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Original Article

# Potential role of uric acid in correlation with epidemics of hypertension and albumin creatinine ratio in diabetic nephropathy

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ABSTRACT

*Background:* Diabetic nephropathy (DN) is a microvascular complication of Type 2 diabetes mellitus. Uric acid (UA) is the end product of purine nucleotide metabolism and its primary mode of clearance is by renal excretion. Modifiable factors such as blood pressure, albuminuria, glycemic control, etc., play an important role in the progression of DN and none of them are curative. Hence, there is a pressing interest to identify other potentially modifiable factors such as UA in the progression of DN.

*Methods:* The present case–control study included 180 subjects, categorized into three groups: Group I, Group II, and Group III. Anthropometric and biochemical parameters were analyzed by standard methods.

*Results:* The mean fasting blood sugar, HbA1c, serum creatinine, spot urine albumin, albumin creatinine ratio, and triglycerides were significantly higher in Group III than in Group I and Group II. In Group I, eGFR, spot urine creatinine, total cholesterol, HDL cholesterol, and LDL cholesterol were statistically significantly higher than in Group II and Group III. Pearson's correlation coefficient of UA with systolic, diastolic blood pressure, and albumin creatinine ratio in Group II and Group III showed positive correlation, and no significant difference was found.

*Conclusion:* UA induces endothelial dysfunction, leading to renal injury in DN. In our study, UA, blood pressure, and ACR did not show significant correlation. Future studies with huge sample size are necessary to evaluate UA and ACR as the genuine markers, which help clinicians to assess the kidney failure in diabetes with these routine biochemical markers.



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*Abbreviations:* SD, standard deviation; BMI, body mass index; OBI, obesity index; WC, waist circumference; HC, hip circumference; WHR, waist hip ratio; SBP, systolic blood pressure; DBP, diastolic blood pressure; FBS, fasting blood sugar; FI, fasting insulin; HbA1c, glycated hemoglobin; TC, total cholesterol; TG, triglycerides; HDL, high-density lipoproteins; LDL, low-density lipoproteins; T2DM, type 2 diabetes mellitus; UA, uric acid; DN, diabetic nephropathy; RAAS, renin angiotensin aldosterone system; ESRD, end stage renal disease; MDRD, modification of diet in renal disease; VEGF, vascular endothelial growth factor; AGE, advanced glycation end products; TGF-β, transforming growth factor-β; NOS, nitrous oxide system.

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## 1. Introduction

Diabetes mellitus (DM), a group of chronic diseases, is characterized by hyperglycemia. Chronic hyperglycemia injures the human body in many ways. One of the chief injuries arising from hyperglycemia is injury to vasculature, which may be either a small vascular injury (microvascular disease) or injury to the large blood vessel of the body (macrovascular disease).[1] A large number of patients diagnosed each year with microvascular and macrovascular complications are attributed to type 2 diabetes mellitus (T2DM).[1] Nephropathy related to type 2 diabetes mellitus is one of the leading causes of end-stage renal disease (ESRD) and is associated with an increased risk of cardiovascular morbidity and mortality. Modifiable risk factors, such as arterial blood pressure, albuminuria, glycemic control, lipid control, and various inhibitors of the renin angiotensin aldosterone system (RAAS) play an important role in the progression of diabetic nephropathy (DN) and it is believed that none of them are curative.[2] Hence, there is a pressing interest to identify other potentially modifiable factors in the progression of DN.

Uric acid (UA), the final product of endogenous and dietary purine nucleotide metabolism, is formed by conversion of xanthine into hypoxanthine, which is catalyzed by enzyme xanthine oxidase. UA is a weak acid with a $pK_a$ of 5.75. In the extracellular compartment at physiological pH of 7.4, 98% of UA is in the ionized form as urate. In the collecting tubules of the kidneys, where the pH can fall to 5.0, UA formation is favored. Renal excretion of UA involves mainly 4 pathways: filtration, reabsorption, secretion, and post-secretory reabsorption. Urate is freely filtered at the glomerulus. An active anion-exchange process in the early proximal convoluted tubule reabsorbs most of it. Most urinary UA appears to be derived from tubular secretion, possibly from the S2 segment of the proximal tubule. Overall, 98–100% of filtered urate is reabsorbed; 6–10% is secreted, ultimately appearing in the final urine. Studies conducted by Tseng et al., reported that increased serum UA levels induces endothelial dysfunction, glomerular hypertension, renal hypertrophy, and decrease renal perfusion leading to kidney injury.[3–5] Studies done by Fukui et al. and Khosla et al. on diabetic patients reported that hyperuricemia is associated with kidney damage, independent of hypertension.[6,7] On the other hand, higher levels of serum insulin may decrease UA clearance by the kidneys.[8] Therefore, diabetic patients are more prone to UA injury. This encouraged us to take up the study to find the association of serum UA levels with blood pressure and albumin creatinine ratio (ACR) in diabetes as well as DN subjects.

## 2. Objectives

1. Comparison of anthropometric and biochemical indices between clinically proven healthy controls (Group I), type 2 diabetes without nephropathy (Group II) and type 2 diabetes with nephropathy (Group III).
2. Correlation of serum UA levels with blood pressure and ACR in diabetes without nephropathy (Group II) and diabetes with nephropathy (Group III) subjects.

## 3. Materials and methods

A total of 180 subjects from the outpatient clinics of Medicine Department at Sri Devaraj Urs Medical College attached to Sri R.L. Jalappa Hospital, Kolar were included in this study. Informed consent was obtained from all the enrolled patients and Institutional ethical clearance was obtained to start the study. These subjects were grouped into three categories

Group I Fifty-nine clinically proven healthy controls.
Group II Sixty-three T2DM subjects without nephropathy.
Group III Fifty-eight DN subjects.

Type 2 diabetes Mellitus was diagnosed based on the World Health Organization criteria.[9] None of the patients had diabetic ketoacidosis at the onset of disease. All of them were being treated by anti-diabetic oral agents or insulin at the time of the study. For those receiving insulin treatment, insulin therapy had not been started in the first year of diagnosis of DM. Patients on treatment with UA lowering agents, or diuretics and patients with acute illness, fever, urinary tract infection, a glomerular filtration rate (GFR) less than 60 ml/min/1.73 $m^2$ were excluded. Patients enrolled in the study were recommended not to have heavy exercise 24 hours before examination. Anthropometric measurements such as body height, weight, hip circumference (HC), waist circumference (WC), obesity index (OBI), and waist hip ratio (WHR) were measured and calculated respectively using standard methods. Body mass index (BMI) was calculated by Quetlet index formula.[10] Right arm's blood pressure was measured in sitting position using mercury sphygmomanometer. After 10 hours of overnight fasting, blood samples were collected and the parameters were estimated by the following methods: fasting blood sugar (FBS) by glucose-oxidase method,[11] serum UA, total cholesterol, high-density lipoproteins, triglycerides, and urine creatinine were measured by an enzymatic methods,[12,13] these variables were analyzed using Johnson & Johnson Vitros-250 dry chemistry Autoanalyzer which works on the principle reflectance Photometry. Fasting Insulin was done by chemiluminiscence[12] and $HbA_1c$ by HPLC methods.[12] The low-density lipoproteins cholesterol (LDLC) and eGFR were calculated using Friedewald formula and modification of diet in renal disease (MDRD) formula, respectively.[14,15] Previous studies conducted and published from our institution did not find any significant difference in the estimated or calculated LDLC.[16] Thus, we calculated the LDLC after considering the limitations of the Friedewald formula. Albumin was measured by early morning urine sample by dipstick method and those with high values or detectable and suspected to be at risk, the microalbumin was estimated by using commercially available kit method and autoanalyser. Urinary albumin–creatinine ratio (ACR) was calculated by dividing the urinary albumin concentration in microgram by the urinary creatinine concentration in milligram. An ACR of 30.0 μg/mg or lower was considered as ''normal,'' an ACR between 30 μg/mg and 299 μg/mg was considered as ''microalbuminuria.'' Very high ratios (ACR ≥ 300 μg/mg) were defined as ''overt albuminuria''.[17]

The differences between the three groups were assessed using analysis of variance (ANOVA). The correlation between

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serum UA concentrations SBP, DBP, and ACR was evaluated by Pearson correlation analysis by using SPSS version 16.0. *P* value of <0.05 was considered significant.

## 4. Results

The mean and standard deviation values for clinical characteristics of 180 subjects enrolled in this study are shown in Table 1. The mean values of anthropometric measurements were significantly higher in Group II and Group III compared to Group I. With respect to physiological characters such as systolic and diastolic blood pressure, the mean value of Group III was higher than Group I and Group II. The mean FBS, HbA1c, serum creatinine, spot urine albumin, albumin–creatinine ratio and triglycerides, were significantly higher in Group III than in Group I and Group II. Whereas, eGFR, spot urine creatinine, total cholesterol, high-density lipoproteins (HDL) cholesterol and LDLC were higher in Group I compared to Group II and Group III; however, significant difference was observed.

Table 2 shows the post-hoc analysis using Bonferroni criterion for significance between the Groups I, II and III. All the anthropometric and biochemical indices were statistically significant among the three groups (with *P* values of <0.001 and <0.005), except for TG and HDL cholesterol significant difference was not observed between Group II vs Group III.

Figs. 1 and 2 show the Pearson's correlation coefficient of UA with systolic and diastolic blood pressure and ACR in T2DM (Group II) and T2DM with DN (Group III), positive correlation was observed with these parameters; however, no significant difference was found.

## 5. Discussion

UA, a metabolite of key interest, may be derived by endogenous or exogenous routes. The endogenous production of UA from purine degradation and tissue catabolism under normal circumstances is relatively constant at 300–400 mg per day.[18] However, the exogenous pool varies significantly with diet. According to Kutzing and Firestein, a diet rich in animal protein contributes significantly to the purine pool and subsequent UA formation by a series of enzymatic reaction involving xanthine oxidase as the final step. The balance between dietary intake, endogenous metabolism of purines and the urinary excretion rate of UA determines plasma UA levels. Almost all serum UA is present in the ionized form – monosodium urate, and only about 5% of urate is protein bound at physiological pH. Renal excretion is the primary mode of UA clearance.[19]

In this study, we studied the relationship between hyperuricemia, hypertension, and albumin–creatinine ratio in T2DM with and without nephropathy.

In the present study, BMI, OBI, and WHR were higher in Group II and Group III compared to Group I. A study done by Atkinson et al. also observed similar findings and stated that obesity and diet such as meat, sugar (fructose) and beer are well known risk factors for hyperuricemia.[20] Most of the studies also suggest that fructose from added sugars increases the risk for hypertension and kidney disease.[21]

**Table 1 – ANOVA results comparing mean and standard deviation of anthropometric, physiological and biochemical indices in Group I (Healthy controls), Group II (T2DM without DN) and Group III (T2DM with DN).**

| Parameters | Group I Mean ± SD | Group II Mean ± SD | Group III Mean ± SD | ANOVA-F-value with significance |
|---|---|---|---|---|
| AGE (years) | 55.40 ± 11.76 | 55.58 ± 11.25 | 55.82 ± 11.04 | 4.13, $P > 0.05$ |
| BMI (kg/m$^2$) | 24.82 ± 3.31 | 30.15 ± 4.23 | 26.62 ± 3.86 | 1.01, $P < 0.05$* |
| OBI | 57.22 ± 8.72 | 63.59 ± 8.88 | 63.22 ± 10.10 | 6.26, $P < 0.001$* |
| WHR | 0.95 ± 0.10 | 0.97 ± 0.17 | 0.98 ± 0.13 | 0.85, $P < 0.05$* |
| SBP (mmHg) | 122 ± 12.31 | 124 ± 15.05 | 128 ± 19.21 | 2.02, $P < 0.05$* |
| DBP (mmHg) | 78 ± 8.22 | 80 ± 11.10 | 88 ± 10.31 | 0.264, $P < 0.05$* |
| FBS (mg/dl) | 98.91 ± 10.00 | 144.18 ± 14.52 | 148.31 ± 16.19 | 9.96, $P < 0.001$** |
| FI (mcU/ml) | 15.84 ± 4.81 | 23.40 ± 6.66 | 17.34 ± 5.71 | 1.44, $P = 0.15$ |
| HbA1c (%) | 6.42 ± 3.65 | 8.98 ± 2.35 | 10.30 ± 2.14 | 7.33, $P < 0.001$** |
| Serum creatinine (mg/dl) | 0.91 ± 0.51 | 1.5 ± 0.63 | 3.5 ± 1.52 | 29.55, $P < 0.001$** |
| Uric acid (mg/dl) | 4.01 ± 1.21 | 5.7 ± 1.28 | 6.9 ± 2.45 | 5.40, $P < 0.001$** |
| Spot urine albumin | 221.05 ± 100.82 | 269.78 ± 112.73 | 705.38 ± 123.14 | 11.08, $P < 0.001$** |
| Spot urine creatinine | 90.96 ± 29.91 | 59.96 ± 16.07 | 56.06 ± 17.30 | 2.22, $P < 0.05$* |
| Albumin creatinine ratio (ACR) | 10.44 ± 3.58 | 15.11 ± 5.23 | 35.11 ± 9.74 | 4.51, $P < 0.05$* |
| eGFR (ml/min/1.73 m$^2$) | 120.36 ± 15.46 | 98.23 ± 16.98 | 85.89 ± 21.78 | 0.46, $P < 0.05$* |
| TC (mg/dl) | 188.71 ± 30.07 | 164.19 ± 35.58 | 175.11 ± 36.47 | 6.60, $P < 0.001$* |
| TG (mg/dl) | 151.19 ± 11.58 | 190.39 ± 14.03 | 220.93 ± 16.47 | 3.49, $P < 0.05$* |
| HDL (mg/dl) | 43.59 ± 10.77 | 37.98 ± 12.89 | 39.37 ± 9.41 | 12.57, $P < 0.001$** |
| LDL (mg/dl) | 113.03 ± 11.07 | 87.73 ± 12.85 | 99.82 ± 10.58 | 8.61, $P < 0.001$** |
| Diet | 1.91 ± 0.28 | 1.96 ± 0.17 | 2.00 ± 0.51 | 2.93, $P < 0.05$* |
| Smoking | 1.61 ± 0.49 | 1.85 ± 0.36 | 2.00 ± 0.56 | 18.27, $P < 0.05$* |
| Alcohol | 1.70 ± 0.45 | 1.89 ± 0.35 | 2.00 ± 0.59 | 12.84, $P < 0.05$* |

* $P < 0.05$ considered as significant.
** $P < 0.001$ considered as highly significant.

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**Table 2 – Post-hoc (Bonferroni test) comparing means of anthropometric and biochemical indices in Group I (Healthy controls), Group II (T2DM without DN), and Group III (Diabetes with DN).**

| Variables | Group I vs Group II, P | Group II vs Group III, P | Group I vs Group III, P |
|---|---|---|---|
| BMI (kg/m$^2$) | <0.001 | <0.001 | <0.001 |
| OBI | <0.001 | <0.001 | <0.001 |
| WHR | <0.001 | <0.001 | <0.001 |
| SBP (mmHg) | <0.001 | <0.001 | <0.001 |
| DBP (mmHg) | <0.001 | <0.001 | <0.001 |
| FBS (mg/dl) | <0.001 | <0.05 | <0.001 |
| HbA1c (%) | <0.001 | <0.001 | <0.001 |
| Serum creatinine mg/dl) | <0.001 | <0.001 | <0.001 |
| Uric acid (mg/dl) | <0.05 | <0.05 | <0.001 |
| Spot urine albumin | <0.001 | <0.001 | <0.001 |
| Spot urine creatinine | <0.05 | <0.05 | <0.05 |
| Albumin creatinine ratio (ACR) | <0.05 | <0.05 | <0.001 |
| eGFR (ml/min/1.73 m$^2$) | <0.001 | <0.05 | <0.001 |
| TC (mg/dl) | <0.001 | <0.05 | <0.001 |
| TG (mg/dl) | <0.001 | >0.05 | <0.001 |
| HDL (mg/dl) | <0.05 | >0.05 | <0.05 |
| LDL (mg/dl) | <0.001 | <0.05 | <0.001 |

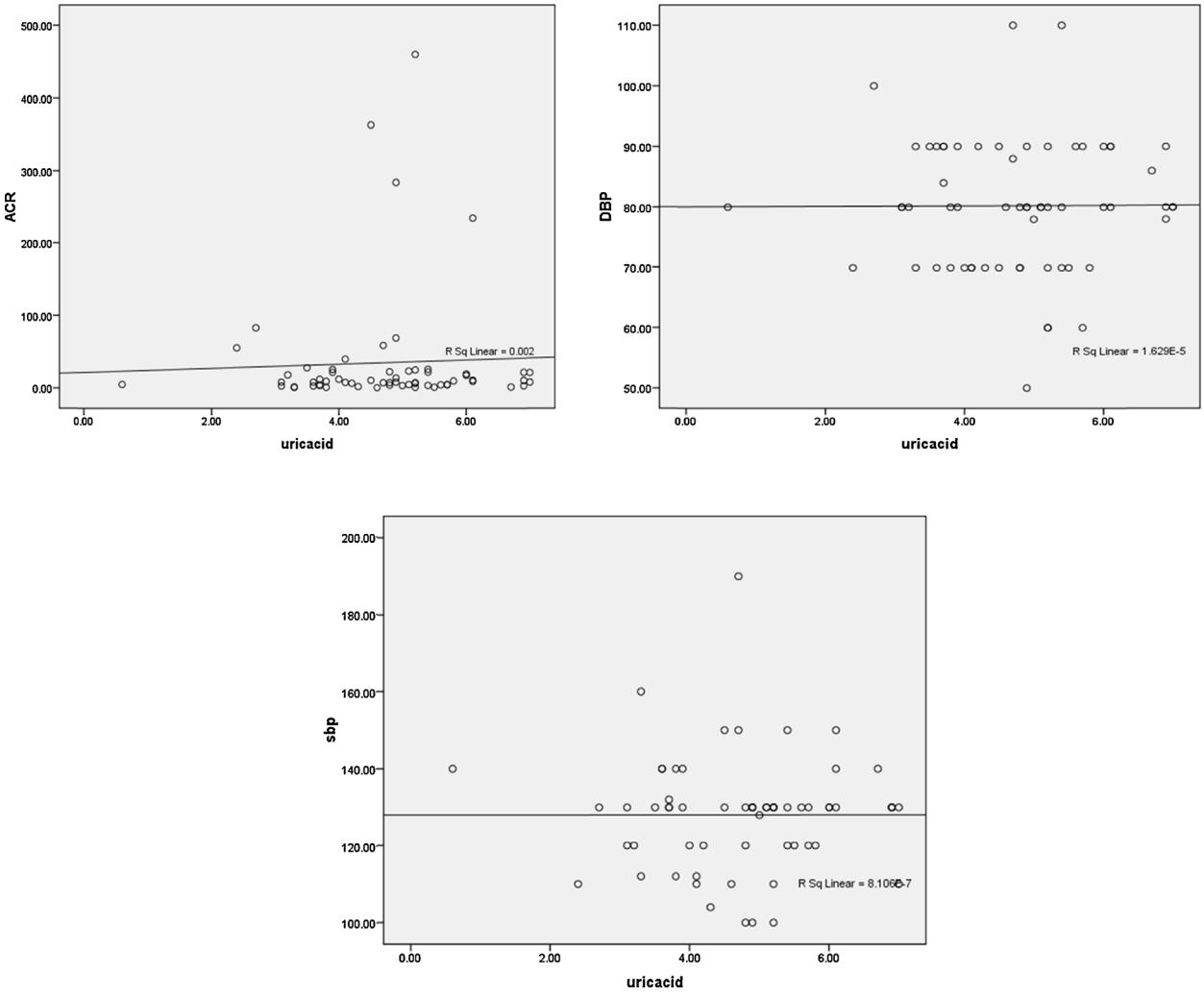


**Fig. 1 – Correlation of uric acid with SBP, DBP and ACR in T2DM without DN.**

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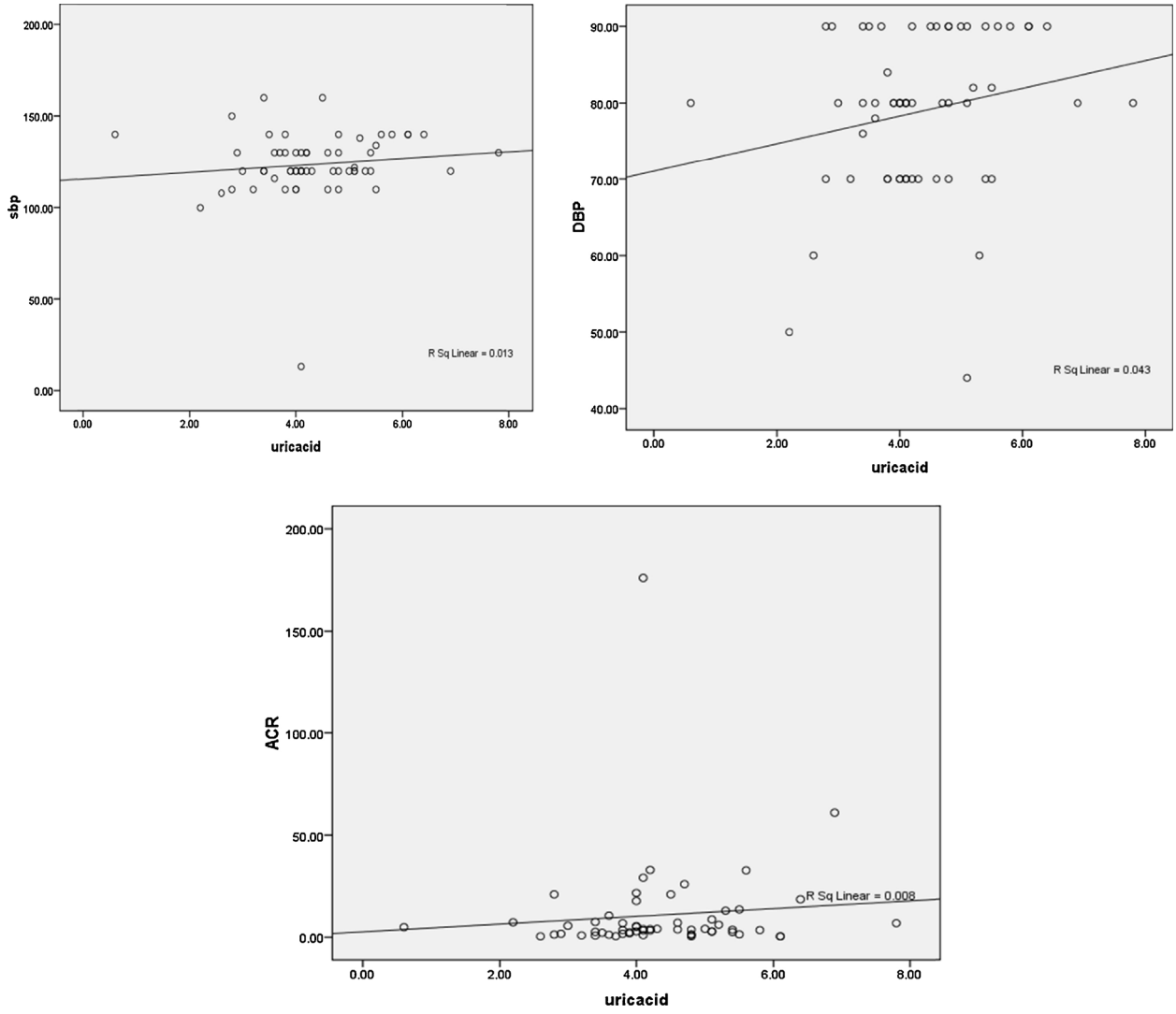


**Fig. 2 – Correlation of uric acid with SBP, DBP and ACR in T2DM with DN.**

Our study showed significant increase of blood pressure in Groups II and III than Group I. Similar results were shown in the study done by Johnson and colleagues who reported hyperuricemia to be a risk factor for hypertension.[18] Recent evidences from animal studies and epidemiology done by Johnson et al., in the year 2005 suggested that hyperuricemia has a primary role in hypertension. Rats that were made hyperuricemic rapidly developed hypertension through activation of the renin-angiotensin system, induction of endothelial dysfunction, and vascular smooth muscle proliferation. Lowering UA in these animals prevented this effect.[18] Longitudinal study conducted by Feig et al., in children, showed a strong correlation between hyperuricemia and the subsequent development of hypertension.[22] However, this is not clear with respect to the population or geography. Because, there is lot of variation in the diet and also other factors that are involved in the UA synthesis or degradation. It has been observed that even the genetics play an important role in the significant alteration of UA levels. Our results were consistent with studies done by Nakagawa and associates, reported that UA has a causal role in metabolic syndrome.[21]

Significant increase of FBS and $HbA_1c$ was found in Group I vs Group II, Group II vs Group III and Group I vs Group III. However, fasting insulin was elevated in Group II compared to Groups I and III and no significant difference was observed in our study. Bo and coworkers reported that hyperuricemia is associated with insulin resistance and onset or progression of nephropathy in type 2 diabetic patients.[7] Even this is consistent with our findings. The reason for this could be that the insulin resistance occurs when the cells become less sensitive to the effects of insulin. This results in rising blood sugar levels and a drop in the energy production. To compensate for the insulin resistance and to keep the blood glucose levels from spiraling out of control, the pancreas tries to restore the balance by producing more insulin. In case, if this is left unchecked, the cells become even more resistant to insulin; as the pancreas secretes ever greater amounts of insulin, in a desperate attempt to bring the system back under control, this results in dangerously high blood levels of insulin. If this is not corrected, the pancreas eventually becomes exhausted, resulting in diabetes.[23] Long-standing hyperglycemia is known to be a

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significant risk factor for the development of DN. Because, hyperglycemia directly results in mesangial expansion and injury results in increase in the mesangial cell glucose concentration. Glucose can also bind reversibly and eventually irreversibly to proteins in the kidneys and circulation to form advanced glycosylation end products (AGEs). AGEs can form complex cross-links over years of hyperglycemia and can contribute to renal damage. It has been noted that mediators of proliferation and expansion, including platelet-derived growth factor, TGF-β and vascular endothelial growth factor (VEGF) are also elevated in DN.[23]

In the present study, serum creatinine and UA levels were elevated in Group III compared to Groups I and II. Similar results were observed by Kentaro et al., stating that elevated UA levels can be a consequence of impaired renal function.[24] However, UA per se can also be detrimental to the kidneys as shown in animal and human studies.[25,26] Elevated UA can induce renin expression from the juxtaglomerular cells and inhibit nitrous oxide system (NOS) expression in the macula densa.[27] UA is also known to impair endothelial function and stimulates the production of cytokines from leukocytes and chemokines from vascular smooth muscle cells.[28] Thus as a result, hyperuricemic rats develop hypertension and result in renal injury consisting of afferent arteriolopathy, mild tubulointerstitial fibrosis, intra glomerular hypertension, glomerular hypertrophy and eventually, glomerulosclerosis with albuminuria.[8,9] Study conducted by Osterby et al., reported that these histopathologic changes induced by elevated UA in animals are also common features of DN in humans.[29]

Study done by Boon et al. reported that spot urine estimations are equivalent to 24-hour urine assessments.[30] Hence, in the present study, we estimated spot urine albumin and spot urine creatinine, and also calculated ACR; statistically significant difference was observed between three Groups. Creatinine is a metabolic byproduct of skeletal muscle creatine and phosphocreatine metabolism and is thus lower in subjects with lower muscle mass, for example, women or the elderly. Appearance of albumin in urine is the first sign of kidney damage and onset of DN in patients with DM.[5] In DN, the activation of the local renin-angiotensin system occurs in the proximal tubular epithelial cells, mesangial cells, and podocytes. Angiotensin II (ATII) itself contributes to the progression of DN and preferentially constricts the efferent arteriole in the glomerulus, leading to higher glomerular capillary pressures. In addition to its hemodynamic effects, it also stimulates renal growth and fibrosis through ATII type 1 receptors, which secondarily upregulate TGF-β and other growth factors. However, in our study, no significant correlation was found between UA and ACR, whereas study conducted by Bonakdaran et al. found positive correlation between these two parameters and reported that elevated serum UA concentration can be a significance of kidney dysfunction.[18]

In our present study, TC, LDL, and HDL cholesterol were higher in Group I than in Groups II and III, where as TG was elevated in Group III compared to Group I and Group II. This pattern of abnormalities is due to several pathogenetic mechanisms. First, urinary protein loss stimulates an increased LDL synthesis by the liver. It is likely that proteinuria with the resultant hypoalbuminemia leads to an upregulation of 3-hydroxy-3-methylglutaryl CoA reductase with a consequent hypercholesterolemia.[31] Second, low HDL with a poor maturation of HDL-3 to cholesterol-rich HDL-2 is due to acquire lecithin-cholesterol acyltransferase deficiency secondary to abnormal urinary losses of this enzyme.[32] However, impaired clearance of chylomicrons and VLDL has emerged as the dominant factor for the increased serum triglyceride concentration.

Limitation of our present study: (1) it was carried out in a single institution; (2) large-scale intervention is required to verify the effectiveness of UA-lowering therapy for renoprotection; (3) the factors involved in alteration of serum UA were not considered, for example, the dietary factors such as diet high in purines (organ meats, shellfish, fatty meats), diet high in fructose (high fructose corn syrup, table sugar, honey), alcohol consumption, and smoking; (4) the patient drug history was not evaluated and the available types of antihypertensive agents, which might affect serum UA levels and finally, urine creatinine concentrations differ between men and women and between different racial/ethnic groups.

## 6. Conclusion

DN, a complex microvascular disease, remains incurable even though several therapeutic options are available for the treatment of patients with DN. UA has several reported effects such as endothelial dysfunction, increased activity of the RAAS, induction of inflammatory cascades, and activation of profibrotic cytokine contributing to the progression of microvascular disease leading to renal injury in DN.

Studies show that UA, blood pressure, and ACR directly link to the progression of kidney disease in DM. However, in our study, these variables did not show significant correlation. Future studies with huge sample size are necessary to evaluate UA and ACR as the genuine markers, which help clinicians to assess the kidney failure in diabetes with these routine biochemical markers.

## Author's contribution

U. Munilakshmi contributed in the Formulation of study, Biochemical analysis, Data collection and is the Principal Investigator. Guidance, Planning, and Correction of the write up was provided by K.N. Shashidhar and is the Corresponding Author. Evaluation and Review of literature was done by K. Prabhavathi, while Data collection and Manuscript editing was done by Madhavi Reddy. Clinical Case finding and overall guidance was provided by V. Lakshmaiah.

## Conflicts of interest

The authors have none to declare.

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