# Study of association between serum uric acid and HbA1c levels in patients with type 2 diabetes mellitus

**Basavaraj R. Patil Raikod and Shridhar S. Patil***

Department of General Medicine, Mahadevappa Rampure Medical College, Sedam Road, Mahadevappa Marg, Kalaburgi-585105, Karnataka, India

**Abstract:** *Background:* Type 2 diabetes mellitus is prevalent in a majority of population in India with approximately 30-35% and is fast gaining the status of a potential epidemic in India with more than 62 million diabetic individuals currently diagnosed with the disease. Plasma uric acid, an end product of purine metabolism, thought to be a metabolically inert end product without any physiological significance. An association between serum uric acid and type 2 diabetes mellitus is said to induce hyperinsulinemia and impaired glucose tolerance. *Objectives:* To identify the levels of serum uric acid in patients with Type 2 Diabetes mellitus and to find out the association between serum uric acid levels and HbA1c levels between patients and controls. *Methods:* A prospective observational study conducted over a period of 18 months from Jan 2018 to June 2019. Serum uric acid and serum glucose concentration were measured in 100 patients of which 50 controls and 50 patients groups. *Results:* Serum uric acid concentration was higher in diabetic group as compared with control group and was significant (p<0.001). *Conclusion:* There is no association between serum uric acid and HbA1c levels in patients with type 2 diabetes when compared with controls and was statistically significant with (p value 0.05).
**Keywords**: HbA1c, Serum Uric Acid, Type 2 Diabetes Mellitus.

## Introduction

Type 2 diabetes mellitus is prevalent in a majority of population in India with approximately 30-35% and is fast gaining the status of a potential epidemic in India with more than 62 million diabetic individuals currently diagnosed with the disease [1]. Although the IDF South-East Asia Region (SEA) comprises only seven countries - India, Bangladesh, Nepal, Sri Lanka, Mauritius, Bhutan and the Maldives it is the second most populous IDF region after the Western Pacific Region (WP). Estimates in 2017 indicate that 8.5% (6.5-10.7%) of the adult population aged 20-79 years has diabetes. This is equivalent to 82.0 (62.6 - 103.2) million people living with diabetes. About 45.8% of these are undiagnosed.

Although only one-third (33.3%) of adults in SEA live in urban areas in 2017, nearly half (48.8%) of all adults with diabetes can be found in cities. Mauritius has the highest adult diabetes prevalence rate in this region (22.0%), followed by Sri Lanka (10.7%) and India (10.4%).

India is home to the second largest number of adults living with diabetes worldwide, after China. People with diabetes in India, Bangladesh, and Sri Lanka make up 98.9% of the region's total adult diabetes population. People from age 50-70 have the highest diabetes prevalence among all ages in this region. In 2017, India is the largest contributor to the regional mortality, with nearly 1 million estimated deaths attributable to diabetes [2]. Diabetes is a syndrome of hyperglycemia and disturbances of carbohydrate, fat and protein metabolism associated with absolute or relative deficiencies in insulin secretion [3].

*Criteria for the diagnosis of diabetes mellitus* [4]:

- Symptoms of diabetes plus random blood glucose concentration ≥11.1 mmol/L (200 mg/dL) [Random is defined as without regard to time since the last meal] or

- Fasting plasma glucose ≥7.0 mmol/L (126 mg/ dL) [Fasting is defined as no caloric intake for at least 8 h] or
- Hemoglobin $A_{1c}$ ≥ 6.5% [Hemoglobin $A_{1c}$ test should be performed in a laboratory using a method approved by the National Glycohemoglobin Standardization Program and correlated to the reference assay of the Diabetes Control and Complications Trial. Point of care hemoglobin $A_{1c}$ should not be used for diagnostic purposes] or
- 2-h plasma glucose ≥ 11.1 mmol/L (200 mg/dL) during an oral glucose tolerance test [The test should be performed using a glucose load containing the equivalent of 75 g anhydrous glucose dissolved in water, not recommended for routine clinical use]

*Note:* In the absence of unequivocal hyperglycemia and acute metabolic decompensation, these criteria should be confirmed by repeat testing on a different day [4].

*Uric Acid:*

Plasma uric acid, an end product of purine metabolism, is related to the purine bases of the nucleic acids. Its levels are genetically determined, but are influenced by multiple environmental factors. It had been thought to be a metabolically inert end product without any physiological significance. Recently, it has been shown that there is a definite relationship between hyperglycemia and uric acid levels. Studies done so far have shown that, in the early stages of diabetes, the levels were high and as the diabetic status progresses, there is a gradual decline of uric acid levels in many patients.

It is also associated with alterations of other organ functions such as kidney and cardiac and uric acid has been implicated in a number of other complications of type 2 diabetes mellitus such as neuropathy, obesity, hypertension and metabolic disorders. An association between serum uric acid, the end product of purine metabolism to type 2 diabetes mellitus as it is said to induce hyperinsulinemia and impaired glucose tolerance. The association between serum uric acid and HbA1c in type 2 diabetes mellitus in comparison with controls is that the levels of HbA1c and serum uric acid are higher for patients compared to controls [5]. Serum uric acid levels is inversely associated with HbA1c in Type 2 diabetes

mellitus patients but positively correlated with HbA1c in normal-glucose subjects [6]. The serum uric acid >7.0mg/dl were significantly seen in case of diabetes where as serum uric acid <or equal to5.0gm/dl was significantly seen in subjects without diabetes mellitus [7]. Serum uric acid levels is found to be increased with increasing HbA1c levels there after decreases with further increase in HbA1c levels.

**Material and Methods**

*Source of data:* Patients, with known diabetes or impaired glucose tolerance / newly detected patients of diabetes or impaired glucose tolerance treated on OPD basis or in patients admitted in B.T.G.H. A detailed history was taken and thorough physical examination was done.

*Methods of collection of data (including sampling procedure, if any):* Patients with known diabetes or impaired glucose tolerance/ newly detected patients of diabetes or impaired glucose tolerance treated on OPD basis or in patients admitted in B.T.G.H a detailed history was taken and thorough physical examination was done. A prospective observational study was conducted on 50 cases of type 2 diabetes mellitus patients. The duration of study was from Jan 2018 to June 2019 (18 months).

*Inclusion criteria:*

- Patients with type 2 diabetes mellitus (irrespective of their glycemic status and duration of diabetes.
- Patients age >40years of either sex.
- Patients who came for routine health checkup and whose HbA1c and uric acid levels were within the normal range with age and sex matched served as controls.

*Exclusion criteria:*

- Patients already on drugs that affecting serum uric acid levels.
- Alcoholics.
- Myeloproliferative Disorders.
- Lymphoproliferative Disorders.
- Pregnancy.
- Gout.

*Sample size:*

- Total of 100 patients.
- 50 patients with diabetes mellitus newly detected or already on treatment.
- 50 normal subjects.

*Specimen Collection and Preparation:* Collect serum using standard sampling tubes. Heparin or EDTA plasma. These 2 samples are taken into autoanalyser and calorimetric analysis done at 546 nm and 660 nm.

*Calculation:* Roche/ Hitachi systems automatically calculate the uric acid concentration of each sample.

*Conversion factor:* mg/dl $\times$59.5 = $\mu$mol/l

### Results

The total number of subjects included in this study was 100. Among these 100 subjects, 50 were patients of type 2 DM and 50 were controls [Table-1].

**Table-1: Details of subjects included in the study**

| Parameter | Type 2 DM | Controls |
|---|---|---|
| Total No | 50 | 50 |
| Age | >40 | >40 |
| Mean Age | 59.74±10.58 | 56.30±8.65 |
| Sex | M=33 F=17 | M=29 F=21 |
| FBS | 191.16±57.09 | 100.84±15.68 |
| PPBS | 240.84±48.91 | 120.18±13.06 |
| RBS | 256.36±98.77 | 128.02±25.98 |
| SUA | 5.39±2.06 | 4.46±1.41 |

Descriptive and inferential statistical analysis has been carried out in the present study. The results were analysed by using SPSS version 18 (IBM Corporation, SPSS Inc., Chicago, IL, USA). Microsoft word and Excel was used to generate graphs, tables etc.

Results on continuous measurements were presented on Mean ± SD (Min-Max). Normality of the data was checked using Shapiro-Wilk Test. Inferential statistics like chi-square test, fischer-exact test and Mann-Whitney U test was used to check difference between the groups. Spearmans correlation was used to check relationship between two variables. Significance was assessed at 5 % level of significance.

**Table-2: HbA1c levels in patients with type 2 DM (Group 1) and controls (Group 2)**

| HbA1c | Group-I n(%) | Group-II n(%) | Total n(%) |
|---|---|---|---|
| <6.5 | 0 (0) | 50 (100) | 50 (50) |
| >6.5 | 50 (100) | 0 (0) | 50 (50) |
| Total | 50 (100) | 50 (100) | 100(100) |
| Mean±SD | 9.44±1.75 | 5.85±0.38 | |
| Chi=100, p = 0.001 | | | |

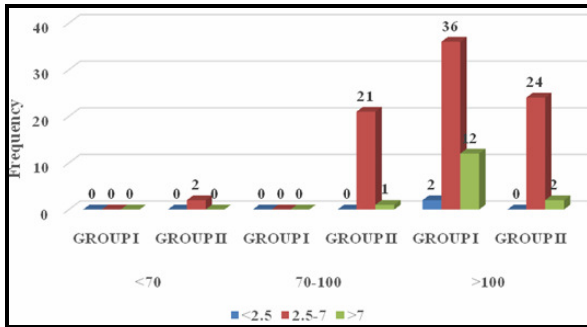*Inference:* There is statistically significant difference between the groups for HbA1c

**Table-3: Uric acid levels in Group 1 and Group 2**

| Uric Acid | Group I n(%) | Group II n(%) | Total n(%) |
|---|---|---|---|
| <2.5 | 2 (4) | 0 (0) | 2 (2) |
| 2.5-7 | 36 (72) | 47 (94) | 83 (83) |
| >7 | 12 (24) | 3 (6) | 15 (15 |
| Total | 50 (100) | 50 (100) | 100(100) |
| Mean±SD | 5.39±2.06 | 4.46±1.41 | |
| Chi=8.858, p=0.012 | | | |

*Inference:* There is statistically significant difference between the groups for uric acid

**Table-4: Uric Acid & HbA1C in Group I & II**

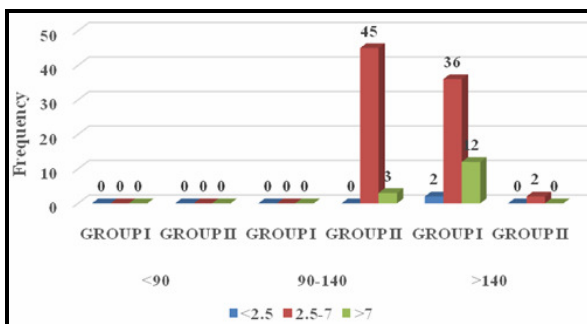| Uric Acid | <6.5 | | >6.5 | |
|---|---|---|---|---|
| | Group I | Group II | Group I | Group II |
| <2.5 | - | - | 2 (4) | - |
| 2.5-7 | 47 (94) | - | 36 (72) | - |
| >7 | 3 (6) | - | 12 (24) | - |
| Total | 50(100) | | 50(100) | |
| P=0.05 | | | | |

*Inference:* No significant difference was noted between two groups.

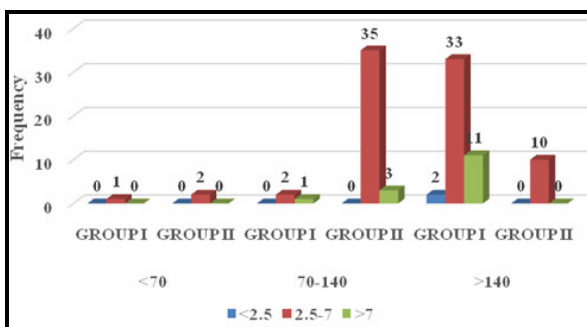**Fig-1:** Uric Acid & FBS in Group I & II



*Inference:* Statistically significant difference was noted between two groups.

**Fig-2:** Uric Acid & PPBS in Group I & II



*Inference:* Statistically significant difference was noted between two groups.

**Fig-3:** Uric Acid & RBS in Group I & II



*Inference:* Statistically significant difference was noted between two groups

### Discussion

The present study of Serum uric acid levels in patients with diabetes or newly diagnosed type 2 diabetes mellitus was carried out in the department of General Medicine, Basaveshwar Teaching and General Hospital from Jan 2018 to June 2019 (18 months). The patients were grouped into study group (patients with type 2

DM) and control group (normal subjects). The purpose of the study was to study the serum uric acid levels and association between serum uric acid and HbA1C levels in patients with diabetes and newly diagnosed type 2 diabetes mellitus in comparison with normal subjects. The main finding of our study was that plasma uric acid levels were elevated in men and women with type 2 diabetes mellitus when compared with control group.

Adlija Causevic, Sabina Semiz, et al [8] showed significantly elevated urine/serum ratio of uric acid (USRUA) levels in patients with Type 2 diabetes, a negative USRUA correlation with the blood glucose levels in diabetic patients, and an effect of sex and age on the uric acid levels. Since literature data suggest a strong genetic effect on uric acid levels, it would be pertinent to perform further, possibly genetic studies, in order to clarify gender and ethnic differences in uric acid concentrations. In our study the mean serum uric acid was high (5.39±2.06) in all patients with type 2 diabetes when compared to controls and the difference was statistically significant [Table-3].

Kodama S Et al [9-10] in their study assessed systematical evaluation of association between serum uric acid level and subsequent development of Type 2 DM and concluded that serum uric acid level is positively associated with development of Type 2 DM regardless of various study characteristics and also concluded that further research should be attempted to determine whether it is effective to utilize serum uric acid level as a predictor of Type 2 DM for its primary prevention. In this study patients with poor metabolic control and longer duration of diabetes were more susceptible to develop various complications including hypouricemia.

Serum uric acid level was found to be increased with increasing HbA1c levels there after decreases with further increase in HbA1c levels. A negative association of plasma uric acid with overt diabetes was found earlier in several other studies [2, 11-12]. Our study results confirm this finding despite the methodological differences and the various diagnostic criteria for diabetes mellitus used

in these studies. In a prospective study of 10,000 Israeli men, it was found that diabetic men had lower plasma uric acid levels than "prediabetic" men, who had higher levels than nondiabetic men [13]. In a cross sectional study conducted on 70 type 2 Diabetes Mellitus patients who attended Primary Health Care in Binjai. by Rusdiana, Sri Suryani Widjaja et al, showed that there is no significant association between HbA1C and serum uric acid [14]. Our study showed that there is no significant association between HbA1C and serum uric acid levels with p value 0.05 among the study subjects [Table-4].

Derek G Cook et al [10], showed that there was a positive relationship between serum glucose and serum uric acid concentrations and at higher levels of glucose, serum uric acid levels decreased. He concluded that serum uric acid probably reflects the biochemical interaction between serum glucose and purine metabolism, with increased excretion of uric acid during hyperglycemia and glycosuria.

In this study 72% (36) patients of type 2 diabetes had serum uric levels between 2.5-7 mg/dL and 24% (12) patients had serum uric acid levels more than 7mg/dL with mean serum uric acid level was *5.39 ± 2.06 and 4.46 ± 1.41* in patients with type 2 diabetes and control group respectively and the difference was statistically significant. Daniel Felg Et al [15-19] in their study concluded that 40-60% subjects with IGT had hyperuricemia.

In this study 72% (36) patients had serum uric acid levels between 2.5-7gm/dl, 24% (12) patients had serum uric acid levels more than 7gm/dl & only 4%(2) patients of Type 2 DM had serum uric acid levels less than 2.5mg/dL. And it shows that lower levels of serum uric acid was seen in patients with longer duration of diabetes when compared with shorter duration of diabetes. The possible reason may be due to increased excretion of uric acid over the years and modification of diet in renal disease [15].

There was no statistically significant difference noted between the study group and control group for age and gender distribution. In this study, there was statistically significant difference noted between the study group and control group for serum uric acid and FBS, serum uric acid and

PPBS, serum uric acid and RBS [Figure-1, 2 & 3 respectively]. In the present study 92%(17) patients had serum uric acid levels between 2.5-7mg/dl and 6% (3) patients had serum uric acid levels more than 7mg/dl with HbA1C less than 6.5% (non diabetics).When it compared to diabetics with HbA1C more than 6.5%, 72% (36) patients had serum uric acid levels between 2.5-7gm/dl, 24% (12) patients had serum uric acid levels more than 7gm/dl and only 4% (2) patients had serum uric acid levels less than 2.5gm/dl.

In the present study no significant difference was noted between gender and serum uric acid levels with p value of 0.05. Higher baseline SUA independently increased the risk for onset of hypertension and elevated UAE. Research is needed to determine whether SUA-lowering therapies can impede development of diabetic kidney disease and hypertension in T2D youth [20].

## Conclusion

- Plasma uric acid levels was increased in patients with Type 2 DM. Plasma uric acid decreased in patients with Type 2 DM of longer duration and the degree of reduced plasma uric acid levels were directly proportional to the duration of Type 2 DM.
- Serum uric acid level is found to be increased with increasing HbA1c levels there after decreases with further increase in HbA1c levels.
- Uric acid level above 4.5mg/dl in general population (considered as 'red flag' sign) was a marker or risk factor for DM, which was present in 58% of study population.
- Serum uric acid levels is inversely associated with HbA1c in overt Type 2 diabetes mellitus.
- There is no association between serum uric acid and HbA1c levels in patients with type 2 diabetes when compared with controls.

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*All correspondences to: Dr. Shridhar S. Patil, Junior Resident, Department of General Medicine, Mahadevappa Rampure Medical College, Sedam Road, Mahadevappa Marg, Kalaburgi-585105, Karnataka, India. E-mail: drshridharpatil519@gmail.com