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RESEARCH ARTICLE

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

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Abstract

This study investigated the prevalence and determinants of hyperuricemia in type 2 diabetes mellitus(T2DM) patients with central obesity. A hospital-based cross-sectional study was carried out at Index Medical College, Hospital and Research Centre, Indore. T2DM patients with central obesity who were aged over 20 years, whose serum uric acid levels were measured, were recruited. Hyperuricemia was defined as serum uric acid >0.42 mmol/L in men and >0.36 mmol/L in women. The purpose of the present study was to investigate the prevalence of hyperuricemia and the association between uric acid levels and the various diabetic risk factors. This study included 100 diabetic 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's coefficient and linear regression model. The prevalence of a serum uric acid level >0.42 mmol/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 diabetic risk factors, in particular serum triglycerides. Hyperuricemia is significantly associated with type II diabetes mellitus and can significantly increase morbidity and mortality from diabetes if not managed in time.

INTRODUCTION

Uric acid is the end product of human purine metabolism. Hyperuricemia is a condition in which the subject has increased serum uric acid levels. Studies have noted that an elevated level of uric acid predicts the development of diabetes, obesity, hypertension and the metabolic syndrome.[1] Uric acid levels tend to decrease with increasing plasma glucose levels in patients with type 2 diabetes mellitus (T2DM).[2] Some cardiovascular risk factors, including obesity, hypertension, dyslipidemia and the metabolic syndrome, are more prevalent in patients with T2DM than in those without T2DM.[3] The prevalence of T2DM is a chronic metabolic disease that is a major public health problem around the world. With rapid economic growth, increases in life expectancy and changes in lifestyle, the incidence of diabetes mellitus has increased. Obesity and weight gain are the recognized causes of T2DM.Diabetes mellitus is considered a cardiovascular risk equivalent, and cardiovascular disease is the most common cause of death in patients with diabetes mellitus.[3]

Hyperuricemia has recently gained attention as it has been reported that it not only plays an important role in the development of metabolic diseases but is also a cardiovascular risk factor.[4-7] However, the prevalence of hyperuricemia and associated risk factors in diabetic patients with central obesity has not been investigated. Therefore, this study was conducted to assess the prevalence of hyperuricemia and associated risk factors in Chinese patients with central obesity.

MATERIAL AND METHODS

One hundred diagnosed patients suffering from diabetes mellitus having type II diabetes mellitus for more than three years were randomly selected from the Outdoor patients department, Index Medical College, Hospital and Research centre, Indore. These patients were then divided in to two groups; obese and non-obese. One hundred healthy individuals were selected to constitute the control group.

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. 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 I (Figure I). BMI, triglycerides and uric acid levels were significantly higher in morbid group than in control group ($p<0.001$) (Figure II).Smoking, alcohol consumption and high triglyceride levels were more common in men than in women (Table I). 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 >0.42 mmol/L in men and >0.36 mmol/L in women [8], 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 75^{th} percentile which gives a cut-off at 0.383 mmol/L for men and 0.354 mmol/L for women. Table 1 also shows the simple correlation coefficients between serum uric acid levels and the various diabetic 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 II shows the association of hyperuricemia with obesity in sex specific highest quartiles. Table III shows the regression model with hyperuricemia.

Risk Factor	unit	Men (n=62)			Women (n=38)		
		Mean±SD	Corr.	P value	Mean±SD	Corr.	P value
URIC ACID	mmol/L	4.97±1.72	1	-	4.6±1.49	1	-
AGE	Years	52.54±11.18	0.131	0.261	51.4±13.45	0.04	0.73
HEIGHT	feet	5.54±0.42	-0.12	0.27	5.19±0.42	0.07	0.58
WEIGHT	Kg	66.97±9.04	0.17	1.12	60.34±12	0.09	0.46
BMI	Kg/m^2	24.95±3.59	0.14	0.2	24.74±5.64	0.05	0.68
WAIST CIRCUMFERENCE	cm	35.35±3.59	0.09	0.4	34.82±5.05	0.07	0.59
GLUCOSE	mmol/L	195.64±89.80	-0.1	0.3	184.8±75.6	-0.27	0.04*
TOTAL CHOLESTEROL	mmol/L	187.14±45.72	0.12	0.28	185.9±36.12	0.07	0.56
HDL-C	mmol/L	44.55±16.57	-0.19	0.08	51.4±16.31	-0.19	0.14
TRIGLYCERIDES	mmol/L	201.46±134.67	0.31	0.006*	194.3±119.04	0.23	0.08*
LDL-C	mmol/L	102.54±39.70	0.02	0.8	94.8±36.7	0.01	0.9
VLDL	mmol/L	40.02±26.78	0.31	0.006*	39.16±24.5	0.20	0.12
γ- GLUTAMYL TRANSFERASE	mmol/L	21.78±24.63	0.14	0.022*	17.4±15.08	0.24	0.06*
UREA	mmol/L	31.56±12.61	0.32	0.005	30.14±11.3	0.23	0.08
CREATININE	mmol/L	1.15±0.35	0.44	0.00	1.03±0.2	0.35	0.007
SMOKING	%	20	-	-	-	-	-
HYPERTENSION	%	46.6	-	-	38.3	-	-
ALCOHOLIC	%	7.7	-	-	-	-	-

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

	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
Weight						
<54Kg	06	3.8		31	27.1	
54-64Kg	32	20.64		26	22.8	
>64Kg	116	74.83	<0.001	59	51.75	<0.001
Uric Acid						
<0.19mmol/L	30	19.35		28	24.56	
0.19-0.28mmol/L	31	20.0		37	28.07	
>0.28mm0l/L	93	60.0	-	43	37.71	-

Table II: Proportion of persons with high uric acid (i.e. in sex-specific highest quartile) showing correlation with obesity, by sex

Explanatory Variables	unit	Men (n=62)			Women (n=38)		
		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 III: linear regression model on serum uric acid by sex.Coeff. : Coefficient of regression, SD: standard deviation, Int.: Intercept.

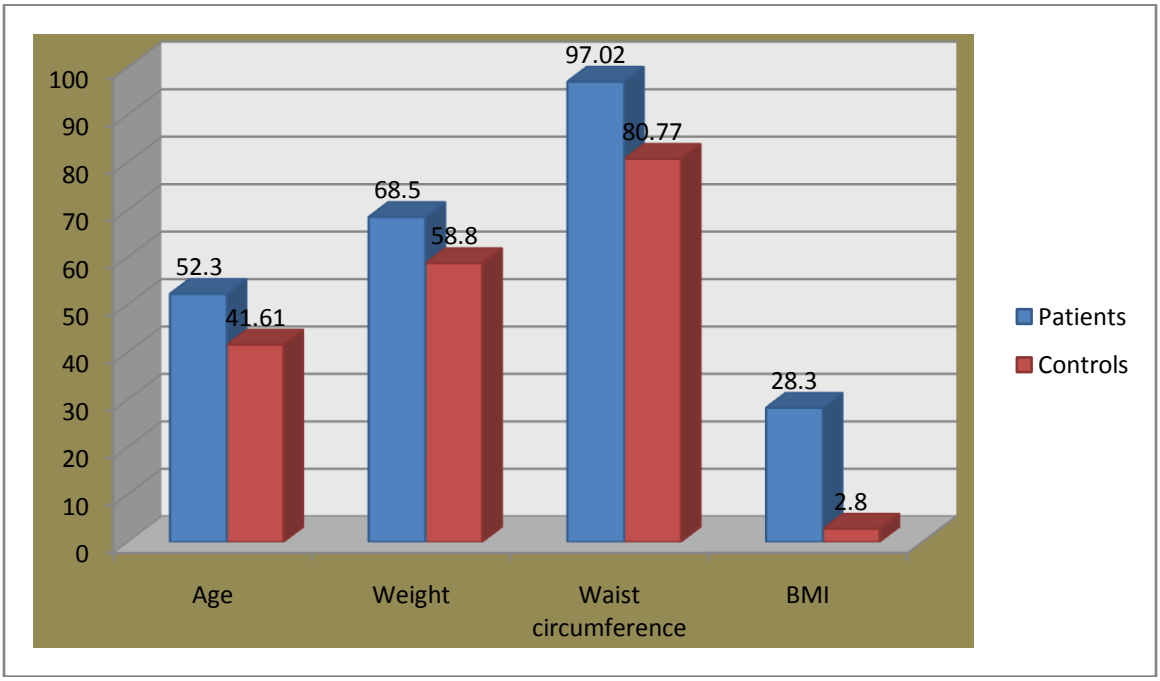

Figure I. Comparison of physical characteristics between diabetic and control group

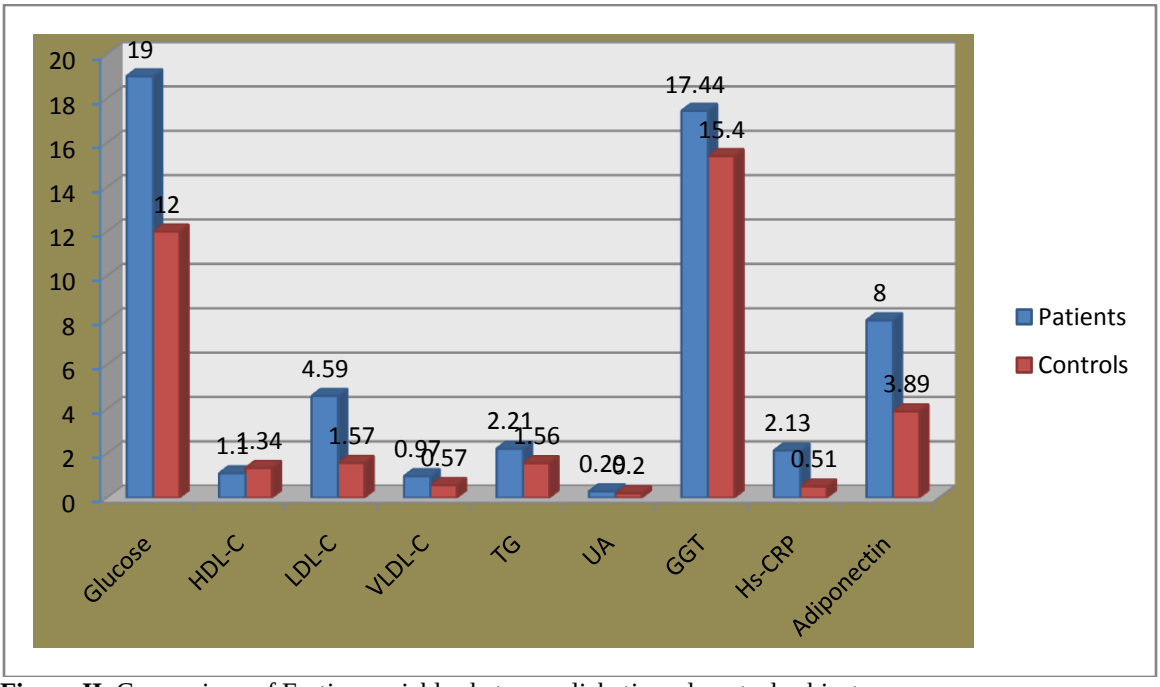

Figure II. Comparison of Fasting variables between diabetic and control subjects

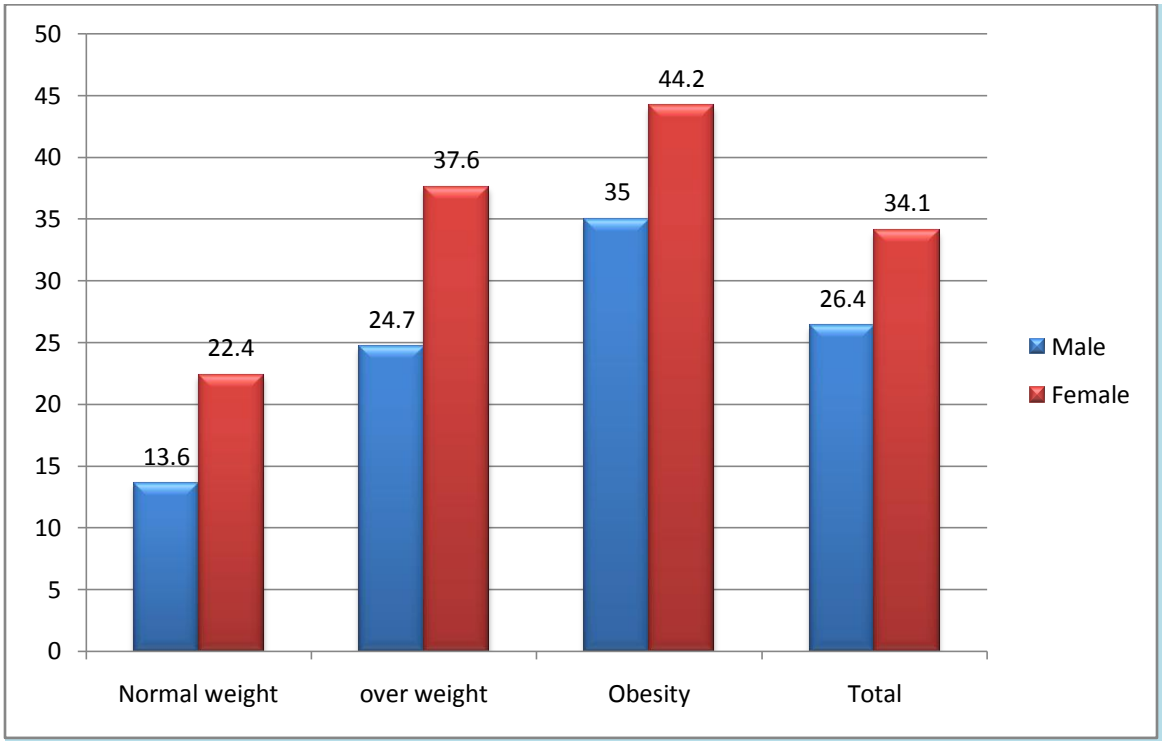

Figure III. Prevalence of hyperuricemia by BMI categories and gender, values represent percentages

DISCUSSION

It was seen that serum uric acid is positively associated with type 2 Diabetes Mellitus. The association was significantly more in females, in obese patients and patients with hyperlipidemia. These results were comparable in most aspects to the similar studies performed by different research workers.[9-14]

Among Chinese T2DM patients with central obesity, the results of the current study showed prevalence of hyperuricemia in women as 36.1% and in men as 28.4%. Liu et al[15] systematically analyzed the prevalence of hyperuricemia in general Chinese populations using the metaanalysis method, and reported that the prevalence in women was 8.6% and 21.6% in men. The prevalence of hyperuricemia in Chinese T2DM patients with central obesity as observed in the current study is dramatically higher than in general Chinese general populations as reported by Liu *et al*.[15] Previous studies have reported that men had a higher percentage of hyperuricemia compared with women.[15,16]

Although a few research workers found a negative association, Ishihara M. et. al[14] studied the association between the urinary excretion of calcium and uric acid in type 2 diabetic patients. They found that in diabetic patients uric acid clearance/creatinine clearance was higher and the serum level of uric acid was lower than in normal subjects. Their analysis showed that diabetic subjects have increased fractional excretion of uric acid. Gonza SL[17] et al observed similar finding in insulin dependant diabetic patients.

The actual mechanism of hyperuricemia in diabetic patients is not known but different theories have been presented. Quiniones et al (1995) [9]observed that hyperuricemia is a frequent finding in insulin resistant states. He found that insulin induces change in fractional uric acid and sodium excretion correlated with one another and physiological hyperinsulinimia acutely reduces urinary uric acid and sodium excretion in coupled patients. Moriwaki et al (1995)[18] studied the effects of glucose infusion on the renal clearances of uric acid, xanthine and oxypurinol and found that effect was not related to osmotic diuresis but induced by glycosuria and/or hyperglycemia.

Muscelli and coworkers (1996) [11]observed the effect of insulin or urinary excretion in normal subjects and found that hyperinsulinimia caused a significant decrease in urinary excretion of uric acid.

The association of uric acid with diabetes mellitus has also been explained on the basis of genetic predisposition. Hyperuricemia may result in acute gouty arthritis, nephrolithiasis and nephropathy. Hyperuricemia with diabetes mellitus may specially give rise to complications like overt nephropathy and stroke.

The main observations of the present study are the following: firstly, hyperuricemia was seen in diabetes mellitus type 2 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.

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 [19-22] 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 [23]. 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 [24, 25], 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 diabetes mellitus and in particular to serum triglycerides. Concentration of serum uric acid was found to be increased in diabetic subjects as compared to healthy controls. In this study particular association of hyperuricemia with obese diabetic patients was noticed. Considering the rapidly increasing incidence of obesity around the World and the potential link between hyperuricemia and diabetes, more emphasis should be put on the evolving prevalence of hyperuricemia in developing countries.

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