Original Research Article

A study on serum uric acid levels in type 2 diabetes mellitus and its association with cardiovascular risk factors

T. Murali Venkateswara Rao[1*], Naga Karthik Vanukuri[2]

[1]Associate Professor, [2]Assistant Professor
Department of General Medicine, NRIGH, Chinakakani, Andhra Pradesh, India
[*]Corresponding author email: **muralivenkateswararao.t@gmail.com**

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Abstract

Introduction: The Morbidity and mortality due to non-communicable diseases specially attributed to diabetes mellitus and coronary heart disease is raising rapidly in India, causing nearly 5.8 million deaths per year annually. Considering the strong association between the levels of serum uric acid and the occurrence of coronary atherosclerosis in subjects with type 2 diabetes mellitus, the current study has been undertaken to assess the factors influencing the serum uric acid levels in patients with type 2 diabetes mellitus

Materials and methods: The study was an analytical cross sectional study, conducted in NRI Medical College and General Hospital, Guntur in Department of General Medicine and Department of Biochemistry, from December 2014 to November 2015. The study has included 70 cases diagnosed with Type 2 diabetes mellitus and 30 healthy controls. Hyperuricemia has been arbitrarily defined as >7.0 mg/dL in men and >6 mg/dL in women.

Results: Among diabetic cases, the proportion of subjects with hyperuricemia was 11.43% and among the controls, none of the controls had hyperuricemia in study population. The mean uric acid level increased from 4.30 ± 0.77 in people with duration diabetes 2 to 4 years to 4.57±1.01 in people with duration of diabetes 5 to 8 years. Among people who had diabetes for 9 to 12 years, the mean uric acid level was 6.47 ± 1.07. The association between duration of diabetes and serum uric acid level was statistically significant. There was a strong positive association between hypertension, Hyperlipidemia and serum uric acid levels.

Conclusions: Serum uric acid levels were significantly elevated in diabetic population. Elevated serum uric acid levels were significantly noted among those with dyslipidemia with high triglycerides,

hypertension. Serum uric acid levels increased with increasing duration of diabetes.

Key words

Uric acid, Type 2 diabetes mellitus, Cardiovascular risk factors.

Introduction

The Morbidity and mortality due to non-communicable diseases specially attributed to diabetes mellitus and coronary heart disease is raising rapidly in India, causing nearly 5.8 million deaths per year annually [1, 2]. Insulin resistance state is associated with diabetes mellitus and metabolic syndrome (MS). The four major players in the MS are hyperinsulinemia, hypertension, hyperlipidemia, and hyperglycaemia. Each member of this deadly quartet has been demonstrated to be an independent risk factor for CHD and capable of working together in a synergistic manner to accelerate both non-diabetic atherosclerosis and the atherosclerosis associated with MS and T2DM [3, 4]. In a like manner, hyperuricemia, hyperhomocysteinemia, ROS, and highly sensitive C- reactive protein (hsCRP) and each of which play an important role in expanding the original Syndrome X described by Reaven in the atherosclerotic process [5]. Many studies in the past have recommended regular screening of all type 2 diabetic subjects, to identify people with higher risk of subsequent atherosclerosis [6]. A strong association was also demonstrated between uric acid levels and various other cardiovascular risk factors [7]. Considering the paucity of studies on the subject in India, 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 levels and cardiovascular risk factors like obesity, hypertension, smoking, dyslipidemia.

Objectives

- To compare the serum uric acid levels among type 2 diabetic subjects with controls.
- To identify factors associated with high serum uric acid levels among type 2 diabetic subjects.

Materials and methods

Study setting: The study was conducted in NRI Medical College and General Hospital, Guntur in Department of General Medicine and Department of Biochemistry.

Study design: The study was analytical cross sectional study.

Study period: The study was conducted from December 2014 to November 2015.

Sample size: The study has included 70 cases diagnosed with Type 2 diabetes mellitus and 30 healthy controls.

Inclusion criteria

- Patients with type 2 diabetes mellitus (irrespective of their glycemic status and duration of diabetes).
- Patient's age > 40 years.
- Both sexes were included.

Exclusion criteria

Patients with the following conditions were excluded from the study

- Renal failure.
- On long term diuretics and steroids.
- Regularly consuming alcohol.
- On antimetabolite and chemotherapy drugs.
- Hepatic disorders.
- Peripheral vascular disease/ cerebrovascular disease/ pulmonary tuberculosis.
- Renal transplant patients.
- Pregnancy and lactating mothers

Ethical considerations

The study was approved by intuitional human ethics committee. Informed written consent was obtained from all study participants. Confidentiality of the study participants was maintained throughout the study.

Study procedure

After informed written consent was obtained, selected data were elicited from the patients and controls and recorded in structured proforma. The data was collected on Socio demographic parameters like age, gender etc. Clinical parameters like Duration of diabetes, Family history of diabetes, Smoking history etc.

Physical examination was done to record anthropometric data like Body weight, height, BMI, WHR etc. Clinical parameters like Systolic and Diastolic blood pressure. 10 ml of blood was collected and sent to the laboratory for assessment of Fasting and postprandial blood sugar levels estimated by using glucosoxidase-peroxidase (GOD/POD) method, Serum lipid profile, Blood urea estimation was done manually by using diacetyl monoxime method (DAM) and serum creatinine estimation was done by using alkaline picrate method.

Estimation of serum uric acid

Serum uric acid was done by using phosphotungstic acid method.

Step 1: Deproteinisation: In a test tube to 1 ml of distilled water, 0.2 ml of serum, 0.4 ml of 2/3 N H2SO4, 0.4 ml sodium turgitate (10%) are added and sample centrifuged for 5 minutes.

Step 2: To 1 ml of the filtrate add 0.75N NaOH, saturated picric acid 0.5 ml mix well & wait for 15 minutes. Reading is taken at 490 nm calorimetrically.

Operational definitions

Diabetes Mellitus [8]

- FPG -126 mg/dl (7.0 mmol/l). Fasting is defined as no caloric intake for at least 8 h.* OR
- Symptoms of hyperglycaemia and casual plasma glucose -200 mg/dl (11.1mmol/l). Casual is defined as any time of day without regard to time since last meal. The classic symptoms of hyperglycaemia include polyuria, polydipsia, and unexplained weight loss. OR
- 2-h plasma glucose -200 mg/dl (11.1 mmol/l) during an OGTT. The test should be performed as described by the World Health Organization, using a glucose load containing the equivalent of 75 g anhydrous glucose dissolved in water. *

*In the absence of unequivocal hyperglycemia, these criteria were confirmed by repeat testing on a different day

Hyperuricemia [9]

Hyperuricemia has been arbitrarily defined as >7.0 mg/dL in men and >6. mg/dL in women.

Statistical Analysis

Descriptive analysis of all the explanatory and outcome variables was done using mean and standard deviation for quantitative variables, frequency and proportion for categorical variables. The quantitative variables were compared across the study groups by independent sample t-test. The categorical variables were compared across the groups by chi square test. P value < 0.05 was considered as statistically significant. IBM SPSS version 21 was used for statistical analysis.

Results

A total of 70 diabetic subjects and 30 controls were included in the study. Both the study groups had no significant differences in terms of baseline sociodemographic and anthropometric parameters.

Both the cases and controls were comparable in age and gender distribution. The mean age of the study participants was about 59 years. The BMI, waist hip ratio, fasting Blood sugar and post prandial blood sugar were higher in Diabetes group, compared to controls. The range of serum uric acid was also higher in diabetes subjects (3.3 to 8.2), compared to healthy controls (2.6 to 5.3) as per **Table – 1**.

There were no statistically significant differences among the cases and controls with respect to the

other CVD risk factors like family history of CAD, smoking status and hypertension (P value > 0.05) as per **Table – 2**.

Among cases, the proportion of subjects with hyperuricemia was 11.43% and among the controls, none of the controls had hyperuricemia in study population (**Table - 3**).

The mean uric acid level increased from 4.30 ± 0.77 in people with duration diabetes 2 to 4 years to 4.57±1.01 in people with duration of diabetes 5 to 8 years. Among people who had diabetes for 9 to 12 years, the mean uric acid level was 6.47 ± 1.07. The association between duration of diabetes and serum uric acid level was statistically significant (**Table - 4**).

The total number of hypertensive in the cases group was 18. The mean serum uric acid level in the hypertensive group was 6.60±1.105. The mean serum uric acid level in the non-hypertensive group was 4.79±1.18. The difference between the two groups was statistically significant. The mean serum uric acid in patients with lipid profile abnormality was 6.37±1.02. The mean serum uric acid in patients without lipid profile abnormality was 4.79±1.18. The difference between the two groups was statistically significant. Number of patients with ischemia was 14. The mean serum uric acid level in ischemia group was 6.75±1.203. Of this only 5 had hyperuricemia which includes 4 males and 1 female. Number of patients with infarction was 4. The mean serum uric acid level in infarction group was 7.3±0.96. The difference in the uric mean uric acid level between ischemia and infarction group were statistically not significant (**Table - 5**).

Table - 1: Comparison of cases and controls with respect to baseline parameters.

Parameters	**Cases (N=70)**	**Controls (N=30)**
Gender	M= 42 F= 28	M= 16 F= 14
Mean Age (Yrs)	59.55	55.8
BMI	24.38±2.80	22.07±2.23
WHR	0.76-1.14	0.65-1.12
FBS (mg/dl)	102-206	86-129
PBS (mg/dl)	162-304	123-198
SUA (mgt/dl)	3.3-8.2	2.6-5.3

Table - 2: Analysis of Cases and Controls in Relation to Selected Cardiovascular Risk Factors.

Risk factor	**Cases***		**Controls**		**P Value**
	Frequency	**Percentage**	**Frequency**	**Percentage**	
Family history CAD	13	18.57	6	20.00	0.9114 (ns)
Smoking among males	18	42.86	4	25.00	0.3421 (ns)
Hyper tension	18	25.71	8	26.67	0.8813 (ns)

Table - 3: Association between hyperuricemia and diabetes mellitus.

Hyperuricemia	**Cases**	**Controls**
	Frequency (%)	**Frequency (%)**
Positive	8 (11.43 %)	0 (0 %)
Negative	62 (88.57 %)	30 (100 %)

Table - 4: Duration of Diabetes (DOD) and Hyperuricemia.

DOD *(Years)	No.of patients	Hyperuricemia		P Value
		Mean	SD	
2-4	12	4.30	0.77	0.356 (ns)
5-8	31	4.57	1.01	0.001
9-12	27	6.47	1.07	0.001

Table - 5: Association between serum uric acid levels and other CVD risk factors among diabetic subjects.

Parameter	No. of Cases	Serum uric acid values		p value
		Mean	SD	
Hypertension				
YES	18	6.60	1.105	0.0001
NO	52	4.79	1.18	
LPA				
YES	26	6.373	1.02	0.0001
NO	44	4.60	1.14	
CAD				
Ischemia	14	6.75	1.203	0.391 (ns)
Infarction	4	7.3	0.96	

Discussion

Considering the strong association between the levels of serum uric acid and the occurrence of coronary atherosclerosis in subjects with type 2 diabetes mellitus, the current study has been undertaken to assess the factors influencing the serum uric acid levels in patients with type 2 diabetes mellitus.

The current study has demonstrated that the proportion of subjects with hyperuricemia was much higer in diabetic population (11.43%) and none of the controls had hyperuricemia. In their review, Katsiki N, et al. have concluded a strong association between the serum uric acid levels and diabetes and it' complications [10]. Keenan T., et al. have reported increased by Serum urate levels were not associated with T2DM, CHD, ischemic stroke, or HF. In contradiction to majority of the published studies on the subject, this particular study has suggested, there is no causal role of uric acid and cardiovascular complications in diabetic population [11].

Choi H. K., et al. have evaluated the correlation between gout and the future risk of type 2 diabetes among men with a high cardiovascular risk profile and confirmed that, among men with a high cardiovascular risk profile with gout, there is a higher risk of future risk of type 2 diabetes independent of other known risk factors [12]. These study findings suggest a reverse causality and raises further questions on nature of the association of diabetes, serum uric acid and the diabetes related complications, especially coronary artery disease. Du L., et al. confirmed the increased risk of disbets related macro vascular complications, including CAD and cerebral infarction. From pooled estimates of 23 studies, the authors concluded that higher serum uric acid levels may contribute to cerebral infarction in patients with type 2 diabetes [13].

In the current study, the mean uric acid level increased from 4.30 ± 0.77 in people with duration diabetes 2 to 4 years to 4.57±1.01 in people with duration of diabetes 5 to 8 years.

Among people who had diabetes for 9 to 12 years, the mean uric acid level was 6.47 ± 1.07. The association between duration of diabetes and serum uric acid level was statistically significant. Studies by Gagliardi A. C., et al. [9], Javorsky, et al. [14], Kramer C. K., et al. [15] have reported similar association, along with strong influence of serum uric acid on future cardiovascular events.

In the present study serum uric acids were significantly raised in patients with hypertension. The mean uric acid levels in diabetics with hypertension and non-hypertensive were 6.6±1.105 and 4.79±1.18 respectively. The difference was statistically significant. Studies by Li Q., et al. [16] Li L. X., et al. [17] have demonstrated similar findings, but the study by Li, L. X., et al.(17) have also suggested , this association of hypertension and hyperuricemia may not translate into increased cardiovascular risk as proposed by many other studies.

The current study also highlighted the strong association between the serum uric acid and other risk factors like Hyperlipedemia. Studis by Lehto S., et al. [18], Li L. X., et al. [17], Nagahama K., et al. [19] and Zoppini G., et al. [20] also have reported similar strong association between hyperuricemia and components o metabolic syndrome. In summary, although there is overwhelming evidence that elevated serum uric acid concentrations are strongly associated with increased cardiovascular risk and poor outcome, prospective population studies are often confounded by co-existent risk factors. In the present study serum uric acid positively correlated with duration of diabetes and cardiovascular risk factors like obesity (high BMI, abnormal waist hip ratio), hypertension, dyspidemia and the results were statistically significant.

Conclusion

Serum uric acid levels were significantly elevated in diabetic population. Significant positive correlation between serum uric acid levels and Body Mass Index as well as Waist Hip Ratio was noted. Elevated serum uric acid levels were significantly noted among those with dyslipidemia with high triglycerides, hypertension. Serum uric acid levels increased with increasing duration of diabetes.

Recommendations

- Multiple factors are associated with increased uric acid levels.
- Routine annual estimation of uric acid among diabetics from the identification of diabetes will help the clinician to find out the adequacy of
    i. Control of glycemic status.
    ii. Control of dyslipidemia.
    iii. Development of hypertension.

Diabetic patients with raised serum uric acid levels should be carefully monitored for CAD as well as other vascular episodes.

- A meticulous control of blood sugar, hypertension, body mass index, dyslipidemia among diabetics bring down elevated uric acid level in diabetics.

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