

# Association of serum uric acid with proteinuria in type 2 diabetic patients

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**Background:** Various findings suggest that uric acid is an inflammatory factor and may have a role in endothelial dysfunction and act as a mediator of diabetic nephropathy. The objective of this study was to evaluate the relationships between serum uric acid level and level of proteinuria in type 2 diabetic (T2D) patients. **Materials and Methods:** A cross-sectional analytical study was conducted in 60 patients with T2D without a history of gout. None was treated with allopurinol. Venous blood samples were obtained in fasting state for determinations of serum creatinine, uric acid, and hemoglobin A<sub>1c</sub> (HbA<sub>1c</sub>) (reference range 3.8-5.5%); 24-h urine proteinuria was also measured. **Results:** Mean age of the patients was 57 ± 8.3 years. Mean ± standard error (SE) of serum creatinine was 0.98 ± 0.028 mg/dL, mean ± SE of serum uric acid was 4.5 ± 0.15 mg/dL, and mean ± SE of proteinuria was 388 ± 28.7 mg/day (median = 303.5 mg/day). There was no significant difference in serum uric acid, HbA<sub>1c</sub>, and creatinine level between males and females ( $P > 0.05$ ). There was a significant positive association between body mass index (BMI) and serum uric acid levels ( $r = 0.428, P = 0.001$ ). After adjustment for weight, a significant positive association of serum uric acid with level of proteinuria was seen ( $r = 0.47, P < 0.001$ ). **Conclusion:** Serum uric acid had a significant positive association with diabetic nephropathy. It might be hypothesized that serum uric acid plays a role in diabetic nephropathy in T2D.

**Key words:** Proteinuria, renal failure, type 2 diabetes mellitus, uric acid

## INTRODUCTION

Despite advances in the care of patients with diabetes, diabetic nephropathy (DN) remains the most common etiology for end-stage.<sup>[1-5]</sup> Various factors have been associated with the development of DN in type 2 diabetic (T2D) patients, including age, poor glycemic control, hypertension, and smoking.<sup>[2-10]</sup> Of them, inflammation and endothelial dysfunction seems to play a basic role in the development of DN. Recent findings suggest that uric acid is an inflammatory factor, may have a role in endothelial dysfunction,<sup>[9-13]</sup> and act as a mediator of DN.<sup>[10-14]</sup> The objective of this study was to find an association between serum uric acid level and proteinuria level in T2D patients.

## MATERIALS AND METHODS

A cross-sectional analytical study was conducted in 2011 on 60 patients (both genders, age range 41-81 years) with T2D. The patients' body weight was stable for at least 3 months before the study. None of the patients had a history of gout and none was treated with allopurinol. Body mass index (BMI) was calculated in kg/m<sup>2</sup>.<sup>[10,15-17]</sup> Patients' history, current medications, insulin doses, tobacco use, and family medical history were obtained. Venous blood samples were obtained in fasting state for determinations of serum creatinine, uric acid, and

hemoglobin A<sub>1c</sub> (HbA<sub>1c</sub>) (reference range 3.8-5.5%); 24-h urine proteinuria was also measured.

Results were expressed as mean ± standard deviation (SD) and were considered as statistically significant when two-sided  $P < 0.05$ . Independent-samples *t*-test was used for comparison variables between male and female. Spearman's rho coefficient correlation test was used for correlation of BMI with serum uric acid and partial correlation coefficient test was used for correlation of proteinuria with serum uric acid.

## RESULTS

A total of 60 T2D patients were enrolled in the study (56.7% female, age range: 41-81 years, mean age: 57 ± 8.3 years). Mean ± SE of serum creatinine was 0.98 ± 0.028 mg/dL, mean ± SE of serum uric acid was 4.5 ± 0.15 mg/dL, and mean ± SE of proteinuria was 388 ± 28.7 mg/day (median = 303.5 mg/day). The results of interested variable are shown in Table 1. In this study, there was no significant difference of serum uric acid, HbA<sub>1c</sub>, and creatinine between males and females ( $P > 0.05$ ). There was a significant positive association between BMI and serum uric acid ( $r = 0.428, P = 0.001$ ). After adjustment for weight, a significant positive association of serum uric acid level with proteinuria level was seen ( $r = 0.47, P < 0.001$ ).

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## DISCUSSION

The etiology of DN is complex and remains to be clarified.<sup>[2,4]</sup> Presently, diabetes is the leading cause of end-stage renal disease in the most parts of the world.<sup>[2-5,14,18-23]</sup> Although the progression of kidney disease can be halted partially, DN is still regarded as an irreversible and progressive disease.<sup>[2-5,14,18-24]</sup> Thus, it has become increasingly essential to find the pathophysiological mechanisms that leads to the development and progression of DN.<sup>[24-26]</sup> In this study, we found the significant positive association of serum uric acid with level of proteinuria, when adjusted for weight. Hyperuricemia and its association with obesity and various components of metabolic syndrome have been documented in previous studies.<sup>[24,25]</sup> Hyperuricemia is also prevalent in patients with chronic renal failure.<sup>[23-29]</sup> Indeed, various studies have shown that hyperuricemia may have a pathogenic role in the development and progression of chronic renal failure, rather than simply reflecting decreased renal uric acid excretion.<sup>[24-27]</sup> In diabetic patients, serum uric acid early in the course of diabetes is significantly associated with later development of persistent macroalbuminuria.<sup>[26-28]</sup> It was shown that kidney damage in hyperuricemic rats is not dependent on blood pressure and instead involves the renin-angiotensin system (RAS).<sup>[25-28]</sup> An association between serum uric acid and early loss of renal function has been shown in patients with type 1 diabetes.<sup>[27-29]</sup> In the study conducted by Fukui *et al.*, positive correlation of serum uric acid and urinary albumin excretion in 343 men with type 2 diabetes mellitus was shown.<sup>[30]</sup> They concluded that serum uric acid concentration is associated with microalbuminuria and subclinical atherosclerosis in men with type 2 diabetes mellitus.<sup>[30]</sup> Similarly, Fu *et al.*, in a study on Chinese diabetic patients, found that hyperuricemia was significantly associated with abnormal albuminuria in patients without diuretics or use of uricosuric agents or alcohol. They concluded that hyperuricemia were significantly related to the presence of albuminuria in patients with diabetes.<sup>[31]</sup> Elevated level of serum uric acid can lead to low-grade kidney injury without deposition of uric acid crystals in animal models.<sup>[32]</sup> Also, hyperuricemia in rats induced arteriopathy of preglomerular vessels, resulting in impaired autoregulation, glomerular hypertension, and endothelial dysfunction.<sup>[27,29]</sup> It was found that microvascular disease in hyperuricemic rats occurs independent of blood pressure and is dependent on activation of the systemic and

local RAS and inhibition of endothelial nitric oxide.<sup>[27,29,33,34]</sup> In the study conducted by Obermayr *et al.*, serum uric acid was found to be a predictor of new onset kidney disease, independent of other risk factors.<sup>[35]</sup> In conclusion, in our study, serum uric acid had a significant positive association with DN. Given this fact, we hypothesized that serum uric acid plays a pathological role in the development of DN in T2D. To approve this hypothesis, we suggest studying of the effect of lowering uric acid with allopurinol on renal function in DN patients in future.

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**Table 1: The results of variables in type 2 diabetic patients**

Variable	Min	Max	Mean±SD
BMI (kg/m <sup>2</sup> )	20.06	41.4	29.9±4
Diabetic duration (years)	3	23	9.2±4.9
Systolic BP (mmHg)	110	170	133±13
Diastolic BP (mmHg)	70	100	84±7.4
HbA <sub>1c</sub> (%)	4.8	9.5	7.4±1.07

BP=Blood pressure; BMI=Body mass index

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