ORIGINAL ARTICLE

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

Saeed Behradmanesh, Mohammad Karami Horestani[1], Azar Baradaran[1], Hamid Nasri[2]

Medical Plants Research Center, [1]Department of Internal Medicine, Shahrekord University of Medical Sciences, Shahrekord, [2]Isfahan Kidney Disease Research Center, Isfahan University of Medical Sciences, Isfahan, Iran

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_{1c} (HbA_{1c}) (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_{1c}, 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.[1-5] Various factors have been associated with the development of DN in type 2 diabetic (T2D) patients, including age, poor glycemic control, hypertension, and smoking.[2-10] 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,[9-13] and act as a mediator of DN.[10-14] 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^2.[10,15-17] 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_{1c} (HbA_{1c}) (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 protenuria 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_{1c}, 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 ($r = 0.47$, $P < 0.001$).

Address for correspondence: Prof. Hamid Nasri, Isfahan Kidney Disease Research Center, Isfahan University of Medical Sciences, Isfahan, Iran.
E-mail: hamidnasri@yahoo.com
Received: 29-09-2012; **Revised:** 18-11-2012; **Accepted:** 12-12-2012

DISCUSSION

The etiology of DN is complex and remains to be clarified.[2,4] Presently, diabetes is the leading cause of end-stage renal disease in the most parts of the world.[2-5,14,18-23] Although the progression of kidney disease can be halted partially, DN is still regarded as an irreversible and progressive disease.[2-5,14,18-24] Thus, it has become increasingly essential to find the pathophysiological mechanisms that leads to the development and progression of DN.[24-26] 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.[24,25] Hyperuricemia is also prevalent in patients with chronic renal failure.[23-29] 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.[24-27] In diabetic patients, serum uric acid early in the course of diabetes is significantly associated with later development of persistent macroalbuminuria.[26-28] It was shown that kidney damage in hyperuricemic rats is not dependent on blood pressure and instead involves the renin–angiotensin system (RAS).[25-28] An association between serum uric acid and early loss of renal function has been shown in patients with type 1 diabetes.[27-29] 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.[30] They concluded that serum uric acid concentration is associated with microalbuminuria and subclinical atherosclerosis in men with type 2 diabetes mellitus.[30] 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.[31] Elevated level of serum uric acid can lead to low-grade kidney injury without deposition of uric acid crystals in animal models.[32] Also, hyperuricemia in rats induced arteriolopathy of preglomerular vessels, resulting in impaired autoregulation, glomerular hypertension, and endothelial dysfunction.[27,29] 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.[27,29,33,34] 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.[35] 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.

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

Variable	Min	Max	Mean±SD
BMI (kg/m^2)	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_{1c} (%)	4.8	9.5	7.4±1.07

BP=Blood pressure; BMI=Body mass index

REFERENCES

1. Tolouian R, Hernandez GT. Prediction of diabetic nephropathy: The need for a sweet biomarker. J Nephropathology 2013;2:4-5.
2. Rahimi Z. ACE insertion/deletion (I/D) polymorphism and diabetic nephropathy. J Nephropathology 2012;1:143-51.
3. Rouhi H, Ganji F. Effect of N-acetyl cysteine on serum lipoprotein (a) and proteinuria in type 2 diabetic patients. J Nephropathology 2013;1:61-6.
4. Jalal DI, Rivard CJ, Johnson RJ, Maahs DM, McFann K, Rewers M, *et al*. Serum uric acid levels predict the development of albuminuria over 6 years in patients with type 1 diabetes: Findings from the Coronary Artery Calcification in Type 1 Diabetes study. Nephrol Dial Transplant 2010;25:1865-9.
5. Baradaran A. Lipoprotein (a), type 2 diabetes and nephropathy; the mystery continues. J Nephropathology 2012;1:126-9.
6. Tavafi M. Diabetic nephropathy and antioxidants. J Nephropathology 2013;2:20-7.
7. Hovind P, Rossing P, Tarnow L, Johnson RJ, Parving HH. Serum uric acid as a predictor for development of diabetic nephropathy in type 1 diabetes: An inception cohort study. Diabetes 2009;58:1668-71.
8. Gheissari A, Hemmatzadeh S, Merrikhi A, Fadaei Tehrani S, Madihi Y. Chronic kidney disease in children: A report from a tertiary care center over 11 years. J Nephropathology 2012;1:177-82.
9. Unsal A, Koc Y, Basturk T, Akgun AO, Sakaci T, Ahbap E. Risk factors for progression of renal disease in patient with diabetic nephropathy. Eur Rev Med Pharmacol Sci 2012;16:878-83.
10. Nasri H. Hypertension and renal failure with right arm pulse weakness in a 65 years old man. J Nephropathology. 2012;1:130-3.
11. Coll-de-Tuero G, Mata-Cases M, Rodriguez-Poncelas A, Pepió JM, Roura P, Benito B, *et al*. Chronic kidney disease in the type 2 diabetic patients: Prevalence and associated variables in a random sample of 2642 patients of a Mediterranean area. BMC Nephrol 2012;13:87.
12. Kari J. Epidemiology of chronic kidney disease in children. J Nephropathology 2012;1:162-3.
13. Lim AK, Tesch GH. Inflammation in diabetic nephropathy. Mediators Inflamm 2012. doi: 10.1155/2012/146154.
14. Gheissari A, Mehrasa P, Merrikhi A, Madihi Y. Acute kidney injury: A pediatric experience over 10 years at a tertiary care center. J Nephropathology 2012;1:101-8.
15. Baradaran A, Behradmanesh S, Nasri H. Association of body mass index and serum vitamin D level in healthy Iranian adolescents. Endokrynol Pol 2012;63:29-33.
16. Nasri H. Association of serum lipoprotein (a) with hypertension in diabetic patients. Saudi J Kidney Dis Transpl 2008;19:420-7.
17. Nasri H, Yazdani M. The relationship between serum LDL-cholesterol, HDL-cholesterol and systolic blood pressure in patients with type 2 diabetes. Kardiol Pol 2006;64:1364-8.
18. Solati M, Mahboobi HR. Paraoxonase enzyme activity and

dyslipidemia in chronic renal failure patients. J Nephropathology 2012;1:123-5.
19. Sánchez Niño MD, Ortiz A. Is it or is it not a pathogenic mutation? Is it or is it not the podocyte? J Nephropathology 2012;1:152-4.
20. Bonakdaran S, Ebrahimzadeh S, Noghabi SH. Cardiovascular disease and risk factors in patients with type 2 diabetes mellitus in Mashhad, Islamic Republic of Iran. East Mediterr Health J 2011;17:640-6.
21. Sahni N, Gupta KL. Dietary antioxidents and oxidative stress in predialysis chronic kidney patients. J Nephropathology 2012;1:134-42.
22. Tayebi KH. Short history about renal transplantation program in Iran and the world: Special focus on world kidney day 2012. J Nephropathology 2012;1:5-10.
23. Khajehdehi P. Turmeric: Reemerging of a neglected Asian traditional remedy. J Nephropathology 2012;1:17-22.
24. Bruno RM, Penno G, Daniele G, Pucci L, Lucchesi D, Stea F, *et al*. Type 2 diabetes mellitus worsens arterial stiffness in hypertensive patients through endothelial dysfunction. Diabetologia 2012;55:1847-55.
25. Doria A, Krolewski AS. Diabetes: Lowering serum uric acid levels to prevent kidney failure. Nat Rev Nephrol 2011;7:495-6.
26. Hovind P, Rossing P, Johnson RJ, Parving HH. Serum uric acid as a new player in the development of diabetic nephropathy. J Ren Nutr 2011;21:124-7.
27. Sanchez-Lozada LG, Soto V, Tapia E, Avilia-Casado C, Sautin YY, Nakagawa T, *et al*. Role of oxidative stress in the renal abnormalities induced by experimental hyperuricemia. Am J Physiol Renal Physiol 2008;295:F1134-41.
28. Kuo CF, Luo SF, See LC, Ko YS, Chen YM, Hwang JS, *et al*. Hyperuricaemia and accelerated reduction in renal function. Scand J Rheumatol 2011;40:116-21.
29. Khosla UM, Zharikov S, Finch JL, Nakagawa T, Roncal C, Mu W, *et al*. Hyperuricemia induces endothelial dysfunction. Kidney Int 2005;*67*:*1739*-42.
30. Fukui M, Tanaka M, Shiraishi E, Harusato I, Hosoda H, Asano M, *et al*. Serum uric acid is associated with microalbuminuria and subclinical atherosclerosis in men with type 2 diabetes mellitus. Metabolism 2008;57:625-9.
31. Fu CC, Wu DA, Wang JH, Yang WC, Tseng CH. Association of C-reactive protein and hyperuricemia with diabetic nephropathy in Chinese type 2 diabetic patients. Acta Diabetol 2009;46:127-34.
32. Kang DH, Nakagawa T, Feng L, Watanabe S, Han L, Mazzali M, *et al*. A role for uric acid in the progression of renal disease. J Am Soc Nephrol 2002;13:2888-97.
33. Mazzali M, Kanellis J, Han L, Feng L, Xia YY, Chen Q, *et al*. Hyperuricemia induces a primary renal arteriolopathy in rats by a blood pressure-independent mechanism. Am J Physiol Renal Physiol 2002;282:F991-7.
34. Assadi F. The epidemic of pediatric chronic kidney disease: The danger of skepticism. J Nephropathology 2012;1:61-4.
35. Obermayr RP, Temml C, Gutjahr G, Knechtelsdorfer M, Oberbauer R, Klauser-Braun R. Elevated uric acid increases the risk for kidney disease. J Am Soc Nephrol 2008;19:2407-13.

How to cite this article: Behradmanesh S, Horestani MK, Baradaran A, Nasri H. Association of serum uric acid with proteinuria in type 2 diabetic patients. J Res Med Sci 2013;18:44-6.

Source of Support: This study was funded by Shahrekord University of Medical Sciences (grant# 898), **Conflict of Interest:** None declared.