ORIGINAL RESEARCH

An analytical study about the corelationof Serum Uric acid with other Cardiovascular risk factors

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ABSTRACT
Introduction: The positive association between serum uric acid and cardiovascular diseases such as stroke or ischemic heart disease has been recognized since the 1950s and has been confirmed by numerous epidemiological studies.Elevated serum uric acid levels are commonly seen in association with glucose intolerance, hypertension and dyslipidemia, a cluster of metabolic and hemodynamic disorders which characterize the so-called metabolic syndrome. The purpose of the present study was to investigate the prevalence and the clinical correlates of hyperuricemia. **Methods:** This Cross Sectional analytical study involved Prior Consent from the patients & was found to be within ethical standards. It was conducted in six months. Simple random sampling technique was used for data collection. An Interview with the help of Predesigned Questionnaire along with detailed clinical Examination was done. Cut-off Limits of various Cardiovascular risk factors was set . 100 Number of Patients were included in the study. **Results:** In both sexes, serum triglycerides and serum uric acid levels were strongly correlated ($p < 0.001$). In women, significant correlations ($p < 0.01$) were also found with almost all metabolic parameters except for alcohol consumption. In men, serum uric acid correlated with blood pressure, body mass Index and total cholesterol ($p < 0.01$). Age, triglycerides, BMI, alcohol consumption and hypertension were the major determinants of the variations in serum uric acid levels in both sexes. **Conclusion:** Hyperuricemia is also closely linked to the various components of the metabolic syndrome and in particular to serum triglycerides. 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.

Key Word: Hyperuricemia , Cardiovascular Risk Factors, Clinical Correlates , Uric Acid

INTRODUCTION

Uric acid is commonly thought to be an inert waste product from purine metabolism. It is synthesized mainly in the liver, intestines, and other tissues such as muscles, kidneys, and the vascular endothelium as the end product of an exogenous pool of purines (derived largely from animal proteins), and the endogenous pool derived from live and dying cells degrading their nucleic acids, adenine, and guanine into uric acid.
Until in the early 1800s, it was discovered that an increased serum uric acid (SUA) level was the cause of gout.[1] Subsequently, associations of uric acid concentration with cardiovascular and renal disorders were also observed.[2]
Experimental studies have suggested that uric acid may penetrate vascular smooth muscle fibers through an organic anion transport system, followed by activation of multiple signal transduction pathways, which culminate in increased expression of inflammatory mediators. The consequences are a rise of arterial pressure, vascular smooth muscle cell hypertrophy, and hypertension.[3,4] In addition, soluble uric acid induces vascular endothelial cell dysfunction, namely, alteration of cell proliferation and induction of cell senescence and apoptosis, via activating the renin-angiotensin system (a hormone

system responsible for regulating plasma sodium concentration and arterial blood pressure) and triggering reactive oxygen and nitrogen species and endoplasmic reticulum stress.[5,6,7]

The positive association between serum uric acid and cardiovascular diseases such as stroke or ischemic heart disease has been recognized since the 1950s and has been confirmed by numerous epidemiological studies since then[8-14]. However, whether uric acid is an independent risk factor for cardiovascular mortality is still disputed as several studies have suggested that hyperuricemia is merely associated with cardiovascular diseases because of confounding factors such as obesity, dyslipidemia, hypertension, use of diuretics and insulin resistance[15,16,17]. Moreover, there is still no well-established pathophysiological link between hyperuricemia and the development of cardiovascular complications.

Elevated serum uric acid levels are commonly seen in association with glucose intolerance, hypertension and dyslipidemia, a cluster of metabolic and hemodynamic disorders which characterize the so-called metabolic syndrome[18,19,20,21,22]. Studies performed in healthy volunteers as well as in subjects with asymptomatic hyperuricemia have suggested that the link between the metabolic syndrome and serum uric acid is related to the ability of insulin to decrease the clearance of uric acid in the renal proximal tubule resulting in an increase in serum uric acid levels[23]. Several population-based studies have also examined the influence of a number of cardiovascular risk factors or components of the metabolic syndrome on serum uric acid levels. Thus, elevated serum uric acid levels have been linked to hypertension, hyperinsulinemia, reduced physical activity, increased body mass index, increased alcohol consumption and decreased HDL cholesterol. [18,19,20,21,22].

The purpose of the present study was to investigate the prevalence and the clinical correlates of hyperuricemia in a developing country

METHEDOLOGY

This Cross sectional analytical study involved Prior Consent from the patients& was found to be within ethical standards. It was conducted in 8 months among patients attending OPD of various health centres & tertiary medical care institutes in Raipur CG for consultation / screening of various Non communicable Diseases Simple random sampling technique was used for patient selection . 100 Number of Patients included in the study.

Patients who didn't wanted to be part of the study &Critically ill patients were excluded from the study.

Detailed Clinical Examination was done & all the patients went through Routine investigations. Patient's history including age, sex, duration of the diabetes was taken. Height and weight and Body Mass Index (BMI) of all patients were calculated. Blood pressure was taken for all the patients for detection of hypertension & Patients were categorised as being hypertensive if they were on antihypertensive treatment or if they had a systolic blood pressure >140 mm Hg and/or diastolic blood pressure >90 mm Hg. Blood was collected for investigation in early morning empty stomach samplesUrine samples were collected in the early morning after an overnight fast.

MEASURES AND CUT-OFF POINTS

DIABETES MELLITUS

The diagnosis of diabetes mellitus was considered when individuals reported to have been told by a doctor to have diabetes or tested positive for glycosuria or the current WHO diagnostic criteria for diabetes – fasting plasma glucose ≥ 7.0mmol/l (126mg/dl) or 2–h plasma glucose ≥ 11.1mmol/l (200mg/dl).

HYPERURICEMIA

Uric acid was measured on a standard autoanalyzer. As data regarding the relationship of uric acid to cardiovascular disease is lacking in developing countries, ad-hoc criteria for hyperuricemia were adopted in this study. Values of uric acid above the sex-specific percentile 75 (i.e. 6 mg/dl for women & 6.8 mg/dl for men) were defined as high.

SMOKING

Smoking habits were classified as followed: persons who did never smoke, ex-smokers designated 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.

WEIGHT AND 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 squared (kg/m^2). Hip and waist were measured to the nearest 1 cm.

ALCOHOL HABITS

Alcohol consumption was assessed in two stages. In the first, persons were categorised according to frequency of alcohol drinking: never, occasionally but less than once a week, once or twice a week, every other day and almost every day. Those declaring a consumption of at least one drink per week were further questioned about their weekly average consumption of the different alcohol beverages available.

BP MEASUREMENTS AND HYPERTENSION

Blood pressure (BP) was measured three times consecutively on the right arm with a standard sphygmomanometer, the subject being in a sitting position after at least 30 minutes of rest. Values, determined as the mean of the last two measurements,

were recorded to the nearest 2 mm Hg, and readings based on Korotkoff first and fifth base sounds. Participants were asked if they had taken drugs for high blood pressure within 2 weeks prior to the examination.

Data was filled in Microsoft Excel&analysed using the Statistical Package for Social Sciences (SPSS) for Windows version 21 &a computer software Epi Info version 6.2 (Atlanta, Georgia, USA).Chi-square test was used to analyze nonparametric or categorical data. For analysis of ordinal scale data, Student's t-test was used. Karl–Pearson correlation coefficient was calculated to observe correlation between variables.P value of 0.05 and less was considered as statistically significant.

For continuous variables, the linear correlation coefficients with uric acid were first calculated and tested against zero. The statistically significant covariates were included in a multivariate linear regression model and a stepwise backward selection procedure was used to determine which covariates contributed to the variation of uric acid independently of the others. Age, triglycerides, body mass index and alcohol consumption were retained in the final parsimonious regression model for both sexes. . For categorical and binary variables, the strength of association with high uric acid was measured using the Mantel-Haenszel test for linear trend and the Pearson chi-square test respectively. A multivariate logistic regression model predicting high uric acid was developed.

RESULTS

A total of 100 patients including 60 males and 40 females were studied. The mean age of the patients was 43.82 ± 9.57 years.

Smoking, alcohol consumption and high triglycerides levels were more common in men than in women.

Serum uric acid levels were significantly higher in men than in women ($p < 0.01$). When using the commonly accepted cut-off values for serum uric acid levels,i.e a serum uric acid > 6.8 mg//dL in men and > 6mg /dL in women[10]

The prevalence of hyperuricemia was 28.33% (17) in men and 5%(2) in women ($p < 0.01$).

The values of different variables / risk factors with gender is given in table no. 1

In both sexes, serum triglycerides and serum uric acid levels were strongly correlated ($p < 0.001$). In women, significant correlations ($p < 0.01$) were also found with almost all metabolic parameters except for alcohol consumption. In men, serum uric acid correlated with blood pressure, body mass Index and total cholesterol ($p < 0.01$).

The multivariate model linear regression model. Age, triglycerides, BMI, alcohol consumption and a treatment for hypertension were the major determinants of the variations in serum uric acid levels in both sexes. All metabolic parameters were strongly associated with serum uric acid levels. The effect of age was particularly prominent in women and the effect of alcohol consumption was more marked in men. Smoking had no effect on serum uric acid levels.

The odds ratio for high uric acid levels according to different levels of age, triglycerides, waist, alcohol consumption and treatment of hypertension.

Table 1: The values of Various risk factors with respect to gender among study subjects

Risk Factors / Variables	Men (n= 60)	Women (n= 40)
Serum Uric Acid	4.35 (SD – 1.85)	3.83 (SD – 1.12)
Age	46.72 ± 8.27 years	42.62 ± 9.91 years
Total Cholesterol	221.53 mg/dl (SD – 44.23)	245.62 mg/dl (SD- 52.79)
Triglycerides	207.28 mg/dl (SD- 63.46)	220.35 mg/dl (SD- 57.28)
Systolic BP	142.6 mm Hg (SD- 25.6)	135.8 mm Hg (SD- 21.54)
Diastolic BP	94.6 mm Hg (SD-15.9)	90.6 mm Hg (13.47)
BMI	26.6 (SD – 4.72)	28.2 (SD –5.92)
Alcohol Intake	60 ml (SD-40.50)	-
Smoking	18.33%(11)	-
Diabetes Cases	11.66% (7 cases)	12.5% (5 Cases)

SD = Standard Deviation

DISCUSSION

The main observations of the study are the following: 1. The prevalence of hyperuricemia is high in cases of male study subjects. 2. Significant relationships between serum uric and the various components of the Cardiovascular risk factors were found in men as well as in women. 3. A relatively strong association was found between serum uric acid levels and triglycerides.

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[15, 24]. 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[25]. Study also found that male subjects have a higher prevalence of hyperuricemia than women. A partial explanation for this could be the alcohol

consumption. Alcohol consumption is significantly associated with elevated uric acid levels.[25] In our multivariate linear regression model, alcohol consumption contributes significantly to uric acid levels in men. Another important factor may be the use of antihypertensive agents such as diuretics which are known to increase serum uric acid levels among known hypertensives and controlled hypertensives subjects.[26,27].

Significant correlations were found between serum uric acid and several components of the metabolic syndrome, such as a higher BMI, waist-to-hip-ratio, blood pressure and 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[26,27] or impaired renal function accompanying hypertension [28,29]. Its an Established fact that the kidney seems to play an important role in the development of the metabolic syndrome [30]. 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[30]. Insulin resistance may increase blood pressure directly via enhanced proximal tubular sodium reabsorption[31,32], or indirectly by the sympatho-adrenal system [33]. 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 Black 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 [18,20,34,35] including in patients with primary gout where a strong correlation was found between urinary uric acid excretion and serum triglycerides particularly among non-drinkers. A strong correlation has even been reported in healthy subjects too[36]. This association could have been explained by confounding factors such as the BMI or other associated variables as suggested previously.

The finding of the present study is has some limitations. Notebly the data analysis was restricted to a cross-sectional &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.

CONCLUSION

Our study showed that hyperuricemia is very frequent in a this part of the world . Alcohol consumption , Dietary factors , Low fluid intake and the use of diuretics appear to play an important role in mediating this hyperuricemia. However, hyperuricemia is also closely linked to the various components of the metabolic syndrome and in particular to serum triglycerides. 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.

Results provide some insights on the role of hyperuricemia (if any) as a risk factor in the development of cardiovascular complications. The demonstration of a close relationship between serum uric acid and parameters of the metabolic syndrome reveals another possible link between serum uric acid and cardiovascular morbidity and mortality.

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Compliance With Ethical Standards.

CONFLICT OF INTEREST

None.

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