



# Serum uric acid and its relation to adenosine deaminase, lipid profile and oxidative stress in Diabetes Mellitus type 2

Shashikala Magadi Dasegowda<sup>1</sup>, Ashok Kumar Jeppu<sup>2</sup>, Kavitha Ashok Kumar<sup>3</sup>, Sushith Sushith<sup>4</sup>

<sup>1</sup>Diabteology, Diacon Hospital Bangalore. 19th main road, 1st block, Rajajinagar, Bangalore, Karnataka 560010, India.

<sup>2</sup>Biochemistry unit, International Medical School, Management and Science University University Drive Off Persiaran Olahraga, Sekysen 13. 40100 Shah Alam, Selangor, Darul Ehsan, Malaysia.

<sup>3</sup>Otolaryngology unit, International Medical School, Management and Science University University Drive Off Persiaran Olahraga, Sekysen 13. 40100 Shah Alam, Selangor, Darul Ehsan, Malaysia.

<sup>4</sup>Department of biochemistry, A J Institute of Medical Sciences, Kuntinana, Mangalore 575004, Karnataka, India.

#### Address for correspondence:

Ashok Kumar Jeppu,  
Biochemistry unit; International Medical School, Management and Science University University Drive, Off Persiaran Olahraga, Sekysen 13. 40100 Shah Alam, Selangor, Darul Ehsan, Malaysia.  
drashokumarj@gmail.com

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## ABSTRACT

**Aim/Background:** Serum uric acid is an end product of purine catabolism. The relationship between the serum uric acid adenosine deaminase, lipid profile and oxidative stress in type 2 diabetes mellitus was studied to evaluate its role as one of the risk factor for coronary artery disease. **Methods:** The serum uric acid level in type 2 diabetes mellitus was compared with controls. The correlation between serum uric acid with adenosine deaminase (ADA), parameters of oxidative stress and serum lipids was also evaluated. **Results:** We observed serum uric acid level ( $5.74 \pm 0.49$ ) mg/dl is significantly ( $p < 0.001$ ) increased in type 2 diabetes mellitus when compared to controls ( $4.38 \pm 0.41$ ) mg/dl. Increase in serum uric acid level is significantly associated with increase in adenosine deaminase, malondialdehyde (MDA), total antioxidant capacity (TAC), serum triglyceride (TG), total cholesterol (TC) and low density lipoprotein cholesterol (LDL Cholesterol). Further we observed a significant negative correlation between HDL cholesterol and the serum uric acid level. **Conclusion:** We conclude that increase in serum uric acid level in type 2 diabetes mellitus acts as pro-oxidant. The endothelial dysfunction, proliferation of smooth muscle cells, oxidative stress will facilitate atherogenesis and its progression. A strong association between serum total cholesterol, LDL cholesterol, serum triglyceride, and the inverse relationship between the high density lipoprotein cholesterol and serum uric acid observed in the present study suggests that serum uric acid has a role in coronary artery disease.

**KEY WORDS:** Uric acid; Malondialdehyde; Total antioxidant capacity; Low density lipoprotein; High density lipoprotein; Cholesterol.

## INTRODUCTION

Diabetes mellitus type 2 (type 2 DM) is a disorder of multiple aetiologies, which is characterized by chronic hyperglycaemia with disturbances of carbohydrate, fat and protein metabolism resulting from deficiency of insulin, deficiency in action of insulin or both. Type 2 DM affects more than 230 million people worldwide and this number is expected to reach 350 million by 2025. Type-2 DM is the most common form of diabetes accounting for 90% of the cases [1]. The chronic hyperglycemia of diabetes is associated with significant long-term sequel, particularly damage and/or dysfunction of various organs, especially the heart, blood vessels, kidneys, eyes and nerves, [2].

Adenosine deaminase (EC 3.5.4.4) is an enzyme involved in the metabolism of purine nucleoside, catalyses the irreversible hydrolytic deamination of adenosine and 2'-deoxyadenosine to inosine and 2'-deoxyadenosine,

respectively. Further metabolism of these deaminated nucleosides leads to formation of hypoxanthine, which is later converted to uric acid by the action of xanthine oxidase. The enzyme is widely distributed in vertebrate tissues and plays a critical role in a number of physiological systems [3].

In diabetes mellitus the serum level of by-product of lipid peroxidation malondialdehyde (MDA) is increased and total antioxidant capacity (TAC) is decreased, which indicate the oxidative stress [4, 5]. There is a direct relationship between the serum adenosine deaminase activity and oxidative stress. [6, 7]

Uric acid is a diprotic acid. It is a product of the metabolic breakdown of purine nucleotides. Serum uric acid is one of the important contributors of antioxidant capacity and acts as antioxidant in the early stages of atherosclerosis [8]. However, during later stages of atherosclerosis when the uric acid level is elevated, it functions as pro-oxidant rather than

antioxidant. The antioxidant and oxidant function of uric acid mainly depends on various factors such as depletion of antioxidants, surrounding oxidant environment, acidity etc. All these factors which make uric acid act as a pro-oxidant is found in the accelerated atherosclerotic-vulnerable plaque of the intima of the arteries [9]. Various epidemiological studies with different study designs – prospective, retrospective, cross-sectional and meta-analysis had been used to examine the relation between the serum uric acid and coronary artery disease. Some of these studies have shown positive association and some others have not shown an independent relationship. The positive association is demonstrated in specific population with a high risk for coronary vascular disease, like type 2 DM [10]

Chronic hyperuricemia has been suggested as independent risk factor for hypertension, metabolic syndrome, chronic kidney disease and cardiovascular disease [11]. So hyperuricemia should be a red flag indicating the overall approach for reducing the risk by global risk reduction program [12]

The present study compared the serum uric acid level between type-2 DM and control group. It also evaluated the correlation between the adenosine deaminase, MDA, TAC, and lipid profile with uric acid levels in type 2 DM.

## MATERIALS AND METHODS

Study group consisted of 100 individuals between the age group of 35-65 years. Of which 50 individuals with type 2 diabetes mellitus were considered as cases. The cases consists of 60 individuals with diabetes mellitus on treatment without any known complications came to outpatient department. The age and sex matched control group consisted of 50 healthy individuals, who came to hospital for general health check-up and found to have normal laboratory parameters and no abnormal findings on physical examination. Their serum uric acid level was compared with the cases. Subjects with tuberculosis, leprosy, acute lymphadenitis, infectious mononucleosis, enteric fever, hepatitis A and B, chicken pox, hematopoietic malignancies like Hodgkin's lymphoma and drug induced lymphadenitis were excluded from the study group. Study was approved by Institutional ethical committee.

After taking the informed consent, patient details were obtained and by aseptic precautions venous blood (5 ml) was collected in a plain vacutainer tube after eight to twelve hours of fasting. Blood was processed immediately to obtain serum.

Serum adenosine deaminase estimations were done by using colorimetric method of Giusti and Galanti [13]. Serum uric acid was estimated by caraway method [14]. Serum MDA was measured by thiobarbituric acid method [15]. Serum TAC was estimated using FRAP (ferric reducing ability of plasma) assay [16]. Serum cholesterol [17], serum triglyceride [18], serum HDL cholesterol [19] were estimated by using commercially available kits and autoanalyser. Serum LDL cholesterol was calculated by using Friedwald's formula [20].

Descriptive and inferential statistical analysis has been carried out in the present study. Results of continuous

measurements are presented on Mean  $\pm$  SD and results on categorical measurements are presented in Number (%). Student t test (two tailed, independent) has been used to find the significance of study parameters on continuous scale between two groups (Inter group analysis) on metric parameters. Pearson correlation between study variables in cases and controls is done

## RESULTS

Gender distribution and age distribution of the study population is shown in table 1 and table 2. Student t test had demonstrated that serum uric acid levels were significantly ( $p < 0.001$ ) increased in type 2 diabetes mellitus ( $5.74 \pm 0.49$ ) mg/dl when compared to controls ( $4.38 \pm 0.41$ ) mg/dl (table 3). Measured levels of ADA, MDA, TAC and serum lipids is shown in table 4. Pearson correlation was used to find the correlation between the uric acid and the study parameters. In type 2 diabetes mellitus serum uric acid level had shown significant ( $p < 0.001$ ) positive correlation with serum adenosine deaminase and malondialdehyde. However significantly ( $p < 0.001$ ) negative correlation between serum uric acid and total antioxidant capacity was observed in type 2 diabetes mellitus. Serum triglyceride, total cholesterol, LDL cholesterol levels had shown statistically highly significant ( $p = < 0.001$ ) positive correlation with serum uric acid, whereas significant ( $p = < 0.001$ ) negative correlation was observed between HDL cholesterol and serum uric acid level (table 5).

**Table 1.** Gender distribution of patients studied

Gender	Cases	Controls	Total
Female	26(43.3%)	27(54%)	53(48.2%)
Male	34(56.7%)	23(46%)	57(51.8%)
Total	60(100%)	50(100%)	110(100%)

Samples are gender matched with  $P=0.265$

**Table 2.** Age distribution of patients studied

Age in years	Cases	Controls	Total
31-40	8(13.3%)	4(8%)	12(10.9%)
41-50	26(43.3%)	20(40%)	46(41.8%)
51-60	22(36.7%)	24(48%)	46(41.8%)
61-70	4(6.7%)	2(4%)	6(5.5%)
Total	60(100%)	50(100%)	110(100%)
Mean $\pm$ SD	49.53 $\pm$ 6.84	51.12 $\pm$ 6.63	50.25 $\pm$ 6.76

Samples are age matched with  $P=0.222$

**Table 3.** Comparison of serum uric acid (U/L) between study groups

Groups	Serum Uric acid mg/dl	p value
1. Controls	4.38 $\pm$ 0.41	<0.001
2. Cases	5.74 $\pm$ 0.49	

p value <0.05 – significant (Student t test (two tailed, independent))

**Table 4.** The serum levels of ADA, MDA, and serum lipid levels in type 2 DM

	Control	Type 2 DM	P value
Adenosine deaminase(ADA) (U/L)	17.86±4.04	50.77 ± 6.95	<0.001
Malondialdehyde (MDA) (nmol/dl)	239.32±23.97	512.13 ± 70.15	<0.001
Total antioxidant capacity(TAC) (mmol/l)	1.66±0.25	0.39 ± 0.15	<0.001
Serum triglyceride (mg/dl)	106.68±17.64	315.52±27.17	<0.001
Serum cholesterol (mg/dl)	162.26±8.28	280.92±45.89	<0.001
LDL cholesterol (mg/dl)	93.88±7.49	191.33±44.71	<0.001
HDL cholesterol (mg/dl)	47.02±4.88	26.63±6.57	<0.001

**P<0.05 = significant** (Student t test ( two tailed, independent ) )

**Table 5.** Pearson correlation of study variables with uric acid in cases and controls

Parameters correlated	Cases		Control	
	r-value	p-value	r-value	p-value
Serum adenosine deaminase vs uric acid	0.875	<0.001	-0.120	0.405
Serum malondialdehyde vs uric acid	0.872	<0.001	0.026	0.860
Total antioxidant capacity vs uric acid	-0.836	<0.001	0.110	0.448
TGL vs Uric acid	0.754	<0.001	-0.275	0.053+
Total cholesterol vs Uric acid	0.812	<0.001	-0.116	0.422
LDL vs Uric acid	0.825	<0.001	-0.016	0.914
HDL vs Uric acid	-0.598	<0.001	0.013	0.929

p value <0.05 – significant

## DISCUSSION

Adenosine deaminase involved in the metabolism of purine nucleoside, catalyses the irreversible hydrolytic deamination of adenosine and 2'-deoxyadenosine to inosine and 2'-deoxyinosine, respectively. Further metabolism of these deaminated nucleosides leads to hypoxanthine, which is transformed into uric acid by xanthine oxidase [3]. Present study was conducted to evaluate serum uric acid level in type 2 diabetes mellitus and its correlation with adenosine deaminase, parameters of oxidative stress and serum lipids. We observed significant ( $p<0.001$ ) increase in serum uric acid in DM type 2 compared to control group. A significant ( $p<0.001$ ) correlation between the serum uric acid and parameters of oxidative stress and lipid profile in cases.

Uric acid can act as a pro-oxidant and it may thus be a marker of oxidative stress, but it may also have a therapeutic role as an antioxidant [20]. We observed that uric acid level was increased in type 2 DM compared to controls. Our findings were in accordance to the study of Kaur A et al [21] which had shown that uric acid is increased in type 2 diabetes mellitus when compared to controls. Serum ADA showed positive correlation with uric acid, which indicates as serum ADA level increases uric acid level also increases.

Xanthine oxidase has been localized in the atherosclerotic plaque. It allow the active purine metabolism on the surface of endothelial plasma membrane as well as in the cytoplasm. This would lead to overproduction of uric acid as well as

excessive generation of reactive oxygen species [22]. Siddiqui S et al, showed that ADA was increased in type 2 diabetics when compared to controls and decreased after antioxidant therapy. ADA can be regarded as a strong indicator of reactive oxygen species production leading to oxidative stress in type 2 diabetics and its level can be modulated by antioxidants. [7, 23].

A statistically significant positive correlation between serum uric acid and MDA as well as the statistically significant negative correlation between serum uric acid level and TAC in our study indicate the association between serum uric acid level and oxidative stress. Oxidative stress is a major factor in pathogenesis of complications in type 2 diabetes mellitus. Uric acid is known to be a pro-oxidant. Uric acid level above the upper 1/3rd of the normal range ( $>4$  mg/dl) and the hyperuricemia ( $>7$ mg/dl) considered as one of the multiple factors that contribute to endothelial dysfunction [24, 25, 26].

Berezin AE and Kremzer.A.A demonstrated the positive correlation between the serum uric acid, LDL cholesterol and serum total cholesterol with CD14<sup>+</sup>CD309<sup>+</sup> cell subset. There was a significant effect of cardiovascular risk factors (Type 2DM, serum uric acid, total cholesterol, hs-CRP, LDL-cholesterol) and Agatston score index on the combined dependent variable (CD45<sup>-</sup>CD34<sup>+</sup>, CD14<sup>+</sup>CD309<sup>+</sup>, and CD14<sup>+</sup>CD309<sup>+</sup>Tie2<sup>+</sup> cell subsets). They postulated that a reduction in circulating CD14<sup>+</sup>CD309<sup>+</sup> and CD14<sup>+</sup>CD309<sup>+</sup>Tei2<sup>+</sup> endothelial progenitor cells is related

to a number of cardiovascular risk factors in asymptomatic patients with known CAD [27].

Berezin AE et al had shown that in asymptomatic patients with coronary artery disease, serum uric acid mildly relates to metabolic factor (type two diabetes mellitus, total cholesterol, and creatinine). Depending on the quartiles of serum uric acid levels in subjects with CHF circulating level of proangiogenic MPCs declines. They suggested that mild elevation of SUA (31.5mmol/L) might be considered a predictor of decline in the number of proangiogenic MPCs in patients diagnosed with CHF [28].

The endothelial nitric oxide synthase (eNOS) enzyme produces nitric oxide (NO). The endothelium becomes a net producer of reactive oxygen species, especially superoxide, when eNOS is uncoupled. The dysfunctional endothelium associated with type 2 DM produces reactive oxygen species [12]. Vascular smooth muscle proliferation is promoted by uric acid. It also upregulate the expression of platelet-derived growth factor and monocyte derived chemotactic protein 1 [29, 30]. This would facilitate the atherogenesis and its progression. It was demonstrated that there is a decreased in excretion of uric acid due to reduced effect of insulin, as a result of insulin resistance. [31, 32].

We also observed statistically highly significant positive correlation between serum triglyceride, total cholesterol and LDL cholesterol (table 5). But serum uric acid and serum HDL cholesterol are negatively correlated, which is statistically highly significant (table 5). Li Qin et al have demonstrated that higher the serum uric acid levels were associated with higher levels of triglyceride, total cholesterol, LDL cholesterol and uric acid. Demonstrating the strongest positive correlation between triglyceride, total cholesterol, LDL cholesterol and uric acid. They have also shown that higher uric acid levels were associated with lower HDL cholesterol level, indicating the negative correlation between them [33, 34].

Tavil Y et al had shown that individuals with hypertension and hyperuricemia had increased carotid intima media thickness compared to individuals with normal uric acid levels. They have also demonstrated a strong relationship between carotid intima media thickness measurement, serum uric acid levels and other major determinants of the atherosclerosis [35]. Goncalves et al. had shown that there is a significant increase in the concentration of serum uric acid in adolescents at an increased risk of coronary vascular disease compared to those with lower risk. Serum total cholesterol and triglyceride levels increased as the uric acid level increased. But HDL cholesterol level decreased with increase in serum uric acid level. They have also demonstrated that for each 1mg/L of serum uric acid increase there is a 4% increased odds of having high cardiovascular risk in both genders [36].

## CONCLUSION

From the present study it is concluded that there is a definite relationship between the activity of the purine catabolizing

enzyme adenosine deaminase and end product of purine catabolism uric acid. Study also indicated the relationship between the oxidative stress and the serum uric acid level, indicating that serum uric acid acts as pro-oxidant. Since increase in serum uric acid is associated with significant increase in serum total cholesterol, LDL cholesterol and serum triglyceride and decrease in HDL cholesterol. It indicates that serum uric acid might facilitate the process of atherogenesis and coronary vascular disease in type 2 diabetes mellitus.

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