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Original Article

Serum Uric Acid Levels and Its Association with Cardiovascular Risk Factors

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Abstract

Background: Although the issue of hyperuricemia as a risk factor for cardiovascular diseases (CVD) has been disputed, several studies have shown an association between hyperuricemia and several CVD risk factors. The aim of this study was to assess distribution of uric acid level in Yazd City, center of Iran, and its association with CVD risk factors.

Methods: From autumn 2004 to summer 2005, 2000 urban population of Yazd City, aging 20-74 years via clustering random sampling were enrolled in this cross sectional study.

Results: Serum uric acid level, systolic blood pressure (SBP), diastolic blood pressure (DBP) and waist/hip ratio were significantly higher in men than in women ($P< 0.001$),moreover, total cholesterol, HDL cholesterol and body mass index (BMI) were significantly higher in women ($P< 0.001$). The prevalence of hyperuricemia and metabolic syndrome in men and women was (17.9%, 11.25% $P= 0.001$) and (11.87%, 19.32% $P= 0.01$), respectively. Hyperuricemia was more prevalent in metabolic syndrome and ischemic heart disease independent of age and sex.

Conclusion: Significant correlations were found between serum uric acid and several components of the metabolic syndrome. Weight, waist circumstance, triglyceride level and DBP, were the major determinants of the variations in serum uric acid levels .This could be attributed to the insulin resistance status .

Keywords: *Hyperuricemia, Metabolic syndrome, Ischemic heart disease, Cardiovascular, Risk Factor*

Introduction

Uric acid is the final breakdown product of purine degradation in humans. Hyperuricemia results from increased production, decreased exertion or a combination of both (1).

During adulthood, plasma concentration rises overtime and vary with height, body weight, blood pressure, renal function, diet and alcohol intake (2-4).

The most recognized complication of hyperuricemia is gouty arthritis and renal problems such as nephrolithiasis, urate nephropathy and uric acid nephropathy (1). Understanding the issue of association with CVD risk factors deserves special attention regarding the progressive prevalence of CVD throughout the world. Considering different aspects of CVD risk factors is necessary. Since hyperuricemia can be a accompaniment disorder with syndrome X (characteristics by abdominal obesity, impaired glucose tolerance, increased LDL Cholesterol & decreased HDL Cholesterol), its presence is an indication of screening and aggressively treating any accompanying obesity, hyperuricemia, diabetes or hypertension (1, 5). Not surprising hyperuricemia resulting from euglycemic hyperinsulinemia may precede the onset of type II diabetes, hypertension, coronary artery diseases, and gout in individual with syndrome X (1).

The current study was undertaken to assess uric acid level and its relationship with CVD risk factors in the Yazd urban population.

Material and Methods

Participants

From autumn 2004 to summer 2005, 2000 urban population of Yazd City, aging 20-74 yr via clustering random sampling were enrolled in this

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cross sectional study .Sample size was estimated according to the prevalence of CVD risk factors in previous studies. This study was analyzed data of first phase of Yazd healthy heart project that is a community based interventional study for determined the prevalence of CVD risk factors and implementing interventional measures to reduce them in Yazd City.

Data collection

Fasting blood sampling was done to qualify uric acid, fasting blood sugar and lipid profiles. Height, weight and waist circumference were measured. BMI was calculated by dividing weight by squared height (kg/m^2). A person was considered smoker if he/she smoked at least 10 cigarettes per day for the last 3 months. Blood pressure was measured 2 times consecutively with 5 min interval in two separate visits. Measuring was performed on the right arm with a standard sphygmomanometer. The subject was in a sitting after resting for at least 15 min. Reading was based on korotkoff first and fifth base sounds and mean of the four measurements was recorded as blood pressure of individual. Participants were asked if they had been taking drugs for high blood pressure at the present. Hypertension was defined as a DBP$\geq$ 90 mmHg and/ or SBP$\geq$ 140 mmHg or current intake of antihypertensive medication. Diabetes mellitus was defined as using glucose lowering agents or insulin injection, fasting blood glucose $\geq$ 126 or the level of glucose $\geq$ 200 after 75 gr oral glucose. Impaired glucose tolerance test was defined as blood glucose >=140 and <200 in patient with fasting glucose <126. Uric acid level above 7 mg/dl for men and 6 mg/dl for women were considered high. 4

Venous blood sampling were obtained after 12 h of fasting, centrifuged within 2 h, and refrigerated at 10 ºC. Biochemical analyses were done at the performed at the Yazd Central Laboratory. Total cholesterol and t riglyceride were determined enzymatically using a PARS AZMOON Kit. HDL cholesterol was quantified similarly after precipitation with magnesium phosphotungstate. Hyperlipidemia was defined as a total cholesterol >=200 or triglyceride >=150 or current intake of lipid lowering medication. Uric acid level was measured on a standard auto analyzer. External controls for the laboratory determinations were regularly conducted. Metabolic syndrome was defined based criteria of NCEP adult panel III, that in defined as 3 or more following criteria: fasting glucose> =110, blood pressure >=130/85 mmHg, HDL cholesterol <40 in men and <50 in women, triglyceride>=150 mg/Dl, waist circumference>=102cm in men and>= 88cmin women.

Statistical Analysis

All statistical analyses were carried out using SPSS software version 12. Linear and logistic regression techniques were used to determine the independent predictors of serum uric acid level and hyperuricemia, respectively. The various components of metabolic syndrome, as well as other established risk factors of hyperuricemia were considered as potential explanatory variables in this model. For continuous variables, the linear and correlation coefficients with uric acid were calculated. The statistical significant covariates were included in a multivariate linear regression model and a stepwise backward procedure was applied used to determine which covariate contributed to the variation of uric acid independent of the others. For categorical and binary variables, Mantel-Haenszel test and Pearson chi square test were used.

Results

The mean level of uric acid was 4.4$\pm$1.2 mg/dl. The baseline characteristics of participants are presented in Table 1.

Serum uric acid level, SBP, DBP and waist/hip ratio were significantly higher in men than in women (P< 0.001). On the other hand, total cholesterol, HDL cholesterol and BMI were significantly higher in women (P< 0.001). The prevalence of metabolic syndrome in men and women was (11.87%, 19.32%, P= 0.01), respectively. Furthermore the prevalence of hyperuricemia was 17.9% in men and 11.5% in women (P= 0.04).

Table 2 displays hyperuricemia prevalence among cardiovascular risk factors. Hyperuricemia was

more prevalent in hypertensive, obese and hyperlepidemic participations and in patients with impaired glucose tolerance test ($P< 0.001$).

Table 3 shows the simple correlation coefficients between serum uric acid levels and the various cardiovascular risk factors in the population. Age, waist, triglyceride, total cholesterol, HDL cholesterol, LDL cholesterol, diastolic blood pressure, systolic blood pressure were strongly correlated (HDL cholesterol had negative correlation) ($P< 0.001$).

The multivariate model linear regression using a step wised backward selection procedure model, showed that weight, waist circumference, triglyceride and diastolic blood pressure, were the major determinants of the variations in serum uric acid levels.

Table 4, and 5 show that age and sex adjusted hyperuricemia was independently more prevalent in subjects with metabolic syndrome and history of angina pectoris (by using rose questionnaire).

Table 1: Mean levels, standard deviations for serum uric acid levels and selected cardiovascular risk factors based on sex

Risk Factors	Unit	Men (n=1000)		Women (n=1000)		
		Mean	SD	Mean	SD	*P*
Serum uric acid	mg/dl	4.8	1.2	4	1	0.001
Systolic BP	mmHg	129	14	127	16	0.001
Diastolic BP	mmHg	83	8.7	81	8.9	0.001
Total cholesterol	mg/dl	191	41	205	46	0.001
HDL cholesterol	mg/dl	51	13	53	13	0.001
LDL cholesterol	mg/dl	103	35	113	37	0.001
Triglyceride	mg/dl	178	112	172	102	0.1
BMI	Kg/m^2	25	3.8	27	4.4	0.001
Waist to hip ratio	Ratio	0.91	0.08	0.90	0.09	0.001

Table 2: Hyperuricemia prevalence in other cardiovascular risk factors

Risk Factor Category	Hyperuricemia (%)	*P*†
Male	17.9	0.04
Female	11.25	
Abdominal obesity		
yes	22.9	<.0001
no	14.8	
Obesity		
Yes	26.1	<.0001
no	15.5	
IGTT		
Yes	29.5	<.0001
No	16.5	
Cholesterol		
>200	21.9	<.0001
<=200	13.7	
Triglyceride		
>150	23.9	<.0001
<=150	11.2	
Smoking		
Yes	14.4	0.08
No	18	
Hypertension		
Yes	25	<.0001
No	12.7	

†: analyzed by qui square test and $P< 0.05$ was considered significant.

Table 3: Simple correlation uric acid levels with selected cardiovascular risk factors

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Risk Factors	Mean (SD)	Unit	*Correlation*	
			r†	*P*
Age	47.8(15)	years	0.1	.001
Systolic BP	128(15)	mmHg	0.18	.001
Diastolic BP	82.2(8.8)	mmHg	0.17	.001
Total cholesterol	198(44)	mg/dl	0.14	.001
HDL cholesterol	53.9(13)	mg/dl	-0.12	.001
LDL cholesterol	108(36)	mg/dl	0.1	<.001
Triglyceride	175(107)	mg/dl	0.24	<.001
BMI	26.1(4.4)	Kg/m2	0.11	<.001
Waist	93.4(12)	Cm	0.46	<.001

†: analyzed by linear regression, $P< 0.05$ was considered significant.

Table 4: Age and sex adjusted of hyperuricemia prevalence in those subjects with metabolic syndrome.

Metabolic syndrome(MS) before and after age and sex adjust	OR†	95% CI	*P*
Metabolic syndrome(MS)	2.2	(1.7-2.8)	<0.001
(MS) age adjusted	2.1	(1.6-2.6)	<0.001
(MS) age & sex adjusted	2.4	(1.8-3)	<0.001

†: analyzed by mantel-haenszel test

Table 5: Age and sex adjust of hyperuricemia prevalence in those subjects with Ischemic heart disease (history of angina pectoralis via rose questionnaire)

Ischemic heart disease before and after age and sex adjustment	OR†	95% CI	*P*
IHD	2.2	(1.2-3.8)	0.007
IHD age adjusted	2.2	(1.2-3.9)	0.006
IHD age & sex adjusted	2	(1-3.7)	0.01
IHD metabolic risk factors adjusted	1.97	(1.1-3.7)	0.03

†: analyzed by mantel-haenszel test

Discussion

We report two major findings from the present analysis of a large body of cross-sectional data, first, prevalence of hyperuricemia in urban Yazd population by sex, second, hyperuricemia association with metabolic syndrome. Although hyperuricemia is well recognized as a risk factor for atherosclerotic diseases such as myocardial infarction and stroke (6, 7), the independence of this association from other confounding factors has remained controversial. This is mostly because serum uric acid is associated with component of metabolic syndrome, such as hypertension, dyslipidemia and obesity (8-10). In the current study, we also found positive correlations between uric acid and weight, waist, diastolic and systolic blood pressure, total and LDL cholesterol and triglyceride levels, and a negative correlation between uric acid and HDL-C levels. Several possible pathophysiological mechanisms have been evoked to explain these associations including insulin resistance (11), the use of diuretics (12, 13) or impaired renal function accompanying hypertension (14-15). Indeed the kidney seems to play an important role in the development of the metabolic syndrome (16). 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 (16). Insulin resistance may increase blood pressure directly via enhanced proximal tubular sodium reabsorption (17, 18), or indirectly by the sympatho-adrenal system (19). 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. Several previous studies have analyzed possible associations between hyperuricemia and coronary heart disease and their independence. Although some studies reported a positive association between hyperuricemia and coronary heart disease (20-22), others did not (23, 24). Most of the studies showing negative results advocated, as expected, that the association between uric acid and coronary heart disease is not truly independent, but it is dependent on other risk factors for coronary heart disease (23-24). On the other hand, it

is possible that uric acid is an independent risk factor for coronary heart disease in some selected populations (25). In our study the association between hyperuricemia and angina pectoris (by rose questionnaire) is independent to hypertension, obesity, diabetes, hyperlepidemia (cholesterol> 200, triglyceride>150) and metabolic syndrome. (*P*= 0.03) odd ratio=1.97(1-3.7) several study demonstrated the association between uric acid and ischemic stroke and reported that this may be independent of other risk factors (23). Because uric acid is also known to have antioxidant activity in the serum, its level may rise as a compensatory mechanism to counteract the increased oxidative stress under the conditions of metabolic syndrome (28) or atherosclerosis (29). It has also been reported that the relationship between uric acid and coronary artery disease might be stronger in women, although independence of the association was not always assessed in these reports (22-27). In accordance with previous studies (22-31), we found that serum uric acid levels are higher in men than in women. 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 (32). In addition, our findings showed significant increasing prevalence of hyperuricemia with age rising in women but not in men. The interpretation of the present results is confronted by some limitations. Firstly, the data analysis was restricted to a cross-sectional study (Yazd healthy heart project). 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.

In conclusion, our data show that hyperuricemia is closely linked to the various components of the metabolic syndrome and independently related to coronary artery diseases. 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 attention should be protected about the increasing burden of hyperuricemia in developing countries.

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