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Serum uric acid levels in type 2 diabetes mellitus among South Indian Urban Population: A cross sectional study

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Abstract:
Background and aim: Hyperuricemia is common in individuals with obesity, metabolic syndrome and type 2 diabetes mellitus. This has been attributed to the hyperinsulinemia due to insulin resistance in T2DM and it's effect on the renal excretion of uric acid. There have been recent studies depicting that hyperuricemia may independently predict the development of diabetes. However, there are conflicting studies of hypouricemia in T2DM as well which may be due to increased glomerular filtration rate with increased renal clearance of uric acid. In order to add further evidence to the existing database of knowledge about uric acid metabolism in T2DM this study was carried out. Material and Methods: This cross sectional study and the subjects were selected according to inclusion and exclusion criteria. Data recorded included serum uric acid, HbA_{1c}, fasting and post prandial plasma glucose, serum creatinine, fasting lipid profile and waist hip ratio. Results: The mean value of serum uric acid was 5.11±1.2 mg/dL in diabetics and 4.59±1.12 mg/dL in non-diabetics, though within the normal reference range was statistically significant (p=0.029). However, the association of hyperuricemia (serum uric acid >7mg/dL) as a risk factor for diabetes mellitus was not significant (p=1.000). Waist circumference in cases was 94.8 ± 10 cm and in controls it was 86.6 ± 11.6 cm (p<0.001). Waist-hip ratio in diabetics was 1.0 ± 0.11 and in non-diabetics 0.9 ± 0.08 (p<0.001). HbA1c, FBS, PPBS, serum creatinine, waist circumference, waist-hip ratio were significantly increased and HDLc was decreased significantly in diabetes mellitus. Conclusion: Increased serum uric acid, decreased HDLc and increased waist-hip ratio are observed in type 2 diabetes mellitus. Steps should be taken to monitor serum uric acid, lipid profile and anthropometric measurements of diabetics and non-diabetics.

Keywords: Uric acid, type 2 Diabetes mellitus

Introduction:

Diabetes mellitus is a metabolic disorder characterized by hyperglycemia leading to damage to all systems of the body and thus, is one of the leading causes of high morbidity and mortality. The hyperglycemia is caused by defective pancreatic insulin production, action or both and results in abnormal carbohydrate, protein and fat metabolism [1]. Hyperuricemia is an independent risk factor for kidney dysfunction among type 2 diabetes mellitus (T2DM). Hyperuricemia is common in individuals with obesity, metabolic syndrome and type 2 diabetes mellitus. This has been attributed to the hyperinsulinemia due to insulin resistance in T2DM and it's effect on the renal excretion of uric acid. Hyperuricemia is also associated with increased progression to overt nephropathy [2], [3]. There have been studies depicting that hyperuricemia may independently predict the development of diabetes [4], [5]. However, there are conflicting studies of hypouricemia in T2DM as well which may be due to increased glomerular filtration rate with increased renal clearance of uric acid [6], [7]. In order to add further evidence to the existing database of knowledge about uric acid metabolism in T2DM this study was carried out.

Objectives:

- To estimate and compare serum uric acid, HbA1c, fasting blood glucose (FBS) post prandial blood glucose (PPBS), fasting lipid profile in type 2 diabetes mellitus patients with non-diabetic controls
- To correlate serum uric acid with HbA1c, fasting blood glucose (FBS) post prandial blood glucose (PPBS), fasting lipid profile in type 2 diabetes mellitus

Materials and methods:

Study design and method

This study is a cross sectional study to determine if an association exists between specific risk factors of diabetes mellitus among patients who reported for follow-up at Sapthagiri Institute of Medical Sciences and Research Center, Bengaluru. These risk factors are specifically serum uric acid in both non-diabetic and type 2 diabetic subjects. In addition, the study also seeks to determine whether there is any correlation between altered serum uric acid and other risk factors, including HbA1c, fasting and post prandial plasma glucose, fasting

lipid profile and waist hip ratio in type 2 diabetic patients. Data was obtained from patient's medical record files and any patient who fitted the following criteria was enrolled in the study after obtaining informed consent. Institutional Ethics Committee had approved the study.

Inclusion criteria:

Diabetics:
50 male and female patients already clinically diagnosed with type 2 diabetes mellitus between the age of 30 and 90 years according to ADA criteria [8]

Non diabetics:
50 male and female subjects not presenting signs and symptoms of type 2 diabetes mellitus between the ages of 30 and 90 years

Exclusion criteria:

- Pregnant women who may have presented with gestational diabetes
- Individuals with estimated glomerular filtration (eGFR) less than 90 mL/min/ 1.73m^2
- Gout
- Malignancy

Biochemical analysis included serum uric acid, HbA1c, fasting plasma glucose (FBS), post prandial plasma glucose (PPBS), serum creatinine and fasting lipid profile. The assays were performed using MerilAutoquant Clinical Chemistry auto analyzer except HbA1c which was measured using Mispa*i2* auto analyzer. The assays were carried out in the clinical chemistry of the central laboratory according to the standard manufacturer's protocols. All laboratory tests were performed after method calibration with the reference standard and internal quality control check. Hyperuricemia is defined as serum uric acid greater than 7mg/dL [9]. Anthropometric measurements included waist circumference and waist-hip ratio by using a measuring tape.

Statistical Analysis
The data collected was tabulated and analyzed using descriptive statistical tool, mean, standard deviation, and comparison between the groups was done using independent't' test. Pearson correlation analysis was done to assess the relationship between serum uric acid and other parameters. Fisher exact test was performed for the association of hyperuricemia and T2DM. Complete analysis was carried out using SPSS package.

Results:

The mean age of diabetics was 54.84 ± 11.64 years and that of non-diabetics was 51.04 ± 10.44 years. The mean value of serum uric acid was 5.11±1.2 mg/dL in diabetics and 4.59±1.12 mg/dL in non-diabetics, though within the normal reference range was statistically significant (p=0.029). Difference of means of HbA_{1c}, FBS, PPBS, serum creatinineand HDLc between diabetics and non-diabetics was statistically significant as shown in Table (1). Waist circumference in cases was 94.8 ± 10 cm and in controls it was 86.6 ± 11.6 cm (p<0.001). Waist-hip ratio in diabetics was 1.0 ± 0.11 and in non-diabetics 0.9 ± 0.08 (p<0.001). Pearson's correlation showed there was significant positive correlation between serum uric acid and serum triglycerides as shown in Table (2). The association of hyperuricemia as a risk factor for diabetes mellitus was not significant as shown in Table (3). HbA1c, FBS, PPBS, serum creatinine, waist circumference, waist-hip ratio were significantly increased and HDLc was decreased significantly in diabetes mellitus.

Table 1: Comparison of biochemical parameters and anthropometric measurements between diabetics and non-diabetics by independent 't' test

	Non-diabetics n=50(mean±SD)	Diabetesmellitus n=50(mean±SD)	t	'p' value
Fasting Blood Glucose (mg/dL)	84.44±31.42	143.32±72.1	5.293	<0.001**
Post Prandial Blood Glucose (mg/dL)	129.58±51.25	237.2±93.8	7.118	<0.001**
HbA_{1c} (%)	6.13±1.37	8.68±2.27	6.795	<0.001**
Serum Creatinine (mg/dL)	0.77±0.19	0.95±0.38	2.894	0.005*
Total cholesterol (mg/dL)	175.4±28.42	170.66±36.7	-0.722	0.472
Triglycerides (mg/dL)	164±79.82	170±94.41	0.319	0.75
HDLc (mg/dL)	39.32±4.67	36.9±4.79	-2.491	0.014*
LDLc (mg/dL)	103.3±28.36	99.44±34.37	-0.612	0.54
Non-HDLc (mg/dL)	136±27.09	132.68±37.86	-0.516	0.607
Uric acid (mg/dL)	4.59±1.12	5.11±1.2	2.213	0.029*
Waist-Hip ratio	1.0±0.11	0.9±0.08	5.167	<0.001**
Waist Circumference (cm)	86.6±11.6	94.8±10	3.757	<0.001**

**p < 0.001 statistically highly significant, *p<0.05 statistically significant

Table 2: Pearson's correlation of serum uric acid with other biochemical parameters and anthropometric measurements in diabetics

Serum uric acid with	r value	'p'value
Fasting Blood Glucose (mg/dL)	0.058	0.691
Post Prandial Blood Glucose (mg/dL)	0.071	0.622
HbA_{1c} (%)	-0.063	0.665
Serum Creatinine (mg/dL)	0.172	0.231
Total cholesterol (mg/dL)	0.09	0.536
Triglycerides (mg/dL)	0.302	0.033*
HDLc (mg/dL)	-0.07	0.629
LDLc (mg/dL)	-0.063	0.661
Non-HDLc (mg/dL)	0.051	0.728
Waist-Hip ratio	0.059	0.698
Waist Circumference (cm)	0.006	0.968

Table (3): Association of hyperuricemia with diabetes mellitusby Fisher Exact test

	Serum Uric acid>7mg/dL	Serum Uric acid<7mg/dL	Total
Diabetes mellitus	2	48	50
Non-diabetics	1	49	50
Total	3	97	100

The two-tailed P value equals 1.0000

Discussion:

In this study the serum uric acid though within the reference range was significantly increased in diabetes mellitus than non-diabetics. A meta-analysis by Lv Q et al, showed in eight prospective cohort studies, including a total of 32016 participants and 2930 incident T2DM, the risk of T2DM was increased by 6% for every 1mg/dL increase in serum uric acid [10]. In a five year prospective cohort study by Liu J et al, it was observed that persistent hyperuricemia was associated with a 75% higher risk of diabetes (RR=1.75, 95% CI= 1.47-2.08). It was also observed that in two years with respect to the changes in serum uric acid, over 10% decline and 30% increase in serum uric acid was associated with lower and higher risk of diabetes mellitus respectively [11]. A meta-analysis by Jia Z et al, of 12 cohort studies assessed the correlation between serum uric acid levels and incident T2DM and impaired fasting glucose (IFG). This meta-analysis revealed that a positive non-linear relationship exists between serum uric acid levels and incident T2DM as well as IFG [12].

In a study by Wu Y et al, it was observed that serum uric acid and 2-hour insulin levels were highest in the impaired glucose regulation (IGR) or the prediabetes group in both men and women. After adjusting for multiple confounding risk factors, the serum uric acids levels significantly correlated with 2-hour insulin levels (odds ratio=1.700, 95% confidence interval=1.390, 2.080, P<0.001) and HOMA-IR scores (odds ratio=2.017, 95% confidence interval=1.671, 2.434, P<0.001) in the impaired glucose regulation (IGR) group [13]. In a study by Babikr WG et al, the serum uric acid levels were found to correlate positively with HbA1c (r=0.135, p=0.026) in diabetics [14].

In a study by Warjukar P et al, the prevalence of microalbuminuria was 37% in cases and 8% in control. Mean value of age, BMI, fasting glucose, post-meal plasma glucose, serum uric acid, microalbuminuria in patients of diabetes mellitus was found to be highly significant as compared to the control group (p<0.0001). Males had higher values of microalbuminuria than females whereas serum uric acid was higher in females than males. There was a positive correlation of microalbuminuria with age, duration of diabetes, BMI, fasting blood sugar (FBS), post meal blood sugar (PMBS), and uric acid (r value=0.32, p-value=0.0013) in diabetics [15].

A study by WoldeamlakB et al, carried out to assess hyperuricemia as a risk for cardiovascular disease amongst diabetics it was observed that prevalence of hyperuricemia among type 2 diabetic patients was 31.5%. The serum uric acid concentration was higher among male (33.1%) compared to female (28.9%) [16].

In a study by Park KJ et al, multiple logistic regression analysis was used to compute odds ratios (ORs) and 95% confidence intervals (CIs). It was observed that prediabetes was more prevalent in the hyperuricemia group compared with the normal-range group among men (OR = 1.51; 95% CI = 1.11-2.05; P < .01) and women (OR = 1.84; 95% CI = 1.01-3.37; P = .04) after adjustment for age, body mass index, abdominal obesity, blood pressure, triglyceride, high-density lipoprotein cholesterol, renal function, alcohol consumption, smoking, and physical activity level [17].

In a study by Haque et al, the pre diabetic and diabetic individuals had a lowered serum uric acid compared to

healthy individuals. Serum uric acid was positively associated with body mass index, triglycerides and total cholesterol but negatively associated with fasting blood glucose [18]. In a study by PavaniBandaru et al, higher serum uric acid was inversely associated with diabetes mellitus in a representative sample of US adults. Serum uric acid levels were categorized into quartiles and multivariable logistic regression models showed that higher serum uric acid levels were inversely associated with diabetes mellitus after adjusting for age, gender, ethnicity, education, smoking, alcohol consumption, body mass index, hypertension and serum total cholesterol. The odds ratio (95% confidence interval) of diabetes mellitus was 0.48 (0.35–0.66; $p<0.001$) when compared with the first quartile of serum uric acid [19]. In a study by Rafiullah et al, serum uric acid level was positively associated with increased incidence of cardiovascular diseases (CVD) in patients with abnormal eGFR (<90 mL/min/1.73 m^2). HbA1c was found to be inversely associated with hyperuricemia in patients with normal eGFR level (≥90 mL/min/1.73 m^2) [20].

Decreased serum uric acid in T2DM may be due to increased glomerular filtration rate with increased renal clearance of uric acid. To conclude hyperuricemia can be explained by the enhanced renal urate reabsorption via stimulation of the urate-anion exchanger URAT1 and/or the sodium-dependent anion co-transporter in brush border membranes of the renal proximal tubule by elevated insulin due to insulin resistance.

Limitations:

In this study only a single measurement of serum uric acid was done which may be affected by diet, alcohol consumption, dehydration and renal excretion of urate. Persistent hyperuricemia may be more appropriate to reflect the risk of diabetes mellitus than a single measurement of serum uric acid. eGFR and renal dysfunction progression also should be considered. Hence, serial recordings of serum uric acid may be warranted to explore the therapeutic use for uric acid lowering agents for reducing the risk of diabetes mellitus.

Conclusion:

- Increased serum uric acid, decreased HDLc and increased waist-hip ratio are observed in type 2 diabetes mellitus. Steps should be taken to monitor serum uric acid, lipid profile and anthropometric measurements of diabetics and non-diabetics.
- Further studies are required to investigate whether serum uric acid can be causally linked to type 2 diabetes mellitus.

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