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Original Research Paper

Biochemistry

SERUM URIC ACID LEVEL IN DIFFERENT GLYCEMIC CONDITIONS: A CROSS-SECTIONAL STUDY IN A TEACHING HOSPITAL OF NORTH-EAST INDIA

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ABSTRACT

Background: Diabetes mellitus is a growing global health issue, with rising prevalence each decade. Although serum uric acid (SUA) is linked to various cardiometabolic risk factors, its direct relationship with diabetes and pre-diabetes is still debated. Our study aims to explore the correlation between SUA levels and fasting blood glucose (FBG), postprandial blood glucose (PPBG), and glycated hemoglobin (HbA1c) levels in non-diabetic healthy individuals, prediabetics, and diabetics visiting a tertiary care teaching hospital in Tripura. **Methods:** This hospital-based cross-sectional study involved 180 patients from the Diabetes Clinic at Agartala Government Medical College. The participants were categorized into three groups: 60 diabetics, 60 pre-diabetics, and 60 non-diabetics. We measured serum uric acid, fasting blood glucose, post-prandial blood glucose, and glycated hemoglobin levels. Statistical analyses included the student's t-test to assess differences between means and pearson's correlation analysis, with a p-value of less than 0.05 considered statistically significant. **Results:** Diabetics had a statistically significant ($p<0.05$) higher mean of serum uric acid (9.81 ± 1.67 mg/dl) as compared to pre-diabetics (6.52 ± 0.23 mg/dl) and non-diabetics (5.29 ± 0.43 mg/dl). Pearson's correlation analysis revealed a statistically significant ($p<0.05$) positive correlation of serum uric acid with all the glycemic parameters (fasting blood glucose, post prandial blood glucose & HbA1c) in the diabetic and pre-diabetic patients. **Conclusion:** The present study found that serum uric acid levels were highest in diabetic patients, followed by pre-diabetics and non-diabetics. A significant positive correlation was observed between serum uric acid and all glycemic parameters, supporting the idea that elevated serum uric acid may contribute to diabetes mellitus development. Thus, serum uric acid could serve as a potential biomarker for predicting pre-diabetes and diabetes.

KEYWORDS : Diabetes, Pre-diabetes, Non-diabetes, Glycemic, Serum uric acid

INTRODUCTION:

Uric acid, the metabolic end product of purine nucleotides, can lead to hyperuricemia when its production exceeds kidney excretion. This condition affects 10-25% of the general population and has been rising globally. Elevated uric acid levels are linked to gout and various health issues such as metabolic syndrome, cardiovascular diseases, and renal dysfunction. While studies show uric acid as a risk factor for hypertension, dyslipidemia, cardiovascular, and kidney diseases; its association with diabetes mellitus remains unclear and controversial, possibly influenced by sex and ethnic differences.[1] Diabetes mellitus (DM) has emerged as a significant health challenge in India, with projections suggesting that by 2030, approximately 87 million Indians could be affected by this disease. Long-standing type 2 DM profoundly impacts multiple organs, reducing quality of life and increasing both morbidity and mortality.[2] A 2011 study by the Indian Council of Medical Research (ICMR) revealed that India has 77.2 million individuals with prediabetes and 62.4 million with diabetes. Prediabetes represents an intermediate stage of glucose regulation characterized by impaired fasting glucose and/or impaired glucose tolerance. This stage is reversible and significantly increases the risk of developing type 2 DM. Therefore, early identification of prediabetes is crucial for preventing the onset of type 2 DM.[3]

Previous research has shown varying findings regarding the association between elevated serum uric acid (SUA) levels and diabetes. Some studies have reported a positive correlation between SUA and diabetes,[4-6] while others have found no relationship[7] or even an inverse association.[8-10] Most studies on this topic have focused on populations with existing co-morbid conditions such as old age, diabetes, or high risk for kidney and cardiovascular diseases. There is a scarcity of research examining SUA levels and their relationship with blood glucose concentrations in apparently healthy adults. Understanding these trends is crucial as hyperuricemia is increasingly linked to modifiable cardiovascular risk factors. Despite reports from various regions worldwide, there remains a lack of information specific to the population of Tripura. Therefore, our study aims to investigate the correlation between SUA levels and fasting blood glucose (FBG), post prandial blood glucose (PPBG) & glycated haemoglobin (HbA1c) levels among non-diabetic healthy individuals, prediabetics, and diabetics in Tripura.

MATERIALS AND METHODS:

A hospital based observational cross-sectional study was conducted in the Department of Biochemistry in collaboration with Department of Medicine, Agartala Government Medical College & Govind Ballabh Pant Hospital. Agartala, Tripura from February, 2024 to July, 2024. The study population was 60 diabetes, 60 pre-diabetes & 60 non-diabetic healthy individuals (n=180) attending the outpatient department (OPD) of Diabetes Clinic, Department of Medicine, Agartala Government Medical College & Govind Ballabh Pant Hospital. Agartala, Tripura. Sample size was calculated in Openepi software with confidence interval of 95%, power of 80% and ratio of 1:1:1 between three groups with a dropout rate of 10%. The study was conducted after obtaining approval from Institutional Ethics Committee (IEC) of Agartala Govt. Medical College. Written informed consent was obtained from all the study participants.

Inclusion Criteria:

a) Patients with type 2 diabetes mellitus (patients were taken irrespective of their glycemic control and their duration of diabetes) attending the Diabetes clinic, AGMC & GBP hospital.
b) Pre-diabetes patients attending the Diabetes clinic, AGMC & GBP hospital.
c) Non-diabetic healthy individuals.
d) Patients aged above 40 years.
e) Both sexes were included.
f) Patients who were willing to take part in this study.

Exclusion Criteria:

a) Patients with renal failure.
b) Pregnancy & lactating mothers.
c) Patients who were on long term diuretics & steroid.
d) Patients who were regularly consuming alcohol.
e) Patients who had hepatic & metabolic disorders.
f) Patients who had PVD/CVA/ Pulmonary Tuberculosis.
g) Renal transplant patients.

Operational Definition:

Individuals were grouped into diabetic, pre-diabetic and non-diabetic category according to American Diabetes Association, 2021 guidelines.[11]

a) **Diabetes-** Diabetic subjects are defined as those having fasting blood glucose ≥126 mg/dl or HbA1c level ≥ 6.5%.
b) **Pre-diabetes-** Pre-diabetic subjects are defined as those having fasting blood glucose level 100-125mg/dl or HbA1c level between 5.7 - 6.4%.
c) **Non-diabetes-** Non-diabetic subjects are defined as those having fasting blood glucose level of less than 100 mg/dl or HbA1c level less than 5.7%.

Collection of blood sample for the study: Under aseptic measures, 6 ml of blood was drawn from the antecubital vein using a sterile needle and syringe. After collection, blood samples were kept in the prefixed containers (fluoride, EDTA, & clot activator container) and then sample was allowed to clot at room temperature and then serum was separated by centrifugation and accordingly proper labelling including coding was done. Whenever possible, analysis of the test was done immediately. In case of any delay, the aliquots of the sample were stored at 2-8° C until analysis.

METHODS:

a) Estimation of fasting blood glucose (FBG) and postprandial blood glucose (PPBG) by Glucose Oxidase-Peroxidase (GOD-POD) method in XL-640 full auto-analyzer.
b) Estimation of Glycated haemoglobin (HbA1c) by Biorad D10 HPLC machine.
c) Estimation of serum uric acid (SUA) by Uricase Trinder method in XL-640 full auto-analyzer.

Statistical Analysis: Data entry and analysis were performed using SPSS version 29.0 in windows PC. Categorical data was presented with the help of text, tables, charts etc. Student t-test for testing the significance of difference between two means and Pearson's correlation analysis were used and p value less than 0.05 was considered statistically significant.

RESULTS:

Table 1- Baseline characteristics of the study population

Variable	Non-diabetic (n=60)	Pre-diabetic (n=60)	Diabetic (n=60)	p value
Age (Years)	48.4 ± 4.78	49.1 ± 4.21	48.8 ± 4.42	>0.05
Sex	Male- 36 (60%) Female- 24	Male- 34 (56.6%) Female- 26	Male- 38 (63.3%) Female- 22	-
	(40%)	(43.4%)	(36.7%)	
BMI (kg/m^2)	21.84 ± 1.34	22.27 ± 1.06	22.1 ± 1.17	>0.05
SBP (mm Hg)	117.4 ± 6.31	119 ± 4.62	119.2 ± 5.11	>0.05
DBP (mm Hg)	76.6 ± 6.12	78.2 ± 4.03	78 ± 5.25	>0.05
Hyperuricemia	03 (5%)	30 (50%)	54 (90%)	0.000*

* p value < 0.05 is considered statistically significant

Table 2- Biochemical parameters among the study population

Variable	Non-diabetic (n=60)	Pre-diabetic (n=60)	Diabetic (n=60)	p value
FBG (mg/dl)	85.2 ± 6.8	119.6 ± 4.23	187.2 ± 45.28	0.000*
PPBG (mg/dl)	121.1 ± 8.34	166.9 ± 13.32	296.6 ± 69.86	0.000*
HbA1c (%)	4.99 ± 0.3	5.99 ± 0.24	7.9 ± 1.07	0.000*
SUA (mg/dl)	5.29 ± 0.43	6.52 ± 0.23	9.81 ± 1.67	0.000*

* p value < 0.05 is considered statistically significant

Table 3- Pearson correlation of serum uric acid (SUA) with other biochemical parameters in the study population

Variable	Non-diabetic (n=60)			Pre-diabetic (n=60)			Diabetic (n=60)		
SUA	FBG	PPBG	HbA1c	FBG	PPBG	HbA1c	FBG	PPBG	HbA1c
	r-0.163 p->0.05	r-0.139 p->0.05	r-0.171 p->0.05	r-0.975 p-0.000*	r-0.991 p-0.000*	r-0.981 p-0.000*	r-0.997 p-0.000*	r-0.998 p -0.000*	r-0.995 p-0.000*

* p value < 0.05 is considered statistically significant

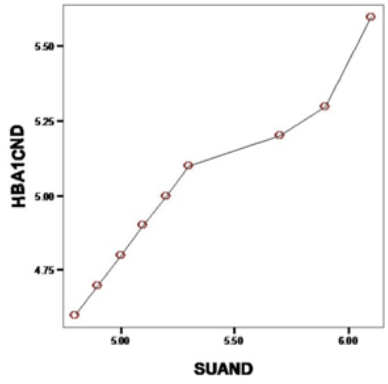

Fig 1: Line diagram showing changes in HbA1c in relation to serum uric acid in non-diabetic healthy individuals HBA1CND- HbA1c (%) in non-diabetic healthy individuals SUAND- Serum uric acid (mg/dl) in non-diabetic healthy individuals

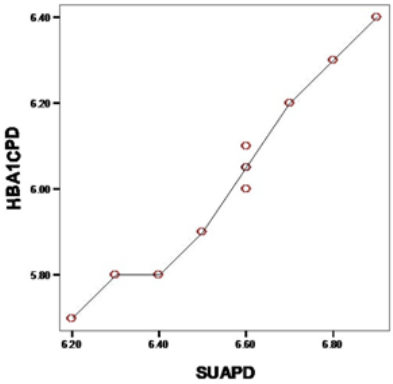

Fig 2: Line diagram showing changes in HbA1c in relation to serum uric acid in pre-diabetic patients HBA1CPD- HbA1c (%) in pre-diabetic patients SUAPD- Serum uric acid (mg/dl) in pre-diabetic patients

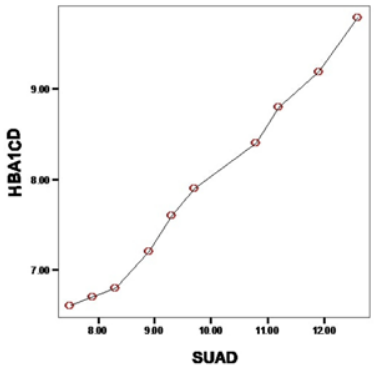

Fig 3: Line diagram showing changes in HbA1c in relation to serum uric acid in diabetic individuals HBA1CD- HbA1c (%) in diabetic individuals SUAD- Serum uric acid (mg/dl) in diabetic individuals

DISCUSSION:

In this study, we sought to compare serum uric acid levels across diabetic, pre-diabetic patients, and non-diabetic healthy individuals. Additionally, we examined the relationship between serum uric acid and glycemic parameters such as fasting blood glucose (FBG), postprandial blood glucose (PPBG), and HbA1c levels. We found statistically non-significant differences in demographic and clinical parameters, including age, BMI, systolic blood pressure (SBP), and diastolic blood pressure (DBP), among the three groups. Hyperuricemia was observed in 90% diabetic patients which was higher than pre-diabetic patients (50% have hyperuricemia) and non-diabetic group (5% have hyperuricemia); this difference was found to be statistically significant ($p<0.05$) [Table 1]. We also observed a statistically significant ($p<0.05$) increase in the serum uric acid level in diabetic patients as compared to pre-diabetic patients & non-diabetic healthy individuals (Table 2). We observed a progressive trend in which uric acid levels were highest in diabetic participants, followed by pre-diabetics, and lowest in non-diabetic participants. Pearson correlation analysis (table 3) revealed a statistically significant positive correlation of serum uric acid with all the glycemic parameters (fasting blood glucose, post prandial blood glucose & HbA1c) in the diabetic and pre-diabetic patients. A progressive increase in the glycated haemoglobin (HbA1c) level in relation to serum uric acid was observed in diabetic, pre-diabetic patients & non-diabetic healthy individuals (Fig 1-3).

The results of our study are consistent with several previous studies. Kodoma S et al[4] conducted an observational cohort study and found that elevated serum uric acid levels are linked to an increased risk of developing type 2 diabetes mellitus. It was also observed that for every 1 mg/dl rise in serum uric acid, the risk of developing type 2 diabetes increases by 17%.

In a meta-analysis study by Jia Z et al[5], a nonlinear relationship was identified between serum uric acid (SUA) levels and the incidence of impaired fasting glucose (IFG) and type 2 diabetes mellitus ($p< 0.01$). The multivariate-adjusted relative risks (RRs) with 95% confidence intervals (CIs) for IFG and T2DM were 1.02 (0.95–1.10), 1.04 (0.94–1.15), 1.10 (0.99–1.22), 1.25 (1.16–1.35), 1.43 (1.31–1.55), 1.50 (1.38–1.63), and 1.49 (1.34–1.67) for SUA levels of 2.5, 3.5, 4.5, 5.5, 6.5, 7.5, and 8.5 mg/dl, respectively. The RR (95% CI) of T2DM for the highest SUA level compared to the lowest was 1.67 (1.51–1.86). In another hospital-based comparative cross-sectional study conducted by Khan SA et al[6], it was found that the average serum uric acid level differed significantly among the three groups ($p = 0.010$), with diabetic patients having the highest level (7.50 ± 2.24 mg/dl) and euglycemic controls having the lowest (6.44 ± 2.06 mg/dl). A positive and significant correlation was found between UA and both FBG ($r = 0.253$, $p = 0.002$) and PPG ($r = 0.134$, $p = 0.048$) among the participants.

Recently, Shrestha J et al[3] conducted a hospital-based comparative cross-sectional study in 2021 and found that serum uric acid levels showed a positive correlation with all glycemic parameters (FBG: =0.320, PPBG: =0.328, and HbA1C: =0.306). These correlations were statistically significant ($p < 0.001$ for all). Additionally, within the diabetic group, serum uric acid levels significantly increased with the duration of diabetes (=0.157, $p = 0.034$).

Uric acid, the final product of purine metabolism, is produced in the liver. Purine nucleotides break down into hypoxanthine and guanine, with some being recycled into nucleotides and the rest converted to uric acid by xanthine dehydrogenase/oxidase. In healthy individuals, uric acid production and excretion are stable. However, excessive uric acid production or impaired excretion can lead to high blood uric acid levels, making body fluids acidic. This acidity can disrupt cellular functions and contribute to metabolic diseases over time.[12-14]

Elevated blood uric acid levels have been shown to increase the expression of interleukin-1 (IL-1), interleukin-6 (IL-6), and tumor necrosis factor- (TNF-),[15] as well as enhance C-reactive protein (CRP) production.[16] Animal studies indicate that uric acid-induced inflammation reduces insulin sensitivity in mice[17] and that uric acid infusion can elevate TNF- levels and activate the classical inflammatory pathway.[18] In human studies, higher serum uric acid levels are positively correlated with TNF- , IL-6, and CRP in healthy individuals.[19]

Excessive uric acid levels can increase the production of reactive oxygen species (ROS), leading to inflammation and dysfunction in blood vessels. While uric acid acts as a potent antioxidant by neutralizing superoxide and hydroxyl radicals in the plasma, it can also exhibit prooxidant effects in vascular tissues by boosting ROS production, such as hydrogen peroxide (H_2O_2). This oxidative stress induced by uric acid can cause lipid peroxidation, DNA damage, and activation of inflammatory factors, ultimately resulting in cellular damage. Additionally, oxidative stress can impair insulin gene expression, reducing insulin secretion.[20,21]

Uric acid directly inhibits the initiation of the insulin signaling pathway by recruiting ectonucleotide pyrophosphatase/phosphodiesterase 1 (ENPP1) at the receptor level.[22]

Our study's major limitation was the selection bias inherent in a hospital-based design, which may affect the applicability of our findings to the general population. Other limitations include small sample size and cross-sectional study. We recommend conducting further community-based prospective studies that include important covariates to address this issue.

CONCLUSION:

In the present study, the concentration of serum uric acid is highest in the diabetic patients, followed by pre-diabetic patients and then non-diabetic healthy individuals. Serum uric acid has a statistically significant ($p<0.05$) positive correlation with all the glycemic parameters (FBG, PPBG, HbA1c). The results of this study support the hypothesis that elevated serum uric acid levels may contribute to the development of diabetes mellitus. Therefore, serum uric acid can be used as a potential biomarker to predict pre-diabetes

and diabetes mellitus. Further research with larger sample size is necessary to evaluate the reliability of using serum uric acid as a predictor for pre-diabetes & type 2 diabetes mellitus.

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REFERENCES:

1. Haque T, Rahman S, Islam S, Molla NH, Ali N. Assessment of the relationship between serum uric acid and glucose levels in healthy, prediabetic and diabetic individuals. Diabetology & metabolic syndrome. 2019 Dec;11:1-8.
2. Gokate M, Gadkari N, Aggarwal A. Can Uric Acid be Used as a Surrogate for Urinary Albumin in Type-2 Diabetes? A Prospective Observational Study Indian Journal of Public Health Research and Development 2023;14(3):150.
3. Shrestha J, Pokhrel BR, Karki M, Gautam N, Tamang B, Palikhey A et al. Comparative study of serum uric acid level in diabetic, pre-diabetic and non-diabetic individuals in a tertiary care centre of Nepal. Journal of Chitwan Medical College.2022;12(41):44-8.
4. Kodama S, Saito K, Yachi Y, Asumi M, Sugawara A, Totsuka K et al. Association between serum uric acid and development of type 2 diabetes. Diabetes care. 2009;32(9):1737-42.
5. Jia Z, Zhang X, Kang S, Wu Y. Serum uric acid levels and incidence of impaired fasting glucose and type 2 diabetes mellitus: a meta-analysis of cohort studies. Diabetes Res Clin Pract. 2013;101(1):88-96.
6. Khan SA, Mandal S. Significance of serum uric acid level in prediabetic and diabetic patients. Prog Med Sci. 2018; 2(2):21-6.
7. Taniguchi Y, Hayashi T, Tsumura K, Endo G, Fujii S, Okada K. Serum uric acid and the risk for hypertension and Type 2 diabetes in Japanese men: The Osaka Health Survey. J Hypertens. 2001;19(7):1209-15.
8. Bandaru P, Shankar A. Association between Serum Uric Acid Levels and Diabetes Mellitus. Int J Endocrinol. 2011:60471-2.
9. Nan H, Dong Y, Gao W, Tuomilehto J, Qiao Q. Diabetes associated with a low serum uric acid level in a general Chinese population. Diabetes Res Clin Pract. 2007; 76(1):68- 74.
10. Haque T, Rahman S, Islam S, Molla NH, Ali N. Assessment of the relationship between serum uric acid and glucose levels in healthy, prediabetic and diabetic individuals. Diabetol Metab Syndr. 2019; 11(1):49-56.
11. American Diabetes Association. 2. Classification and Diagnosis of Diabetes: Standards of Medical Care in Diabetes-2021. Diabetes Care. 2021 Jan; 44 (1):15-33.
12. Bonakdaran S, Kharaqani B. Association of serum uric acid and metabolic syndrome in type 2 diabetes. Current diabetes reviews. 2014 Mar 1;10(2):113-7.
13. Li Y, Xie H, Musha H. "-e risk factor Analysis for type 2 diabetes mellitus patients with nonalcoholic fatty liver disease and positive correlation with serum uric acid," Cell Biochemistry and Biophysics, vol. 72, no. 3, pp. 643–647, 2015.
14. Viazzi F, Leoncini G, Vercelli M, Deferrari G, Pontremoli R. Serum uric acid levels predict new-onset type 2 diabetes in hospitalized patients with primary hypertension: the MAGIC study. Diabetes care. 2011 Jan 1;34(1):126-8.
15. Johnson RJ, Kang DH, Feig D, Kivlighn S, Kanellis J, Watanabe S et al. Is there a pathogenetic role for uric acid in hypertension and cardiovascular and renal disease?. hypertension. 2003 Jun 1;41(6):1183-90.
16. Kang DH, Park SK, Lee IK, Johnson RJ. Uric acid–induced C-reactive protein expression: implication on cell proliferation and nitric oxide production of human vascular cells. Journal of the American Society of Nephrology. 2005 Dec 1;16(12):3553-62.
17. Chaudhary K, Malhotra K, Sowers J, Aroor A. Uric acid-key ingredient in the recipe for cardiorenal metabolic syndrome. Cardiorenal medicine. 2013 Jan 27;3(3):208-20.
18. Maahs DM, Caramori L, Cherney DZ, Galecki AT, Gao C, Jalal D et al. Uric acid lowering to prevent kidney function loss in diabetes: the preventing early renal function loss (PERL) allopurinol study. Current diabetes reports. 2013 Aug;13: 550-9.
19. Kirilmaz B, Asgun F, Alioglu E, Ercan E, Tengiz I, Turk U et al. High inflammatory activity related to the number of metabolic syndrome components. The Journal of Clinical Hypertension. 2010 Feb;12(2):136-44.
20. Yu MA, Sánchez-Lozada LG, Johnson RJ, Kang DH. Oxidative stress with an activation of the renin–angiotensin system in human vascular endothelial cells as a novel mechanism of uric acid-induced endothelial dysfunction. Journal of hypertension. 2010 Jun 1;28(6):1234-42.
21. Matsuoka TA, Kajimoto Y, Watada H, Kaneto H, Kishimoto M, Umayahara Y et al. Glycation-dependent, reactive oxygen species-mediated suppression of the insulin gene promoter activity in HIT cells. The Journal of clinical investigation. 1997 Jan 1;99(1):144-50.
22. Tassone EJ, Cimellaro A, Perticone M, Hribal ML, Sciacqua A, Andreozzi F et al. Uric acid impairs insulin signaling by promoting Enpp1 binding to insulin receptor in human umbilical vein endothelial cells. Frontiers in endocrinology. 2018 Mar 26;9:98.