

A Study of Association of Hyperuricemia with Progressive Diabetic Nephropathy

NS Neki*, Himanshu Gupta**, Ramraj MEena**, Tamil Mani**

Department of Medicine, Govt. Medical College and Guru Nanak Dev Hospital, Amritsar, India.

Abstract: Diabetes mellitus is the most common endocrinological disorder. It affects almost all the organs of the body. Diabetic nephropathy is a major complication of diabetes and hyperuricemia is a common finding in diabetic nephropathy. This study attempts to find precise relationship of hyperuricemia with progression of nephropathy in patients of diabetes mellitus. Four hundred (400) known diabetics with or without various degree of renal dysfunction were enrolled for the study. Patients were grouped on the basis of their renal albumin excretion rate. Serum levels of creatinine and uric acid were measured along with the urinary albumin and uric acid using standard colorimetric assay. Statistical analysis was done by standard statistical methods. Serum uric acid shows highly significant positive correlation ($p < 0.001$) with diabetic nephropathy, especially those with macroalbuminuria; levels systolic blood pressure and diastolic blood pressure levels also had positive correlation with uric acid values in diabetic patients with nephropathy. **Conclusion:** Serum uric acid positively correlates with the progressive diabetic nephropathy.

INTRODUCTION

Diabetes mellitus is a heterogeneous group of metabolic disorders characterized by chronic hyperglycemia with disturbances of carbohydrate, fat and protein metabolism resulting from defects in insulin secretion, insulin action or both¹. The metabolic changes associated with diabetes mellitus further lead to pathophysiological changes in multiple organ system which are responsible for various acute and long term complications of diabetes mellitus. Among the microvascular complications, kidney is the organ which is most seriously and commonly affected¹. The natural history in the development of diabetic nephropathy (DN) includes glomerular sclerosis, intra-glomerular hypertension, hyperfiltration, intermittent microalbuminuria and finally frank proteinuria^{2,3}. If microalbuminuria stage remains unchecked and uncontrolled, it culminates in end stage renal disease^{4,5}. Microalbuminuria means significant increase in albumin excretion rate (AER). It is defined as 30-300 mg albumin in a 24-hr urine collection or 30-300 ug albumin/mg creatinine in a spot collection (preferred method)⁶. Microalbuminuria is the first manifestation of injury to the glomerular filtration barrier and predicts the development of overt nephropathy⁷. Elevated serum uric acid is frequently associated with hypertension, cardiovascular and renal disorder. Various studies find uric acid as a predictor of hypertension, cardiovascular and renal disorder despite controlling associated risk factors^{8,9,10,11}.

Several studies indicate that uric acid has some role in type 2 diabetes mellitus, since the hyperglycemia was shown to correlate with the development of renal dysfunction in type 2 diabetes^{12,13}. The observed hyperuricemia in DN could be explained by several mechanisms that may operate singly or in combination. There are two possibilities of increase in blood uric acid levels. It could be increased production or decreased excretion of uric acid. Higher serum uric acid in DN is most likely due to abnormality in uric acid excretion. Hyperuricemia may result from increased net tubular reabsorption.¹⁴

Although several experimental studies suggest that uric acid may act as risk factor for development of renal dysfunction, it remains unclear if uric acid is a risk factor for progression in subjects with established renal disease¹⁵. Therefore, the present study was designed to evaluate the influence of hyperglycemia and hypertension in the development of DN and to define relationship of uric acid levels in the progression of DN. The aim was to study the association between hyperuricemia and progressive diabetic nephropathy in diabetic patients.

MATERIAL & METHODS

The present study was conducted on 400 known diabetic subjects of both sex in age range of 25 to 85 yrs. This was a randomized open study

Correspondence: Prof. N.S.Neki, Deptt. of Medicine, Govt. Medical College/ Guru Nanak Dev Hospital, Amritsar-143001, Punjab, India
e-mail : drnsneki_123@yahoo.com

which was conducted over indoor & outdoor patients of Guru Nanak Dev Hospital attached to Government Medical College, Amritsar. Patients were grouped according to their renal albumin excretion rate (RAER) into 3 groups. In group A 200 diabetic patients without nephropathy and in group B 100 patients of diabetes mellitus with nephropathy having microalbuminuria while in group C 100 diabetic patients with nephropathy with macroalbuminuria were recruited. Patients having past history and blood glucose level suggestive of diabetes without any renal involvement were included in this group (group A). Patients giving history suggestive of diabetes and high fasting blood glucose with duration of diabetes more than five years with involvement of kidneys, were included.

Patients with any evidence of renal failure from any other cause, nephrotic syndrome, urinary tract infection, urolithiasis, acute illness and/or any other renal disorder, physiological and abnormal stress, exercise, high altitude hypoxia, myocardial ischaemia and ketonuria, all were excluded from the study, as these can cause microalbuminuria.

A written informed consent was obtained. A fasting blood sample was collected from all the patients for the determination of blood urea, serum creatinine, serum uric acid. 24 hour urinary sample was collected for measurement of 24 hr urinary albumin while fresh mid stream morning urinary sample was obtained to measure urinary uric acid level. Serum uric acid levels were compared in all the groups. These tests were done by using standard procedures.

RESULTS

Disease characteristics of the three (3) groups alongwith the number of patients studied is given in table 1.

Table 1: Showing allocation of patients in different group

Group	Disease characteristic	No. of Patients
A	Diabetic without Nephropathy	200
B	Diabetic Nephropathy with Microalbuminuria	100
C	Diabetic Nephropathy with Macroalbuminuria	100

In our study it was observed that, values of BU and serum creatinine gradually increased as the proteinuria progressed. Mean BU was 27.21% in group-A, 38.34mg% in group-B, 94.98mg% in group-C ($p < 0.05$). Similarly SC was 0.9mg% in group-A, 1.44mg% in group-B and 5.3mg% in group-C. ($p < 0.05$).

Table 2: Blood pressure and laboratory parameter of the various groups

Group	Systolic BP Mean \pm SD	Diastolic BP Mean \pm SD	Proteinuria Mean \pm SD	S. Uric acid Mean \pm SD	U. Uric acid Mean \pm SD
A	134.26 \pm 11.56	83.02 \pm 7.65	0.00 \pm 0.00	3.80 \pm 0.31	423.99 \pm 18.17
B	144.60 \pm 23.59	85.84 \pm 9.01	190.31 \pm 84.22	5.20 \pm 0.63	282.31 \pm 18.69
C	162.70 \pm 22.20	90.72 \pm 9.16	565.03 \pm 169.20	7.10 \pm 0.79	204.26 \pm 16.77
B+C	153.65 \pm 24.58	88.28 \pm 9.39	377.67 \pm 230.33	6.15 \pm 1.19	243.28 \pm 42.95

It was also observed that with the progression of proteinuria, SUA progressed as well as evident by values of mean SUA (mg%) from 3.2 in group-A to 5.1 in group-B to 7.2 in group-C ($p < 0.05$) whereas level of urinary uric acid reciprocally decreased as the values of SUA rose. Mean UUA in group-A was 423, in group-B 282 & in group-C 204 ($p < 0.05$).

Table 3: Serum and urine uric acid levels of different groups

Group	Age Mean \pm SD	Blood Urea Mean \pm SD	S. Creatinine Mean \pm SD	S. Uric acid Mean \pm SD	U. Uric acid Mean \pm SD
A	54.89 \pm 10.67	27.21 \pm 4.87	0.90 \pm 0.147	3.80 \pm 0.31	423.99 \pm 18.17
B	57.07 \pm 10.67	38.34 \pm 15.18	1.44 \pm 0.850	5.20 \pm 0.63	282.31 \pm 18.69
C	57.48 \pm 10.31	94.98 \pm 34.11	5.3 \pm 2.77	7.10 \pm 0.79	204.26 \pm 16.77
B+C	57.28 \pm 10.46	66.66 \pm 38.72	3.37 \pm 2.81	6.15 \pm 1.19	243.28 \pm 42.95

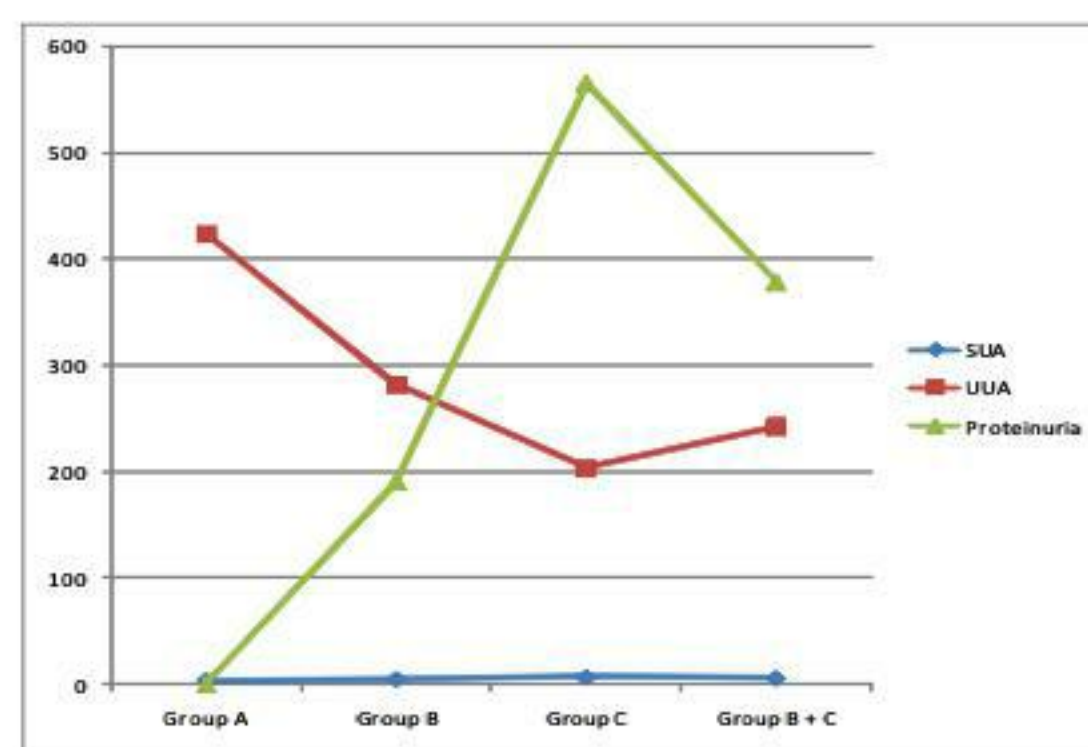


Figure 1: Showing progressive increase in Serum uric acid and Progressive decrease in urinary uric acid and increasing proteinuria in all groups

DISCUSSION

The present study was conducted to find the association of progressive diabetic nephropathy with serum uric acid level in type 2 diabetes mellitus. Group A involved 200 patients with type 2 diabetes mellitus without nephropathy and group B consisted of 100 patients of diabetic nephropathy with microalbuminuria and group C included 100 patients of diabetic nephropathy with macroalbuminuria

It was found that blood urea & serum creatinine of patients in group A was less than that of group B and group B levels were less than that of group C. Comparison of BU & serum creatinine in all groups is statistically highly significant ($p < 0.001$). The results of the present study are in concordance with the study done by Bhagwat and Mane¹⁴.

This study shows that mean serum uric acid of patients in group A, group B and group C were high & the difference in the values of serum uric acid amongst all groups was statistically highly significant ($p < 0.001$). The serum uric acid levels in diabetics without nephropathy were $3.12 \text{ mg\%} \pm 2.10$ and that of patients with microalbuminuria were 5.38 ± 2.12 and in patients with macroalbuminuria group was $6.80 \text{ mg\%} \pm 3.43$ and these results are in agreement with that of Bhagwat and Mane¹⁴.

Regarding urinary uric acid (UUA) levels in patients of group A, group B & group C they were found to be highly significant ($p < 0.001$). These results were comparable with the study conducted by Bhagwat and Mane¹⁴ in which urinary uric acid was $303.22 \text{ mg\%} \pm 21.9$ in group A, $281.78 \text{ mg\%} \pm 42$ in group B & $210 \text{ mg\%} \pm 64.3$ in group C and these values were significant ($p \text{ value} < .05$).

Regarding BP, mean SBP & DBP of patients in group B & C was statistically highly significant ($p < 0.001$). Similar results were found in

the study by Bhagwat and Mane¹⁴.

Reduction in GFR in diabetic nephropathy, increases serum uric acid levels by several mechanisms. Hyperuricemia may result from increased net tubular absorption. After filtration, uric acid undergoes both re-absorption and secretion in the proximal convoluted tubules and this process is mediated by urate/anion exchanger and a voltage sensitive urate channel¹⁶. Organic anion such as lactic acid thus suppresses uric acid excretion and consequently leads to hyperuricemia. Additionally, in DN, sympathetic activity may produce alteration in renal sodium handling leading to increased arterial blood pressure and decreased renal blood flow¹⁷. This also lowers uric acid excretion.

CONCLUSION

This study reveals that levels of serum uric acid have linear positive correlation with the amount of proteinuria, Diabetic nephropathy can be suspected by increasing serum uric acid levels and it is seen that serum uric acid level correlates well with proteinuria, blood urea and serum creatinine level.

BIBLIOGRAPHY

1. Ayodele OE, Alebiosu CO, Salako BL et al. Diabetic nephropathy: a review of the natural history, burden risk factors and treatment. *J Natl Med Assoc* 2004;96:1445-54.
2. Alderman M, Aivyer KJV. Uric acid: Role in cardiovascular disease and effects of losartan. *Curr Med Res And Opinion* 2004;20(3):369-79.
3. Bhagwat VR, Mane SD. Hyperuricemia and progressive diabetic nephropathy. *Biomedicine* 2010;30(2):235-41.
4. Chin-Hsiao Tseng. Correlation of uric acid and urinary albumin excretion rate in patients with type 2 diabetes mellitus in Taiwan. *Kidney Int* 2005;68:796-01.
5. Danziger J. Importance of low Grade Albuminuria, In: *Mayo Clinic proceedings*. July 2008; 83(7): 806-12.
6. Dunloop M. Aldose reductase and role of the polyol pathway in diabetic nephropathy. *Kidney Int* 2000;77:S3-S12.
7. Enomoto A, Kimura H, Chairoungdua A, Shigeta Y, Jutabha P, Cha SH. Molecular identification of a renal urate-anion exchanger that regulates blood urate levels. *Nature* 2002;417:447-52.
8. Franse LV, Pahor M, Bari MD, Shorr RI, Wan JY, Somes GW et al. Serum uric acid, diuretic treatment and risk of cardiovascular events in the systolic hypertension in the elderly program. *J Hypertension* 2000;18(8):1149-54.
9. Harris M, Klein R, Welborn T, and Knuimar M. Onset of NIDDM occurs at least 4-7 years before clinical diagnosis. *Diabetes care* 1992; 15: 815-19.
10. Hsu CY, Iribarren C, McCulloch CE et al. Risk factors for end-stage renal disease. *Arch Intern Med* 2009;169(4):342-50.
11. Johnson RJ, Kang DH, Feig D, Kivlighn S, Kanellis, Watanabe S. Is there a pathogenetic role for uric acid in hypertension and cardiovascular and renal disease? *Hypertension* 2003;41:1183-90.
12. Lebovitz HE. Oral antidiabetic agents. In Kahn CR, Weir GC, editors. *Joslin Diabetes Mellitus*. Philadelphia: Lippincott Williams and Wilkins; 2006:686-704.
13. Lewis JB, Neilson EG. Glomerular diseases. In: Fauci A, Braunwald E, Kasper DL, Hauser SL, Longo DL, Jameson, JL, editors. *Harrison's Principle of Internal Medicine*. 17th ed. New York: McGraw Hill Company; 2008: 1782-96.
14. Power AC. Diabetes Mellitus. In: Fauci A, Braunwald E, Kasper DL, Hauser SL, Longo DL, Jameson JL, editors. *Harrison's principle of internal medicine*. 17th ed. New York: McGraw Hill Company 2008;17(2):2288-89.
15. Reichard P, Berglund B, cars I, Nilson BY, Rosenquist U. Intensified conventional insulin treatment retards the microvascular complications of IDDM: the Stockholm Diabetes Intervention study after 5 years. *J Intern Med* 1991; 230:101-08
16. Sowers JR, Epstein M and Frohlich ED. Diabetes, hypertension and cardiovascular disease; an update. *Hypertension* 2001;37:1053-59.
17. Watts GF, Bennett JE, Rowe DJ et al. Assessment of immunochemical methods for determining low concentrations of albumin in urine. *Clinical Chemistry* 1986; 32 (8): 1544-48.

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