

Is Serum Uric Acid an Added Risk Factor for Micro-Vascular Complications of Diabetes Mellitus? – A Prospective Study

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ABSTRACT

Introduction: Diabetes is the leading cause of adult blindness due to retinopathy, end stage renal disease due to nephropathy and foot ulcers and lower limb amputation due to neuropathy. Serum uric acid levels independently predict the development of micro vascular complications. In this study, we analyse the association of serum uric acid with the micro vascular complications of diabetes.

Material and methods: In this hospital based observational study, hundred diabetic patients were included; of which fifty had micro vascular complications, the remaining fifty had no complications. Blood investigations including fasting(FBS) and post prandial blood sugars(PPBS), glycosylated haemoglobin (HbA1C), and serum creatinine and serum uric acid were done in all patients. All the parameters were compared between the two groups.

Results: Females presented with significantly higher complications as compared to males. The mean age of the patients presented with and without complications was 56.4 ± 9.3 and 59.9 ± 10.3 respectively. HbA1C had a positive correlation with the serum uric acid (SUA) ($r=0.327$, $P = 0.001$). Mean uric acid levels were higher among patients with complications (5.96 ± 2.16) compared to patients without complications (4.95 ± 2.04) which was statistically significant (P value =0.021). Patients with nephropathy and neuropathy had significant elevation in serum uric acid levels than those without; however this significance was not noted in those with retinopathy.

Conclusion: Patients with micro vascular complications had higher levels of serum uric acid compared to those without complications. Also there was positive correlation between HbA1C and serum uric acid levels.

Keywords: Serum Uric Acid, Micro Vascular Complications, Diabetic Retinopathy, Diabetic Neuropathy, Diabetic Nephropathy, Glycosylated Haemoglobin.

INTRODUCTION

Diabetes mellitus is the most challenging health problem in this century. Diabetes is the leading cause of adult blindness due to retinopathy, end stage renal disease due to nephropathy and foot ulcers and lower limb amputation due to neuropathy.¹

Uric acid (UA) is primarily a purine metabolic waste product. About 70% of it gets excreted by the kidneys. Hyperuricemia has gained importance as many studies have reported that it not only has an important role in the development of metabolic syndrome but also micro vascular risk factor.²⁻⁵ Elevated serum uric acid is a feature of hyperinsulinemia or insulin resistance.⁶

Many studies have suggested that inflammation and oxidative stress results from the metabolism of uric acid, leading to vascular injury. The rate limiting step of uric acid production is an enzymatic reaction of the xanthine oxidase (XO) enzyme that oxidises hypoxanthine – xanthine into uric acid. UA synthesis is accompanied by the generation of reactive oxygen species (ROS). XO in the vascular endothelium is associated with ischemia reperfusion injury. It has also been suggested that XO inhibitors improve endothelium-dependent vascular relaxation in blood vessels of hyperlipidemic rabbits.⁷ XO as the source of ROS in ischemia/reperfusion injury has been discovered 30 years ago.^{8,9}

In recent years there has been a debate regarding the association of hyperuricemia with diabetic complications. If this association is conclusively established, therapeutic interventions aiming to reduce uric acid synthesis might help to retard the progression of micro vascular complications of diabetes. Hence this study was conducted aiming to show the association of uric acid levels with diabetic complications.

MATERIAL AND METHODS

This is a hospital based observational study conducted in a tertiary care centre at Coimbatore from April 2015 to April 2016. Patients with Type 2 Diabetes Mellitus of the age group of 20 to 80 years admitted in the medical wards were included in the study. Patients admitted with acute complications like diabetic ketoacidosis and hyperosmolar coma and patients with gestational diabetes were excluded

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from the study. Informed consent was obtained from the patients. Before commencement of the study, approval was obtained from the Institutional Ethics Committee.

A detailed history and physical examination was done. Baseline investigations including fasting and post prandial blood sugars, HbA1c and serum creatinine were done. The diagnosis of diabetes was based on American Diabetic Association criteria. The presence of micro vascular complications was established by fundus examination by an ophthalmologist to assess retinopathy, Urine spot Protein/creatinine ratio (PCR) to assess nephropathy and nylon monofilament test to assess neuropathy. Serum uric acid was done in all patients. Hyperuricemia was defined as serum uric acid greater than 7 mg/dl.

The study population was divided into two groups: group I patients with diabetes and without any vascular complications; group II patients with diabetes and any one or more of vascular complications.

STATISTICAL ANALYSIS

Descriptive statistics were reported as mean and standard deviation; categorical variables were presented with number and percentages. Chi-square test was used to test the association between the variables. Independent t test was used to compare the blood parameters between diabetes with complications and without complications. P value less than 0.05 was considered statistically significant.

RESULTS

Among the 100 diabetic patients studied, there were 62 males and 28 females; 50 had presented with complications and 50 had no complications in the study group. Out of 50 with diabetes related micro-vascular complications, there were 24 males and 26 females. There was a significant difference in the presence of complications and sex; Females presented with significantly higher complications as compared to males (P= 0.004). The mean age of the patients presented with and without complications was 56.4 ± 9.3 and 59.9 ±

Microvascular complication		Serum uric acid level (mg/dL)	P value
Diabetic retinopathy	Present	5.97 ± 2.14	0.97
	Absent	5.95 ± 2.20	
Diabetic neuropathy	Present	6.56 ± 2.30	0.004
	Absent	4.73 ± 1.10	
Diabetic nephropathy	Present	7.05 ± 2.13	0.006
	Absent	5.33 ± 1.94	

Table-3: Serum uric acid levels in micro vascular complications

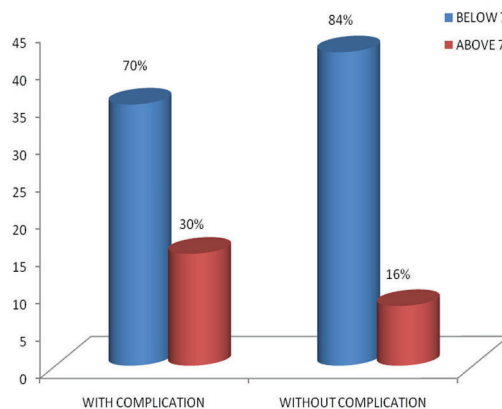


Figure-1: Frequency distribution of serum uric acid(mg/dl) in Diabetes mellitus with and without complications.

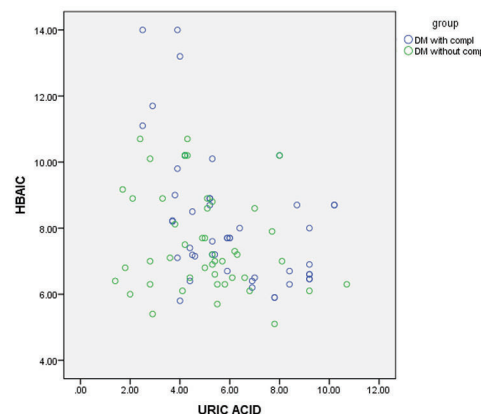


Figure-2: Co-relation of HbA1C with the Serum uric acid levels

	Present (%)	Absent (%)
Diabetic Retinopathy	19(38)	31(62)
Diabetic Neuropathy	16(32)	34(68)
Diabetic Nephropathy	19(38)	31(62)

Table-1: Distribution of Micro vascular complications

	Diabetes with complications	Diabetes without complications	P value
Sex			
Male	24 (39)	38 (61)	0.004*
Female	26 (68)	12 (32)	
Age	56.4 ± 9.3	59.9 ± 10.3	0.084
HbA1c	8.28 ± 2.00	7.55 ± 1.50	0.044*
FBS	137.8 ± 44.5	133.5 ± 46.6	0.644
PPBS	210.1 ± 60.3	187.7 ± 52.7	0.028*
Uric acid	5.96 ± 2.16	4.95 ± 2.04	0.021*

Table-2: Comparison of age, sex, HbA1c and uric acid levels in diabetic patients with and without micro-vascular complications.

10.3 years respectively; although not significant (P= 0.084), patients who presented with complications were younger than those without complications.

The distribution of micro vascular complications is shown in Table 1. Both retinopathy and nephropathy were equally prevalent and slightly more than neuropathy. Hyperuricemia (Serum uric acid >7 mg/dl) was more prevalent among patients with complications (30%) compared to patients without complications (Fig 1). As shown in Table 2, mean uric acid levels were higher among patients with complications (5.96 ± 2.16 mg/dl) compared to patients without complications (4.95 ± 2.04 mg/dl) which was statistically significant (P value = 0.021). HbA1C had a positive correlation with the serum uric acid levels (r=0.327, P = 0.001) as shown in Fig 2.

Table 3 represents the prevalence of hyperuricemia in patients with retinopathy, neuropathy and nephropathy, as compared to those without these complications. It can be seen that nephropathy and neuropathy patients had significantly more hyperuricemia than those without. However there was no statistically significant difference seen in the group with retinopathy. This suggests that high uric acid levels are associated with microangiopathies in Type 2 Diabetes.

DISCUSSION

Increasing amounts of uric acid in the serum causes Gout and this is the most significant cause of lifestyle-related disorder. Uric acid is primarily a product of purine metabolism. Serum uric acid (UA) levels are determined by a balance between Uric acid production and excretion. The rate-limiting step of UA production is an enzymatic reaction of the xanthine dehydrogenase/xanthine oxidase (XDH/XO) enzyme that oxidizes hypoxanthine-xanthine into UA. It is expressed in the liver and small intestine of XDH/XO-rich parenchyma cells¹⁰ and is thought to be the major source for UA. The enzyme is also expressed in adipose tissue, the vascular endothelium, and macrophages, all of which are implicated in lifestyle-related diseases.¹¹ The UA production rate is based on the amount of substrate and/or XO activity. Since the generation of reactive oxygen species (ROS) depends on XO activity, XO is one of the major sources of oxidative stress in cells along with nicotinamide adenine dinucleotide phosphate oxidase, myeloperoxidase, lipoxygenase, and nitric oxide synthase.¹²

The kidney is an important regulator of circulating UA levels and is responsible for 60%-70% of total body UA excretion.¹³ The remaining UA is secreted into the intestine, followed by bacterial uricolysis.¹³ UA excretion in the kidney consists of urate secretion and reabsorption, and earlier research suggests the involvement of hyperfiltration.⁶ Ninety percent of UA filtered by the kidney is reabsorbed.¹³

In patients with diabetes, the SUA level is low due to increased urate clearance.¹⁴ In these patients, hypouricemia is associated with glycosuria¹⁵, decreased metabolic control, hyperfiltration, and a late onset of disease, while elevated SUA is a feature of hyperinsulinemia or insulin resistance.⁶ Development of vascular complications was predicted independently by serum uric acid.¹⁶ In a study conducted by Poonam Agrawal et al., it was concluded that the Uric acid levels are raised in patients with diabetic retinopathy when compared to those without retinopathy.¹⁷ A study conducted by Ching-Chao Liang et al., concluded that there were increased serum uric acid levels which correlated with the severity of diabetic Retinopathy in patients with type 2 DM.¹⁸ Vitreous UA and glucose concentrations were higher in proliferative than in non-proliferative DR. Focal UA production in the vitreous is thought to be involved in the pathogenesis and progression of DR.¹⁹

UA is lowered in Diabetes mellitus (DM) due to hyperfiltration²⁰, but decreased UA excretion during renal dysfunction raises SUA levels. Nazir Shah et al.²¹ conducted a study in 2013 in 163 patients of diabetes mellitus (type 2)

and proposed that elevation in the levels of uric acid was more in the diabetic patients with nephropathy (50%). In a study conducted in 60 diabetic patients by Nasri et al.²², it was proved that there was a significant association between diabetic nephropathy and the levels of uric acid in the patient's serum. Petter Bjornstadet al²³ stated that there is a relation between the uric acid level elevation and development of diabetic nephropathy. Su-Mi Kim et al.²⁴ demonstrated that high UA contributes to the development of nephropathy in diabetic patients.

Several recent studies have been investigating therapeutic interventions to delay nephropathy progression.²⁵⁻²⁷ Allopurinol therapy significantly decreases serum UA levels in hyperuricemic patients with mild to moderate CKD. Its use is safe and has been shown to help preserve kidney function when used for a duration of 12 months.²⁵ Febuxostat has a higher renoprotective effect than allopurinol, inhibits oxidative stress, has anti-atherogenic activity, reduces blood pressure, and decreases pulse wave velocity and left ventricular mass index, most likely due to a strong serum UA lowering effect.²⁷ In animal diabetic nephropathy model, allopurinol attenuated transforming growth factor-beta1-induced Smad pathway activation in tubular cells.²⁸

The prevalence of diabetic peripheral neuropathy shows a significant correlation with increased UA levels.²⁹ Several studies demonstrated that, when controlled for confounding factors such as age, gender, BMI, renal function, and/or diabetic duration, Serum UA levels were high in patients with diabetic polyneuropathy and sudomotor dysfunction.^{30,32}

The pathophysiology of diabetic neuropathy is not completely understood, and multiple metabolic imbalances underlie the development of diabetic neuropathy.³³ Hyperglycemia, dyslipidemia, and cardiovascular dysfunction are all independent risk factors for neuropathy. Probable etiologic factors include the polyol pathway, non-enzymatic glycation, free radicals, oxidative stress, and inflammation. Oxidative stress and inflammation are involved in XDH/XO activity. It is therefore speculated that UA generation by XDH/XO plays a role in diabetic neuropathy.

In a study conducted by Yili Xu et al., it was concluded that the patients with vascular complications had increased serum uric acid levels. He also said that this could be an independent predictor of vascular complications.³⁴ We found similar results in our study.

CONCLUSION

Diabetic patients with micro vascular complications have higher serum uric acid levels than those without complications. Also there was positive correlation between HbA1C and serum uric acid levels.

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