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Uric acid levels in Saudi females with type 2 diabetes mellitus

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ABSTRACT

Background and Aim: Many studies have shown a relationship between hyperuricemia, metabolic syndrome (MetS), and cardiovascular disease. However, there is a dearth of studies identifying this relationship in those with type 2 diabetes mellitus (T2DM). Therefore, in the current study, we assessed the prevalence of hyperuricemia in Saudi females with T2DM and studied the correlation between risen serum uric acid levels and MetS. *Methods and Results:* We adopted an epidemiological, cross-sectional design. Participants were women aged ≥35 years old (n = 200) living in Al Madinah Al Munawarah city. Biochemical factors relevant to diabetes were measured. These included serum uric acid levels, glucose levels, HbA1c, and lipid profiles. In female T2DM patients,

the prevalence of hyperuricemia and MetS were 80% and 70%, respectively. We found positive correlations between cholesterol, triglyceride, fasting blood glucose (FBG), glycosylated hemoglobin (HbA1c), fasting insulin levels, and serum uric acid in our T2DM sample. A multiple linear regression model showed the risk of MetS to be positively correlated with higher levels of uric acid, triglycerides, and glucose, and with higher BMIs. *Conclusion:* Elevated levels of serum uric acid were associated with a higher incidence of MetS and associated symptoms in T2DM Saudi females. Routine evaluation of uric acid may help to prevent MetS-related T2DM complications.

Keywords: Body Mass Index, Lipoprotein, Metabolic Syndromes, Type 2 Diabetes Mellitus, Uric acid.

1. INTRODUCTION

Diabetes mellitus (DM) is an umbrella term for an array of metabolic diseases marked by elevated blood glucose levels (hyperglycemia) that lead to impaired insulin production, insulin action, or both (Diabetes Care., 2020). According to the International (IDF), the prevalence of adult diabetes in the Kingdom is currently 18.3%. The IDF also ranked Saudi Arabia as the country with the seventh-highest number of new cases of diabetes per year (Hu., 2011; IDF., 2019). Although a variety of factors can contribute to the development of type 2 diabetes, lifestyle habits typically associated with urbanization are likely the most significant (Hu., 2011).

World Health Organization (WHO.,2020) and International Diabetes Federation (IDF., 2020) have described metabolic syndrome (MetS) as a cluster of co-occurring conditions, including obesity, cardiovascular disease, dyslipidemia, hypertension, and glucose intolerance. The WHO criteria for MetS are hyperinsulinemia, hyperglycemia, and two or more of the following: dyslipidemia (high triglycerides or low HDL cholesterol), hypertension, or taking blood pressure medication, and a waist circumference greater than 94 cm (IDF., 2020; WHO., 2020). The NCEP ATP III standards for MetS diagnosing are three of these: high fasting triglyceride levels, low high-density lipoprotein levels, high fasting blood glucose levels, hypertension, and a waist circumference greater than 102 cm (NCEP., 2001). MetS involves 20%-25% of the world's population and its prevalence is rising. The incidence of MetS varies widely between the populations of different countries, extending from 8% to 43% in men and from 7% to 56% in women across the world (NCEP., 2001; WHO., 2020).The high rate of MetS in Saudi Arabia may be due to low HDL cholesterol among the population (Al-Nozha et al., 2004 & 2005). Al-Nozha et al. (2005) found the incidence of MetS between 1995 and 2000 to be almost 40% among Saudi Arabian adults. This finding has been replicated by more recent epidemiological studies, which have confirmed an elevated rate of MetS in Saudi Arabia (Aljohani et al., 2014; Aljabri et al., 2018).

Uric acid delivered from purine catabolism, uric acid levels increase in patients that known as hyperuricemia (Bhole et al., 2010). With an increase in uric acid levels comes an increased likelihood that diabetes, obesity, hypertension, or MetS will develop (Bhole et al., 2010; Cibičková et al., 2017). Therefore, the comorbidity of MetS and hyperuricemia is high (Johnson et al., 2015; Reilly et al., 2003). Despite this, raised uric acid levels are not among the criteria for MetS. Whether or not hyperuricemia is associated with the development of MetS or is simply an end-product of the purine metabolic pathway is still controversial [Krishnan et al., 2012; Lv et al., 2013). Despite several studies demonstrating a relationship between hyperuricemia and MetS, it is not known whether hyperuricemia can be used as a predictor of MetS in Saudi women. Also, while a correlation between hyperuricemia and MetS has been demonstrated, the particular aspects of MetS that raised serum uric acid levels are related to has not been determined. Thus, we aim to study the relationship between serum uric acid and MetS in Saudi females with T2DM. High serum levels of uric acid have been linked to depression, cardiovascular disease, and chronic renal disorder in previous studies (Liang et al., 2016; Ridi et al., 2017). Hyperuricemia is common in T2DM patients with central obesity and has been positively correlated with female gender; cardiovascular risk factors such as obesity, hypertension, and dyslipidemia; and low glomerular filtration rates (GFR) Liang et al., 2016; Ridi et al., 2017). However, the association between DM and hyperuricemia remains to be debatable. Many studies suggest that hyperuricemia is a risk factor for the development of DM, particularly within the context of hypoglycemic agent resistance (Johnson et al., 2015; Lv et al., 2013). We intend to investigate the concordance between uric acid levels, MetS components, and glycemic status in Saudi females with T2DM.

2. MATERIALS AND METHODS

Subjects and Inclusion/Exclusion Criteria

We conducted an epidemiological, cross-sectional study between January 2018 and January 2019. Subjects were Saudi women aged ≥ 35 years old with T2DM, living in Al Madinah Al Munawarah city. Women in our sample had no history of type 1 diabetes, parathyroid or calcium-related diseases, endocrine diseases, major renal, liver, heart, neurological, or pancreatic disease. They had

no history of gout (inflammatory arthritis) and bone disease. Patients on supplements such as calcium, allopurinol, and vitamin D were excluded. Details of age, medication history, menstrual cycle, and course of DM for each patient, as well as any diabetic complications experienced were obtained for each patient in the sample from their medical records. All participants gave informed consent and appropriate consent forms were obtained.

Specimen Collection

Venous blood samples (3 ml) were collected from the research subjects after a 12-hour overnight fast. Using immunoassay technology (ARCHITECT c4000, Abbott, USA), as per the manufacturer's instructions, levels of fasting blood glucose (FBG), glycated hemoglobin (HbA1c), and uric acid were measured, and a lipid profile taken from each blood sample. The presence of MetS was determined based on the published criteria (Grundy et al., 2004; IDF., 2019). A patient was deemed to suffer from MetS when, in addition to the DM present in all patients in our sample, there was also an FBG level of ≥110 mg/dl, together with two of the following characteristics:a BMI >30 Kg/m^2, hypertriglyceridemia with triglyceride (TG) >150mg/dl, HDL-C <39 mg/dl, and BP >140/90 mm of mercury (Hg) or documented evidence of anti-hypertensive drug therapy. The definition of hyperuricemia was the levels of uric acid more than 0.35 mmol/l, based on previous studies (Ridi et al., 2017).

Other Physical Measurements

Each participant was given a physical examination. The information recorded was height (cm), weight (kg), BMI (weight divided by the square of the height, expressed as kg/m^2). BP was recorded twice, five minutes apart, and the average of these two measurements was used for later BP analysis. Hypertension was identified as systolic blood pressure (SBP) ≥140 mm Hg, or diastolic blood pressure (DBP) ≥ 90 mm Hg.

Statistical Analysis

Once data was collected, we analyzed it using Graph Pad Prism 7 software (GraphPad Software, CA, USA). Quantitative data were expressed as mean ± standard deviation (SD), frequencies, and percentages. Pearson's correlation coefficient was calculated to assess the degree of correlation between the key variables. A multivariate analysis based on a multiple logistic regression model was run to predict the risk of MetS for T2DM women, using a 95% confidence interval and odd ratios.

3. RESULTS

The clinical characteristics of the study cohort are summarized in Table 1. Our results found hyperuricemia in 80% of the T2DM patients and MetS in 70%. Compared with average values, the diabetic females in our sample had higher lipid profiles, uric acid levels, fasting insulin levels, and higher BMI (Table 1).

Table 1: The clinical characteristics of the study samples

Parameter	**Diabetic Females N= 200**
MetS %	140 (70%)
Non-Mets %	60 (30%)
Uric acid (mmol/l)	**0.55±0.19***
Hyperuricemia % (>0.35 mmol/L)	160 (80%)
FBG (mmol/L)	10.35±3.35
HbA1c (%)	7.65±2.52
Fasting insulin uIU/mL	**12.70±3.03***
LDL-cholesterol (mmol/L)	**4.79±0.85***
HDL-cholesterol (mmol/L)	**0.8±0.17***
Total cholesterol (mmol/L)	**7.59±0.87***
Triglycerides (mmol/L)	**3.89±1.82***
Systolic BP, mm Hg	125±15.50
Diastolic BP, mm Hg	70±9.8
Weight (kg)	71.80±10.98
Length (cm)	157.67±5.55

BMI (kg/m2)	**26.35±6.5***
The mean concentrations ± standard deviation for the biochemical markers of the study population were determined. These markers were BMI (body mass index), FBG (fasting blood glucose), fasting insulin, lipid profile, TG (triglyceride), LDL-C (low-density lipoprotein-cholesterol), CHOL (total cholesterol), HDL-C (high-density lipoprotein-cholesterol), uric acid, HbA1c (glycated hemoglobin), and systolic and diastolic blood pressure (BP). Table shows the percentage of patients in the study population with MetS and hyperuricemia. The High levels of certain biomarkers and BMI significantly beyond the normal range in healthy women are marked with an asterisk (*) on the table.	

The correlations found between serum uric acid level and other biomarkers in the T2DM patients are presented in Table 2. The columns show correlation coefficients (r) and the corresponding *P*-value. Levels of uric acid were found to be inversely correlated with HDL (r= −0.411, *P*= 0.02). Significant positive correlations were observed between FBG and uric acid levels (r = 0.431, *P*= 0.01) and between HbA1c and uric acid levels (r=0.455, *P*= 0.03). There was also a significant positive correlation between triglycerides and uric acid levels (r= 0.622, *P*= 0.002) (Table 2).

Table 2: Association of uric acid level and other markers in Type 2 diabetic females.

Parameter	**Uric acid**	
	r	***p***
FBG	0.431	**0.01***
HbA1c %	0.455	**0.03***
Fasting insulin	0.461	**0.02***
LDL-cholesterol	0.334	**0.07**
HDL-cholesterol	-0.411	**0.02***
Total cholesterol	0.112	**0.07**
Triglycerides(TG)	0.622	**0.002****
SBP	0.422	**<0.001****
DBP	0.429	**<0.001****
BMI	0.333	**0.06**
Data were analyzed using the Pearson correlation test. The correlation coefficient for each variable was r versus the serum concentration of uric acid. *P*< 0.05*, *P*<0.001**.		

We applied a multivariate logistic regression model, with serum uric acid, FBG, triglycerides, systolic and diastolic BP, and high BMI as the independent variables predicted to increase the risk of MetS in T2DM patients (Table 3). As can be seen in Table 3, the odds ratios were statistically significant for uric acid, FBG and triglycerides. A one-unit change in the dependent factor, female MetS risk, increases the odds of higher BMI, systolic, and diastolic BP by factors of 5.03, 3.98, and 3.88 respectively (Table 3).

Table 3: Multivariate analysis for blood biomarkers and BMI in women with T2DM and MetS.

Parameter	**β**	**OR (95% CI)**	***P*-value**
Uric acid (mmol/l)	0.667	7.89 (0.156 to 13.165)	**<0.001****
FBG (mmol/L)	0.557	3.89 (0.9437 to 9.14)	**<0.001****
HbA1c (%)	1.001	1.02 (0.9395 to 1.017)	0.25
Fasting insulin uIU/mL	0.113	0.598 (0.0861 to 2.282)	0.81
LDL-cholesterol (mmol/L)	0.266	1.976 (0.972 to 1.05)	0.78
HDL-cholesterol (mmol/L)	0.257	0.882(0.822 to 1.170)	0.23
Total cholesterol (mmol/L)	0.113	1.162 (0.993 to 1.129)	0.42
Triglycerides (mmol/L)	0.687	8.973 (0.993 to 9.005)	**<0.001****

Systolic BP, mm Hg	0.584	3.981 (0.903 to 6.19)	**0.03***
Diastolic BP, mm Hg	0.565	3.884 (0.663 to 4.185)	**0.02***
BMI (kg/m2)	0.537	5.023 (1.001 to 6.019)	**<0.001****
Multiple logistic regression showed odd ratios (OR), with a 95% CI, and standardized beta coefficient (β) values for the biomarkers and BMI. Statistically significant was at a level of $P \leq 0.05$* or ≤0.001**.			

4. DISCUSSION

In this cross-sectional study of Saudi women with T2DM, we observed associations between serum levels of uric acid and the parameters of MetS. Specifically, dyslipidemia (low levels of HDL-C and elevated TG) and insulin resistance were highly correlated with uric acid levels (Table 2). Our data support other recent research on the relationship between serum uric acid levels and MetS (Sluijs et al., 2015; Sun et al., 2015). Ameta-analysis of prospective studies reported a positive linear association between serum uric acid levels and a predisposition to MetS (Sluijs et al., 2015; Sun et al., 2015; Yuan et al., 2015). Multivariate regression analyses for our data defined well-established markers of MetS as independent factors predicting the risk of MetS. Also, in the current work, our multivariate regression added uric acid as an independent factor that contributes to the risk of MetS in women with T2DM. This association reached a significance level of $P<0.001$ in the multiple regression model (Table 3). This supports previous data indicating a close relationship between high serum uric acid levels and biochemical MetS criterion (Sluijs et al., 2015; Sun et al., 2015; Tang et al., 2010).

The correlation between uric acid levels insulin resistance and DM has not been well studied. Our data showed a strong correlation between the parameters of insulin resistance (hyperglycemia and high insulin levels) and uric acid levels.

The biological mechanisms underlying the relationship between serum uric acid levels and diabetes remains controversial. However, hyperuricemia may result in insulin resistance and thereby, diabetes, which has been attributed to endothelial dysfunction and nitric oxide inhibition (Sun et al., 2015; Tanaka et al., 2020). Supporting this is data from two generations of the Framingham Heart Study showing that higher serum uric acid levels, even in younger adults, increases the risk of T2DM, in the absence of other known risk factors (Grundy et al., 2004). This was confirmed by a 15-year follow-up that reported an escalated incidence of diabetes and prediabetes among individuals with higher serum urate levels [Krishnan et al., 2012; Seungmin et al., 2020). Our study is in agreement with these results as we found a positive relationship between high levels of uric acid and both increased FBG and fasting insulin levels. This information may help to reduce the complications associated with T2DM.

In the current study, the association between high serum uric acid levels and high BP, a major factor of MetS, was also investigated. A strong relationship was found, suggesting that high serum uric acid levels may predispose an individual to cardiovascular disease. Nevertheless, additional investigations are needed to clarify this point.

5. CONCLUSION

In conclusion, this study confirmed a correlation between serum uric acid levels and MetS criteria in T2DM Saudi females. In particular, dyslipidemia (low HDL-C and high TG) and insulin resistance were positively correlated with high uric acid levels. Uric acid levels were higher in T2DM patients than average levels in healthy population. An association was also noticed between uric acid levels and BP. Therefore, high serum uric acid levels may correspond to an increased risk of cardiovascular disease. The present study is the first to provide insight into the role of serum uric acid in assessment of the MetS predisposition of the female Arab population with T2DM. Future studies, given the confounding factors, however, further research may be required to determine causality and expand on the present findings.

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Authors' contributions

WM: Conceptualization, study design, software, data curation, analysis and interpretation, original draft preparation and formal analysis, reviewing and editing. Author significantly contributed to this research and hold responsibility for its quality and content. Author has critically reviewed and approved the final draft and is responsible for the content and similarity index of the manuscript.

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Conflict of interest
There is no conflict of interest.

Ethics approval
This study was accepted by the Medical Ethical Committee of the Faculty of Applied Medical Sciences at Taibah University (MLT 201621).

Informed consent
Written & Oral informed consent was obtained from all individual participants included in the study. Additional informed consent was obtained from all individual participants for whom identifying information is included in this manuscript.

Abbreviations
T2DM= Type 2 Diabetes Mellitus, MetS = Metabolic Syndromes, HDL= High-Density Lipoprotein, LDL= Low-Density Lipoprotein, TG= Triglyceride, CRP= C - reactive protein, CVD= Cardiovascular disease, DM= Diabetes Mellitus, T1DM= Type 1 Diabetes Mellitus, BMI= Body Mass Index, DBP= Diastolic Blood Pressure, SBP= Systolic Blood Pressure, FBG= Fasting Blood Glucose.

Data and materials availability
All data associated with this study are available upon request to the corresponding author.

Peer-review
External peer-review was done through double-blind method.

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