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Original Research Article

Serum uric acid is no more a by-stander for risk of cardiovascular diseases in metabolic syndrome: a prospective study

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ABSTRACT

Background: Cardiovascular diseases have become the fastest growing health issue in India and worldwide. Population with metabolic syndrome is known to be pre-disposed to several chronic disorders along with higher risk of experiencing cardiovascular events. The role of uric acid as a cardiovascular risk factor in metabolic syndrome was not well studied in the literature, which made us to undertake the present study.
Methods: All the patients aged between 18 to 75 years (both gender) who approached Madhavbaug cardiac care clinics located in Maharashtra, India for assessing risk of heart disease from January 2015 to January 2017 were screened. Risk factors for metabolic syndrome have been evaluated among the study population and categorised into metabolic syndrome positive (≥3 risk factors) and negative groups (<3 risk factors). Statistical analysis was done using SPSS software version: 21.0.
Results: Our study includes 2294 subjects who met the inclusion and exclusion criteria. Males outnumbered the females and sex ratio was 2.89:1. Females had lower serum uric acid levels compared to males irrespective of metabolic component. Gender and serum uric acid levels (high and low) were used stratification of the subjects. Serum uric acid is an independent predictor of cardiovascular diseases with an Odds ratio of 1.13 (95% confidence interval).
Conclusions: Serum uric acid level is one of the important predictor for cardiovascular risk in metabolic syndrome. Raised uric acid is not an innocent by-stander and one of the major contributors in development of cardiovascular diseases.

Keywords: Hyperuricemia, Metabolic syndrome, Cardiovascular diseases

INTRODUCTION

Cardiovascular diseases (CVD) have become the fastest growing health issue in India and worldwide. In order to prevent the progression of the disease there is need of constant research to learn about: the metabolites and/or processes contributing to the disease pathophysiology, better diagnostic markers, tools and algorithms that may help to shed the light on areas to target to prevent disease progression and eventually and a better management therapy.

Though the pathophysiology of cardiovascular diseases is well studied, newer metabolites or molecules are constantly being added to the list of one's related to that of CVD. One such metabolite is uric acid (UA). UA is one of the weak acid produced by the liver, muscles, and

intestine[1]. In the pathogenesis of kidney and gout, UA was claimed as one of the prime role. It's been more than an era that high serum uric acid (SUA) has been put forward as an association with other chronic diseases such as hypertension (HTN).[1,2] In 1951 the association between hyperuricemia and CHD has been reported for first time in the literature.[3]

Population with metabolic syndrome (MS) is known to be pre-disposed to several chronic disorders along with higher risk of experiencing cardiovascular events. MS is a mixed entity of clinical and laboratory abnormalities. The diagnostic criteria for MS requires three or more of the following manifestations which includes; waist circumference >90 and 80 cm in men and women respectively; (2) serum triglyceride >150 mg/dl; (3) high-density lipoprotein cholesterol (HDLc) <40 and 50 mg/dl in men and women respectively, blood pressure (BP) >130/85 mmHg; and fasting blood sugar >100 mg/dl.[4] The manifestations are attributed to excess deposition of fat in adipose tissue.[5]

Higher levels of serum uric acid (>10mg/dl) has more association with MS by 10 times in adults with normal body mass index.[6] In a study, children of age 10-15 years at baseline were followed for 10 years, which showed high SUA as a predictor for MS in males.[7] In contradictory to above study, elderly hypouricemic subjects above 65 years when followed showed that female subjects have high incidence of MS comparatively.[8]

METHODS

Study population

All the patients aged between 18 to 75 years (both gender) who approached Madhavbaug cardiac care clinics located in Maharashtra, India for assessing risk of heart disease from January 2015 to January 2017 were screened. Participants who agreed to assess their serum UA levels and provide a signed consent for data publication were screened. Participants with no metabolic risk factor were enrolled in without metabolic syndrome ($MetS^-$) group and those with 3 or more metabolic risk factors were enrolled in with metabolic syndrome ($MetS^+$) group.

Study method

The metabolic syndrome status was determined using five point guidelines from The National heart, lung, and blood institute (NHLBI) health topics. According to which participants with at least three metabolic risk factors is to be diagnosed as $MetS^+$. The metabolic risk factors are: abdominal obesity, fasting plasma glucose (FPG) ≥100 mg/dl (5.6 mmol/l) or h/o of type 2 diabetes mellitus (DM).

TG level ≥150 mg/dl (1.7 mmol/l), or specific treatment for this lipid abnormality, HDL cholesterol <40 mg/dl (1.03 mmol/l) in males and <50 mg/dl (1.29 mmol/l) in females, or specific treatment for this lipid abnormality and systolic BP ≥130 or diastolic BP ≥85 mmHg, or treatment of hypertension.

Three millilitre of blood was collected in plain vacutainer and later centrifuged to obtain serum. Serum UA levels were estimated using kit from ACCUREX Biomedical Pvt. Ltd. performed in fully automated analyzer (DS-302). Current study was conducted in accordance with the ethical principles in the declaration of Helsinki and consistent with good clinical practices.

Statistical analysis

The variables were reported as mean (SD) or median (range) according to the distribution of the data. The difference between the means across the group was calculated using independent t-test while Mann Whitney u' test was used to compare non-parametric variables across the group, p=0.05 was considered to be significant. SPSS software 21.0 was used to analyse the data.

RESULTS

In the present study, 2294 participants were enrolled based on the study inclusion and exclusion criteria. The demographic and clinical details of the enrolled participants are reported as in (Table 1). Majority of the participants in both the study groups were male 1705 (74.3%), $MetS^-$ 726 (76.9) and $MetS^+$ 979 (71.1). We observed the data based on the four metabolic syndrome components and studied the SUA levels between the genders (Table 2). Irrespective of the metabolic component female participants consistently showed lower SUA levels as compared to the male participants.

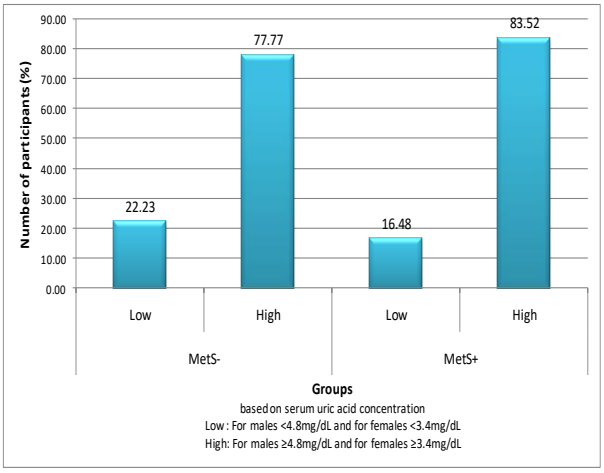

Figure 1: Cut off values of SUA indicating the metabolic syndrome status of the participants.

Two cut-offs values were used of SUA each for a gender to stratify the participants into low and high SUA levels. The cut off was set to 4.8 for males (low: <4.8 and high: ≥4.8) and 3.4 for females (low: <3.4 and high: ≥3.4). These cut offs may help shed the light on role of SUA level on the metabolic syndrome status of the participants (Figure 1).

Majority of the participants in both the study groups had high level of SUA. In the present study we had also taken odds ratio for SUA as a risk factor for CAD depending on angiographic evidence which showed a significant, Odds ratio 1.13 (95% confidence interval).

DISCUSSION

Current study was driven to make an analysis of the trend in serum uric acid levels in metabolic syndrome population as compared to their counterparts. The study was also focused to sort the difference if any between the genders in terms of serum uric acid levels in context to varied metabolic syndrome components. This kind of analysis was a requisite in a large population similar to the current study that is representative of Maharashtra, India. About 45.5% of the current study population classified as having hyperuricemia.

Table 1: Demographic and clinical parameters.

Study parameters	Metabolic syndrome status						P value
	Absent			Present			
	N	Mean	SD	N	Mean	SD	
Age (years)	943	58.74	11.71	1377	57.43	10.02	0.005
Serum uric acid	941	5.63	1.79	1371	6.06	1.93	0.0001
Abdominal girth (cm)	944	85.96	10.6	1372	98.20	9.62	0.0001
Fasting blood sugar (mg/dl)	940	115.07	40.45	1367	143.93	54.70	0.0001
Triglyceride (mg/dl)	945	105.93	32.90	1369	168.79	79.90	0.0001
HDL-cholesterol (mg/dl)	945	49.23	11.38	1372	39.14	10.12	0.0001
SBP	348	140.81	13.98	471	139.94	13.68	0.374

Table 2: Metabolic syndrome components comparison between gender.

Metabolic syndrome components	Uric acid (mg/dl)					
	N	Women	P value	N	Men	P value
Abdominal girth (cm)						
<88/102	236	5.31±1.93	0.013	1277	5.92±1.83	0.002
≥88/102	375	5.70±1.88		417	6.25±1.89	
Fasting blood sugar (mg/dl)						
<110	235	5.56±1.90	0.990	739	6.11±1.75	0.033
≥110	377	5.56±1.93		959	5.92±1.92	
Triglyceride (mg/dl)						
<150	353	5.25±1.85	0.0001	1101	5.81±1.78	0.0001
≥150	259	5.98±1.95		598	6.36±1.93	
HDL-cholesterol (mg/dl)						
<50/40	420	5.56±1.84	0.978	838	6.14±1.90	0.003
≥50/40	191	5.56±2.10		860	5.87±1.80	

The females in the current study population had significantly lower SUA levels as compared to males. One of the hypothesis justifying low SUA levels in females is related to uricosuric effect of estrogen that increases excretion of uric acid from the body. However, in the current study the estrogen levels were not studied and hence the low SUA levels can't be directly attributed to the uricosuric effect of estrogen.

A prospective study which analysed a group of 1511 subjects both men and women , between age group of 55-80 years who were not affected initially by any manifestation of MS. Subjects were followed up which demonstrated significant higher incidence of many manifestations of MS like , hypertriglyceridemia, low HDL, and HTN in subjects with highest sex-adjusted quartile of UA.[9] It's still a topic of debate whether SUA is merely a marker or a risk factor for CV disease, or whether hypouricemic agents affect outcomes.[10]

The confounding factors which are frequently encountered in cardiac patients namely HTN,

dyslipidemia, DM, alcohol consumption, hypothyroidism and diuretic use show association between SUA and different CVD.[11] Type 2 DM hyperuricemic patients who were treated with allopurinol showed reduction of carotid intimal thickening.[12] In contradictory to present study, some studies failed to demonstrate UA as independent CVD risk factor.[13] A study conducted in Framingham including 6763 participants failed to demonstrate a significant association between SUA and coronary heart disease (CHD)and cardiovascular (CV) mortality.[14] SUA was measured in 705 cases of both sexes that underwent coronary angiography. 41% of cases had normal angiography and were considered the control group. A significant positive correlation between SUA and the severity of CHD score was encountered.[15] But most of the, data collected in recent years are in favor of association with SUA. SUA is a significant predictor of poor outcomes in AMI patients complicated with reduced LV function, heart failure (HF), or both.[16] The pooled data from eleven studies that evaluated the prognostic importance of SUA demonstrated that hyperuricemia can significantly predict all-cause mortality in HF patients.[17] These data are also observed in HF patients with preserved ejection fraction and inpatients hospitalized with severely decompensated acute HF.[18-20] A recent meta-analysis of six studies, including more than 200,000 patients showed that hyperuricemia independently increases the risk of mortality from CVD and CHD.[21] Increased SUA was appointed as independent risk factor for overall mortality and CV mortality.[22,23]

CONCLUSION

The current study reiterates use of SUA levels as the predictor for cardiovascular risk due its strong association with number of factors involved in metabolic syndrome. This study is fairly sized to highlight the changes in SUA levels in metabolic syndrome patients. However, it lacks the follow-up period which may highlight the relationship with future cardiovascular events. It is also important to note that our study supports the hypothesis that uric acid is not an innocent by-stander and thereby has its contribution in development of CVD.

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Conflict of interest: None declared
Ethical approval: The study was approved by the Institutional Ethics Committee

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