

Uric acid in Type 2 Diabetes mellitus with nephropathy

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Abstract

Introduction: Uric acid is an important antioxidant that contributes for around 60% of free radical scavenging capacity of serum. Its role has been controversial in type 2 diabetes mellitus. Earlier studies have reported that renal disease leads to elevation of uric acid in DM, but recently high uric acid levels are reported to be risk factor for the development of diabetes mellitus. Aim of our study is to compare uric acid in type 2 DM with renal disease with non-diabetics and also to compare its levels among patients in different stages of diabetic nephropathy.

Methodology: The case control study was conducted in medical college hospital in coastal Karnataka. Data of serum uric acid, renal profile and demographic profiles of 89 type 2 diabetes mellitus patients was collected from the clinical biochemistry laboratory in the year 2016. Data of 80 non-diabetic controls was taken. Transasia XL-640 was used for the estimation. Estimated GFR (eGFR) was calculated using MDRD formula.

Results: We found an elevation in uric acid and creatinine levels, extremely significantly lower eGFR in diabetics (P = 0.0195, P=0.0078 and P =0.0001 respectively). Odd's ratio was 3.128 between uric acid and diabetic nephropathy. A highly significant (P < 0.0016) differences was observed in uric acid levels among patients of different stages of diabetic nephropathy.

Conclusion: Hyperuricemia was found in diabetic nephropathy patients. There was a significant difference in uric acid was observed among different stages of nephropathy. However causal relationship is inclusive. Prospective studies need to be designed with a serial monitoring of uric acid, GFR and microalbuminuria in diabetics till the development of nephropathy to establish which the cause is and which is effect among these two factors (uric acid and diabetic nephropathy).

Keywords: Uric acid, eGFR, Diabetes mellitus, Nephropathy

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Introduction

Uric acid is the end product of purine catabolism, formed by the action of the enzyme, xanthine oxidase. It has a physiological free radical scavenging property^[1]. It is an important anti-oxidant at its normal reference interval, which contributes significantly to total anti-oxidant capacity of serum. It acts paradoxically at higher levels, i.e. when above 6 mg/dl in females and more than 6.5–7 mg/dl in men, uric acid acts like pro-oxidant. It has therapeutic role as anti-oxidant, but can be a marker of oxidative stress as well.

As uric acid is a known anti-oxidant, it has a beneficial role in diseases^[2,3]. But it has been found that elevated levels of uric acid are associated with high risks of cerebrovascular complication of type 2 diabetes mellitus^[4]. Studies have reported a strong association between elevated uric acid levels and obesity, metabolic syndrome, diabetes mellitus, hypertension, cardiovascular and renal disorders^[5].

Decline in uric acid levels have been reported in type 2DM in several studies^[6,7]. However contradictory

reports are also available with elevated uric acid levels^[8]. There are a few reports available which study the role of uric acid in diabetic nephropathy.

Objectives of our study is to compare uric acid levels in type 2 DM patients with renal disease as compared to non-diabetic controls. We also aim to compare its levels among patients in different stages of diabetic nephropathy.

Material and Methods

The case control study was conducted in medical college hospital in coastal Karnataka. The approval of institutional ethics committee was sought prior to the study. Data of serum uric acid, renal profile and demographic profiles of 89 type 2 diabetes mellitus patients who had attended the teaching hospital was collected from clinical biochemistry laboratory, from January 2015 to May 2016. Diabetes mellitus (DM) is diagnosed as per American Diabetic Association guidelines 2016^[9]. Data of 80 non-diabetic controls was taken. Patient group consisted of 34% females and 66% males whereas control group consisted of 42% females and 58% males. Patients had a mean age of 52.84±2.04 years and controls 49.21±2.47 years, expressed as mean±SEM.

Exclusion criteria: Liver disorders, Alcoholics, Smokers, Gout cases.

Data was obtained from our clinical biochemistry laboratory attached to the 400 bedded teaching hospital. Transasia XL-640 was used to estimate random blood sugar, uric acid, urea and creatinine.

Estimated GFR (eGFR) was calculated using MDRD formula, as follows:

$$eGFR = 186 \times [\text{serum creatinine}]^{-1.154} \times [\text{Age}]^{-0.203} \times 0.742$$

eGFR was taken as a tool to diagnose renal disease associated with diabetes mellitus. Patients were graded in to different stages of chronic renal failure based on eGFR values.

Statistical Analysis

Statistical analysis was carried out by using Graph pad InStat software. Mann Whitney U test was used to compare the continuous variables between the groups. Kruskal Wallis test was used to compare uric acid and bilirubin levels between different stages of diabetic nephropathy, followed by a post test, Dunn's multiple comparison test. Correlation studies were done between uric acid and creatinine, uric acid and eGFR. Odd's ratio was calculated to find the association between elevated uric acid and renal disorder of diabetes mellitus.

Results

We found an elevation in uric acid and creatinine levels, extremely significantly lower eGFR in diabetics as represented in Table 1.

Table 1: Comparison of parameters between type 2 DM with non-diabetic controls

Parameter (mg/dl)	Type 2 DM (n=89) Mean±SEM	Controls (n=80) Mean±SEM	P value
Random Blood Sugar	213.38±10.15	102.13±1.77	<0.0001**
Uric acid	7.61±0.48	6.81 ±0.89	0.0195*
Urea	42.1±5.4	28.96±3.4	0.02*
Creatinine	1.52±0.16	1.14±0.2	0.0078**
eGFR	68.32±3.99	95.62±5.79	0.0001**

*significant

**extremely significant

No significant gender difference was seen in uric acid levels among diabetic patients.

We found a highly significant (**P < 0.0016**) differences in uric acid levels among patients of different stages of diabetic nephropathy as shown in Table 2. Among all the groups, only group V had significantly (P<0.01) high uric acid levels as compared to the other groups.

Table 2: Comparison of uric acid levels in different stages of diabetic nephropathy

Stage	Description	eGFR	No. of DN patients	Uric acid Mean ± SEM (Mg/dl)
I	Normal/elevated GFR	≥90	17	6.04 ± 1.1
II	Mildly ↓ GFR	60-89	25	7.85±0.52
III	Moderately ↓ GFR	30-59	15	7.03±0.78
IV	Severely ↓ GFR	15-29	15	5.14±0.89
V	Kidney failure	<15	15	13.62±1.75

An insignificant negative correlation was found between uric acid and eGFR. But uric acid and creatinine showed a significant (P=0.0023) positive correlation.

Odd's ratio was calculated to find the association between uric acid and diabetic nephropathy, which was 3.128.

Discussion

We have found an elevation in uric acid levels in diabetic patients with nephropathy. Similar results were obtained by Ansari et al^[10]. Yan et al reports that increased uric acid levels is a risk factor for the

development of diabetic nephropathy^[11]. He also opines that uric acid is independently associated with diabetic kidney disease. But controversial reports exist, which suggest that low uric acid levels were implicated in the development of diabetic nephropathy. Cause and effect relationship between uric acid and nephropathy seem to be inter-changeable^[12]. Even though old reports suggest that uric acid is not associated with chronic kidney disease, now it has been suggested to be independently associated with CKD^[13-16].

It has been well accepted that uric acid increases as a consequence of kidney disease. Diminished GFR, tubular excretion and increased reabsorption of uric

acid that occur in renal insufficiency elevate uric acid levels^[17]. This explains elevated uric acid levels seen in our patients of diabetic nephropathy with compromised glomerular functions, as evident from eGFR values. Hyperinsulinemia that occur in insulin resistant state decrease renal excretion of uric acid, contributing to the elevated levels^[18,19].

As there is an elevation in uric acid levels, its beneficial role as antioxidant might not be expected in our patients. Popular anti-oxidant and pro-oxidant shuttle of uric acid explains that at higher levels, uric acid is paradoxically a pro-oxidant. Diabetes mellitus is a known oxidative stress state. Hyperglycemia induces free radical production through various mechanisms like, non-enzymatic glycosylation, glucose auto-oxidation and polyol pathways^[20]. The oxidative stress will be added upon by elevated uric acid. It has been also been argued that high uric acid is a compensatory elevation to combat oxidative stress^[21]. We can justify our result in this way as well.

Odd's ratio suggests that risk of diabetic nephropathy in elevated uric acid levels is three times as compared to controls.

We have certain limitations in our study design. As it is a retrospective study, we could not get data on BMI, blood pressure and several confounding factors.

Conclusions

We found an elevated uric acid levels in type 2 DM as compared to non-diabetics. There was significant difference in uric acid levels among patients of different stages of diabetic nephropathy and also a significantly high risk factor was established between the two. Prospective studies need to be designed with a serial monitoring of uric acid, GFR and microalbuminuria in diabetics till the development of nephropathy to establish which is the cause and which is effect among these two factors (uric acid and diabetic nephropathy).

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Conflicts of interest: None

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