MetS components increases the risk of cardiovascular disease (CVD)[2] and type 2 diabetes mellitus (T2DM)[3]. The prevalence of MetS is increasing in both advanced and developing countries, making it a major public health concern in the modern world with the spread of the Western lifestyle worldwide[4]. Statistically, the global prevalence of MetS varies from 12.5% to 31.4% and is considered to be significantly higher in the Eastern Mediterranean Region and the Americas[5]. MetS may affect approximately 1 in 4 people in the Middle East[6]. The identification of novel biomarkers for MetS that complement existing biomarkers may help identify more individuals at risk and better understand the complex pathogenesis of MetS[7].

Serum uric acid (SUA) is the final product of endogenous and exogenous purine catabolism in humans[8]. It is the most potent antioxidant in human plasma, scavenging free radical activity and chelating iron[9]. However, SUA has both antioxidant and pro-oxidant properties[10], which may be caused by its dual role as an antioxidant in plasma or a pro-oxidant intracellularly[11].

Hyperuricemia, a condition of elevated blood levels of uric acid, is the most important risk factor for developing gout[12]. In recent years, there has been renewed interest in the association of hyperuricemia with many clinical disorders other than gout, such as atherosclerosis, cardiovascular disease, metabolic syndrome, and chronic kidney disease[13]. However, the nature of the relationship between SUA and these diseases remains unclear, but several pathophysiological

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mechanisms of their relationship have been postulated. Hyperuricemia may play a detrimental role by stimulating oxidative stress and contributing to endothelial dysfunction and inflammatory responses[14]. There are few published data on the relationship between SUA and MetS in Middle Eastern populations. Therefore, we conducted a cross-sectional study to assess SUA levels in Syrian patients with metabolic syndrome and to examine the relationship between SUA and components of MetS.

MATERIALS AND METHODS

Participants and study design

This study was conducted between September 2021 and November 2021 at Al Baath University in Homs, Syria. Subjects between the ages of 40 and 70 were enrolled in this study. The sample of participants consisted of 66 subjects with metabolic syndrome and 20 healthy controls. Patients with metabolic syndrome were selected from patients attending Karm Al Shame Health Center, and controls were selected from the patients' companions. All procedures performed in this study adhered to the ethical standards of the Declaration of Helsinki and were approved by the committee of Research Scientific Ethics of Al-Baath University.

Diagnostic criteria

Based on the consensus definition[15], an individual must have at least three of the following risk factors to be diagnosed with metabolic syndrome:-

1) Elevated waist circumference (WC): > 94 cm in men and > 80 cm in women.
2) Elevated triglycerides (TG): > 150 mg/dl.
3) Reduced high-density lipoprotein cholesterol (HDL-C): < 40 mg/dl in men and < 50 mg/dl in women.
4) Elevated blood pressure: systolic blood pressure (SBP) > 130 mmHg or diastolic blood pressure (DBP) > 85 mmHg, or use of antihypertensive drugs.
5) Elevated fasting blood glucose (FBG): >100 mg/dl or use of antidiabetic agents.

Hyperuricemia was defined when the levels of uric acid exceeded 7 mg/dl (417 μmol /l) in men and 6 mg/dl (357 μmol/ l) in women.

Exclusion criteria

Pregnant and breastfeeding women, patients with alcoholism, kidney or liver disease, thyroid disease, cardiovascular disease, cancer, gouty arthritis, type 1 diabetes, and patients using urate-lowering drugs or diuretics usage were excluded from this study.

Measurements

After inviting the participants, written informed consents were obtained, the purpose of the research was clearly explained, and questionnaires including demographic data, medical history, drug information and physical and anthropometric indicators were completed.

Anthropometric and blood pressure measurement

Waist circumference was measured with non-stretching tape and placed halfway between the lower ribs and the iliac crest without applying pressure on the body surface. Weight was measured using an analog mechanical scale and height was measured using an inelastic tape meter while subjects were standing barefoot. Body mass index was calculated by dividing the weight in kilograms by the square of height in meters (kg/m2). Blood pressure was measured twice on the participant's left arm after resting for 5-10 minutes in a sitting position using an automatic blood pressure monitor (OMRON).

Biochemical markers measurement

A 5.0 ml overnight fasting venous blood sample was collected and serum was used to measure biochemical parameters. Fasting blood glucose (FBG), total cholesterol (TC), triglycerides (TG), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), and serum uric acid (SUA) were measured by colorimetric methods using single-beam spectrophotometer (SIMITRONICS), with (BioSystem) kits.

Statistical analysis

All analyzes were performed using the Statistical Package for the Social Sciences (SPSS) version 24. Descriptive values were

presented as mean ± standard deviation (SD). Comparisons between groups were performed using t-test. Bivariate (Pearson) correlation was used to compare correlations between SUA and BMI, WC, SPB, DPB, FBG, TG, TC, HDL-C and LDL-C. *P*-value less than 0.05 was considered statistically significant.

Ethical approval

All procedures performed in this study adhered to the ethical standards of the Declaration of Helsinki and were approved by the committee of Research Scientific Ethics of Al-Baath University (approval date: 1/9/2020. approval no. 2573).

Informed Consent

All the study participants have provided written informed consent to participate in this study.

RESULTS AND DISCUSSION

Basic clinical characteristics of subjects according to the presence or absence of metabolic syndrome

A total of 86 subjects (40 males and 46 females) were enrolled in the study, 66 were diagnosed with metabolic syndrome based on our study criteria, and 20 participants were enrolled as controls. **Table 1**. compares the main characteristics of the two groups and the *P*-values obtained from t-tests. The MetS group tended to have significantly greater BMI and WC and higher levels of SPB, DPB, FBG, TG, TC, LDL-C compared to controls. In contrast, controls had significantly higher levels of HDL-C than the subjects in the MetS group (all $P < 0.05$).

Basic clinical characteristics of MetS patients according to the presence or absence of hyperuricemia

Hyperuricemia was found in 28.78% (19) of MetS patients. T-test was used to analyze the relationship between variables in groups with and without hyperuricemia. **Table 2**. shows that among MetS patients, the mean values of (age, BMI, WC, TC and LDL) were significantly higher in the hyperuricemia group, whereas t-test revealed no significant difference in SPB, DPB, FBG, TG, and HDL-C mean levels between the two groups. Hyperuricemia was higher in MetS women than in MetS men.

Table 1: Characteristics of study subjects based on the presence or absence of MetS**.**

Parameters	**MetS**	**controls**	**-**
N	66	20	**-**
Gender (Female/Male)	(34/32)	(12/8)	**-**
Parameters	**MetS (Mean ± SD)**	**Controls (Mean ± SD)**	***P***
Age	55.76 ± 9.19	54.65 ± 9.22	**0.638**
BMI (kg\m^2)	31.73 ± 5.37	25.16 ± 2.85	**0.000**
WC (cm)	109.27 ± 10.51	81.00 ± 7.50	**0.000**
SPB (mmHg)	139.24 ± 15.67	121.00 ± 8.90	**0.000**
DPB (mmHg)	81.39 ± 11.96	74.30 ± 7.33	**0.014**
FBG (mg\dl)	140.90 ± 41.11	87.83 ± 10.90	**0.000**
TG (mg\dl)	197.64 ± 73.86	107.96 ± 28.96	**0.000**
TC (mg\dl)	196.89 ± 41.81	162.31 ± 18.33	**0.001**
HDL-C (mg\dl)	37.22 ± 9.33	53.99 ± 5.82	**0.000**
LDL-C (mg\dl)	109.11 ± 24.38	84.79 ± 13.51	**0.000**
SUA (μmol\l)	348.27 ± 78.23	258.13 ± 88.35	**0.000**

Abbreviations: body mass index (BMI), waist circumference (WC), systolic blood pressure (SBP), diastolic blood pressure (DBP), fasting blood glucose (FBG), triglycerides (TG), total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), low density lipoprotein cholesterol (LDL-C), serum uric acid (SUA).

Table 2: Clinical characteristics of metabolic syndrome patients based on uric acid status.

Parameters	**MetS with hyperuricemia**	**MetS without hyperuricemia**	**-**
N	19	47	-
Gender (F/M)	(14/5)	(20/27)	-
Parameters	**MetS with hyperuricemia (Mean ± SD)**	**MetS without hyperuricemia (Mean ± SD)**	***P***
Age	60.37 ± 8.36	53.89 ± 8.92	**0.009**
BMI (kg\m^2)	34.01 ± 5.71	30.80 ± 4.99	**0.027**
WC (cm)	114.74 ± 8.48	107.06 ± 10.51	**0.006**
SPB (mmHg)	142.53 ±18.39	137.91 ± 14.44	**0.283**
DPB (mmHg)	84.11± 14.04	80.30 ± 10.99	**0.245**
FBG (mg\dl)	151.91 ± 44.86	136.44 ± 39.13	**0.168**
TG (mg\dl)	222.58 ± 63.04	187.56 ± 76.11	**0.081**
TC (mg\dl)	218.56 ± 36.08	188.13 ± 41.09	**0.006**
HDL-C (mg\dl)	34.04 ± 8.34	38.50 ± 9.49	**0.078**
LDL-C (mg\dl)	123.66 ± 19.01	103.22 ± 23.99	**0.002**

Abbreviations: body mass index (BMI), waist circumference (WC), systolic blood pressure (SBP), diastolic blood pressure (DBP), fasting blood glucose (FBG), triglycerides (TG), total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), low density lipoprotein cholesterol (LDL-C).

Association between serum uric acid levels and the number of MetS components

MetS patients were divided into three groups according to the number of MetS components. One-way ANOVA test was used to compare the mean values of SUA levels among the three groups, and multiple comparison test was applied to examine the difference in mean values between any two groups (see ‹**Fig. 1.**). There were statistically significant differences in SUA levels between and within groups, with increasing SUA levels in patients having higher numbers of MetS components. The mean values of SUA were (292.12, 349.12, 397.14) µmol\l for patients with three, four, and five MetS components, respectively.

Pearson correlation analysis of SUA and variables in MetS patients

Pearson correlation test was performed to assess the relationship between baseline variables and SUA levels in MetS patients. As shown in **Table 3.,** there was a significant positive correlation between SUA levels and WC, DBP, FBG, TG, TC and LDL-C, while a negative correlation with HDL-C (all $P < 0.05$) was noted. However, BMI and SBP were not correlated with SUA levels.

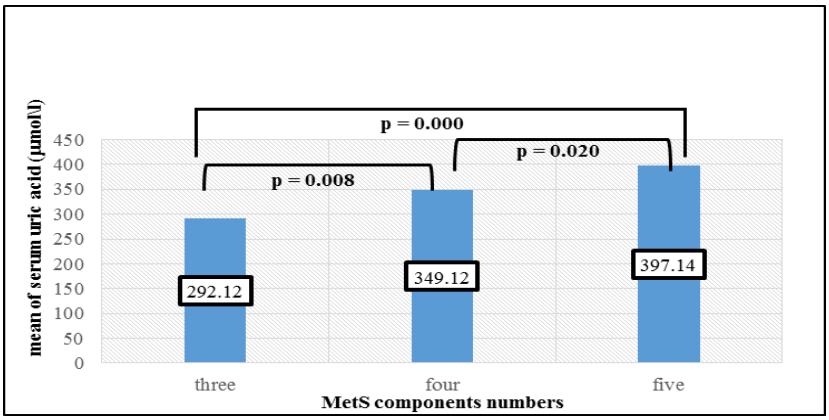

Fig. 1: Association between serum uric acid levels and number of MetS components using multiple comparisons.

Table 3: Pearson correlation analysis of serum uric acid and other risk variables in metabolic syndrome patients.

parameters	Pearson Correlation	*P*
BMI (kg\m^2)	0.218	**0.079**
WC (cm)	0.251	**0.042**
SPB (mmHg)	0.173	**0.166**
DPB (mmHg)	0.286	**0.020**
FBG (mg\dl)	0.281	**0.022**
TG (mg\dl)	0.424	**0.000**
TC (mg\dl)	0.350	**0.004**
HDL-C (mg\dl)	-0.460	**0.000**
LDL-C (mg\dl)	0.336	**0.006**

Abbreviations: body mass index (BMI), waist circumference (WC), systolic blood pressure (SBP), diastolic blood pressure (DBP), fasting blood glucose (FBG), triglycerides (TG), total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), low density lipoprotein cholesterol (LDL-C).

Discussion

Metabolic syndrome is a concordance of cardiovascular risk factors[16]. Therefore, it is not surprising that WC, BMI, SBP, DBP, FBG, TC, LDL-C and TG were all higher, while HDL-C was lower in the MetS group compared to controls, especially since most of them are biomarkers used to identify people with MetS. The same findings were reported in other comparative studies[17–19.] An interesting finding in our study was that MetS patients had higher levels of SUA than the control group. The incidence of hyperuricemia was also higher in MetS patients than in controls, 28.87% and 10%, respectively, but this was slightly lower than reported by (J. Xu *et al.*), which was 16.1% in the control group and 33.3% in MetS group[20]. Hyperuricemia has historically been thought to be a secondary consequence of MetS because insulin resistance can reduce the urinary excretion of uric acid. However, recent studies have shown that elevated SUA levels often precede the development of insulin resistance[21], and that it may play a contributing causal role in MetS[22]. In support of this hypothesis, (M. Takir *et al.*) found that subjects with hyperuricemia who were prospectively administered allopurinol showed improvements in insulin resistance and systemic inflammation compared with controls[23].

Another finding regarding the study of MetS and hyperuricemia was that all risk factors were elevated in the hyperuricemic MetS group, in which obesity (WC and BMI) as well as TC and LDL-C levels being the most significant differences compared to MetS patients with normal SUA. Although there is growing evidence supporting the association between gout and MetS and its components[24], our study has shown that even asymptomatic hyperuricemia may correlate with MetS components. Literature indicates that asymptomatic hyperuricemia is important as a silent trigger of the innate immune system[25]. Furthermore, it can predict the development of hypertension[26], T2DM[27,28], and chronic kidney disease[29] by inducing an inflammatory response. Also, the pro-inflammatory role of uric acid, even in its soluble state, may increase the risk of MetS[25]. Our findings broadly support the work of other studies in this field that have linked hyperuricemia to MetS components[30,31]. Additionally, a higher prevalence of hyperuricemia was confirmed in females than in males in the present study. This result is in contrast with previous studies[20,32]. One possible explanation for this may be that most of the women in the current study were postmenopausal and may have experienced hormonal changes during menopause and consequently reduced uricosuric effects of estrogen[33].

Moreover, elevated SUA levels were associated with an increased number of MetS components. The significance of these results lies in the fact that an increased number of MetS components implies an increased risk of developing cardiovascular disease. According to (Y.G.S. Barbalho *et al.*), cardiovascular risk, as measured by the Framingham Risk Score, is

amplified by 30% in the presence of 4 MetS components and by 40% in the presence of 5 MetS components compared with 3 or fewer MetS components ($P < 0.001$)[34]. Experimental studies have demonstrated the role of SUA as a pro-oxidant that induces endothelial dysfunction and stimulates the renin-angiotensin system and systemic inflammation, indicating a further contribution to cardiovascular injury[35].

Turning to obesity parameters, the present study demonstrated a significant relationship between SUA and WC in MetS patients. This association is consistent with previous observations[31,36]. There are many potential mechanisms underlying this relationship in which hyperuricemia contributes to adipocyte lipogenesis and inflammation[37]. Intracellular uric acid plays a pro-oxidant role by stimulating the NADPH oxidase enzyme. Additionally, increased fat deposition in adipocytes may be triggered by xanthine oxidoreductase, an enzyme involved in uric acid production[37]. On the other hand, adipose tissue produces and excretes uric acid and this production increases in the case of obesity[38]. However, no significant correlation was found between BMI and SUA. Comparing the two results, it can be seen that uric acid is primarily associated with central obesity, as WC is a more important determinant of visceral obesity than BMI. This is confirmed by the hypothesis that SUA levels are significantly more associated with visceral fat than with subcutaneous fat[39].

Our results also showed that SUA is correlated with FBG. These results are consistent with other studies that have found a direct link between SUA and blood glucose[36,40]. A possible mechanism is that elevated uric acid levels may increase hepatic gluconeogenesis by reducing the activity of the energy sensor enzyme adenosine monophosphate (AMP) kinase (AMPK)[41]. In addition to its role in reducing insulin sensitivity by increasing inflammatory interleukin expression and oxidative stress[42]. Some Studies have reported that SUA can be used as a biomarker to estimate the risk of developing T2DM in the future[42].

Regarding lipid profile, our results showed that SUA had a positive correlation with TC, TG and LDL-C, and a negative correlation with HDL-C, implying its association with dyslipidemia which was also described by other studies[43,44]. These effects are mainly attributed to the role uric acid plays in regulating fructokinase expression in hepatocytes, leading to an enhanced lipogenic impact of fructose. Nevertheless, uric acid may act independently by increasing hepatocyte fat production by stimulating mitochondrial oxidative stress, and consequently blocking aconitase, increasing citric acid and thereby stimulating lipogenesis [45].

With reference to the relationship between SUA and BP, previous studies have shown that uric acid is an independent risk factor for the development of systolic and diastolic hypertension[46,47], It has been traced to the role of SUA in impairing endothelial function by decreasing the phosphorylation of endothelial nitric oxide synthase under hypoxic conditions[48]. However, the results of our study were controversial, with a noted correlation only with DBP and not with SBP. A possible explanation for this discrepancy may relate to age. One study found that SBP increased with age in MetS patients, whereas DBP decreased after the age of 50, and since the mean age of subjects enrolled in our study was 55, therefore age may have had a greater contribution in developing high SBP compared to SUA[49]. Similar to our study, one study (F.Li *et al.*) found that uric acid was only associated with DBP and not with SBP[30].

Conclusion

Our results showed that MetS patients had higher levels of SUA. Furthermore, MetS components correlated with SUA levels. Although the current study was based on a small sample of participants, these results suggest that elevated SUA levels may be a potential therapeutic target for the control of MetS disorders. Further longitudinal studies are needed to determine the causal role of uric acid in MetS.

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ارتباط حمض البول المصلي بمكونات المتلازمة الاستقلابية عند السكان السوريين

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هدفت الدراسة الحالية إلى معرفة الارتباط بين مستويات حمض البول المصلي والمتلازمة الاستقلابية ومكوناتها لدى المرضى البالغين من مدينة حمص السورية. شملت هذه الدراسة ٨٦ عينة مقسمة إلى مجموعتين: ٢٠ من الضوابط الأصحاء و٦٦ مريضاً يعانون من المتلازمة الاستقلابية. تم تسجيل معلومات الفحص البدني وضغط الدم، وتم قياس كل من حمض البول المصلي (SUA)، غلوكوز الدم الصيامي (FBG)، الكولسترول الكلي (TC)، الشحوم الثلاثية (TG)، كولسترول البروتين الشحمي مرتفع الكثافة (HDL-C)، كولسترول البروتين الشحمي منخفض الكثافة (LDL-C). بيّنت النتائج أن مرضى المتلازمة الاستقلابية لديهم مستويات أعلى بكثير من SUA مقارنة بالضوابط ($P < 0.001$). كما أن مرضى المتلازمة الاستقلابية الذين يعانون من فرط حمض بول الدم لديهم مؤشر كتلة الجسمBMI ، محيط خصر WC، TC وLDL-C أعلى من أولئك الذين لديهم مستويات طبيعية من حمض البول ($P < 0.05$). علاوة على ذلك، فإن الأشخاص الذين يملكون عدد أكبر من مكونات المتلازمة الاستقلابية لديهم مستويات أعلى من حمض البول. من ناحية أخرى، ارتبط SUA ارتباطاً إيجابياً مع WC وDBP وFBG وTG وTC وLDL-C وسلباً مع HDL-C ($P < 0.05$). بشكل عام، يبدو أن ارتفاع مستويات SUA يرتبط بشكل إيجابي بمكونات المتلازمة الاستقلابية لدى السكان السوريين ويمكن اعتباره هدفاً علاجياً للسيطرة على اضطرابات المتلازمة الاستقلابية.