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ASSOCIATION BETWEEN SERUM URIC ACID LEVEL AND METABOLIC SYNDROME COMPONENTS

Dr. Deepak Varshney

Assistant Professor, Department of Medicine, Muzaffarnagar Medical College, Opp. Begrajpur Industrial Area, Ghasipura, Muzaffarnagar-2512023 (U.P.)

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Corresponding Author:

Dr. Deepak Varshney

Assistant Professor, Department of Medicine, Muzaffarnagar Medical College, Opp. Begrajpur Industrial Area, Ghasipura, Muzaffarnagar-2512023 (U.P.)

ABSTRACT

BACKGROUND:
Metabolic syndrome (MetS) consists of several risk factors including central obesity, elevated blood pressure, hyperglycemia, high triglycerides, and reduced high-density lipoprotein cholesterol. MetS is associated with an increased risk of type 2 diabetes, cardiovascular disease (CVD), and mortality. Several population-based studies showed an increased risk of CVD in individuals with MetS compared to those who do not have the syndrome. Besides the traditional risk factors, other factors including microalbuminuria, inflammatory markers, and hyperuricemia have been suggested to be involved in the Mets. Along with MetS, obesity has also been found as an important risk factor for CVD. Furthermore, a link has been found between obesity and hyperuricemia in various studies. The prevalence of MetS is increasing at an alarming rate both in developed and developing countries. MetS is highly prevalent among Bangladeshi adults and has increased rapidly in the last few decades. A recent review reported a high prevalence of MetS (30%) in the Bangladeshi population with 32% in females and 25% in males.

AIM: The aim of the study is to Association between Serum Uric Acid Level and Metabolic Syndrome Components.

MATERIAL AND METHOD: This is a cross-sectional study conducted in the Department of General Medicine. The eligibility criteria consisted of being aged 30–49 years, and having no history of cardiovascular disease, diabetes, cancer, stroke, kidney disease, and gout. Of selected individuals, 3 who had heart failure and kidney disease were not included in the study, and the participants consisted of 30 persons in the MetS group and 30 as controls. Subjects who were taking antihypertensive or antidiabetic agents, lipid-lowering agents, and hypouricemic agents were excluded. Participants were asked to take a vegetable diet in the three days before they received the examination. All participants provided written informed consent before inclusion in the study.

RESULTS: After adjustment for confounding factors, serum uric acid was significantly higher in the MetS group than in the non-MetS group. Subjects in the MetS group had higher BMI, WC, lean body mass (LBM), body fat mass (BFM), trunk fat mass, SBP, DBP, FPG, insulin, HOMA index, TG, TC, LDL, and lower HDL levels than the subjects in the non-MetS group. In this study, the mean serum uric acid was significantly higher in the MetS group than that in the non-MetS group, even after adjustment for age, sex, and BMI. There were increases in ORs after adjustment for age and gender. The result of the regression model showed that in model III (age, sex, and BMI adjusted) for every 1 mg/dl elevation in the serum uric acid level, the odds ratio for developing metabolic syndrome increased approximately 2-fold.

CONCLUSION: Serum uric acid had an independent association with MetS components and increased the risk of MetS by near two folds. Regarding the high prevalence of obesity and MetS as well as the potential link between hyperuricemia and CVD, future studies should be conducted to clarify the role of uric acid in the pathogenesis of Mets and the clinical significance of the current findings. This study shows serum uric acid is markedly associated with metabolic syndrome and its components, in particular serum triglycerides and waist circumference.

KEYWORDS: Uric acid, Metabolic syndrome, Insulin resistance and Body composition

INTRODUCTION

Metabolic syndrome (MetS) is defined by a cluster of risk factors, including obesity, dyslipidemia, hypertension, and insulin resistance.[1] When occurring together, they increase the risk of developing cardiovascular disease (CVD) and diabetes.[2] Previous studies have shown that the defined MetS risk factors cannot explain all CVD

events observed in these subjects. Therefore, several other risk factors such as inflammatory markers, microalbuminuria, hyperuricemia, and disorders of coagulation have been debated to be included in the MetS definition.[3,4] The prevalence of MetS is increasing worldwide including in Asian countries,[5] and a high prevalence of MetS (30.1 %) has been reported in Iran.[6]

MetS has gradually become a global epidemic and a serious public problem affecting human health. According to the National Health and Nutrition Examination Survey (NHANES) survey data, the overall crude prevalence of MetS in the USA increased from 32.5% to 36.9% from 2011–2012 to 2015–2016. The Asia Pacific region is also facing a serious epidemic with a rapidly increasing incidence of MetS.[7] In China, the overall age-standardized prevalence is about 20% in 2009. A 2018 review reported that nearly one billion people across the globe now suffer from MetS. In addition, a large body of literature has demonstrated that MetS increases the risk of type 2 diabetes, cancer, cardiovascular disease, and all-cause mortality.[8,9]

Serum uric acid (SUA) is the end product of purine metabolism or purine nucleotide catabolism.[10] When the regulation of SUA production and excretion is out of balance, the levels of SUA become abnormal. It has been strongly demonstrated that elevated SUA level is closely related to diabetes, hypertension, obesity, renal function decline, and cardiovascular disease, most of which are principal contributors to the development and progression of MetS.[11] Serum uric acid is a final enzymatic product of purine metabolism in humans, and it is suggested that hyperuricemia is associated with MetS, and they may have common pathophysiology.[12] In addition to MetS, elevated concentrations of uric acid are associated with a variety of cardiovascular conditions.[13] However, the association of uric acid and MetS remains controversial and limited experience exists in this relationship.

A meta-analysis of 11 cohort studies suggested that the combined RR of MetS risk was 1.72 (1.45, 2.03) comparing the top SUA level category to the lowest SUA level category, and dose–response analysis indicated that the risk of developing MetS increased by 1.30 (1.22, 1.38) times for per 1 mg/dL SUA increment.[14] Even though the relationship between higher SUA levels and increased MetS was widely reported, most previous studies were conducted using cross-sectional or cohort designs, with SUA levels measured once at baseline. It is still unclear whether the temporal dynamic change of SUA is an independent risk factor for MetS, especially for those with baseline SUA levels within the normal reference range. The prevalence of hyperuricemia has been increasing in recent years, not only in advanced countries but also in developing countries, along with the development of their economies. It has been suggested that hyperuricemia is associated with metabolic syndrome. Furthermore, a link has been found between obesity and hyperuricemia in various studies.[15,16] The prevalence of MetS is increasing at an alarming rate both in developed and developing countries. Recent epidemiological studies have demonstrated an association of serum uric acid (SUA) with MetS and its components in different populations.[17,18]Some other studies have also found that elevated SUA levels are an independent predictor of the components of MetS, such as high blood pressure and hyperglycemia. Given the high prevalence of MetS in the present study we evaluated the association of serum uric acid levels and MetS components in the present study.

MATERIAL AND METHODS

This is a cross-sectional study conducted in the Department of General Medicine. The eligibility criteria consisted of being aged 30–49 years, and having no history of cardiovascular disease, diabetes, cancer, stroke, kidney disease, and gout. Of selected individuals, 3 who had heart failure and kidney disease were not included in the study, and the participants consisted of 30 persons in the MetS group and 30 as controls. Subjects who were taking antihypertensive or antidiabetic agents, lipid-lowering agents, and hypouricemic agents were excluded. Participants were asked to take a vegetable diet in the three days before they received the examination. All participants provided written informed consent before inclusion in the study. All steps in the methods section were performed in accordance with the relevant guidelines and regulations.

The inclusion criteria were: both genders, aged above 25 years, free from severe chronic illness, and willing to participate.

Exclusion criteria were: pregnant women, lactating mothers, and participants with a history of hepatotoxic drug intake, kidney disease, alcohol

intake, and self-reported evidence of acute or chronic hepatitis.

Measurement methods: To measure waist circumference, locate the top of the right iliac crest. Place a measuring tape in a horizontal plane around the abdomen at the level of the iliac crest. Before reading the tape measure, ensure that the tape is snug but does not compress the skin and is parallel to the floor. Measurement is made at the end of a normal expiration.[1] Blood pressure was measured using a sphygmomanometer after the subjects had rested for more than 5 min. For those with a systolic blood pressure ≥140 mmHg and a diastolic blood pressure ≥90 mmHg, blood pressure was measured on a further 2 occasions after resting, and average values were then taken.

Blood sample collection:

Venous blood samples were collected after an overnight fast from each subject. The blood samples were centrifuged and stored the isolated serum at −20°C until laboratory analysis. HDL-C was measured similarly after precipitation with magnesium phosphotungstate. LDL-cholesterol was calculated using Friedewald's formula. FPG was measured using the glucose oxidase method, and immunoreactive insulin (IRI) was measured by radioimmunoassay.

Laboratory analyses: Participants provided an overnight fasting venous blood sample. Serum samples were used to determine participants' lipid profiles and fasting blood glucose using an automatic analyzer. Serum triglyceride concentration was determined by standardized enzymatic procedures using glycerol phosphate oxidase assay. High-density lipoprotein-cholesterol (HDL-C) was measured by a chemical precipitation technique using dextran sulfate. Fasting plasma glucose was measured using the hexokinase method. Serum uric acid concentrations were measured using the uricase EMST method. Having at least three of the following components: high serum triglycerides (TG) concentrations (≥150 mg/dl and/or use of lipid-lowering medication); low serum HDL- cholesterol (HDL-C) concentrations (89 cm in men and > 91 cm in women, based on guidelines for the First Nationwide Study of the Prevalence of Metabolic Syndrome.[6]

Diagnosis Criteria:

1. Hyperuricemia is defined as serum uric acid level ≥7 mg/dl (in men) or ≥6.0 mg/dl (in women).
2. We assessed metabolic syndrome according to AHA/NHLBI criteria. The presence of metabolic syndrome was defined as those patients having ≥3 of the following 5 items: (1) waist circumference ≥90 cm for males (≥80 cm for females); (2) serum triglyceride levels ≥150 mg/dl or on drug treatment for elevated triglycerides; (3) serum HDL-C levels <40 mg/dl for males (<50 mg/dl for females), or on drug treatment for reduced HDL-C; (4) systolic blood pressure ≥130 mmHg or diastolic blood pressure ≥85 mmHg or antihypertensive drug treatment in a patient with a history of hypertension; (5) fasting blood glucose ≥110 mg/dl or on drug treatment for elevated glucose.[1]

STATISTICAL ANALYSIS

Results are expressed as mean ± standard deviation (SD). Kolmogorov Smirnov test was used to examine the normality of variables of interest. Continuous variables were compared by T-test. The relationship between uric acid level and other variables including MetS components were assessed by Pearson's correlation coefficients. A logistic regression analysis was performed to examine the relationship between serum uric acid and the diagnosis of MetS.

RESULT: -

The average age of the study population was 36.3 ± 5.0 years. The clinical and metabolic characteristics of the study participants are summarized in Table 1.

Table 1: Characteristics of the participants with or without metabolic syndrome.

Variables	MetS group (*n* = 30)	Non-MetS group (*n* = 30)
Age, years	36.3 ± 5.0	37 ± 5.57
Body mass index, kg/m2	23.62 ± 2.63	22.69 ± 2.60
Waist circumference, cm	89.7 ± 13.14	85.60 ± 6.52
Fat-free mass, kg	53.48 ± 10.12	48.25 ± 8.23
Fat mass, kg	22.82 ± 6.5	17.22 ± 5.44
Trunk fat mass, kg	11.33 ± 2.84	8.39 ± 2.21
Systolic blood pressure, mmHg	111.5 ± 10.1	108.4 ± 11.3
Diastolic blood pressure, mmHg	80.4 ± 8.2	75.2 ± 10.23

Fasting glucose, mg/dl	98.6 ± 11.1	93.4 ± 5.7
Fasting insulin, µU/ml	11.4 ± 4.57	7.8 ± 3.26
HOMA-IR	2.24 ± 1.39	2.06 ± 1.04
Triglyceride, mg/dl	196.1 ± 120.1	99.2 ± 52.2
Total cholesterol, mg/dl	198.8 ± 40.7	175.4 ± 25.3
LDL-C, mg/dl	113.5 ± 28.4	104.1 ± 20.1
HDL-C, mg/dl	32.5 ± 5.2	43 ± 9.6
Uric Acid, mg/dl	4.77 ± 1.42	2.75 ± 1.21

Subjects in the MetS group had higher BMI, WC, lean body mass (LBM), body fat mass (BFM), trunk fat mass, SBP, DBP, FPG, insulin, HOMA index, TG, TC, LDL, and lower HDL levels than the subjects in the non-MetS group. In this study, the mean serum uric acid was significantly higher in the MetS group than that in the non-MetS group, even after adjustment for age, sex, and BMI.

Table 2: Association between uric acid level (mg/dl) and metabolic syndrome in logistic regression models.

Serum uric acid	OR (95 % CI)
Model I	1.60(1.23-2.33
Model II	1.25 (1.49-3.81)
Model III	1.09 (1.30-3.41)

Model I, the Crude model; Model II, adjusted for age and sex; Model III, furtheradjusted for BMI

Table 2 shows the association of serum uric acid level for the diagnosis of MetS in the logistic regression analysis. There were increases in ORs after adjustment for age and gender. The result of the regression model showed that in model III (age, sex, and BMI adjusted) for every 1 mg/dl elevation in the serum uric acid level, the odds ratio for developing metabolic syndrome increased approximately 2-fold.

DISCUSSION

In this study, we evaluated the associations of serum uric acid levels with MetS components in individuals with or without MetS. Serum uric acid levels were significantly higher in the MetS group compared to healthy individuals after considering covariates like gender, age, and BMI. This finding is in line with some other studies.[22] Although hyperuricemia is well recognized as a risk factor for atherosclerotic diseases such as myocardial infarction and stroke, its independent association with cardiometabolic risk factors remained controversial. Hyperuricemia is an increasingly common medical problem not only in the advanced countries but also in the developing countries. It has been described that hyperuricemia is associated with metabolic syndrome components, such as obesity, dyslipidemia, hyperglycemia, and hypertension.[19]

Higher serum uric acid levels, even within the normal ranges, were associated with an increased odds ratio of MetS and remained significant even after adjusting for confounding factors. It is speculated from this study that serum uric acid is one of the determinants of the Mets. With a one-unit increase of serum uric acid, the odds of developing MetS approximately doubled. Similar findings have shown that individuals with high uric acid levels have 1.6 times higher odds of developing MetS.[20] However, the precise biological mechanisms underlying the association between serum uric acid and the development of MetS remain unclear, although the reduction in endothelial nitric oxide bioavailability by uric acid is likely to be involved. Nitric oxide seems to play an important role in the development of insulin resistance, and its deficiency is believed to reduce blood flow to insulin-sensitive tissues, i.e., skeletal muscle, liver, and adipose tissue, leading to blocking the action of insulin.[21]

Conen et al. 2004[22] and **Schachter 2005**[23] showed the same results. Hyperuricemia and hypertriglyceridemia are suggested to be associated with insulin resistance syndrome, and many investigators are studying the mechanisms of the emergence of this syndrome. The association between insulin resistance syndrome, hyperuricemia, and hypertriglyceridemia is complicated. A study done by **Krishnan et al.2007**[24] found that men with hyperuricemia had more risk

for incident hypertension. Each unit increase in serum uric acid was associated with a 9% increase in the risk for incident hypertension. Although the mechanism by which uric acid plays a pathogenetic role in hypertension was unclear, hyperuricemia is associated with deleterious effects on endothelial function, platelet adhesion, aggregation, or oxidative metabolism

These results showed that the body fat mass, especially trunk fat mass, could be related to serum uric acid. Some studies reported the relationship between body fat mass and serum uric acid. **Hikita et al.2007**[25] reported that there were significant relations between serum uric acid and both visceral fat and total fat mass; in particular, serum uric acid was more closely related to visceral fat. It is considered that insulin resistance caused by the accumulation of visceral fat is the underlying mechanism.

Yoo et al.2005[26] and **Becker and Jolly 2006**[27] reported that hyperglycemia was a remarkable risk factor for hyperuricemia. In a study of 3681 Japanese adults, it was found that an elevation of serum uric acid concentration in males increased the risk of type 2 diabetes. It was concluded that hyperuricemia was positively associated with hyperglycemia. Insulin resistance may be the link between them, but we found there was no statistical significance between elevated fasting glucose and uric acid concentration. A statistically significant positive correlation was noted for serum uric acid concentration with log-transformed fasting plasma glucose only in women.

The study also found that the longitudinal increase of SUA was positively linked with the MetS incidence, independent of baseline SUA. What we observed was roughly in line with the results of baseline SUA. The similarity is that in a population-based study of 6083 Norwegian adults, the risk of MetS incidence was increased 1.28-fold per 59 µmol/L increase of longitudinal SUA among all populations.[28] Another retrospective cohort study among 407 Japanese community-dwelling women manifested that the risk of MetS increased 2.49 fold comparing the third tertial to the first tertial of longitudinal increase in SUA.[29]

The limitations of this study warrant consideration. Firstly, this study is limited due to its cross-sectional nature, since a causal association between uric acid and MetS could not be derived. Secondly, the sample size in this study was relatively small which could limit the generalization of our findings. It is also possible that unmeasured confounding variables may exist.

CONCLUSION:

Serum uric acid had an independent association with MetS components and increased the risk of MetS by near two folds. Our findings propose that uric acid can be considered a component of MetS. Regarding the high prevalence of obesity and MetS as well as the potential link between hyperuricemia and CVD, future studies should be conducted to clarify the role of uric acid in the pathogenesis of Mets and the clinical significance of the current findings. This study shows serum uric acid is markedly associated with metabolic syndrome and its components, in particular serum triglycerides and waist circumference. Considering the growing incidence of obesity and metabolic syndrome worldwide and the potential link to hyperuricemia, more emphasis should be put on the evolving morbidity prevalence of hyperuricemia in our country.

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