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## RESEARCH ARTICLE

# SERUM URIC ACID IN TYPE 1 DIABETES MELLITUS

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**ABSTRACT**

Uric acid is elevated in type1 diabetes mellitus. It has also been associated with diabetic complications. Objectives were to study the significance of glycemic control and serum uric acid levels in Type 1 Diabetes Mellitus and to correlate between duration of diabetes and serum uric acid levels in Type 1 Diabetes Mellitus. 50 cases with type 1 diabetes mellitus with 50 age and sex matched controls were selected and Serum uric acid (SUA) levels were estimated by the uricase method. Our results showed significantly increased levels of SUA levels in type 1 diabetic cases mean 3.62mg/dl compared to controls mean 2.11mg/dl. SUA was also significantly increased in poor glycemic control (HbA1c >10) mean 4.33mg/dl. The mean SUA levels in diabetes with more than 10 years duration is 5.16±1.89. It was concluded that increased levels of serum uric acid levels are seen in type 1 diabetic patients irrespective of age and sex. In poorly controlled diabetics the serum uric acid was significantly increased. There was significant increase of serum uric acid in diabetic patients of more than 10years duration indicating chronic complications. So large number of studies is required to conclude that serum uric acid can be an early marker for diabetic complications, but this can be used as a prognostic marker along with other markers.



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## INTRODUCTION

Type 1 diabetes mellitus is characterized by abrupt onset of severe diabetic symptoms and total reliance on exogenous insulin for survival (International Textbook of Diabetes Mellitus). Type 1 Diabetes comprises ~10% of all cases of diabetes mellitus (Belfiore, 2000). Although type 1 diabetes mellitus most commonly develops before the age of 30, an autoimmune beta cell destructive process can develop at any age. There is considerable geographic variation in the incidence of type 1 Diabetes mellitus with the incidence of 1 to 3/100,000 per year (Fauci *et al.,* 2008). Elevated serum uric acid levels and significant renal clearance have been associated with early impaired renal function (Elizabeth *et al.,* 2008; Gołembiewska *et al.,* 2005) and poor glycemic control[5]. Several studies in type 2 diabetes mellitus have shown the association of high serum uric acid levels as a strong and early predictor of the disease. This study was done to study the significance of serum uric acid in Type 1 Diabetes mellitus, which also helps to know the relationship between glycemic control, duration of diabetes mellitus and uric acid levels. Early raise of these parameters may help in early diagnosis and management of diabetic complications and may help in preventing further progression of the complications in Type 1 Diabetes mellitus. Objectives are to Study the significance of serum uric acid levels in Type 1 Diabetes Mellitus, and to assess the correlation between serum uric acid levels and Glycemic control in Type 1 Diabetes Mellitus. The overall age-adjusted incidence of type 1 diabetes varied from 0.1/100,000 per year (in China and Venezuela) to 36.8/100,000 per year in Sardinia and 36.5/100,000 per year in Finland (Marjatta Karvonen *et al.,* 2000). In most populations, the incidence increased with age and was the highest among children 10–14 years of age (Kumar *et al.,* 2008). The overall incidence/prevalence of Type 1 DM in Karnataka per 100,000 persons was 3.8(0.32/year) [males 3.7(0.31/year) and females 4(0.33/year)] (Kumar *et al.,* 2008). Diabetes Mellitus produces 'vasculopathy' which may involve the capillary circulation leading to 'microvascular complications'. It can also accelerate and progress to 'macrovascular complications'. The potential mechanisms contributing to the initiation and development of the chronic complications include glycation of proteins leading to advanced glycated end (AGE) products, the Polyol Pathway where glucose is reduced to sorbitol and the Haemodynamic Hypothesis. In 1993, researchers announced the DCCT's main findings: intensive glucose control greatly reduces the complications of type 1 diabetes (Diabetes Control and complications Trial, 1993). Long term studies like UKPDS has proved that maintaining euglycemia significantly reduces microvascular complications in type1 Diabetics (UK

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Prospective Diabetes Study, 1998). The severity of the metabolic abnormality can progress, regress, or stay the same. Thus, the degree of hyperglycemia reflects the severity of the underlying metabolic process and its management. Over recent years there has been renewed debate about the association between raised serum uric acid concentration and diabetic complications. Several large studies have identified the value, in populations, of serum uric acid concentration in predicting the risk of cardiovascular events, such as MI. This has directed several research studies towards the potential mechanisms by which uric acid might have direct / indirect effects on the diabetic complications.

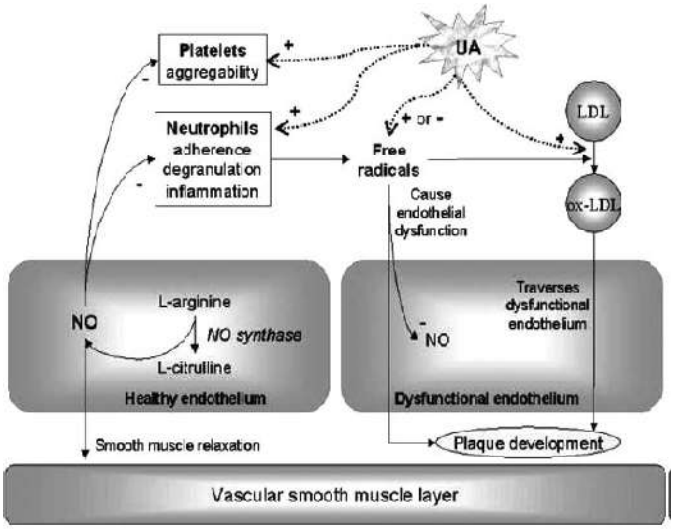


**Figure 1. Schematic representation of potential mechanisms through which high SUA could impair vascular function, and thereby promote development of atherosclerosis or increase cardiovascular risk**

Xanthine oxidase activity is increased in the setting of ischemia or oxidative stress. The consequences are an increase in uric acid production and raised SUA concentrations, and increased hydrogen peroxide synthesis, which stimulates further liberation of free radicals (Waring *et al.,* 2000; William *et al.,* 2005). Uric acid can stimulate vascular adherence of neutrophils and their subsequent degranulation, so that peroxide and superoxide free radicals are liberated in close proximity to the endothelium and impair vascular endothelial function through leukocyte activation (William *et al.,* 2005. Hyperglycemia induces both an oxidative stress (glucose autoxidation and advanced glycosylation endproducts (AGE) – ROS oxidation products and a reductive stress through pseudohypoxia with the accumulation of NADH and NAD(P)H in the vascular intima. This redox stress consumes the natural occurring local antioxidants. Once these local intimal antioxidants are depleted uric acid can undergo the paradoxical antioxidant – prooxidant switch or the urate redox shuttle (Melvin *et al.,* 2004). E. Gołembiewska showed that in type 1 diabetes there is significant renal uric acid clearance, pronounced with poor glycemic control which leads to hypouricemia despite an approximately two fold uric acid synthesis (Gołembiewska *et al.,* 2005). Serum uric acid levels, related with CRP levels in chronic kidney disease patients was shown by Caravaca, 2005. With M. Suliman, serum uric acid levels showed a high association with all-cause mortality. Moreover, uric acid level was associated with calcium/phosphate metabolism, dyslipidemia, and inflammation (Suliman *et al.,* 2006; Carlos *et al.,* 2007). CRP and UA are associated with an increase of arterial stiffness in male and female subjects, was shown by Nobukazu Ishizaka *et al.,* 2005. Mild hyperuricemia was shown to significantly increase renal tubular injury and inflammation in a model of CP-induced ARF in the rat. Serum uric acid concentration in the high-normal range is associated with impaired renal function in patients with type 1 diabetes was shown by Elizabeth T. Rosolowsky (Elizabeth *et al.,* 2008). Further, it is proposed that fructose- and purine-rich foods that have in common, the raising of uric acid may have a role in the epidemic of metabolic syndrome and renal disease that is occurring throughout the world (Pietro Cirillo *et al.,* 2006). Hyperuricaemia is also associated with possible confounding factors including elevated serum triglyceride and cholesterol concentrations, fasting and post-prandial plasma insulin concentrations, waist-hip ratio and body mass index (Green *et al.,* 1992; Gołembiewska *et al.,* 2005; Seppo Lehto *et al.,* 1998; Waring *et al.,* 2000). About one quarter of hypertensive patients have co-existent hyperuricaemia (Kumar *et al.,* 2008) and, interestingly, asymptomatic hyperuricaemia predicts future development of hypertension, irrespective of renal function was explained by Richard J Johnson *et al.,* 2003. Uric acid also has a predictive role in high-risk patient groups. For instance, diabetes mellitus is a very powerful risk factor for cardiovascular disease, and a prospective study of 1017 Type 2 DM patients showed that serum uric acid concentration >295 µmol/l conferred a hazard ratio of 1.91 of fatal or non-fatal stroke during 7-year follow-up study (Seppo Lehto *et al.,* 1998).

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. It remains unclear whether uric acid is an independent predictor of poor cardiovascular outcome (Waring *et al.,* 2000). Paolo Verdecchia study demonstrates a strong independent association between SUA and CV risk in initially untreated and asymptomatic adult subjects with essential hypertension (Paolo Verdecchia *et al.,* 2000). Elevated serum uric acid is a consistent feature of the insulin resistance syndromes, which are also characterized by elevated plasma insulin level, blood glucose concentration, serum triglyceride concentration, raised body mass index and waist-hip ratio (Bonora *et al.,* 1996; Agamah *et al.,* 1991). Uric acid concentrations were significantly higher in subjects with impaired glucose metabolism according to Vaidotas Urbanavicius *et al.,* 2008

## MATERIALS AND METHODS

The study comprised of type 1 Diabetes Mellitus cases visiting the inpatient and outpatient at Kempegowda Institute of Medical Sciences and Bangalore Diabetic Hospital, Bangalore. Age and sex matched healthy volunteers served as controls. Total Number of Subjects was 100, with 50 controls and 50Type 1 Diabetes Mellitus cases. Inclusion Criteria was patients with Type 1 Diabetes Mellitus on treatment in all age groups. Exclusion Criteria was Type 1 Diabetes Mellitus with established micro & macro vascular complications. Patients on drugs which alters serum uric acid levels. All conditions which increase/decrease serum uric acid levels. Blood - samples were collected after an informed written consent. Study design was Comparative study with random sampling. Data for the study was collected from all those who fulfilled the inclusion and exclusion criteria after taking a detailed case history and obtaining a written informed consent. Baseline data including

age and sex, detailed medical history including conventional risks factors, clinical examinations and relevant investigations were included as part of the methodology. 5 ml plain venous blood sample after overnight fasting and 2 hour postprandial were obtained by venepuncture. For $HbA_{1C}$ estimation 2 ml of EDTA blood sample was collected. This was followed by centrifugation and processed immediately. Determinations of Serum uric acid was estimated by uricase method (Lawrence, 2010), Glycosylated haemoglobin by immunoturbidimetric method, Fasting and post prandial blood sugars by glucose oxidase / peroxidase method. The statistical software using SPSS 17, Systat 8.0, MS word and MS Excel were used for the analysis of data.

## RESULTS

Out of 50 cases and 50 controls, 25 were male and 25 female cases and 22 male and 28 female controls.

**Table 1. Number of subjects in controls and study groups**

| | Controls | | | Study group | | |
|---|---|---|---|---|---|---|
| | M | F | Total | M | F | Total |
| Children (0 – 17 yrs) | 14 | 7 | 21 | 14 | 13 | 27 |
| Adults (≥ 18 yrs) | 8 | 21 | 29 | 11 | 12 | 23 |
| Total | 22 | 28 | 50 | 25 | 25 | 50 |

Among cases the average age of diabetic person is 17.96±5.39 yrs. The numbers of male subjects were higher than female subjects in controls, compared to study group. Though statistically non-significant, the controls and cases were age and sex matched as far as possible.

**Table 2. Descriptive Statistics of cases and controls**

| Cases | N | Min | Max | Mean | SD |
|---|---|---|---|---|---|
| AGE in yrs | 50 | 7 | 31 | 17.96 | 5.39 |
| DM duration in yrs | 50 | 0.2 | 23.0 | 7.78 | 5.00 |
| FBS mg/dl | 50 | 37 | 505 | 183.7 | 112.6 |
| PPBS mg/dl | 50 | 44 | 532 | 218.1 | 128.2 |
| HbA1c % | 50 | 6.0 | 15.4 | 9.94 | 2.26 |
| SUA mg dl | 50 | 0.8 | 8.8 | 3.63 | 1.93 |
| Controls | | | | | |
| AGE | 50 | 9 | 30 | 18.98 | 5.59 |
| RBS | 50 | 54 | 106 | 74.54 | 13.36 |
| HbA1c | 50 | 4.0 | 5.8 | 4.77 | 0.53 |
| SUA | 50 | 0.5 | 3.5 | 2.11 | 0.86 |

Statistically, the mean age of duration of diabetes is 7.78±5.0 and HbA1c is 9.9%. The mean serum uric acid (SUA) is 3.63 mg/dl in study group compared to controls 2.11±0.86.

**Table 3. Correlations between diabetic duration, HbA1c & SUA in Cases**

| | | HbA1c % | SUA mg/dl |
|---|---|---|---|
| DM duration in yrs | Pearson Correlation | 0.299* | 0.650** |
| | Sig. (2-tailed) | 0.035 | 0.000 |
| | | DM duration in yrs | SUA mg/dl |
| HbA1c % | Pearson Correlation | 0.299* | 0.312* |
| | Sig. (2-tailed) | 0.035 | 0.027 |

*. Correlation is significant at the 0.05 level (2-tailed).
**. Correlation is significant at the 0.01 level (2-tailed).

There was statistically significant correlation at 5% level between duration of diabetes and serum uric acid (SUA) indicating SUA increases with the duration of diabetes mellitus. SUA also increased with increase in HbA1c indicating increase in SUA levels with poor control of diabetes.

**Table 4. Paired Samples Test of SUA and HbA1c of cases & controls**

| | | Mean | SD | Sig. (2-tailed) |
|---|---|---|---|---|
| Pair 1 | SUA_Control | 2.11 | 0.86 | .000 |
| | SUA mg dl | 3.63 | 1.93 | |
| Pair 3 | HbA1c_Control | 4.77 | 0.53 | .000 |
| | HbA1c % | 9.94 | 2.26 | |

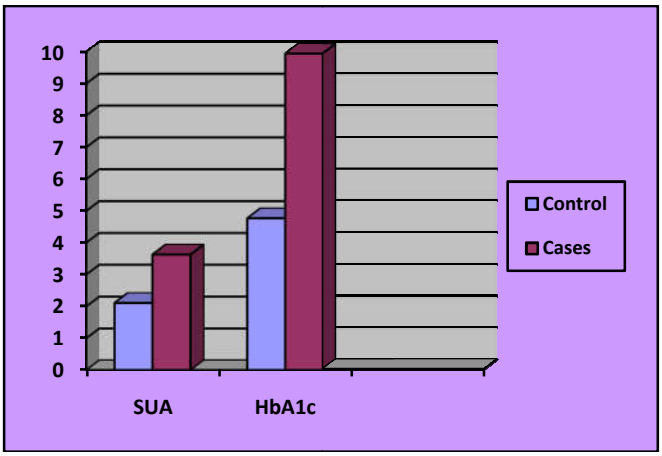


**Figure 2. Distribution of cases and controls of SUA and HbA1c**

When t – test is applied we get significant 2 tailed correlations between SUA and HbA1c with their respective controls at 5% level. This indicates increased uric acid levels in diabetics compared to controls. It is further significantly increased in uncontrolled diabetics compared to controlled diabetics.

**SUA depending on diabetic duration:** When only diabetic duration is considered irrespective of age and sex the results are as follows

**Table 5. Paired Samples Test of SUA depending on duration of diabetes**

| | | N | Mean±SD | Sig. (2-tailed) |
|---|---|---|---|---|
| Pair 1 | SUA Control | 17 | 2.43±0.95 | 0.564 |
| | SUA cases ≤ 5 | 17 | 2.23±0.90 | |
| Pair 2 | SUA Control | 19 | 2.47±0.90 | 0.004 |
| | SUA cases 5 to 10 | 19 | 3.74±1.77 | |
| Pair 3 | SUA Control | 14 | 2.49±0.94 | 0.001 |
| | SUA cases ≥ 10 | 14 | 5.16±1.89 | |

When diabetic patients are grouped depending on the duration of diabetes, there exists significant mean difference in SUA at 5-10 yr, >10yr of diabetic duration compared to controls at 5% level.

**At different levels of HbA1c:** To know the significance of glycemic control and serum uric acid levels are studied at different levels of HbA1c <6%, 7-9% and >10%.

**Table 6. Descriptive Statistics of SUA at different levels of HbA1c**

| | N | Min | Max | Mean | SD |
|---|---|---|---|---|---|
| < 6 %_ Controls | 50 | 0.5 | 3.5 | 2.11 | 0.86 |
| < 6 % Cases | 2 | 2.2 | 2.3 | 2.25 | 0.07 |
| 7 - 9 % Cases | 21 | 1.5 | 5.0 | 2.84 | 1.21 |
| > 10 % Cases | 27 | 0.8 | 8.8 | 4.34 | 2.17 |

There is significant increase SUA levels for cases 4.34±2.17 with HbA1c >10% compared to controls 2.11±0.86. The levels of serum uric acid was also increased for cases with HbA1c 7-9%. But there was not much difference in cases with HbA1c <6%.

**Table 7. Paired Samples Test of SUA with respect to HbA1c**

| | | Mean | N | SD | Sig. (2-tailed) |
|---|---|---|---|---|---|
| Pair 1 | < 6 % Controls | 2.05 | 2 | 0.78 | 0.795 |
| | < 6 % Cases | 2.25 | 2 | 0.07 | |
| Pair 2 | < 6 % Controls | 2.08 | 21 | 0.87 | 0.062 |
| | 7 - 9 % Cases | 2.84 | 21 | 1.21 | |
| Pair 3 | < 6 % Controls | 2.02 | 27 | 0.87 | 0.000 |
| | > 10 % Cases | 4.34 | 27 | 2.17 | |

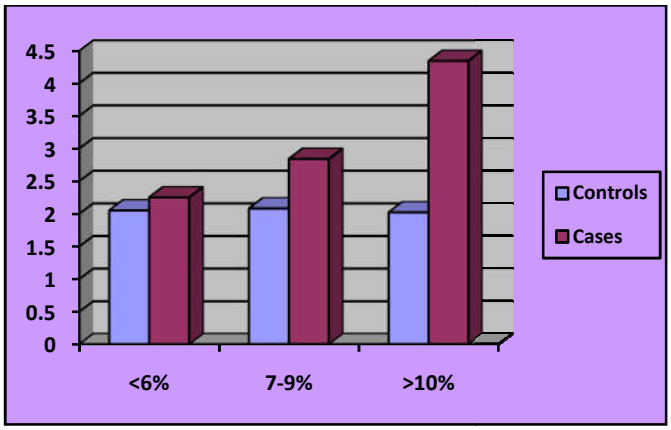


**Figure 3. Distribution of SUA in cases & controls depending on glycemic control (HbA1c)**

The serum uric acid levels increased significantly with increase in HbA1c levels. At HbA1c >10, the levels are statistically significant compared to controls.

## DISCUSSION

Comprehensive results obtained from various studies conducted upon patients with diabetes mellitus point towards a close relationship between serum levels of acute-phase reactants like uric acid and diabetes mellitus. Several studies have implicated hyperurecemia in the pathogenic process leading to endothelial dysfunction, which contribute to various local and systemic complications in long-term diabetes. Hyperuricemia has been shown to be linked to a number of conditions and disorders like gout, hypertension and diabetes mellitus. Several mechanisms have been proposed on how uric acid is elevated, reabsorption from kidney. Elevated levels of uric acid have been shown to be an independent marker in many conditions like hypertension (Carmine Zoccali *et al.,* 2006), DM, stroke, cardiovascular disease and renal disease. It remains unclear whether an increased UA level is the cause or a consequence of some of these conditions. In this background, an assessment of serum uric acid in relation to type 1 diabetes mellitus patients has been made. The present study was carried out on 50 type 1 diabetes mellitus cases and serum uric acid was measured spectrophotometrically. There was significant elevation in the serum uric acid levels in type 1 diabetics, compared to healthy controls. Higher levels were observed in patients with poor control of diabetes even though the values were not in pathological levels. Serum uric acid levels were directly related to serum glucose levels and with HbA1c. Increased serum uric acid levels were directly proportional to the duration of diabetes.

In our study 27 cases of type 1 diabetes had HbA1c >10% indicating poor control and there was significant mean difference at 5% level of serum uric acid compared to controls indicating increasing serum uric acid levels with poor control of diabetes. Similar finding was found with Nobukazu Ishizaka *et al.,* 2005 and by Golembiewska *et al.,* 2005 In this study, serum uric acid concentration in the high-normal range is associated with poor glycemic control and increasing duration of diabetes in Type 1 diabetes mellitus. Poor glycemic control is associated with increased serum uric acid levels and with increasing duration of type 1 diabetes. A positive correlation was observed between serum uric acid levels in the study group. Hence this study highlights the facts that all type 1 diabetes should be screened periodically for serum uric acid levels and blood sugars to detect and to prevent future complications. Since type 1 diabetes mellitus is an inflammatory process, elevated levels of acute phase reactants like serum uric acid probably act as diagnostic marker for the development of pan systemic complications, and act as diagnostic and early marker for the development of diabetic complications. Follow up studies are needed to confirm that this level of serum uric levels is a risk factor for diabetic complications in type 1 diabetes and to determine whether its reduction would prevent the complications.

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