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Prevalence of Hyperuricemia and Relation of Serum Uric Acid with Cardiometabolic Risk Factors

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Abstract

Cardiometabolic diseases like metabolic syndrome (Mets), cardiovascular disease (CVD) and type 2 diabetes mellitus have several risk factors in common. Several biochemical markers are in current use as laboratory diagnostic aids for these disorders. Many more such markers will emerge in the future as a result of current research. Serum uric acid (SUA) has emerged as a common candidate involved in these three cardiometabolic disorders.The purpose of the present study was to investigate the prevalence of hyperuricemia and the association between uric acid levels and the various cardiometabolic risk factors. This study included 150 cardiometabolic subjects aged 25 to 80 years. The body mass index (BMI), waist circumference, total and HDL cholesterol, serum triglycerides and serum uric acid were measured. Data were analyzed using student t-test, pearson'scoefficient and linear regression model .The prevalence of a serum uric acid level >0.42mmol/L in men was 18.32% and the prevalence of a serum uric acid level >0.36 mmol/L was 15.9% in women. Serum uric acid was strongly related to serum triglycerides in men as well as in women ($r = 0.255$ in men and $r = 0.254$ in women, $p < 0.001$). Uric acid levels were also significantly associated but to a lesser degree with age, BMI and waist circumference. This study shows that serum uric acid is markedly associated with parameters of the metabolic syndrome, in particular serum triglycerides. Considering the growing incidence of obesity and metabolic syndrome worldwide and the potential link between hyperuricemia and cardiovascular complications, more emphasis should be put on the evolving prevalence of hyperuricemia.

Key words: *Cardiometabolic disease, Hyperuricemia, Metabolic syndrome*

INTRODUCTION

Cardiometabolic disease includes a wide range of indications leading to heart and coronary disease. Today, it affects more than 100 million people in the developed world and represents the leading cause of death in the world, before cancer and accidents. Even if patient care is improving, the disease continues to grow to epidemic proportions, with the continued prevalence of a variety of risk factors including dyslipidemia, obesity and diabetes. It is defined as an array of metabolic, hemodynamic and renal abnormalities. The syndrome is also associated with essential hypertension, abnormalities in the circadian rhythm of blood pressure and heart rate, the diabetic dyslipidemic syndrome, hypercoagulability and increased cardiovascular inflammation, all of which contribute to an increased risk of cardiovascular disease, morbidity and mortality. Cardiometabolic diseases like metabolic syndrome (Mets), cardiovascular disease (CVD) and type 2 diabetes mellitus have several risk factors in common. Several biochemical markers are in current use as laboratory diagnostic aids for these disorders. Many more such markers will emerge in the future as a result of current research. Serum uric acid (SUA) has emerged as a common candidate involved in these three cardiometabolic disorders. A "common soil" hypothesis has been proposed implicating the role of uric acid in the three disorders [(1)].

The topical role of serum uric acid being a risk factor is currently controversial. The role of uric acid and its relation to cardiovascular disease, renal disease and hypertension is rapidly evolving. It's important role both historically and currently in the clinical clustering phenomenon of the metabolic syndrome, type 2 diabetes mellitus, atherosclerosis and non-diabetic atherosclerosis is of great importance.

Uric acid can act as a pro-oxidant, particularly at increased concentrations, and may thus be a marker of oxidative stress [(2,3)], but it may also have a therapeutic role as an antioxidant [(4,5)]. Plasma uric acid concentrations correlate with longevity in primates and other mammals [(6),] a characteristic that is presumably a function of urate's antioxidant properties. Thus it is unclear whether increased concentrations of uric acid in diseases associated with oxidative stress, such as atherosclerotic coronary heart disease (CHD), Stroke, and peripheral arterial occlusive disease, are a protective response or a primary cause. Some researchers have proposed that hyperuricemia-induced oxidative stress represents a cause of metabolic syndrome [(7).] Hyperuricemia has been found to be associated with obesity and insulin resistance, and consequently with type II diabetes [(8, 9)]. The association between concentrations of uric acid and these three cardiometabolic disorders remains incompletely understood and uric acid presents one of the candidates that may be involved in these three cardiometabolic disorders. The present study was aimed to establish a diagnostic and prognostic value of serum uric acid in these cardiometabolic disorders.

METHODS

Cases were divided into four groups namely, Group 1: normal, healthy adults as control group, Group 2: patients with type 2 diabetes mellitus, Group 3: patients with known history of CHD, and Group 4: patients with metabolic syndrome (diagnosed as per NCEP-ATP III criteria)(10).A total of 150 cases were selected which included 69 metabolic syndrome cases, 51 cases of diabetes mellitus type 2 and 30 cases with cardiovascular disease.

The following five criteria were used for the diagnosis of metabolic syndrome, as described by NCEP-ATP III committee.

1. Elevated triglycerides (>150 mg/dl) or specific treatment for this lipid abnormality.
2. Reduced HDL cholesterol (<40 mg/dl in males and <50 mg/dl in females) or specific treatment for this lipid abnormality.
3. High blood pressure (>130/85 mm/Hg) or on treatment for hypertension.
4. Raised fasting blood glucose (>100mg/dl or 5.6 mmol) or already having type II diabetes.
5. Obesity- measured as waist circumference >35 inches in women and >40 inches in men or BMI 25-30 Kg/m^2 (obesity or overweight).

If three of the above mentioned five criteria were present in the patient, he/she was considered as the case of metabolic syndrome.

Renal function was assessed by doing creatinine clearance and blood urea measurements and only cases with normal renal function were included for further study. All participants were subjected to a detailed questionnaire and a medical examination at the study centre was performed.

Measures and cut-off points

Weight, Height and Body Mass Index

Height and body weight were measured with participants standing without shoes and heavy outer garments. Body mass index (BMI) was calculated as weight divided by height (Kg/m^2). Waist circumference was measured to the nearest 1cm.

Blood Pressure

Patients were queried about for the existence of hypertension. Hypertension was defined as diastolic BP $\geq$ 95 and/or current intake of antihypertensive medication.

Smoking

Smoking habits were classified as persons who never smoked, ex-smokers designated as persons who reported no current smoking but regular smoking in the past, occasional smokers referred to persons reporting non-daily consumption of cigarettes and regular smokers currently smoking at least one cigarette per day.

Alcohol habits

Alcohol consumption was assessed according to the frequency of alcohol drinking as never, occasionally and regular.

Dietary Habits

The participants were classified as vegetarians and non-vegetarians according to the type of regular diet.

Diabetes

The diagnosis of diabetes mellitus was considered when individuals reported to have been told by a doctor or tested positive for glycosuria. All the patients were tested for serum glucose level after an overnight fast and also 2hrs after taking regular meal.

Dyslipidemia

The lipid profile of all the patients was tested after an overnight fast which included testing of total cholesterol, triglyceride, HDL, LDL, VLDL levels and calculation of risk factor. The patients with hypertriglyceridemia and lower HDL-cholesterol levels were considered.

Biochemical Analysis

Only blood samples collected in the Clinical Biochemistry laboratory were used for in vitro biochemical analysis. The samples were collected by standard procedures under aseptic conditions. Standard procedures were followed for the preservation and storage of samples before analysis. Total cholesterol was determined enzymatically using an ERBA test kit (CHOD/PAP method)(11). Similarly HDL-cholesterol(Direct enzymatic method) (12), Triglyceride (GPO/PAP method)(13) and uric acid(Uricase/POD method)(14) levels were measured using standard autoanalyser. The values of LDL-cholesterol and VLDL-cholesterol and the risk ratio was calculated using Friedwald formula. Internal quality control for the laboratory determinations was regularly performed.

Statistical Analysis

All statistical analyses were carried out separately by sex using the unpaired student t-test. P-value <0.05 was considered as significant. Linear regression technique was used to determine the independent predictors of serum uric acid. The various components (CVD, Diabetes mellitus type 2 and metabolic syndrome) of the cardiometabolic disease, as well as the other established risk factors of uric acid, were considered as potential explanatory variables in this model. Values of uric acid above the sex-specific percentile 75 (i.e. >0.383 mmol/L for men and >0.354 mmol/L for women) were defined as high.

RESULTS

The characteristics of the participants are presented in Table 1. BMI, triglycerides and uric acid levels were significantly higher in morbid group than in control group ($p<0.001$)(Figure 1).Smoking, alcohol consumption and high triglyceride levels were more common in men than in women (Table 2). As shown in this table and in Figure 2, serum uric acid levels were significantly higher in men than in women ($p < 0.05$). When using the commonly accepted cut-off values for serum uric acid levels, i.e. a serum uric acid >0.42mmol/L in men and >0.36mmol/L in women [15], the prevalence of hyperuricemia would be 18.32% in men and 15.9% in women (p

< 0.05). In this analysis, however, we have used the sex-specific 75th percentile which gives a cut-off at 0.383mmol/L for men and 0.354mmol/L for women. Table 2 also shows the simple correlation coefficients between serum uric acid levels and the various cardiometabolic risk factors in the population. In both sexes, serum triglycerides and serum uric acid levels were strongly correlated (p < 0.001). In women, significant correlations (p < 0.001) were also found with almost all metabolic parameters except for alcohol consumption. In men, serum uric acid correlated with body weight, total cholesterol, waist and BMI (p<0.001).

Table 3 shows the linear regression model. Age, triglycerides, BMI and waist circumference were the major determinants of the variations in serum uric acid levels in both sexes. Table 4 presents the proportion of persons with high uric acid in sex-specific highest quartiles according to selected cardiometabolic risk factors. As shown in this table, all metabolic parameters were strongly associated with serum uric acid levels.

Table 1: Comparison of cardiometabolic risk factors with control subjects, (* denotes p value < 0.001, ** denotes p <0.01), SD: Standard Deviation

FACTORS	UNIT	MORBID GROUP (n=150) Mean±SD	CONTROL GROUP (n=50) Mean±SD
AGE	Years	52.3±12.3*	41.61±11.8
WEIGHT	Kg	68.5±11.4*	58.8±10.43
BMI	Kg/m^2	28.3±11.8**	22.5±4.67
WAIST CIRCUMFERENCE	cm	97.02±12.57*	80.77±15.41
TOTAL CHOLESTEROL	mmol/l	4.78±1.07	4.44±1.03
HDL-C	mmol/l	1.20±0.44	1.34±0.43
TRIGLYCERIDES	mmol/l	2.21±1.40**	1.56±0.75
URIC ACID	mmol/l	0.29±0.09*	0.20±0.04
SMOKING	%	12	-
HYPERTENSION	%	43.3	-
HISTORY OF DIABETES	%	56.6	-
ALCOHOLIC	%	10	-

Table 2: Mean levels, standard deviations and correlations with uric acid for selected cardiometabolic risk factors by sex. SD: standard-deviation, Corr: correlation coefficient with serum uric acid

		Men (n=90)		Women (n=60)	
Risk Factor	**unit**	**Mean±SD**	**Corr.**	**Mean±SD**	**Corr.**
URIC ACID	mmol/L	0.30±0.10	1	0.27±0.09	1
AGE	Years	53.43±11.8	0.172	50.8±13.02	0.113
WEIGHT	Kg	68.6±10.2	0.173	60.8±11.8	0.064
BMI	Kg/m^2	25.5±14.5	0.132	25.03±4.0	0.106
WAIST CIRCUMFERENCE	cm	89.91±12.24	0.030	88.64±8.86	0.130
TOTAL CHOLESTEROL	mmol/L	4.74±1.14	0.055	4.83±0.96	0.067
HDL-C	mmol/L	1.12±0.41	-0.238	1.32±0.44	-0.280
TRIGLYCERIDES	mmol/L	2.23±1.46	0.255	2.20±1.32	0.254
SMOKING	%	20	-	-	-
HYPERTENSION	%	46.6	-	38.3	-
HISTORY OF DIABETES	%	54.4	-	55	-
ALCOHOLIC	%	7.7	-	-	-

Table 3: linear regression model on serum uric acid by sex.Coeff. : Coefficient of regression, SD: standard deviation, Int.: Intercept.

		Men (n=90)			Women (n=60)		
Explanatory Variables	**unit**	**Coeff.**	**SD**	**Int.**	**Coeff.**	**SD**	**Int.**
AGE	Years	0.0256	1.72	3.76	0.0132	1.65	4.59
BMI	Kg/m^2	0.0161	1.74	4.73	0.040	1.55	3.98
WAIST CIRCUMFERENCE	cm	0.0109	1.75	4.75	0.0569	1.63	3.30
TRIGLYCERIDES	mmol/L	0.0034	0.019	4.46	0.0033	0.016	3.97

Table 4: Proportion of persons with high uric acid (i.e. in sex-specific highest quartile) according to selected cardiometabolic risk factors, by sex.

	Men			Women		
	n	**%**	**p**	**n**	**%**	**p**
Age Group						
30-45 years	27	30		22	36.6	
46-65 years	48	53.3		31	51.6	
66-85 years	15	16.6	<0.001	07	11.6	<0.001
Waist circumference						
<77 cm	10	11.1		14	23.3	
77-88 cm	28	31.1		18	30	
>88 cm	52	57.7	<0.01	28	46.6	<0.001
Body Mass Index						
<25 Kg/m^2	52	57.7		32	53.3	
25-30 Kg/m^2	31	34.4		16	26.6	
>30 Kg/m^2	7	7.7	<0.001	12	20	<0.001
Total Cholesterol						
<5.18 mmol/L	60	66.6		44	73.3	
5.18-6.19mmol/L	17	18.8		09	15	
>6.19 mmol/L	13	14.4	<0.001	07	11.6	<0.001
Triglycerides						
<1.69 mmol/L	36	40		27	45	
1.69-5.0 mmol/L	50	55.5		30	50	
>5.0 mmol/L	04	4.44	<0.001	03	05	<0.001
HDL						
>1.54 mmol/L	17	18.8		18	30	
1.02-1.54mmol/L	35	38.8		26	43.3	
<1.02 mmol/L	38	42.2	<0.001	16	26.6	<0.001
History of diabetes						
No	41	45.5	-	27	45	-
Yes	49	54.4		33	55	

Hypertension						
No	48	53.3	-	37	61.6	-
Yes	42	46.6		23	38.3	
Smoking						
No	72	80	-	-	-	-
Yes	18	20				
Alcoholics						
No	83	92.2	-	-	-	-
Yes	07	7.7				

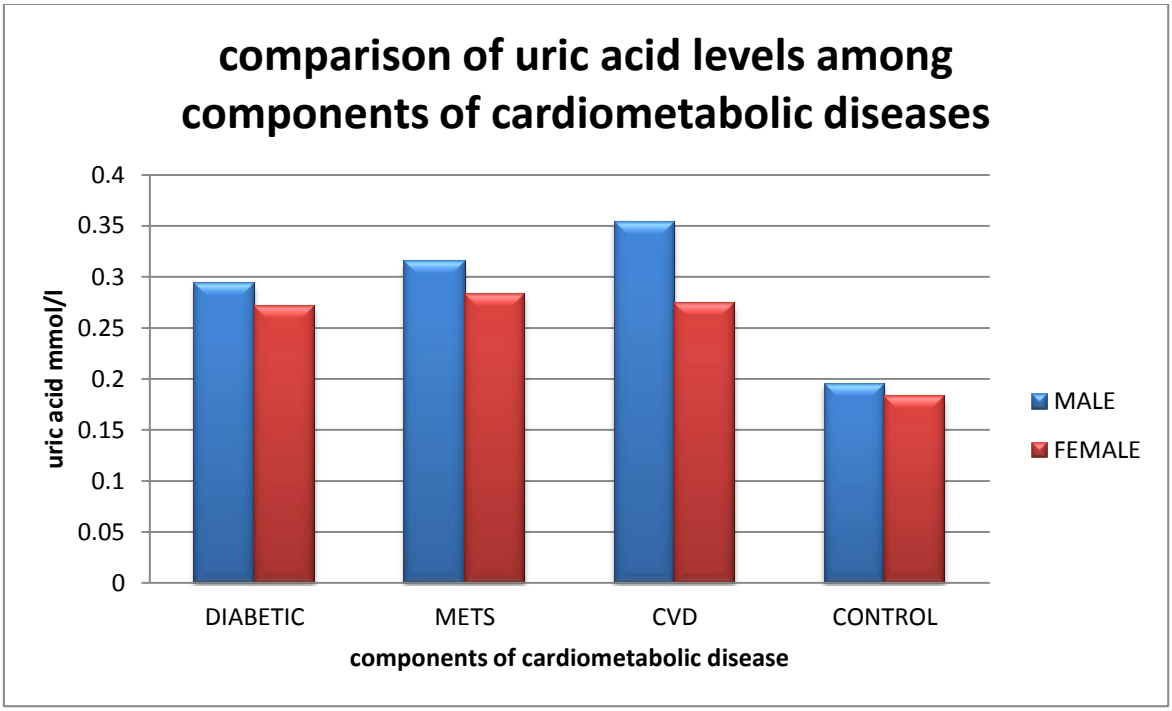

Figure 1: Comparison of serum uric acid levels among components of cardiometabolic disease by sex.

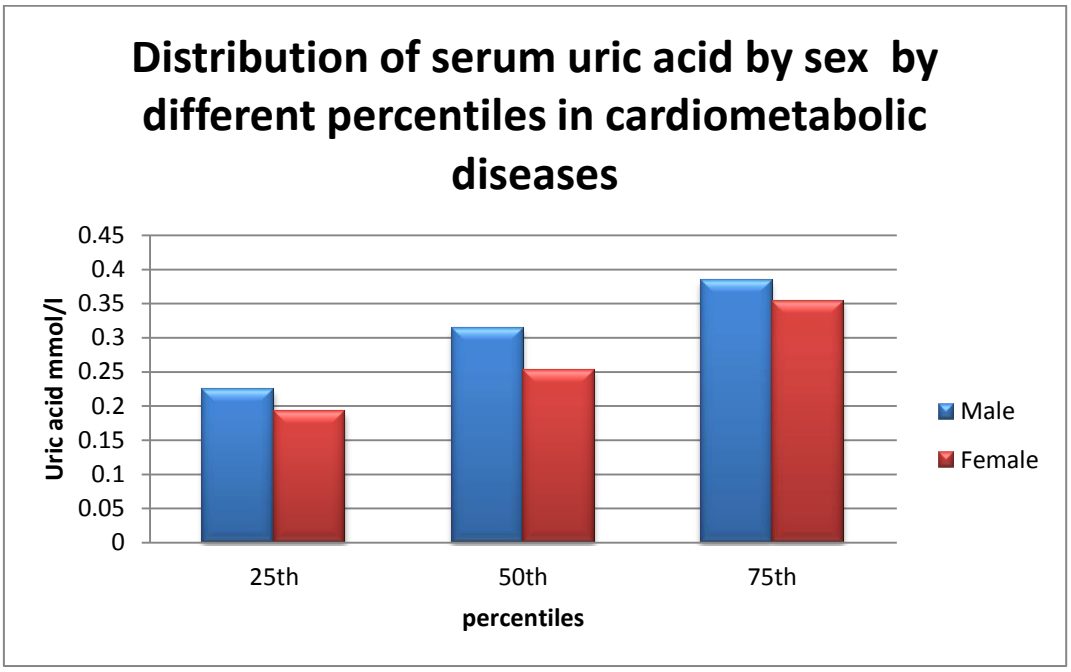

Figure 2: Distribution of serum uric acid by sex by different percentiles.

DISCUSSION

The main observations of the present study are the following: firstly, hyperuricemia was seen in the group of cardiometabolic disease comprising diabetes mellitus type 2, cardiovascular disease and metabolic syndrome as compared to healthy control subjects. Secondly, the prevalence of hyperuricemia is higher in males, significant relationships between serum uric and the various components of the metabolic syndrome were found in men as well as in women. Thirdly, a particularly strong association was found between serum uric acid levels and triglycerides. This association persisted after full adjustment in a linear regression model suggesting a close link between serum uric acid and serum triglycerides levels.

According to previous studies, it is clear that hyperuricemia is associated with the group of cardiometabolic diseases.

In accordance with previous studies, we found that serum uric acid levels are higher in men than in women, although uric acid levels in women tend to increase above the age of 50 [16-18]. These sex differences of serum uric acid levels and the increase after the menopause in females have been reported previously and attributed to the influence of sexual hormones [19]. We also found that male subjects have a higher prevalence of hyperuricemia than women.

Significant correlations were found between serum uric acid and several components of the metabolic syndrome, such as a higher BMI, blood pressure and lower HDL-cholesterol in both men and women. Several possible pathophysiological mechanisms have been evoked to explain these

associations including insulin resistance [20,21], the use of diuretics [22,23] or impaired renal function accompanying hypertension [24,25]. Indeed the kidney seems to play an important role in the development of the metabolic syndrome [26]. Insulin-resistant individuals secrete larger amounts of insulin in order to maintain an adequate glucose metabolism. The kidney which is not insulin-resistant responds to these high insulin levels by decreasing uric acid clearance, probably linked to insulin-induced urinary sodium retention [26]. Insulin resistance may increase blood pressure directly via enhanced proximal tubular sodium reabsorption [27,28], or indirectly by the sympatho-adrenal system [29]. Thereby, the kidney has been implicated as the potential link between muscle insulin resistance and compensatory hyperinsulinemia and the development of hyperuricemia and eventually hypertension.

The most striking association found in our study is certainly the close relationship between serum triglycerides and serum uric acid levels and hyperuricemia. These observations were made in both sexes, with higher correlation levels in males. Interestingly the association was obtained even within the normal range of serum triglycerides. The correlation of triglycerides with uric acid has been found previously in several groups of patients [20,30,31,32,] including in patients with primary gout where a strong correlation ($r = 0.68$, $n = 44$) was found between urinary uric acid excretion and serum triglycerides particularly among non-drinkers. A strong correlation ($r = 0.541$) has even been reported in healthy subjects [33]. This association could have been explained by confounding factors such as the BMI or other associated variables as suggested previously. However, in our partially corrected correlations, the high statistical significance persisted although the coefficients were lower probably under the influence of age and BMI. In our linear regression model, age combined with BMI, waist circumference and triglycerides accounted for most of the variability of serum uric acid levels. The mechanism for the strong association of triglycerides values and serum uric acid levels are still not elucidated. Although, genetic factors have been associated with the concurrence of gout and hypertriglyceridemia [34,35], most investigators tend to conclude that hyperuricemia and hypertriglyceridemia reflects more the lifestyle of the patient, as part of the metabolic syndrome, than genetic factors.

The interpretation of the present results is confronted by some limitations. Firstly, the data analysis was restricted to a cross-sectional study. Only a prospective study could confirm the interdependencies of changes in the metabolic syndrome components and serum uric acid levels. Secondly, no serum insulin levels were measured as an index for insulin resistance. As insulin resistance is believed to play a major role in the metabolic syndrome, the inclusion of this variable in our statistical analysis would have been important. On the other hand it is unlikely that adjustment for insulin resistance could significantly influence our strongest association of serum uric acid and triglycerides, nor let disappear the differences found in men and women.

CONCLUSION

In conclusion, hyperuricemia is closely linked to the various components of the cardiometabolic diseases and in particular to serum triglycerides. Concentration of serum uric acid was found to be increased in diabetic subjects as compared to healthy controls but the increase was relatively low when compared with metabolic syndrome and cardiovascular cases individually. Considering the rapidly increasing incidence of obesity and metabolic syndrome around the World and the potential link between hyperuricemia and coronary heart disease or stroke, more emphasis should be put on the evolving prevalence of hyperuricemia in developing countries. Indeed, several studies have found that uric acid is a prognostic marker for cardiovascular mortality and stroke [36,37]. Our results also provide some insights on the possible role of hyperuricemia as a risk factor in the development of cardiovascular complications.

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