


## Original Research Article

# The association of Hyperuricemia with progressive Diabetic Nephropathy in patients with Type II Diabetes mellitus

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## Abstract

**Background:** Diabetic nephropathy (DN) is a progressive kidney disease caused by the damage to the capillaries in the kidneys' glomeruli. Uric acid is the end product of purine catabolism and is excreted in the urine. Uric acid can serve as an inflammatory factor and is attributed to bring about endothelial dysfunction. The causal role of uric acid in the development of diabetic nephropathy is unknown. This study aimed to evaluate the association of serum uric acid level and low levels of estimated glomerular filtration rate (eGFR) which is an indicator of renal disease progression in patients with Type II (T2D) diabetes mellitus.

**Methods:** A cross sectional analytical observational study was conducted on 150 patients with T2D. Since the study was an observational study it involved no medical intervention. Venous blood samples were obtained in fasting state for determination of random blood sugar, serum creatinine, uric acid, (HbA1c) hemoglobin A1c (reference range 3.8-5.5%); and blood urea nitrogen (BUN). Using MDRD formula eGFR was calculated as =  $186 \times [\text{serum creatinine}]^{-1.154} \times [\text{Age}]^{-0.203} \times 0.742$ . The association of renal disease with T2D and the grading of the patients into different stages of renal failure was analysed by eGFR values.

**Results:** Hundred and fifty diagnosed cases of T2D were included in the present study. The mean age of the study population was  $63 \pm 12.2$ . No significant age and gender related variation in serum uric acid level was noted in the study population. The prevalence of Hyperuricemia was 19.33%. The mean BMI was significantly higher among hyperuricemic subjects in comparison with normouricemic patients. Hyperuricemia was evident in 75% (n=18) of the subjects with diabetic nephropathy. Stage IV and stage V patients were associated with significantly very high ( $p < 0.01$ ) uric acid levels.

**Conclusions:** Serum uric acid has a significant positive association with diabetic nephropathy ultimately resulting in end stage renal disease. Treatment intervention is out of the scope of this study.

## Key words

End stage renal disease, Type II diabetes mellitus, Proteinuria.

## Introduction

Diabetes mellitus (DM) is a chronic disease that occurs either when the pancreas does not produce enough insulin or when the body cannot effectively use the insulin it produces. The prevalence of diabetes is swiftly increasing over the globe at an alarming rate. 69 million people in India are estimated to be diabetic, thus making India the second diabetic capital after China [1].

DN is classically defined by the presence of proteinuria and occurs in a significant percent of patients with type 1 as well as type 2 DM [2]. It can be ascribed to glycosylation of circulating and intra-renal proteins and abnormal intra-renal hemodynamics. Hyperglycemia may result in an increase in mesangial cell glucose concentration and glycation of matrix proteins, which in turn leads to increased matrix production and mesangial cell apoptosis [3].

Hyperuricemia is defined by serum uric acid concentration greater than 7 mg/dl in men and 6 mg/dl in women [4]. Various studies have shown that hyperuricemia can cause various damages like the arteriopathy of preglomerular vessels, impaired auto-regulation, glomerular hypertension, endothelial dysfunction and microvascular disease [5-8]. Uric acid serves as an independent biomarker of hypertension, diabetes mellitus, obesity, and renal disorders [9-11].

Persons who have diabetes in addition to chronic kidney disease have a ~50% higher risk of end stage renal disease (ESRD) and death than those at a similar level of estimated glomerular filtration rate [12]. Clinical investigations have demonstrated improvement in endothelial dysfunction upon lowering the uric acid with allopurinol in hyperuricemic, hypertensive and

type 2 diabetic patients [13, 14]. The progression of kidney damage can be partially halted but is irreversible and cannot be completely halted or reversed.

## Materials and methods

A cross sectional analytical observational study was conducted in the department of medicine of a tertiary care hospital between December 2015 and March 2017 in Hyderabad, Telangana. Hundred and fifty subjects with T2D were included in the present study. Patients with history of hypothyroidism, alcoholism, urinary tract infections, glomerulonephritis, myeloproliferative disorders and gout or on drugs capable of inducing Hyperuricemia were excluded from the study. Written informed consent was obtained from all subjects included in our study.

Patient population included both males and females above the age of 18 years. Demographic characteristics collected included age, gender, body weight, height, and duration of diabetes. All patients underwent a thorough clinical examination followed by investigations for urine routine examination, macroalbumin, blood urea nitrogen, random blood sugar, Complete blood count, serum uric acid, HbA1c and renal function tests including creatinine clearance (GFR). MDRD formula was applied for the calculation of eGFR:

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

The association of renal disease with T2D and the grading of the patients into different stages of renal failure were based on the eGFR values.

Hyperuricemia was defined as serum uric acid  $\geq$  7 mg/dl in males and  $\geq$  6.5mg/dl in females. T2D subjects with proteinuria and eGFR  $<$  90 were

labeled as DN patients. Statistical analysis of the data was performed by SPSS statistical software (version 22) and statistical significance was calculated by percentage analysis and p-value interpretation. *P* value > 0.05 was considered insignificant and < 0.05 was regarded as significant.

## Results

Hundred and fifty (150) patients diagnosed with type 2 diabetes mellitus were enrolled as cases for the study. Fifty two percent were males

(n=78) and forty eight percent (n=72) were females. The age of the population under study ranged from 40 years to 92 years. The mean age of presentation was  $64 \pm 12.2$ . There was no significant variation in the age and gender between normouricemic and hyperuricemic patients as documented in table-1. The duration of diabetes did not show any association with the serum uric acid levels. The mean BMI of the population under study was found to be  $28 \pm 6.45$  (**Table - 1**).

**Table - 1:** Comparative analysis of variables between normouricemic and hyperuricemic patients.

Variable analysed	Normouricemic patients (n=121)	Hyperuricemic patients (n=29)	p value
Age (years)	$63 \pm 11.8$	$65 \pm 12.6$	0.419
Male : Female	61:60	17:12	-
BMI (kg/m <sup>2</sup> )	$26.2 \pm 6.7$	$29.8 \pm 6.2$	0.0093
Duration of T2D (mean)	6	6.2	0.335
FBS (mg/dl)	148	162	0.0001

**Table - 2:** Comparison of laboratory parameters.

Laboratory findings	Normouricemic patients (n=121)	Hyperuricemic patients (n=29)	p value
serum creatinine	$1.02 \pm 0.04$	$1.48 \pm 0.12$	<0.0001
blood urea nitrogen	$27.38 \pm 3.2$	$44.06 \pm 4.8$	<0.0001
serum uric acid	$6.59 \pm 1.3$	$7.4 \pm 1.6$	0.0046
eGFR	$64.56 \pm 2.86$	$96.24 \pm 3.57$	<0.0001

**Table - 3:** Comparison of uric acid levels in different stages of diabetic nephropathy.

Stage	Description	eGFR	No of patients	Mean uric acid (mg/dl) $\pm$ SD
I	Normal/elevated GFR	$\geq 90$	5	$7.43 \pm 0.52$
II	Mildly reduced GFR	60-89	14	$7.56 \pm 0.6$
III	Moderately reduced GFR	30-59	7	$7.06 \pm 1.3$
IV	Severely reduced GFR	15-29	2	$8.34 \pm 0.8$
V	Kidney Failure	<15	1	14.84

The overall prevalence of Hyperuricemia was 19.33% (n=29) and the mean serum uric acid level was  $7.4 \pm 1.6$  (**Table - 2**). Amongst the hyperuricemic patients 58.62% (n=17) were males and 41.38% (n=12) were females. There was no significant variation in the serum uric acid levels between female and male hyperuricemic subjects. No significant difference

was observed in the glycosylated hemoglobin and renal functions between males and females (*P* > 0.05).

Diabetic nephropathy was evident in 16% (n=24) of the population under study. Hyperuricemia was evident in 75% (n=18) of the population with diabetic nephropathy. There was no

evidence of diabetic nephropathy among 37.93% (n=11) of the hyperuricemic subjects. There was a definitive positive correlation between serum uric acid and end stage renal disease ( $P < 0.001$ ) as depicted in **Table - 3**.

## Discussion

Diabetes is a leading cause of end stage renal disease in most parts of the world [15]. DN is an irreversible and progressive disease with complex etiology. The pathogenesis of DN is attributed to mesangial cell apoptosis, inflammatory cytokines, glomerular hypertension and hyperfiltration [3, 16]. The antioxidant property of Uric acid is attributed to its physiological free radical scavenging property [17]. However at levels higher than the reference range, uric acid paradoxically functions as a pro-oxidant and serves as a marker of oxidative stress.

This study showed an elevation in uric acid levels in 19.33% of diabetic patients in comparison to studies, which show 3-13% association of hyperuricemia with general population [18]. In the present study 75% of the patients with diabetic nephropathy were found to have hyperuricemia. Studies by Ansari, et al. [19]; Adiga, et al. [20]; Behradmanesh, et al. [21] and Zoppini, et al. [22] also showed a positive correlation between hyperuricemia and diabetic nephropathy.

A study by Behradmanesh, et al. [21] proves that serum uric acid has a pathological role in the development of DN in T2D. However the most convincing hypothesis is that higher levels of serum insulin due to insulin resistance decrease the uric acid clearance by the kidneys resulting in hyperuricemia [23].

The study also found well-established association of hyperuricemia with obesity and chronic renal failure. Several documented studies prove that hyperuricemia may have a pathogenic role in development and progression of chronic renal failure [24, 25].

Xanthine oxidase inhibitors such as allopurinol have been tried for slowing the progression of renal failure in diabetic patients [26]. The mechanism of beneficial action is by the prevention of uric acid-induced renal inflammation. However the use of allopurinol only partially halts the disease progression, as DN is an irreversible and progressive disease. The applicability of allopurinol in hyperuricemic patients is outside the scope of the present study.

## Conclusion

Hyperuricemia finds a fairly common association with T2D. Hyperuricemic patients show a stronger predilection to progress towards DN and end stage renal disease. Further studies are required to assess the applicability of xanthine oxidase inhibitors in the management of T2D patients with Hyperuricemia.

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