DOI : 10.35124/bca.2019.19.2.4445

Biochem. Cell. Arch. Vol. 19, No. 2, pp. 4445-4449, 2019 | www.connectjournals.com/bca | *ISSN 0972-5075*

ASSESSMENT OF URIC ACID IN PATIENTS OF END-STAGE RENAL DISEASE WITH HYPERTENSION AND DIABETIC NEPHROPATHY AND THE RISK OF CARDIOVASCULAR DISEASES

Shatha Abdul Wadood AL-Shammaree

Department of Chemistry, College of Science, University of Baghdad, Baghdad, Iraq
e-mail: shath_a@yahoo.com

(Received 12 March 2019, Revised 17 May 2019, Accepted 31 May 2019)

ABSTRACT : The relationship of hyperuricemia to kidney disease, diabetes, hypertension and the risk of cardiovascular diseases remain controversial. The aim of this study is to evaluate the use of uric acid (UA) levels to find the higher risk of cardiovascular disease (CVD) in patients with end stage renal disease that have diabetic nephropathy (DN), nephropathy with hypertension (NH) and patients with both diabetic nephropathy with hypertension (DNH). This study deals with 115 patients with end-stage renal disease under hemodialysis sub-grouped into 35 patients with (DN), 40 patients with (NH), and 40 patients with (DNH). Some biochemical parameters were determined in the serum of all participants such as HbA1c, fasting blood glucose (FBG), UA, urea, serum creatinine, total serum protein, calcium, phosphate, albumin, and globin levels. The present study revealed a significant increase ($P<0.05$) in HbA1c, FBG, urea and creatinine in DN and DNH patients compared to NH group. However, non-significant difference was found in total serum protein, serum albumin, globulin, calcium, and phosphate levels between the groups. A positive correlation was found between UA level with FBG, HbA1c and creatinine in DN and DNH groups in comparison to NH group. Levels of UA can be considered as a reliable marker, which is less expensive and helps clinicians in controlling the progression to microvascular complications. The early detection of any complication and adopting the appropriate treatment to reduce the risk of CVD can reduce morbidity and mortality.

Key words : Hyperuricemia, diabetes mellitus, hypertension, cardiovascular diseases, end stage renal disease.

INTRODUCTION

End-stage renal disease (ESRD) is the final stage of chronic kidney disease where the kidney fails to remove the final products of metabolic pathways because of the decreased rate of glomerular filtration (GFR). This stage is caused by many factors included genetic or oxidative stress (Bellomo *et al*, 2004; Yun *et al*, 2014; Xue *et al*, 2014).

Many diseases may cause or are associated with chronic kidney diseases such as smoking, dyslipidemia, chronic inflammation, hypertension, proteinuria, and diabetes mellitus (DM). These diseases may develop to cause CVD (Mikolasevic *et al*, 2017; Yacoub *et al*, 2010; Tsuruya *et al*, 2014).

Structural kidney abnormalities are characteristic of DM although many risk factors are associated with both DM and DN; the explanation of this association is still unrevealed. The progression of DN may take a long period before the symptoms appear or increased albuminuria as a clinical DN and loss of kidney functions. Therefore, search for good biomarkers is of important before the onset appearance of DN symptoms or earlier therapy before renal function decline (Lewis and Maxwell, 2014).

Many studies linked the elevation of uric acid (UA) in renal disease progression and diabetes complications and they considered it as a potential target (Liu *et al*, 2018; Lytvyn *et al*, 2015). The deleterious effects of UA on blood pressure and renal function has been demonstrated even when baseline UA levels are within the normal range. The UA activates the renin-angiotensin-aldosterone system (RAAS), increases oxidative stress, and promotes inflammation (Filiopoulos *et al*, 2012). Consequently, higher UA levels are associated with metabolic abnormalities, cardiovascular disease and kidney dysfunction (Lewis and Maxwell, 2014; Sochett *et al*, 2006; Stanton, 2014).

The UA has a dual role in oxidative stress status; it is considered an antioxidant since it scavenges some free radicals such as superoxide anion and hydroxyl radical. In another hand, UA plays a role in vascular cells of smooth muscle as pro-oxidant that lead to increased oxidative status (Yu *et al*, 2010). This study aimed to

assess UA level in ESRD patients with hypertension, T2DM and T2DM with hypertension to predict which of the patients' groups have higher CVD risk.

MATERIALS AND METHODS

Selection of subjects and blood sampling

This study was conducted during the period from September 2017until February 2018 when approved by the ethical committee of College of Science, University of Baghdad. The number of the participant was 115 patients with end-stage renal disease under hemodialysis treatment sub-grouped into 35 patients with diabetic nephropathy (DN), 40 nephropathy patients with hypertension (NH) and 40 diabetic nephropathy patients with hypertension (DNH). Hypertension was defined as SBP ≥ 140 or DBP ≥ 90 mm Hg. The patients' age range was (38-72) who were attending the Baghdad Medical City Hospital, Baghdad.

Their glomerular filtration rate was lower than 60 mL/ min/1.37 m^2.

Patients with hypertension were treated with losartan, or rosuvastatin, pravastatin, and atorvastatin. All diabetic patients were taking glucose lowering drugs such as metformin or a mix of glibenclamide and metformin or Insulin.

Blood samples were taken from patients according to the instruction of the nephrologist after taking their informed consent. The blood was obtained after fasting from all patients before hemodialysis, transferred into a plain tube, allowed to clot for 15 min at room temperature, then centrifuged at 3000 rpm for 15 minutes. The resulting serum was sub-divided, and stored at -20°C.

This study excluded patients on medication that effect UA level such as allopurinol, and salicylate. Also, patients with vascular disease, hepatic disease, inflammatory diseases, or smokers were excluded.

Clinical analysis

Body mass index of all patients was recorded by dividing weight (in Kg) on height in square meter (m^2). Biochemical parameters were determined including UA by uricase method using a kit from Linear chemical, Spain. HbA1c was measured by kit from Genrui (China). Level of FSG and albumin were measured using a commercial kit from Spinreact (Spain). Total protein and phosphate concentration were determined using a kit from Linear chemical (Spain). Globin level was calculated from total protein and albumin levels. The kit from Biomérieux (France) was used for the determination of calcium. A kit from Randox (UK) was used to determine creatinine level.

Data analysis

The statistical package SPSS (version 17) (SPSS Inc. Chicago, IL, USA) was used to perform the statistical analysis. The normal distribution of the variables was determined using the Kolmogorov Smirnov test. Data with normal distribution were expressed as mean ± standard deviation (SD). To compare qualitative variables between the groups, one-way ANOVA, chi-square test and Pearson correlation were used. P values less than 0.05 were considered significant.

RESULTS

General characteristics and biochemical parameters of the patients are shown in Table 1. The mean age of the patients in the DN group was (49.39 ± 11.91), NH group was (50.93±15.87) years and of DNH group was (52.75± 8.85). All variables did not show a significant difference in all groups except for HbA1c, and FBG, which was significantly higher in DN and DNH groups in comparison to that of NH group ($P<0.05$) and blood pressure was higher in NH group in comparison to that of other groups ($P<0.05$).

The mean serum UA level was significantly higher ($P<0.05$) in DNH group when compared with NH and DN groups (9.88±0.96 vs. 5.18±0.75 and 6.56± 0.42 respectively), as shown in Fig. 1.

Pearson correlation of UA in all groups with the measured parameters in this study showed significant positive correlation ($P< 0.05$) with HbA1c, FBG as presented in Table 2. The correlation between UA and creatinine was positively weak in DN and in NH group while it was intermediate in DNH group (Fig. 2: A,B,C). Non- significant association was found with other parameters.

DISCUSSION

The results in this study revealed that patients with diabetic nephropathy and hypertension have hyperuricemia higher than the other groups.

Although many researchers pointed to the association between increased UA and many diseases such as chronic kidney disease (Borghi *et al*, 2014), hypertension (Feig *et al*, 2013; Grayson *et al*, 2011), and metabolic syndrome/T2DM (Borghi and Cicero, 2017) however, the exact mechanism for this association is unknown.

This result is in agreement with many studies that found elevated UA levels and suggested UA, in comparison to other inflammatory markers, may predict CVD risk (Rothenbacher *et al*, 2012; Kiani *et al*, 2014).

Serum UA was higher in a significant pattern in 90 diabetic patients as compared to healthy individuals but,

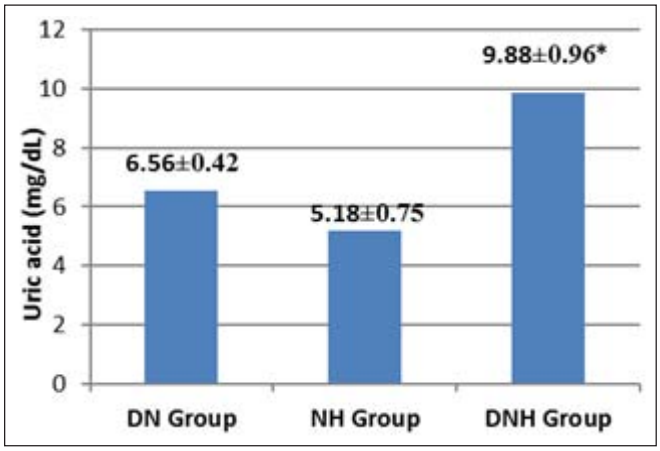

Fig. 1 : Mean (±SD) of UA levels in sera of patient's groups.

Table 1 : Characteristics and some biochemical parameters of patient´s groups.

Groups / Parameters	DN group	NH group	DNH group
No. of patients	35	40	40
Age (years)	49.39±11.91	50.93±15.87	52.75±8.85
Gender (m/f)	20/15	18/22	15/25
BMI (kg/m^2)	27.54± 2.56	27.14± 2.67	28.10± 1.21
Duration of the disease (years)	11. 6± 4.54	11.12± 3.21	13± 2.45
FBG mg/dl	144±75.19*	98±47.92	148±62.92 *
HbA1c %	9.34± 1.45*	6.04± 0.54	*8.91±2.41
SBP (mm Hg)	130 ± 11.05	154 ± 12.23	166 ± 11.89*
DBP(mm Hg)	77± 3.24	96 ± 5.45	96± 6.92*
B. Urea (mg/dl)	70.06±54.44	119.36±40.92	186.60±60.30**
Creatinine (mg/dl)	5.97± 1.77	6.64 ±3.37	9.91± 1.95
Calcium (mg/dl)	7.52± 1.65	7.91±2.26	8.29± 1.17
Phosphate (mg/dl)	4.68± 1.50	4.30± 1.39	4.16 ±1.74
Total protein (g/dl)	6.37± 1.32	7.06± 0.94	6.56±0.96
Globin (g/dl)	2.66±1.30	3.26 ± 1.03	2.95±0.74
Albumin (g/dl)	3.58±0.62	3.80± 0.73	3.61±0.56

*Values are expressed as mean (± SD). Significant difference when P<0.05. BMI: Body Mass Index; DBP: Diastolic Blood Pressure; FBG: Fasting Blood Sugar; HbA1c: glycated hemoglobin; SBP: Systolic Blood Pressure.

elevated UA levels were found significantly in T2DM in comparison to T1DM (Khalaf, 2010). Lytvyn *et al* (2015) found higher UA levels in T2DM, their results support the suggestion of using UA as a potential biomarker of CVD risk in T2DM, and it may be a good treatment target to reduce morbidity and mortality.

Also, an association between UA and HbA1c in 50 T2DM patients was found by the study of Pavithra *et al*

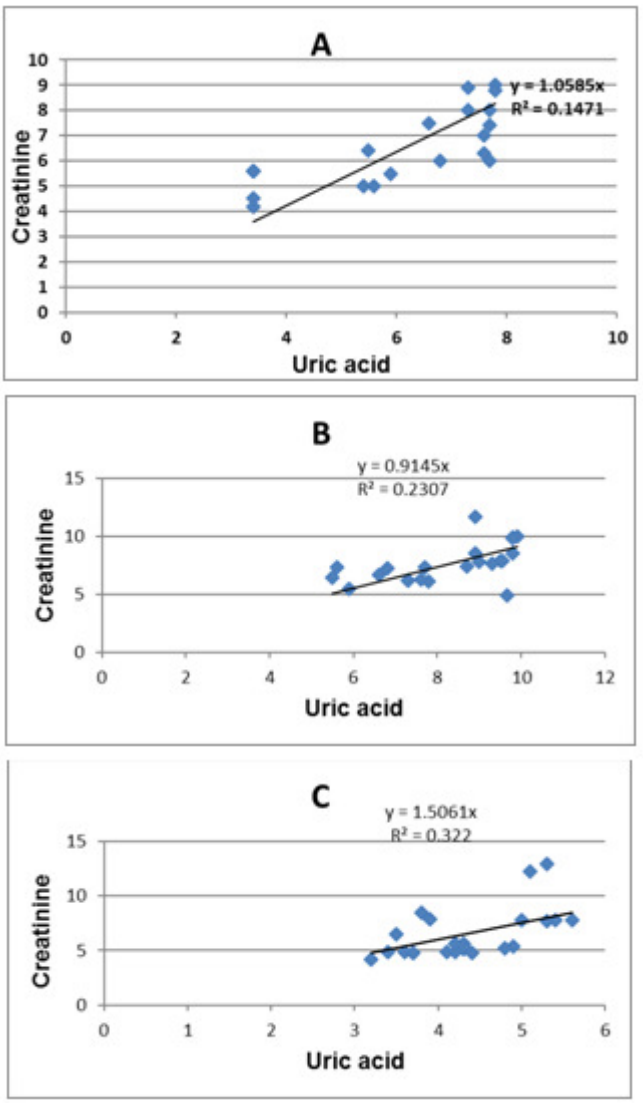

Fig. 2 : Pearson correlation between UA level and creatinine in A: DN, B: NH, C: DHN groups.

Table 2 : Pearson correlation of UA with biochemical indices of the diseases.

Parameters	DN	NH	DNH
HbA1c	0.42*	0.12	0.45*
FBG	0.47*	0.33	0.53*
Creatinine	0.38*	0.48*	0.56*

*Correlation is significant at the 0.05 level.

(2016) they also recommended the inclusion of UA measurement along with diabetic profile tests for T2DM patients.

The role of serum UA was revealed in a study of Kiani *et al* (2014). They mentioned that increase of UA with coronary heart disease, vascular disease, peripheral arterial disease, and stroke was shown in some studies (Daskalopoulou *et al*, 2004; Shankar *et al*, 2008). Regarding the microvascular complications of diabetes, the role of UA in the onset and progression of diabetic

nephropathy or albuminuria was shown in some studies (Hovind *et al*, 2009; Jalal *et al*, 2010). Also, the increase of UA level was reported in diabetic foot patients with retinopathy (Sochett *et al*, 2006).

It is well known that long-term hyperglycemia has many adverse outcomes in diabetic patients that lead to known complications such as diabetic neuropathy, nephropathy, diabetic foot ulcer along with other factors. Some studies observed the role of UA and its contribution in progression of DN or CVD (Lewis and Maxwell, 2014; Rothenbacher *et al*, 2012; AL-Shammaree, 2017).

Several studies have reported an association between UA and hypertension. A prospective observational study included 23,525 subjects, who had been followed up for at least 5 years found that high UA was significantly associated with the incidence of hypertension in non-metabolic syndrome subjects and they proposed management of UA and blood pressure levels to prevent cardiovascular events (Qing Chen *et al*, 2018).

The mechanism that explains the relation of UA and hypertension was explained through animal-based studies (Mazzali *et al*, 2001; Kanellis *et al*, 2005). When rats induced Hyperuricemia; many events lead to the renal and RASS activation also, changing the oxidative-antioxidant balance in favour of oxidative stress and decrease of endothelial nitric oxide production. These events lead to the development of mild hypertension that over time will cause changes in microvascular of the kidney, reduce renal blood flow and eventually hypertension independent of UA (Mazali *et al*, 2012). Experimental studies also confirmed the role of UA in animal models of diabetic nephropathy disease, calcineurin inhibitor nephrotoxicity, and acute kidney injury (Lytvyn *et al*, 2015; Kim *et al*, 2015).

CONCLUSION

This study revealed that ESRD patients have high UA levels and they are at high risk of CVD progression. The patients with diabetic nephropathy and hypertension (DNH) show higher risk than others. UA is a good marker to predict progression to CVD and may be good therapeutic target in ESRD.

ACKNOWLEDGMENTS

The author is very grateful to the staff of the Baghdad Medical City Hospital and laboratory for their collaboration.

REFERENCES

AL-Shammaree S A, Abu-ALkaseem B A and Salman I N (2017) Procalcitonin levels and other biochemical parameters in patients with or without diabetic foot complications. *J Res. Med. Sci.* **22**, 95-100.

Bellomo R, Ronco C, Kellum J A, Mehta R L and Palevsky P (2004) Acute renal failure–definition, outcome measures, animal models, fluid therapy and information technology needs: the Second International Consensus Conference of the Acute Dialysis Quality Initiative (ADQI) Group. *Critical Care* **8**(4), R204.

Borghi C and Cicero A F G. (2017) Serum UA and cardiometabolic disease: another brick in the wall? *Hypertension* **69**(6), 1011-1013.

Borghi C, Rosei E A, Bardin T, Dawson J, Dominiczak A, Kielstein J T and Mancia G (2015) Serum UA and the risk of cardiovascular and renal disease. *Journal of Hypertension* **33**(9), 1729-1741.

Daskalopoulou S S, Athyros V G, Elisaf M and Mikhailidis D P (2004) UA levels and vascular disease. *Current Medical Research and Opinion* **20**(6), 951-954.

Feig D I, Madero M, Jalal D I, Sanchez-Lozada L G and Johnson R J (2013) UA and the origins of hypertension. *The Journal of Pediatrics* **162**(5), 896-902.

Filiopoulos V, Hadjiyannakos D and Vlassopoulos D (2012) New insights into UA effects on the progression and prognosis of chronic kidney disease. *Renal Failure* **34**(4), 510-520.

Grayson P C, Kim S Y, LaValley M and Choi H K (2011) Hyperuricemia and incident hypertension: a systematic review and meta analysis. *Arthritis care and Research* **63**(1), 102-110.

Hovind P, Rossing P, Tarnow L, Johnson R J and Parving H H (2009) Serum uric acid as a predictor for development of diabetic nephropathy in type 1 diabetes: an inception cohort study. *Diabetes* **58**(7), 1668-1671.

Jalal D I, Rivard C J, Johnson R J, Maahs D M, McFann K, Rewers M and Snell-Bergeon J K (2010) 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. *Nephrology Dialysis Transplantation* **25**(6), 1865-1869.

Kanellis J and Kang D H (2005) Uric acid as a mediator of endothelial dysfunction, inflammation, and vascular disease. In *Seminars in Nephrology* **25**(1), 39-42. WB Saunders.

Khalaf S J (2010) Study of some biochemical markers in diabetic patients. *Medical Journal of Tikrit* **2**(162), 84-87.

Kiani J, Habibi Z, Tajziehchi A, Moghimbeigi A, Dehghan A and Azizkhani H (2014) Association between serum UA level and diabetic peripheral neuropathy (A case control study). *Caspian Journal of Internal Medicine* **5**(1), 17.

Kim S M, Lee S H, Kim Y G, Kim S Y, Seo J W, Choi Y W and Won K Y (2015) Hyperuricemia-induced NLRP3 activation of macrophage contributes to the progression of diabetic nephropathy. *American Journal of Physiology-Renal Physiology* **308**(9), F993-03.

Lewis G and Maxwell A P (2014) Risk factor control is key in diabetic nephropathy. *Practitioner* **258**(1768), 13-17.

Liu X, Zhai T, Ma R, Luo C, Wang H and Liu L (2018) Effects of UA-lowering therapy on the progression of chronic kidney disease: a systematic review and meta-analysis. *Renal Failure* **40**(1), 289-297.

Lytvyn Y, Perkins B A and Cherney D Z (2015) UA as a biomarker and a therapeutic target in diabetes. *Canadian Journal of Diabetes* **39**(3), 239-246.

Mazali F C, Johnson R J and Mazzali M (2012) Use of uric acid-lowering agents limits experimental cyclosporine nephropathy.

Nephron Experimental Nephrology **120**(1), e12-e19.

Mazzali M, Hughes J, Kim Y G, Jefferson J A, Kang D H, Gordon K L and Johnson R J (2001) Elevated uric acid increases blood pressure in the rat by a novel crystal-independent mechanism. *Hypertension* **38**(5), 1101-1106.

Mikolasevic I, •utelija M, Mavrinac V and Orlic L (2017) Dyslipidemia in patients with chronic kidney disease: etiology and management. *International Journal of Nephrology and Renovascular Disease* **10**, 35.

Pavithra V, Revathy K and Swaminathan S (2016) Association between UA and HbA1c in type 2 Diabetes Mellitus in Comparison with Controls. *Int. J. Curr. Microbiol. App. Sci.* **5**(4), 585-589.

Qing Chen, Yuan-Jun Yin, Wei-Yan Chen, Jian-Nong Wu and Xuan Huang (2018) Assessment of the association between serum UA levels and the incidence of hypertension in nonmetabolic syndrome subjects. *Medicine* **97**, 1-6.

Rothenbacher D, Kleiner A, Koenig W, Primatesta P, Breitling L P and Brenner H (2012) Relationship between inflammatory cytokines and UA levels with adverse cardiovascular outcomes in patients with stable coronary heart disease. *PloS One* **7**(9), e45907.

Shankar A, Klein B E, Nieto F J and Klein R (2008) Association between serum UA level and peripheral arterial disease. *Atherosclerosis* **196**, 749-755.

Sochett E B, Cherney D Z, Curtis J R, Dekker M G, Scholey J W and Miller J A (2006) Impact of renin angiotensin system modulation on the hyperfiltration state in type 1 diabetes. *Journal of the American Society of Nephrology* **17**(6), 1703-1709.

Stanton R C (2014) Clinical challenges in diagnosis and management of diabetic kidney disease. *American Journal of Kidney Diseases* **63**(2), S3-S21.

Tsuruya K, Yoshida H, Nagata M, Kitazono T, Hirakata H, Iseki K and Asahi K (2014) Association of the triglycerides to high-density lipoprotein cholesterol ratio with the risk of chronic kidney disease: analysis in a large Japanese population. *Atherosclerosis* **233**(1), 260-267.

Xue C, Nie W, Tang D, Yi L and Mei C (2013) Apolipoprotein E gene variants on the risk of end stage renal disease. *PloS One* **8**(12), e83367.

Yacoub R, Habib H, Lahdo A, Al Ali R, Varjabedian L, Atalla G and Albitar S (2010) Association between smoking and chronic kidney disease: a case control study. *BMC Public Health* **10**(1), 731.

Yu M A, Sánchez-Lozada L G, Johnson R J and Kang D H (2010) Oxidative stress with an activation of the renin–angiotensin system in human vascular endothelial cells as a novel mechanism of UA-induced endothelial dysfunction. *Journal of Hypertension* **28**(6), 1234-1242.

Yun Z, Yu-Ping Y, Zong-Wu T, Yang S, Fang Y and Fang S (2014) Association of endothelial nitric oxide synthase gene polymorphisms with end-stage renal disease: a systematic review and meta-analysis. *Renal Failure* **36**(6), 987-993.