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Association of Serum Uric Acid Levels with Components of Metabolic Syndrome: A Cross-Sectional Analysis in a Saudi Adult Population

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Abstract

Background: This study aimed to investigate the possible relations between serum uric acid (UA) and metabolic syndrome (MetS) and its components in a Saudi adult population sample.

Methods and Results: This cross-sectional study enrolled consecutive adult MetS and non-MetS subjects (90 subjects in each group). Glycemic control indices (fasting blood sugar (FBS), HbA1c, insulin, HOMA-IR index), lipid profile/ratios, and renal function tests were also evaluated.

Findings showed that serum UA was significantly higher in the MetS group (322±98.9) than non-MetS group (286±61.2) µmol/L. The fourth quartile of serum UA showed a higher frequency of MetS (73.3%) and central obesity (82.2%), and higher mean values of triglycerides and FBS as well as lower mean values for HDL-C relative to the first quartiles. Data stratification by sex showed consistent associations of BMI, abdominal obesity, HDL-C, TG/HDL-C, and serum creatinine levels with serum UA in both men and women. Serum UA at 310 µmol/L concentration might be a good predictor for MetS/its components in men. In contrast, at a cut-off level of 275.0 µmol/L, it could significantly predict only obesity and high FBS in women.

Conclusion: Serum UA levels are associated with MetS and may predict MetS and/or its components at specific levels in a sex-dependent pattern in the study population. (**International Journal of Biomedicine. 2020;10(4):457-466.**)

Key Words: metabolic syndrome • uric acid • lipid profile • insulin resistance • Saudi adults

Abbreviations

AUC, area under curve; **BMI**, body mass index; **BP**, blood pressure; **BUN**, blood urea nitrogen; **CRE**, serum creatinine; **FBS**, fasting blood sugar; **HbA1c**, glycated hemoglobin; **HDL-C**, high-density lipoprotein cholesterol; **HOMA-IR**, Homeostasis Model Assessment – IR index; **IDL-C**, intermediate-density lipoprotein cholesterol; **IR**, insulin resistance; **IGT**, impaired glucose tolerance; **LDL**, low-density lipoprotein; **LDL-C**, low-density lipoprotein cholesterol; **MetS**, metabolic syndrome; **TC**, total cholesterol; **TG**, triglycerides; **UA**, uric acid; **VLDL-C**, very low-density lipoprotein cholesterol; **WC**, waist circumference

Introduction

Uric acid (2,6,8-trioxypurine) is the final oxidation product of purine metabolism. The formation of uric acid (UA) is through the enzyme xanthine oxidase, which oxidizes oxypurines (xanthine and hypoxanthine) (https://druginfo.nlm.nih.gov/m.drugportal/rn/69-93-2). For a long time, UA was just considered as a risk for the development of gout and kidney stones.[1] Since the 1900s, however, the accumulated evidence, based mainly on epidemiological studies, has linked serum UA levels to metabolic syndrome (MetS), chronic kidney disease, and cardio-cerebrovascular events.[2-4] A growing body of evidence has suggested that UA may not only be considered as a risk factor of MetS but also an independent predictor of cardio-metabolic diseases and mortality.[1,5,6]

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Moreover, in animal models, decreasing UA levels can prevent or reverse features of MetS.[7, 8]

Although UA can function as an antioxidant, it might be an inexpensive marker of the effects of oxidative stress because its antioxidant activity can be overcome by the pro-oxidant and pro-inflammatory effects on cells.[1, 5] In experiments with cultured vascular cells, UA induces cellular proliferation, inflammation, oxidative stress, and the activation of the local renin-angiotensin system.[1]

In MetS, hyperuricemia has been assigned to hyperinsulinemia and to decline in uric acid excretion associated with kidney dysfunction and is not acknowledged as the main mediator of metabolic syndrome, renal disease, and cardiovascular disorder development. However, more recent investigations have altered this traditional view and shown by providing compelling evidence to support an independent link between hyperuricemia and increased risk of MetS, diabetes, hypertension, kidney disease, and cardiovascular disorders. Despite these emerging findings, controversy regarding the exact role of uric acid in inducing these diseases remains to be uncovered.[6, 9] Interestingly, we have previously identified a high rate of obesity and type 2 DM with their complications.[10, 11] In this sense, this study aimed to investigate the possible relations between serum uric acid (UA) and metabolic syndrome (MetS) and its components in a Saudi adult population sample.

Subjects and Methods

Study population

A total of 180 Saudi adult non-smoker participants aged between 24 and 70 years, presenting at the General Central Hospital, were recruited between June 2017 and December 2017 for this study. All participants were allocated into 2 study groups. The MetS group included 90 individuals with MetS; the non-MetS group included 90 individuals without MetS. MetS was defined according to the revised version of the third report of the National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III),[12] i.e. having any 3 of the following 5 diagnostic criteria: (i) Elevated WC (≥92 cm in men and ≥87 cm in women based on the Saudi Abnormal Glucose Metabolism and Diabetes Impact Study (SAUDI-DM);[13] (ii) Elevated TG (≥1.7 mmol/L or on drug treatment for elevated TG; (iii) Reduced HDL-C (≤1.03 mmol/L in men and ≤1.3 mmol/L in women or on drug treatment for reduced HDL-C); (iv) Elevated BP (SBP ≥130 mmHg or DBP ≥85 mmHg or on antihypertensive drug treatment in a patient with a history of hypertension); (v) Elevated fasting glucose (≥5.6 mmol/L) or on drug treatment for elevated glucose.[14,15] Exclusion criteria were participants aged <18 years, pregnancy or breastfeeding, subjects with a history of chronic disease (cardiovascular disease, cancer, stroke, kidney diseases, blood disorders, and gout), treatment with drugs that can affect the results of the study.

Trained nurses through the respective hospital were specified for questionnaire data filling (e.g. age, sex, history of diabetes, hypertension, and dyslipidemia, etc.), anthropometric measurements (height, weight, WC) using Digital Pearson Scale (ADAM Equipment Inc., USA), BP measurement (3 times by using a mercury blood pressure device after the subjects had rested longer than 5 min),[16] and blood sampling following standard protocols to ensure accurate and complete demographic and clinical information for each included participant.

This study was checked against the STROBE (Strengthening the Reporting of OBservational Studies in Epidemiology) checklist and conducted following the "ethical standards of the institutional and national research committee" and with the Helsinki Declaration and its later amendments or comparable ethical standard. It was reviewed and approved by the Medical and Bioethics local committee. Each participant signed informed consent before taking part.

Sample collection and the biochemical analysis

Overnight fast venous blood samples were collected in plain tubes (5 mL) for centrifugation (2500 rpm × 15 minutes) and EDTA tubes (2 mL) for automated glycated hemoglobin (HbA1c) estimation (COBAS, INTEGRA, Roche Diagnostics, USA). The separated sera were divided into aliquots and stored at -80 °C until the time of biochemical analysis. Routine laboratory measurements, including blood urea nitrogen (BUN), serum creatinine (CRE), serum uric acid (UA), fasting blood sugar (FBS), and lipid profile (i.e. TC, HDL-C, LDL-C and TG) were done using commercially available kits on Cobas Integra 400 plus Biochemical analyzer (Roche Diagnostics)". The ratios TC/HDL-C and TG/HDL-C which indicate "the balance between all atherogenic cholesterols (VLDL-C, IDL-C, and LDL-C), and antiatherogenic cholesterol (HDL-C)", were calculated as determinants of cardiovascular risk.[17] Non-HDL-C (i.e. TC – HDL-C) was also calculated as a valuable predictor of premature atherosclerosis and coronary events.[18]

Serum insulin was measured by "Electrochemi-luminescence Immunoassay (Cobas, Roche Diagnostics, USA)" according to the instructions recommended by the manufacturer. Insulin resistance was assessed using HOMA-IR. The calculation formula was as follows: HOMA-IR=(fasting insulin [μIU/mL]×fasting glucose [mmol/L])/22.5.[19, 20]

All the quality control measurements were followed during the laboratory work including running the appropriate calibrators and controls before each run to ensure the performance of the assay.

Statistical analysis

All patient data were coded and anonymized before the analysis. The normally distributed continuous values (i.e. checked by Kolmogorov-Smirnov test) were expressed as mean ±standard deviation (SD) and compared using the Student's t-test (for two groups). One-way analysis of variance (ANOVA) on a rank test (> two groups) followed by Bonferroni multiple comparison tests were also applied. Categorical variables were presented as frequencies (percentages) and compared by Chi-square or Fisher's exact tests. Moreover, Pearson's correlation coefficient was used to test correlations between serum UA and other study variables. Logistic regression analysis was applied to calculate the odds ratios (OR) and 95% confidence intervals (CI) for variables in the study groups, which were adjusted for significant confounding factors as age, parameters of glycemic control, lipid profile, and kidney function test. Receiver operating characteristics (ROC) analysis was used to calculate the area

under the curve (AUC) for serum UA and to find the best cutoff values associated with maximum sensitivity and specificity to identify MetS and its components. Calculation of the study power using "G power-3 software version 3.0.10 (http://www.gpower.hhu.de/)", showed that with the specified study design, and allowable error rate; alpha error = 0.05 with sample size 90 for each group can give 89% power with nearly an effect size = 0.44. The optimal cutoff value for each clinical-laboratory measurement to predict MetS was calculated. Results with $P<0.05$ were considered statistically significant. Data analysis was done by the Statistical Package for the Social Sciences software (IBM SPSS Statistics for Windows, Version 22.0. Armonk, NY).

Results

Baseline characteristics of study participants

The baseline clinical and biochemical characteristics of the study subjects were summarized in Tables 1 and 2. Also, the associations of these parameters with MetS components were presented. As shown in Table 1, individuals older than 45 years had higher odds (OR=3.28; 95% CI: 1.76-6.13) of having MetS compared with those less than 45 years old. The odds ratios of central obesity, hypertension, diabetes mellitus, hyperglycemia, dyslipidemia, hypercholesterolemia, hypertriglyceridemia, elevated LDL-C, and increased IR were 5.61, 27.9, 5.20, 4.33, 11.2, 2.21, 14.8, 4.37, and 2.91, respectively, (all $P<0.05$) for risk to develop MetS relative to ones who do not have any of these disorders. As expected, subjects in the MetS group had significantly higher values of glycemic parameters (FBG, HbA1c, insulin, and HOMA-IR index), lipid profile and ratios (TC, TG, LDL-C, TC/HDL-C, TG/HDL-C, and Non-HDL-C), BUN, and UA than ndividuals in the non-MetS group (Table 2).

Prevalence of MetS components among the study participants

Of the 180 study subjects, central obesity was observed in 112(62%) of participants in whom women had 3.8 times susceptibility for getting this MetS component than men (95% CI: 1.96-7.54; $P<0.001$). In contrast, low HDL-C levels were more prominent in men (64%) than women (32%). Other MetS components (i.e. hypertension, hypertriglyceridemia, and IGT) show consistency among men and women (Table 3).

Table 1.
Clinical and biochemical characteristics of the study participants

Variables		Non-MetS	MetS	*P*	OR (95% CI)
Number		(n=90)	(n=90)		
Age	Mean ± SD	37.3 ± 16.3	43.1 ± 12.0	0.004 [b]	
	≤45 years	66 (73.3)	41 (45.6)	<0.001 [a]	Reference
	>45 years	24 (26.7)	49 (54.4)		3.28 (1.76-6.13)
Sex	Male	23 (25.6)	30 (33.3)	0.252 [a]	0.68 (0.36-1.30)
	Female	67 (74.4)	60 (66.7)		
Weight, kg	Mean ± SD	79.3 ± 16.3	90.8 ± 19.1	<0.001 [b]	
Height, cm	Mean ± SD	160.3 ± 8.4	163.3 ± 9.17	0.025 [b]	
BMI, kg/m^2	Mean ± SD	30.9 ± 6.4	33.9 ± 6.6	0.001 [b]	
Abdominal obesity	Negative	51 (56.7)	17 (18.9)	<0.001 [a]	Reference
	Positive	39 (43.3)	73 (81.1)		5.61 (2.86-11.0)
Hypertension	Negative	78 (86.7)	17 (18.9)	<0.001 [a]	Reference
	Positive	12 (13.3)	73 (81.1)		27.9 (12.4-62.4)
Diabetes mellitus	Negative	78 (86.7)	50 (55.6)	<0.001 [a]	Reference
	Positive	12 (13.3)	40 (44.4)		5.20 (2.49-10.85)
High FBS	Negative	78 (86.7)	54 (60.0)	<0.001 [a]	Reference
	Positive	12 (13.3)	36 (40.0)		4.33 (2.06-9.08)
High insulin	Negative	81 (90.0)	74 (82.2)	0.195 [a]	Reference
	Positive	9 (10.0)	16 (17.8)		1.94 (0.81-4.67)
Dyslipidemia	Negative	25 (27.8)	3 (3.3)	<0.001 [a]	Reference
	Positive	65 (72.2)	87 (96.7)		11.15 (3.22-38.5)
High TC	Negative	62 (68.9)	45 (50.0)	0.015 [a]	Reference
	Positive	28 (31.1)	45 (50.0)		2.21 (1.20-4.06)
High TG	Negative	85 (94.4)	48 (53.3)	<0.001 [a]	Reference
	Positive	5 (5.6)	42 (46.7)		14.8 (5.51-40.1)
High LDL-c	Negative	42 (46.7)	15 (16.7)	<0.001 [a]	Reference
	Positive	48 (53.3)	75 (73.3)		4.37 (2.19-8.74)
Low HDL-c	Negative	52 (57.8)	53 (58.9)	0.880 [a]	Reference
	Positive	38 (42.2)	37 (41.1)		0.95 (0.52-1.72)
HOMA-IR	IS	79 (87.8)	64 (71.2)	0.009 [a]	Reference
	IR	11 (12.2)	26 (28.8)		2.91 (1.34-6.35)

[a] *Fisher's Exact or Chi-square tests were used for qualitative variables, and* [b] *Student's t-test was used for quantitative data. According to HOMA-IR all participants were divided into insulin-sensitive (IS) and insulin resistance (IR, >1.9) groups (Vogeser et al., 2007).*

Table 2.
Biochemical characteristics of the study participants

Variables	Non-MetS (n=90)	MetS (n=90)	*P*
FBS, mmol/L	5.6 ± 1.9	6.8 ± 3.1	0.002
HbA1c, %	5.36 ± 1.1	6.7 ± 1.65	<0.001
Insulin, mIU/mL	4.49 ± 2.7	5.82 ± 3.8	0.008
HOMA-IR	1.15 ± 0.9	1.6 ± 1.0	0.001
TC, mmol/L	4.7 ± 1.09	5.2 ± 0.86	0.002
TG, mmol/L	1.14 ± 0.4	1.68 ± 0.9	<0.001
LDL-C, mmol/L	2.9 ± 1.0	3.3 ± 0.8	0.003
HDL-C, mmol/L	1.22 ± 0.3	1.19 ± 0.3	0.583
TC/HDL-C	4.11 ± 1.4	4.69 ± 1.4	0.009
TG/HDL-C	1.0 ± 0.52	1.5 ± 1.07	<0.001
Non-HDL-C	3.57 ± 1.1	4.05 ± 0.9	0.002
BUN, mmol/L	5.13 ± 1.9	6.5 ± 2.2	<0.001
CRE, mmol/L	64.1 ± 14.8	67.4 ± 16.0	0.148
UA, mmol/L	286 ± 61.2	322 ± 98.9	0.004

Table 3.
Prevalence of components of metabolic syndrome among the study participants

Component	Total (n=180)	Men (n=53)	Women (n=127)	*P*	[a]OR (95%CI)
Central obesity	112	21 (39.6)	91 (71.1)	<0.001	3.85 (1.96-7.54)
Hypertension	85	29 (54.7)	56 (44.1)	0.251	0.65 (0.34-1.24)
High TG	47	17 (32.1)	30 (23.6)	0.266	0.65 (0.32-1.32)
Low HDL-C	75	34 (64.2)	41 (32.3)	<0.001	0.26 (0.13-0.52)
IGT	52	16 (30.2)	36 (28.3)	0.857	0.91 (0.45-1.84)

[a]OR (95% CI): adjusted odds ratio for age (95% confidence interval).

Prevalence of MetS and its components among serum UA quartiles

Figure 1 shows the prevalence of MetS and its components among the four quartiles [Q1:< 248.3, Q2: 248.3- <290, Q3: 290- <361.7, Q4: ≥ 361.7) of serum UA.

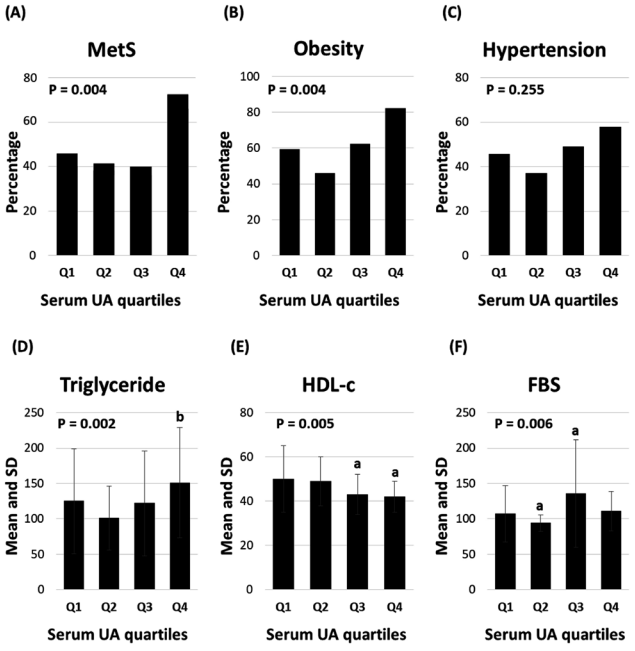

Fig. 1. Overall analysis of the prevalence of MetS and its components by quartiles (Q1-Q4) of serum UA. *Data are presented as percentages (A-C) or mean and SD (D-F).*

Overall, individuals in the Q4 of serum UA showed a significantly higher frequency of MetS (73.3%) and central obesity (82.2%) relative to the ones in the Q1-Q3 (UA-Q1 to UA-Q3; 45.5%, 41.3%, 40.0% of MetS frequency, and 59.1%, 45.7%, and 62.6% of central obesity frequency, respectively).

Furthermore, higher mean values of TG and FBS and lower mean values for HDL-C were observed in UA-Q4 relative to the first ones (Table 4). Data stratification by sex showed a central obesity prevalence increase in UA-Q4 for both males and females. At the same time, subjects with higher mean TG levels and lower mean HDL-C levels were more frequent in UA-Q4 of men relative to that in women (Table 4).

Association between serum UA and the clinical-laboratory parameters

Correlations between serum UA and the clinical-laboratory parameters are summarized in Table 5. Overall analysis showed that serum UA was correlated with age (r=0.174, *P*=0.019), weight (r=0.318, *P*<0.001), height (r=0.236, *P*=0.001), BMI (r=0.175, *P*=0.018) and abdominal obesity (r=0.216, *P*=0.004). In the current study, we found an inverse correlation between serum UA and HDL-C levels (r=-0.259, *P*<0.001) and significant positive correlations between serum UA and other laboratory parameters, including the glycemic variables (FBS, HbA1c, insulin, and HOMA-IR), the lipid profile-related variables and ratios (TC/HDL-C, TG/HDL-C, and non-HDL-C), and kidney function test-related variables (BUN and CRE) as shown in Table 5. Interestingly, data stratification by sex showed consistent associations of BMI, abdominal obesity, HDL-C, TG/HDL-C, and serum creatinine levels with serum UA in both men and women.

Evaluation of serum UA concentration and other clinical-laboratory parameters in diagnosing MetS and its components

An overall analysis has revealed that serum UA at a cut-off point of 295.05 µmol/L could predict MetS, central obesity, high levels of TG, and low HDL-C in the total study participants (Figure 2).

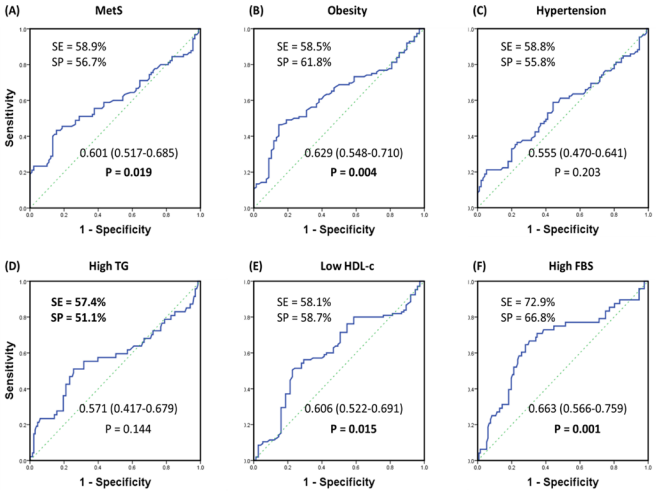

Fig. 2. An overall analysis of the ROC curve for serum UA concentration predicting MetS and its components. *(A) Metabolic syndrome, (B) Central obesity, (C) Hypertension, (D) Hypertriglyceridemia, (E) Low HDL-C, (F) High FBS.*

Table 4.

Prevalence of MetS and its components by quartiles (Q1-Q4) of serum UA stratified by sex

Component	UA-Q1	UA-Q2	UA-Q3	UA-Q4	*P*
Overall					
MetS	20 (45.5)	19 (41.3)	18 (40.0)	33 (73.3)	0.004
Central obesity	26 (59.1)	21 (45.7)	28 (62.2)	37 (82.2)	0.004
Hypertension	20 (45.5)	17 (37.0)	22 (48.9)	26 (57.8)	0.255
TG	1.4 ± 0.8	1.14 ± 0.5	1.4 ± 0.8	1.7 ± 0.9 [b]	0.002
HDL-C	1.3 ± 0.4	1.3 ± 0.3	1.1 ± 0.2 [a]	1.1 ± 0.2 [a]	0.005
FBS	6.0 ± 2.2	5.2 ± 0.7 [a]	7.6 ± 4.2 [a]	6.2 ± 1.6	0.006
Men (n=53)					
MetS	4 (57.1)	4 (40.0)	8 (44.4)	14 (77.8)	0.139
Central obesity	2 (28.6)	0 (0.0)	8 (44.4)	11 (61.1)	0.014
Hypertension	2 (28.6)	5 (50.0)	11 (61.1)	11 (61.1)	0.455
TG	1.3 ± 0.5	0.9 ± 0.4	1.5 ± 90.8	2.0 ± 1.1	0.008
HDL-C	1.3 ± 0.2	1.4 ± 0.1	1.1 ± 0.2	1.1 ± 0.2	0.002
FBS	5.4 ± 1.0	5.4 ± 0.6	9.6 ± 5.8	5.9 ± 1.3	0.359
Women (n= 127)					
MetS	16 (43.2)	15 (41.7)	10 (37.0)	19 (70.4)	0.055
Central obesity	24 (64.9)	21 (58.3)	20 (74.1)	26 (96.3)	0.007
Hypertension	18 (48.6)	12 (33.3)	11 (40.7)	15 (55.6)	0.313
TG	1.4 ± 0.9	1.2 ± 0.5	1.3 ± 0.7	1.5 ± 0.6	0.107
HDL-C	1.3 ± 0.4	1.2 ± 0.3	1.1 ± 0.3	1.1 ± 0.2	0.084
FBS	6.1 ± 2.4	5.2 ± 0.7	6.2 ± 1.9	6.4 ± 1.8	0.006

Data are presented as frequency (percentage) or mean and SD. Pearson Chi-square and Kruskal-Wallis tests were applied, followed by Bonferroni multiple comparison test. a: statistically significant relative to UA-Q1, b: statistically significant relative to UA-Q2.

Table 5.

Correlation analysis between serum UA level and the clinical-laboratory parameters

Clinical data	Total subjects	Men	Women
Age, years	0.174 (0.019)	-0.056 (0.693)	0.230 (0.009)
Weight, kg	0.318 (<0.001)	0.555 (<0.001)	0.274 (0.002)
Height, cm	0.236 (0.001)	0.312 (0.023)	0.083 (0.354)
BMI, kg/m^2	0.175 (0.018)	0.495 (<0.001)	0.178 (0.046)
Abdominal obesity	0.216 (0.004)	0.446 (0.001)	0.249 (0.005)
Hypertension	0.095 (0.204)	0.235 (0.090)	0.006 (0.946)
Diabetes	0.122 (0.104)	0.071 (0.612)	0.114 (0.200)
Dyslipidemia	0.063 (0.402)	0.006 (0.963)	0.139 (0.118)
Laboratory tests			
FBS, mmol/L	0.221 (0.003)	0.119 (0.395)	0.260 (0.003)
HbA1c, %	0.243 (0.001)	0.025 (0.858)	0.343 (<0.001)
Insulin, mIU/mL	0.169 (0.023)	0.361 (0.008)	0.088 (0.325)
HOMA-IR	0.246 (0.001)	0.392 (0.004)	0.147 (0.100)
TC, mmol/L	0.094 (0.207)	0.439 (0.001)	-0.004 (0.964)
TG, mmol/L	0.243 (0.001)	0.432 (0.001)	0.148 (0.097)
LDL-C, mmol/L	0.122 (0.103)	0.380 (0.005)	0.059 (0.510)
HDL-C, mmol/L	-0.259(<0.001)	-0.459 (0.001)	-0.200 (0.024)
TC/HDL-C	0.243 (0.001)	0.481 (<0.001)	0.165 (0.063)
TG/HDL-C	0.299 (<0.001)	0.464 (<0.001)	0.213 (0.016)
Non-HDL-C	0.167 (0.025)	0.467 (<0.001)	0.071 (0.427)
BUN, mmol/L	0.211 (0.004)	0.049 (0.726)	0.210 (0.018)
CRE, mmol/L	0.502 (<0.001)	0.646 (<0.001)	0.427 (<0.001)

Data are presented as the correlation coefficient (P-values).
Abdominal obesity: WC ≥92 cm in men and ≥87 cm in women.

On stratified analysis by sex, serum UA at approximately 310 μmol/L concentration was found to be a good predictor for MetS and all its components in men. While at a cut-off level of 275.0 μmol/L, serum UA could significantly predict obesity and high FBS among all MetS components in women [AUC (95%CI): 0.659 (0.566-0.753), and 0.691 (0.522-0.831), respectively] (Table 6).

On investigating the optimal cutoff values of the clinical-laboratory parameters in the prediction of MetS, the BMI was the best anthropometric measurement to predict MetS [AUC (95% CI): 0.689 (0.609-0.769)] with sensitivity (80%) and specificity (60%) which moderately minimizes the false-positive/-negative cases. The positive likelihood ratio (PLR) was equivalent to 2.0, suggesting that those subjects with BMI ≥30.4 kg/m^2 may present approximately twice the chance of a positive diagnosis being true. In contrast, the negative likelihood ratio (NLR) corresponded to 0.33, which is close to three times the chance of a negative diagnosis confirming the absence of MetS. The PLR and NLR of UA were 1.36 and 0.72, respectively, at 295 μmol/L serum level (Table 7).

Discussion

Given the growing prevalence of obesity, prediabetes, and diabetes, [21, 22] the study of factors that interplay with MetS and/or its components becomes an essential area of public health concern.

Table 6.

Evaluation of serum UA concentration in diagnosing MetS and its components stratified by sex

Variable	AUC	95% CI	S	*P*	Cut-off (mmol/L)	SE	SP	LR+	LR-
OVERALL									
MetS	0.601	0.517-0.685	0.04	0.019	295.0	58.9%	56.7%	1.36	0.752
Obesity	0.629	0.548-0.710	0.04	0.004	295.0	58.5%	61.8%	1.53	0.67
Hypertension	0.555	0.470-0.641	0.04	0.203	295.0	58.8%	55.8%	1.33	0.73
High TG	0.571	0.417-0.679	0.05	0.144	295.0	57.4%	51.1%	1.17	0.83
Low HDL-C	0.606	0.522-0.691	0.04	0.015	295.0	58.1%	58.7%	1.40	0.71
High FBS	0.663	0.566-0.759	0.04	0.001	295.0	72.9%	66.8%	2.19	0.40
Men									
MetS	0.675	0.531-0.820	0.07	0.030	310.5	66.7%	61.9%	1.75	0.54
Obesity	0.763	0.626-0.901	0.07	0.001	310.5	81.0%	62.5%	2.16	0.30
Hypertension	0.636	0.486-0.787	0.08	0.090	310.5	62.1%	54.2%	1.36	0.70
High TG	0.798	0.652-0.944	0.07	0.001	310.5	82.4%	58.3%	1.98	0.30
Low HDL-C	0.783	0.661-0.905	0.06	0.001	310.5	84.2%	61.8%	2.20	0.26
High FBS	0.536	0.377-0.696	0.08	0.660	310.5	65.0%	51.5%	1.34	0.68
Women									
MetS	0.561	0.457-0.665	0.05	0.237	275.0	58.3%	44.8%	1.06	0.93
Obesity	0.659	0.566-0.753	0.05	0.005	275.0	63.7%	61.1%	1.64	0.59
Hypertension	0.504	0.398-0.609	0.05	0.946	275.0	53.6%	40.8%	0.91	1.14
High TG	0.451	0.323-0.579	0.07	0.420	275.0	50.0%	41.2%	0.85	1.21
Low HDL-C	0.608	0.505-0.711	0.05	0.050	275.0	62.8%	56.1%	1.43	0.66
High FBS	0.691	0.522-0.831	0.07	0.002	275.0	75.0%	49.5%	1.49	0.51

S: standard error, SE: sensitivity, SP: specificity, LR+: positive likelihood ratio [=SE/(1-SP)], LR-: negative likelihood ratio [=(1-SE)/SP].

Table 7.

The optimal cut-offs of clinical and laboratory variables in the prediction of MetS

Variable	AUC	95% CI	S	*P*	Cut-off (mmol/L)	SE	SP	LR+	LR-
Age, years	0.634	0.551-0.716	0.04	0.002	40.5	62.2%	64.4%	1.75	0.59
Weight, Kg	0.693	0.615-0.771	0.04	<0.001	82.5	66.7%	61.1%	1.71	0.55
Height, cm	0.590	0.507-0.673	0.04	0.037	160.5	57.8%	59.0%	1.41	0.72
BMI, kg/m^2	0.689	0.609-0.769	0.04	<0.001	30.4	80.0%	60.0%	2.00	0.33
UA, mmol/L	0.601	0.517-0.685	0.04	0.019	295	58.9%	56.7%	1.36	0.72
FBS, mmol/L	0.625	0.542-0.707	0.04	0.004	5.5	52.2%	73.3%	1.96	0.65
HbA1c, %	0.673	0.594-0.752	0.04	<0.001	5.0	65.6%	57.8%	1.55	0.60
Insulin, mlU/mL	0.598	0.515-0.680	0.04	0.024	4.29	54.4%	53.4%	1.17	0.85
HOMA-IR	0.664	0.585-0.743	0.04	<0.001	1.23	56.7%	63.3%	1.54	0.68
TC, mmol/L	0.633	0.551-0.715	0.04	0.002	4.97	62.2%	60.0%	1.56	0.63
TG, mg/dL	0.666	0.587-0.745	0.04	<0.001	1.3	54.4%	66.7%	1.63	0.68
LDL-C, mmol/L	0.648	0.565-0.730	0.04	0.001	3.14	56.7%	65.6%	1.65	0.66
HDL-C, mmol/L	0.514	0.429-0.598	0.04	0.753	1.16	50.0%	51.1%	1.02	0.98
TC/HDL-C	0.614	0.532-0.696	0.04	0.008	4.2	61.1%	60.0%	1.53	0.65
TG/HDL-C	0.660	0.580-0.741	0.04	<0.001	1.0	57.8%	60.0%	1.45	0.70
Non-HDL-C, mmol/L	0.635	0.554-0.717	0.04	0.002	3.8	60.0%	64.4%	1.69	0.62

S: standard error, SE: sensitivity, SP: specificity, LR+: positive likelihood ratio [=SE/(1-SP)], LR-: negative likelihood ratio [=(1-SE)/SP].

The present study evaluated the associations of serum UA levels with MetS and its components in a sample of adult Saudi residence in the Northern area of Saudi Arabia. This region, as part of the "Middle East and North African (MENA)" region, is known for its high prevalence of MetS as recently supported by Al-Rubean et al.' s study, which revealed "a prevalence of 39.9% at specifically 45.0% in men and 35.4% in women" according to the same criteria the authors applied in the present study (i.e. NCEP ATP III criteria).[16] The authors preferred to apply the latter criteria rather than that of the International Diabetes Federation (IDF) [23] which mandates the presence of central obesity as one of the MetS components, contributing to apparently less disease prevalence and missing of several risky individuals who have other MetS components.

Currently, participants older than 45 years showed three times the odds of having MetS compared with those less than 45 years old. This could be attributed in part to the association of the age with the increased central obesity, hormonal changes, and IR,[24,25] as well as the analogous increase in the prevalence of specific MetS components (e.g. diabetes and hypertension) with age in the current population.[26,27]

In the present study, the serum UA level was higher in the MetS group compared to non-MetS one. This finding was consistent with the previous studies in other areas of the world.[28-32] Although serum UA has been reported to have a potent antioxidant capacity (i.e. conferring nearly 50%-60% of the total plasma antioxidant activity) in the circulation,[33] it can promote oxidative and inflammatory stress in the intracellular context[34-36] by several mechanisms detailed previously[37-39] which lead to endothelial cell dysfunction and contribute to MetS biogenesis.[34-36]

The overall analysis revealed that participants in the fourth quartile of serum UA showed a significantly higher frequency of MetS and central obesity relative to the ones in the first quartiles. This finding could support the mutual relations that could be present between serum UA and MetS/ components, which have been debated recently.[40] Chronic hyperuricemia found to be implicated in the pathogenesis of metabolic perturbation that could lead to MetS. Its control may prevent or reverse the course of MetS and/or its components.[41,42] Previously, Zhang et al.'s longitudinal cohort study, and a study by Chen et al. revealed that individuals with a higher concentration of serum UA, have 1.6 times the risk of developing MetS.[43,44] Furthermore, Nejatinamini et al. showed that higher serum UA levels, "even within the normal ranges", were associated with increased odds to have MetS (nearly double risk per one unit increment in serum UA), and could be considered as one of the determinants of the MetS.[31] Our findings are also consistent with that of Choi and Ford 's study on a nationally-representative sample of US adults.[45] They found that MetS prevalence and its individual components increase with increasing grades of hyperurecemia, and they recommended more intensive clinical investigation for a potential coexistence of the MetS in cases presented with high serum UA levels.[45] The close relation of hyperuricemia with MetS might be supported by the fact that UA biosynthesis is linked to glycolysis that is regulated by insulin. A decrease in the glycolytic enzyme glyceraldehyde-3-phosphate dehydrogenase (GA3PDH) activity in case of insulin resistance leads to shifting of glucose utilization from glycolysis into other pathways like the pentose phosphate pathway which is the main source of ribose-5-phosphate, the building unit of phosphoribosyl pyrophosphate (PRPP), which participates in the synthesis of nucleic acids including the purines and, consequently, increases its degradation products and the emergence of hyperuricemia.[46] In this respect, the latter mechanism could also explain the current finding of the high frequency of central obesity in high UA level quartiles as it is known that the visceral fat to be specifically associated with more insulin resistance than other types of adiposity due to the combined effect of increase free fatty acids released and adipokine secretion deregulation.[47]

Although overall correlation analysis showed that serum UA was correlated with age, BMI, and abdominal obesity, stratification analysis by sex revealed a consistent correlation of both BMI and central obesity with serum UA in both sexes. Still, a significant correlation with age was only evident in females. Interestingly, this finding is in line with recent findings of Sun et al., who revealed correlations between UA, hyperuricemia, and coronary artery diseases only in females, but not in men.[48] Additionally, several previous studies in different areas of the world supported this association like the National Health and Nutrition Examination Survey (NANHES) on the US general population,[49] the Italian Pro. V. A. study[50] and the community-based study in China.[51] Although the exact cause of this association is still undefined, the postmenopausal decline of the protective estrogens might explain in part this relation and the consistent correlation of serum UA with the glycemic variables (FBS and HbA1c %) in the present enrolled women.[52]

The present study identified an inverse correlation between serum UA and HDL-C levels and significant positive correlations between serum UA and other laboratory parameters, including the lipid profile-related variables and ratios (TC/HDL-C, TG/ HDL-C, non-HDL-C, and TG/HDL-C) in overall analysis with consistent associations with HDL-C and TG/HDL in both men and women after stratification by sex. This finding expands the previous studies that correlate serum UA with dyslipidemia and an increase in the risk of developing high LDL-C and hypertriglyceridemia.[53,54] The TG/HDL-C ratio is known to be a practical approach for identifying individuals who have insulin resistance, as concluded previously.[55,56] Given the role of HDL-C in the reverse transport of cholesterol from the peripheral tissues to the liver, the inhibitory effect on LDL oxidation, attenuation of platelet aggregation, and stimulation of prostacyclin secretion, HDL-C has a protective role against atherogenicity.[57] As previously indicated that it is hard to estimate the "LDL particle size" increment, which is associated with the hypertriglyceridemia risk,[58] TG/ HDL ratio is considered an accurate and putative marker for atherogenicity,[55] and prediction of the cardio-metabolic risk.[59, 60]

Remarkably, on testing the predictive capacity of serum UA to predict MetS and/or its components, the current results were largely in line with the available literature concerning

adult subjects.[61, 62] These studies including ours, suggest that hyperuricemic individuals could develop MetS at specified cut-off values among different sexes. It is noteworthy that these cut-off values (310 μmol/L and 275.0 μmol/L in the enrolled men and women, respectively) are less than those proposed for the gout treatment[63], which can decrease the chance of missing individuals with high risk to cardiovascular diseases (including MetS individuals) as supported by Cicero et al.[62] Although overall serum UA discriminating value was not the best one among other predictors for MetS, its cut-off point was associated with moderate sensitivity and specificity values, which minimize the false-positive and the false-negative included cases.

Collectively, it is evident that there is a significant association of serum UA levels with MetS and its components, including those associated with an increase in the risk of cardiovascular diseases. At specific cut-off levels, serum UA might predict MetS and/or its components in a sex-specific pattern in the study population that deserves great concern for careful monitor and control. It is worth noting that some limitations should be considered. The study design is a cross-sectional with a modest sample size that enrolled patients with relatively health awareness who were routinely attending the Medicine outpatient clinics at the general hospital, which could add some source of selection bias as it does not represent the general population. Not all the confounding factors could be adjusted (e.g. the physical activity, nutritional status, etc.) as the related data were not complete. Also, the direct causal relation of UA with MetS could not infer from the current study. Longitudinal follow-up studies with larger sample size and with different ethnicities are recommended.

Conclusion

The study findings suggest that levels of serum UA in the Saudi population might be associated with the risk of MetS and its components. In this sense, modifying the lifestyle and early management of hyperuricemia could be a useful strategy for lowering the MetS burden in this region. It is highly recommended to explore the causal relationship between hyperuricemia and MetS in future large-cohort studies.

Competing Interests

The authors declare that they have no competing interests.

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