Original Research Article

Serum uric acid level in type 2 diabetes mellitus

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ABSTRACT

Background: Diabetes mellitus is the most important risk factor associated with two to four fold increased incidence of coronary artery disease. The major risk factors for CAD are hypercholesterolemia, hypertension, diabetes mellitus, and cigarette smoking Objectives: To study the level of serum uric acid in type 2 diabetes mellitus and the correlation between elevated serum uric acid level and the component of metabolic syndrome like obesity, hypertension, dyslipidemia.

Methods: The study was done as descriptive analytical study among the diabetic patients in a tertiary care setting during the period January 2018 to February 2019. The inclusion and exclusion criteria were clearly defined and the study participants were recruited for the study after getting the informed consent. The socio demographic profile, clinical and laboratory data were collected from the blood sample obtained from the patients with the standardized procedures. Data was entered in Microsoft excel spread sheet and analyzed statistically using SPSS statistical software. Student 't' test and Chi-square test values were applied for significance.

Results: Serum uric acid in the study population and control varied from 3.0 to 8.1 and 2.7 to 5.5 mg/dl respectively. The mean and standard deviation of uric acid among cases was 5.08 ± 1.42 while in control it was 3.55 ± 0.62 respectively. The serum uric acid level of diabetics was very much elevated compare with controls and it was highly significant. Significant correlation was noticed between serum uric acid and BMI as well as WHR. Elevated uric acid levels were significantly noticed among those with hypertension, dyslipidemia, coronary artery disease and chronicity of the diabetes.

Conclusions: Uric acid was significantly elevated in diabetic population and the mean value of serum uric acid level was higher in longer duration of diabetes, hypertension, dyslipidemia, central obesity which are the components of metabolic syndrome.

Keywords: Coronary artery disease, Duration of diabetes, Hypertension, Hyperuricemia, Obesity, Serum uric acid, Type 2 diabetes

INTRODUCTION

Cardiovascular disease is an epidemic of modern society. Type 2 diabetes mellitus is an epidemic in India for the past few decades. Diabetes mellitus is the most important risk factor associated with two to four fold increased incidence of coronary artery disease. Nearly 120 years have elapsed since uric acid was first described as a potential risk factor in the development of cardiovascular disease.[1] Hyperuricemia is one of the component of syndrome-X.[2] Serum uric acid is a potential cardiovascular disease risk factor has ballooned in the last several years with numerous abstracts and research

papers, multiple editorials, and review articles. The four major risk factors for CAD viz., hypercholesterolemia, hypertension, diabetes mellitus, and cigarette smoking which were present in Framingham's cohort are difficult to explain among Indians with CAD. CAD in Indians is present even with low cholesterol level. Obesity, systemic hypertension, hypercholesterolemia is associated with NIDDM, as a result of insulin resistance state. Much but not all epidemiological research identifies hyperuricemia is an independent risk factor for the development of cardiovascular disease and renal disease, particularly patients with hypertension or congestive heart failure and in women.[3] Some have found a significant and specific independent association between uric acid level and cardiovascular mortality and morbidity, while others have come to an opposite conclusion. Thus, despite abundant epidemiological evidence, the role of increased serum uric acid and cardiovascular risk is controversial. Here an attempt has been made to study the level of serum uric acid in type 2 diabetes mellitus and the correlation between elevated serum uric acid level and the component of metabolic syndrome like obesity, hypertension, dyslipidemia.

The aims and objectives of this study was to identify the level of uric acid in patients with type 2 diabetes mellitus, and to identify whether any association exist between age, sex, anthropometric measurements (BMI, WHR), hypertension, dyslipidemia and coronary artery disease with serum uric acid level.

METHODS

This was descriptive analytical study conducted in Government Sivagangai Medical College, Sivagangai. The Collaborative Department was Department of Biochemistry, Madurai Medical College, Government Sivagangai Medical College, Sivagangai. The period of study was January 2018 to February 2019 with sample size of 70 cases. The present project was approved by the Ethical committee

Inclusion criteria

- Patients with type 2 diabetes mellitus (patients were taken irrespective of their glycemic control and their duration of diabetes)
- Patients who were above 40 years were included
- Both sexes were included.

Exclusion criteria

- Patients with renal failure
- Pregnancy and lactating mothers
- Patients who were on long term diuretics and steroid.
- Patients who were regularly consuming alcohol
- Patients who were on anti-metabolite and chemotherapy drugs
- Patients who had hepatic and metabolic disorders
- Patients who had PVD/CVA/Pulmonary tuberculosis

- Renal transplant patients.

Controls

Subjects who were above 40 years and had normal blood sugar and who met the above exclusion criteria.

Consent

The study group thus identified by the above criteria (inclusion and exclusion) were first instructed about the nature of study. Willing participants were taken up after getting a written informed consent from them.

Materials

A total of 70 cases who satisfied the inclusion and exclusion criteria above were taken up for subsequent study and 30 age and sex matched normal patients were kept as control.

Methods and tools

Selected socio-demographic, clinical, laboratory data were elicited from the patients and controls and recorded in proforma.
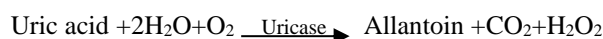
Socio demographic data

- Age
- Sex.

Clinical data

- Body weight
- Height
- BMI, waist hip ratio (WHR)
- Systolic diastolic blood pressure
- Cardiovascular risk factors
- Clinical examination.

Laboratory data

- Blood urea estimation was done manually by using diacetyl monoxime method (DAM)
- Serum creatinine estimation was done by using COBAS auto analyzer
- Serum uric acid was done by using semi auto analyzer.

Principle

Uric acid is converted by uricase to allantoin and hydrogen peroxide in the presence of peroxidase (POD) oxidizes the chromogen to a red coloured compound which is read at 500mm.

$$\text{Uric acid} + 2H_2O + O_2 \xrightarrow{\text{Uricase}} \text{Allantoin} + CO_2 + H_2O_2$$

$$2H_2O_2 + 4\text{aminophyrine} \xrightarrow{\text{DHBS POD}} \text{Red quinolone} + H_2O + HCl$$

(DHBS 3, 5-Dichloro-2 hydroxy benzene sulphonic acid)

Statistical analysis

Data was entered in Microsoft excel spread sheet and analyzed statistically using standard statistical software. Student 't' values was applied for significance. Significance was considered, if the 'P' value was below 0.05.

RESULTS

The total number of subjects included in this study was 100. Among those 100 subjects, 70 were cases (type 2 Diabetes mellitus) and 30 were controls (Non-Diabetic).

Table 1: Frequency distribution of the study population.

	Cases	Controls
Total No.	70	30
Gender	M=46 F=24	M=18 F=12
Age (years)	41 to 75	43 to 73
Mean Age(years)	60	56
BMI	19.4-29.2	18.4-26.0
WHR	0.76-1.14	0.76-1.10
FBS (mg/dl)	128-196	84-122
PPBS (mg/dl)	154-323	136-184
SUA (mg/dl)	3.0 to 8.1	2.7 to 5.5

The age of the subjects in the study group ranged from 41 to 75 years. The mean and standard deviation for age of the cases and controls were 60.1±8.82 and 56

.27±7.84 respectively, there was no significant difference among the cases and controls with reference to the age. Among 70 cases studied, there were 46 males and 24 females. Among 30 controls there were 18 males and 12 females. Among 70 cases and 30 controls screened for BMI, non were obese.

The mean and standard deviation for BMI of the cases and controls were 24.1±2.98 and 21.6±2.3 respectively. The Mean and Standard deviation for fasting blood sugar was 144.28±38.21 similarly for post prandial blood sugar was 212.01±42.13 among diabetics.

Thus, showing that their diabetic status was under poor control (Table 1).

Distribution of cases and controls in relation to mean serum uric acid level (SUA)

Serum uric acid in the study population and control varied from 3.0 to 8.1 and 2.7 to 5.5 mg/dl respectively.

The mean and standard deviation of uric acid among cases was 5.08±1.42 while in control it was 3.55±0.62 respectively (Table-2).

Table 2: Serum Uric Acid level in diabetics and controls.

Serum uric acid*	Cases		Controls	
	Mean	S.D	Mean	S.D
	5.08	1.42	3.55	0.62

P value: 0.0001 (significant).

The serum uric acid level of diabetics was very much elevated compare with controls and it was highly significant. Similarly, the details in relation to the cut off values of serum uric acid 4mg is shown in the Table 3 given below with statistical significance P=0.0001. 74.3% of the diabetic patients have more than 4 mg serum uric acid levels than the control population and it was highly significant.

Table 3: Cases and controls in relation to uric acid.

Serum uric acid	Cases		Controls	
	No.	%	No.	%
<4MG	18	25.7	23	76.7
>4MG	52	74.3	7	23.3

P value = 0.0001 significant.

Hyperuricemia in cases and controls

Hyperuricemia is defined as SUA level ≥8 mg/dL in males and ≥6 mg/dL in females. 7 cases had hyperuricemia while none in controls which clearly shows that the prevalence of hyperuricemia more in diabetic patients when compared to controls.

- The mean value of serum uric acid was 4.77±1.4 in males and 5.68±1.3 in females, in the study group mean uric acid values were higher in females than males and the difference was statistically significant (P=0.0196).
- The mean value of serum uric acid was 6.35±0.82 in those with BMI>25, it was significantly higher when compared to those having BMI<25. The mean value of serum uric acid in BMI<25 was 4.01±0.81 (P=0.0001).
- Mean uric acid level was positively correlated with BMI. (P=0.0001) Uric acid level increases with increasing WHR. The WHR abnormality was considered in 36 cases based on, WHR as 1.0 and above for men, 0.90 and above for women and correlated with uric acid level, it was significant (P=0.0001).
- The mean value of serum uric acid level was slightly higher among smokers 4.80±1.12 when compared to nonsmokers 4.56±1.06, but the difference was not significant statistically (P>0.05).

Table 4: Serum uric acid values in relation to certain variables among cases.

Variables	Variables Groups	Number	Mean	SD	P value
Gender	Male	46	4.77	1.4	0.0196
	Female	24	5.68	1.3	
BMI	<25	38	4.01	0.81	0.0001
	>25	32	6.35	0.82	
WHR Abnormality	Yes	36	6.12	0.72	0.0001
	No	34	3.97	0.43	
Hypertesion	Yes	15	6.15	0.92	0.0001
	No	55	4.79	1.4	
Lipid Profile Abnormality	Yes	20	6.49	0.85	0.001
	No	50	4.52	1.2	
Duration of Diabetes	2-4 years	13	3.88	0.93	0.001
	4-8 years	34	4.69	1.27	
	8-12 years	23	6.34	0.84	

- The mean serum uric acid level in the hypertensive group (6.15±0.92) was significant more than non-hypertensive group (5.15±1.40) in the cases and the results (P=0.0001).
- The mean serum uric acid level in patients with lipid profile abnormality was 6.49±0.85, while it was 4.52±1.20 in patients without lipid profile abnormality, and it was highly significant (P=0.001).
- Mean value of serum uric acid level was higher in longer duration (8-12 years) of diabetes 6.34±0.84, when compared to shorter duration (2-4years) of

diabetes 3.88±0.93. Uric acid level increases with increasing duration of diabetes and it was statistically significant (P=0.001).

Table 5 was showing number of patients with ischemia: 10, of these only 2 had hyperuricemia with equal sex distribution (1:1), Number of patients with infarction was 5, of these only 3 had hyperuricemia, all are female patients (0:3), Percentage of hyperuricemia in infarction is higher than in ischemia, and female patients were more involved in CAD than males in relation to hyperuricemia.

Table 5: CAD and Hyperuricemia.

Type of CAD	No. of patients	Total no. of hyperuricemia	Sex	%
Ischemia	10	2	1M+1F	20%
Infarction	5	3	0M+3F	60%

DISCUSSION

Diabetes is the most common risk factor for cardiovascular disease, and it is present in nearly 25% adults and increases in prevalence with age. Hyperuricemia is one of the component of metabolic syndrome. In the absence of gout the presence of hyperuricemia in patients with type 2 diabetes mellitus is an important marker as well as an added risk factor for atherosclerosis". In this study the relation between serum uric acid level and diabetes was examined. Uric acid is a marker for CAD in combination with other risk factors among diabetics. Though uric acid level and age was independent, it is possible that duration of the illness may have an impact on uric acid levels. In the present study females have higher uric acid level when compared to males. The mean uric acid value in males 4.71±1.4 while in females it was 5.68±1.3, and the difference was

statistically significant in this study. The possible reasons for such difference may be attributable to increased BMI and increased WHR among women.

In the present study serum uric acid correlated well with body mass index (BMI). The mean uric acid in those subjects with BMI>25 were higher than those with BMI <25 (6.35±0.82 Vs 4.01±0.81) and the difference was statistically significant which was similarly supported by many studies.[4,5] Rathman (1997) assessed the various components of insulin resistance syndrome in young black and white adults. They concluded body mass index showed strongest positive correlation with the uric acid among insulin resistance components.[6] In our study the mean uric acid value in patients with waist hip ratio abnormality and patients without waist hip ratio abnormality was 6.12±0.72 and 3.97±0.43 respectively and the difference was statistically significant.

So, it has become evident that the central obesity is an important risk factor for the development of raised serum uric acid levels. Strong epidemiologic data have linked serum uric acid to hypertension in humans and experimental animal data suggests hyperuricemia causes hypertension.[7,8,9] The Olivetti heart study had shown an independent positive association between serum uric acid and development of hypertension.[10] When the level of serum uric acid in hypertensive patients was compared with non-hypertensive patients in cases, the difference was significantly higher in the present study. The present observation on uric acid among diabetic hypertensives is in consistent with other studies. Elevated triglycerides which is the most important risk factor in acceleration of atherosclerosis.[11] There is a significant relationship between serum uric acid and dyslipidemia.[12] In the present study dyslipidemia was noticed as a risk factor in those with CAD, who had significantly elevated serum uric acid levels. "Uric acid stabilizes the platelet aggregation and enhances thrombotic tendency", thus suggested hyperuricemia as a strong predictor of myocardial infarction and stroke and all causes of mortality. Patients with poor metabolic control and longer duration of diabetes were more susceptible to develop various complications including hyperuricemia as observed in the present study. Our study also shows that higher level of serum uric acid was seen in patients with longer duration of diabetes when compared with shorter duration of diabetes. This difference was statistically significant. Uric acid >4 mg/dL should be considered as a "Red flag" in those patients at risk for cardiovascular disease. In this study 74.3% of diabetic patients have serum uric acid level >4 mg/dL, while only 23.3% of the control have serum uric acid >4 mg/dL. In these patients the clinician should strive to utilize global risk reduction Programme to reduce the complications of atherogenic process. The association of serum uric acid with cardiovascular disease has been appreciated for nearly half a century.[1] However, its role as a cardiovascular risk factor remains controversial. The Framingham heart study concluded that uric acid does not have a causal role in the development of coronary artery disease and death from cardiovascular disease.

In an epidemiologic follow up study an association between serum uric acid and cardiovascular disease was shown. The recent PIUMA study also concluded that raised serum uric acid is a powerful risk marker for subsequent cardiovascular disease and all-cause mortality.[13] Of the 70 cases of type 2 diabetes mellitus serum uric acid was elevated in 7 patients which accounts for 10% of cases. Canon showed a prevalence of hyperuricemia in 25% of longstanding uncontrolled diabetes. But in this study, many of the cases were on treatment which might have affected the results. A large Body of evidence links uric acid with metabolic syndrome of insulin resistance, obesity, hypertension, and dyslipidemia. In this study relationship between obesity, hypertension, dyslipidemia and hyperuricemia was statistically significant.

CONCLUSION

Uric acid was significantly elevated in diabetic population. The serum uric acid level was independent of age and smoking status in males. Significant correlation was noticed between serum uric acid and BMI as well as WHR. Significant elevation of uric acid level was observed more among females. Elevated uric acid levels were significantly noticed among those with hypertension, dyslipidemia, coronary artery disease and chronicity of the diabetes. Uric acid level above 4mg/dl in diabetic population (considered as a "Red flag" sign) was a marker or risk factor for CAD, which was present in 70% of study population. So, its suggested that the clinician should have high suspicion to screen the diabetic patients for the serum uric acid levels.

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