European Review for Medical and Pharmacological Sciences 2018; 22: 506-511

Correlations between blood uric acid and the incidence and progression of type 2 diabetes nephropathy

G.-X. LI[1], X.-H. JIAO[2], X.-B. CHENG[3]

[1]Department of Endocrinology, The First People's Hospital of Wujiang District Suzhou, Suzhou, China
[2]Department of Endocrinology, Wujiang Hospital Affiliated Nantong University, Suzhou, China
[3]Department of Endocrinology, First Hospital Affiliated Suzhou University, Suzhou, China

Gengxu Li and Xuehua Jiao contributed equally to this work

Abstract. – OBJECTIVE: To investigate the relationships between blood uric acid (BUA) level and the incidence, progression and deterioration of diabetic nephropathy (DN) in patients with type 2 diabetes mellitus (T2DM).

PATIENTS AND METHODS: A total of fifty patients with T2DM alone whose glycosylated hemoglobin (HbA1c) were under normal range (4-6.5%) at their admission to our hospital were randomly selected as diabetes mellitus (DM) group. Fifty patients with hyperuricemia alone were randomly selected as hyperuricemia (HUA) group. Fifty patients with T2DM complicated with hyperuricemia who were admitted to the hospital with HbAlc of 4-6.5% were randomly selected as diabetes mellitus hyperuricemia (DM-HUA) group. In addition, fifty healthy persons who passed the health examination were randomly selected as normal control (NC) group. The general data such as name and body mass index (BMI), metabolic-related indexes such as fasting blood glucose (FBG), total cholesterol (TC) and triglyceride (TG) as well as kidney-related indexes such as blood urea nitrogen (BUN), creatinine (Cr) and albumin-creatinine-ratio (ACR) in four groups were tested and recorded at the same time. The interrelationships between uric acid (UA) and the above indexes were statistically analyzed.

RESULTS: In DM-HUA group, serum TC, TG and low density lipoprotein (LDL) as well as urine ACE were greatly increased ($p<0.05$) compared with the other three groups, high-density lipoprotein (HDL) was significantly decreased compared with the remaining three groups ($p<0.05$), and BMI and Cr were increased compared with those in NC group and DM group ($p<0.05$). There were no significant differences in metabolic indexes and renal functions in DM group and HUA group. Compared with NC group, TC, LDL, serum β2 macroglobulin and BMI in above two groups were greatly increased ($p<0.05$); BUN and Cr in HUA group were slightly higher than those in NC group ($p<0.05$). Multiple linear regression analysis showed that UA level was the main factor affecting ACR ($R^2=0.636$, $p<0.001$).

CONCLUSIONS: UA level is an independent risk factor for early renal disease in patients with T2DM, which can promote the progression and deterioration of renal disease in T2DM patients.

Key Words:
Hyperuricemia, Type 2 diabetes mellitus (T2DM), Diabetic nephropathy (DN), Urine albumin-creatinine-ratio (ACR).

Introduction

Diabetic nephropathy (DN) is one of the common chronic micro-vascular complications (MVC) of Type 2 diabetes mellitus (T2DM). It is the main cause of end-stage renal failure, which is also one of the important causes of death and disability in diabetes mellitus (DM) patients[1-3]. The increase of microalbuminuria in diabetic patients is a characteristic of DN, and it is also a common indicator in prediction of renal function of DN. The detection of albumin creatinine ratio (ACR) in morning urine of diabetic patients is a common method for clinically screening the incidence of renal diseases in diabetic patients[4-6]. Serum β2 microglobulin can reflect the filtration function of kidney, which is a sensitive and specific index to determine the early renal damage[7,8]. The combined detection of serum β2 microglobulin and ACR in the morning urine has important significance in the early detection of the occurrence of diabetic glomerular and tubular lesions so as to timely control the occurrence and progression of DN. Previous researches[9,10] have shown that hyperuricemia is closely related

Corresponding Author: Xuehua Jiao, MM; e-mail: 1178336323@qq.com

to metabolic syndrome and cardiovascular and cerebrovascular diseases. However, there are few researches on the relationships between hyperuricemia and the occurrence and progression of renal diseases, especially DN. Therefore, this study focuses on the relationships between the level of blood uric acid (BUA) and the occurrence and progression of renal lesions in T2DM patients with stable blood glucose.

Patients and Methods

Patients

T2DM patients under stable control of blood glucose (HbA1c 4-6.5% checked at admission) admitted to our hospital from January 2015 to January 2017, patients with hyperuricemia (male > 430 umol/L, female > 360 umol/L) and normal population passed the healthy examination were collected, in which 50 patients with T2DM alone were randomly selected as DM group, patients with T2DM complicated with hyperuricemia were randomly selected as DM-HUA group, and 50 cases of healthy people were randomly selected as normal control (NC) group. This investigation was approved by the Ethics Committee of Wujiang Hospital Affiliated Nantong University. Signed written informed consents were obtained from all participants before the study.

Methods

The medical history was collected to define the age, gender and course of disease; the height, weight and blood pressure was measured. Roche cobos701 fully automatic biochemical analyzer was used to determine levels of uric acid (UA), glycosylated hemoglobin (HbAlc), triglyceride (TG), serum total cholesterol (TC), low density lipoprotein cholesterol (LDL-c), high density lipoprotein cholesterol (HDL-c), blood urea nitrogen (BUN), serum creatinine (Cr) and serum β2 microglobulin on the next day with empty stomachs of patients. The detection of UA levels required to acquire two fasting blood samples on different days and take the average value. The mid-stream urine ACR was detected by the Norway AS001 fully automatic biochemical analyzer through gold labeling method, and the mid-stream urine was retained after six months to take the average value.

Statistical Analysis

All statistics were performed using Statistical Product and Service Solutions (SPSS) 20.0 software (IBM, Armonk, NY USA). Normality analysis and homogeneity of variance was analyzed at first. Normal distributed data were analyzed by one-way analysis of variance, the quantitative data was expressed as $\bar{x}\pm s$, and *t*-test was performed for the comparison between groups. Non-normal distribution data were expressed as median and analyzed by non-parametric statistics (Kruskal-Willas). Single factor analysis was used to evaluate the relationship between urinary albumin serum creatinine ratio (ACR) and relevant risk factors. The statistically significant factors were screened for multivariate Logistic regression analysis. $p<0.05$ suggested that the difference was statistically significant.

Results

Comparisons of Physical Examination Indexes Among Groups

There were no statistical differences in gender composition, age composition, course of diabetes and blood pressure in four groups ($p>0.05$, Table I). BMI in DM-HUA group was higher than those in NC group and DM group ($p<0.05$, Table I); BMIs in DM group and HUA group were higher than that in NC group ($p<0.05$, Table I); BMI in HUA group was higher than that in DM group ($p<0.05$, Table I).

Table I. Baseline characteristic of included subjects.

	Age (year)	Male (%)	DUR (year)	BMI (kg/m^2)	SBP (mmHg)	DBP (mmHg)
NC	52.18±10.78	23(46)	-	22.93±0.71	126±22	80±21
HUA	54.36±9.76	23(46)	-	27.55±0.78ac	129±18	82±19
DM	55.05±7.67	25(50)	7.16±4.31	26.42±0.45a	130±23	82±22
DM-HUA	56.24±8.93	26(52)	7.56±6.61	27.96±0.96ac	132±20	85±24

Abbreviation: NC, normal control; HUA: hyperuricemia; DM, diabetes mellitus; DM-HUA, diabetes-hyperuricemia; BMI, body mass index; SBP: systolic blood pressure, DBP: diastolic blood pressure. Note: [a], $p<0.05$ in comparison with NC group; [b], $p<0.05$ in comparison with HUA group; [c], $p<0.05$ in comparison with DM group.

Table II. Metabolism related indicators of included subjects

	FBG (mmol/L)	HbA1c (%)	UA (umol/L)	TC (mmol/L)	TG (mmol/L)	HDL-c (mmol/L)	LDL-c (mmol/L)
NC	6.08±1.98	6.68±1.76	275.26±64.50	3.47±0.18	1.42±0.89	1.22±0.04	1.60±0.15
HUA	6.44±2.16	6.86±1.95	521.74±131.18	4.58±0.20[a]	1.79±0.37	1.16±0.06	2.82±0.19[a]
DM	6.86±2.47	6.95±1.84	309.19±75.63	4.41±0.23[a]	2.14±0.41	1.09±0.27[a]	2.54±0.17[a]
DM-HUA	7.05±2.33	6.99±1.92	504.85±80.29	5.11±0.21[abc]	3.11±0.45[abc]	0.92±0.03[abc]	3.43±0.18[abc]

Abbreviation: NC, normal control; HUA: hyperuricemia; DM, diabetes mellitus; DM-HUA, diabetes-hyperuricemia; FBG, fasting blood sugar; HbA1c, glycated hemoglobin; UA, Uric acid; TC, total cholesterol; TG, triglycerides; HDL-c, high-density lipoprotein cholesterol; LDL-c, low-density lipoprotein cholesterol. Note: [a], $p<0.05$ in comparison with NC group; [b], $p<0.05$ in comparison with HUA group; [c], $p<0.05$ in comparison with DM group.

Table III. Kidney related indicators of included subjects.

	BUN (mmol/L)	Scr (umol/L)	β2-microglobulin (mmol/L)	ACR (mg/mmol/L)
NC	4.32±0.31	55.36±3.47	1.76±0.17	0.82±0.09
HUA	5.96±0.65[a]	94.72±10.51[ac]	2.48±0.32[a]	1.89±0.31
DM	5.61±0.36	72.24±5.69	3.05±0.24[a]	2.44±0.42[a]
DM-HUA	6.64±0.49[a]	90.65±4.84[ac]	3.53±0.38[ab]	6.53±0.97[abc]

Abbreviation: NC, normal control; HUA: hyperuricemia; DM, diabetes mellitus; DM-HUA, diabetes-hyperuricemia; FBG, fasting blood sugar; HbA1c, glycated hemoglobin; UA, Uric acid; TC, total cholesterol; TG, triglycerides; HDL-c, high-density lipoprotein cholesterol; LDL-c, low-density lipoprotein cholesterol. Note: [a], $p<0.05$ in comparison with NC group; [b], $p<0.05$ in comparison with HUA group; [c], $p<0.05$ in comparison with DM group.

Comparisons of Metabolic-Related Indexes Among Groups

In DM-HUA group, TC, TG and LDL-C were significantly higher than those in other three groups, and HDL-C was significantly decreased compared with that in other three groups ($p<0.05$, Table II). TC and LDL-C in DM group and HUA group were higher than those in NC group ($p<0.05$, Table II). HDL-C in DM group was lower than that in NC group ($p<0.05$, Table II).

Comparisons of Renal Damage Indexes Among Groups

Compared with other three groups, urine ACR in DM-HUA group was significantly increased ($p<0.05$, Table III); compared with NC group and DM group, its Cr was increased ($p<0.05$, Table III). Serum β2 microglobulin in DM-HUA group was only higher than those in NC group and HUA group ($p<0.05$, Table III); the blood BUN was only higher than that in NC group ($p<0.05$, Table III). Only urine ACR and blood BUN in DM group were increased compared with those in NC group ($p<0.05$, Table III). Compared with NC group and DM group, Cr in HUA group was increased ($p<0.05$, Table III); blood BUN and blood β2 microglobulin in HUA group were only higher than those in NC group ($p<0.05$, Table III).

Related Results of Regression Analysis

The urine ACR was taken as dependent variable; age, gender, BMI, fasting blood glucose (FBG), UA, TC, TG, HDL-C, LDL-C, BUN, Cr and serum β2 microglobulin were regarded as independent variables; BMI, UA, TG, BUN, Cr and serum β2 microglobulin factors showed by univariate logistic regression analysis were influencing factors of urine ACR ($p<0.05$, Table IV). The above factors were used as independent variables to conduct multivariate logistic regression analysis, and the results showed that UA was the main influencing factor of urine ACR ($F=30.528$, $R^2=0.636$, $p<0.000$, Table V).

Discussion

The detection of ACR is a simple and convenient operation. It can accurately reflect the excretion of microalbuminuria in diabetic patients and improve the detection rate of early DN[4-6]. Therefore, it is widely used in screening and follow-up of DN patients.

UA is the product of human purine metabolism. The increase of UA in the body or (and) the decrease in excretion of UA can cause the increase of BUA level. In the studies on the rela-

Table IV. Univariate Logistic regression analysis

	BMI	UA	TG	BUN	Scr	β2-microglobulin
B	0.224	0.015	0.302	0.216	0.239	0.328
p	<0.01	<0.01	<0.01	<0.05	<0.01	<0.01

Abbreviation: BMI, body mass index; UA, uricemia; TG, triglycerides; BUN, blood urea nitrogen; Scr, serum creatinine. Note: $p<0.05$ suggested statistical significance.

Table V. Multivariate logistic regression analysis.

	B	SE	Standard β	*t*	F	R^2	*p*
UA	0.014	0.02	0.913	6.125	30.528	0.6136	<0.001

Abbreviation: UA, uricemia. Note: $p<0.05$ suggested statistical significance.

tionship between UA and kidney disease, some have shown that hyperuricemia is closely related to kidney disease and long-term hyperuricemia can lead to damage and deterioration of renal function[11-14]. HUA may aggravate the development of DN. But there are many factors that affect the incidence and progression of DN, including a variety of confounding factors, among which the course of diabetes and the control of blood glucose are contained. If blood glucose control is unstable, the greater the fluctuation is, the more severe the blood vessel damage in diabetic patients will be. As a result, the more serious DN will be. At the same time, the course of diabetes also affects the incidence and development of kidney disease. The longer the course of disease is, the greater the damage made by kidney disease will be. Therefore, in the case of the correction on the blood glucose fluctuation and the duration of diabetes, T2DM patients with stable glucose control and disease duration showing no significant differences were selected to conduct the comparisons of kidney and metabolism-related indexes. A study showed that the level of BUA is negatively related to islet β cell function in diabetic patients, suggesting that the level of UA is closely related to diabetes[12,15]. In addition, studies[11,14] have suggested that BUA can be used to monitor early pathological changes of DN and to predict the prognosis of DN. Some researches have suggested that UA is closely related to DN that occurs shortly after hyperuricemia in patients with type 1 diabetes mellitus (T1DM), which can independently predict its occurrence[15]. However, the relationship between BUA and renal disease in T2DM patients is not much researched. Some studies have shown that hyperuricemia is an important predictor of 24 hours abnormality of the urine microalbumin (Alb) in T2DM patients[16]. It also shows that hyperuricemia can independently predict the risk of chronic kidney disease (CKD) in T2DM patients with normal or near normal renal function. Studies have reported that long-term hyperuricemia is closely related to type 2 diabetic nephropathy (T2DN), which can cause kidney damage in T2DM patients. Moreover, T2DM patients with hyperuricemia are more likely to have kidney damage. Studies[11,14] of participants with normal or near normal renal function in T2DM showed that hyperuricemia can independently predict the risk of CKD. At the same time, some observational experiments have confirmed that the treatment by reducing BUA level in diabetic patients can be used to prevent the decline of renal function in diabetic patients[17]. It was confirmed in this work that BUA is closely associated with T2DM and it is an independent risk factor for the incidence and progression of T2DN, which is consistent with the results of the above studies.

Animal experiments have shown that hyperuricemia cannot only cause glomerular hypertrophy in mice, but also lead to glomerular sclerosis[18]. At the same time, the model study of T2DM showed that hyperuricemia can lead to the renal tubular and interstitial injury in mice model of T2DM; renal tubulointerstitial damage is alleviated by the reduction of UA through allopurinol therapy. The predicted mechanism may be the blockage of inflammation reaction process in kidney induced by UA. Basic research also supports that microinflammation plays a role in renal vascular endothelial injury induced by UA, suggesting that the mechanism of UA affecting kidney disease may be mediated by inflammatory reaction.

However, the exact mechanism of how UA affects the incidence and progression of nephropathy in diabetic patients is unknown. Therefore, a large number of animal experiments and large-scale clinical observations and experiments are needed to elucidate. To sum up, BUA is closely related to T2DN and there may be many unknown relationships. Therefore, further exploration and more thorough research are needed to confirm how BUA promotes the incidence and development of renal disease.

Conclusions

Hyperuricemia is associated with abnormal metabolism of blood lipid and overweight. It is a risk factor for abnormal metabolism of blood lipid and overweight. UA is the main factor affecting the urine ACR, which is an independent risk factor for the early pathological changes of DN in T2DM patients. The degree of renal damage in patients with T2DM complicated with hyperuricemia is more severe than that in patients with T2DM alone. Hyperuricemia can promote the progression and deterioration of renal disease in T2DM patients.

Acknowledgements

This study was supported by the Project of Boosting Health-Care through Science and Education of Suzhou, Jiangsu Province (KJXW2015058).

Conflict of Interest

The Authors declare that they have no conflict of interests.

References

1) Shen Z, Fang Y, Xing T, Wang F. Diabetic nephropathy: from pathophysiology to treatment. J Diabetes Res 2017; 2017: 1-2.
2) Taghizadeh M, Soleimani A, Bahmani F, Moravveji A, Asadi A, Amirani E, Farzin N, Sharifi N, Naseri A, Dastorani M, Asemi Z. Metabolic response to mulberry extract supplementation in patients with diabetic nephropathy: a randomized controlled trial. Iran J Kidney Dis 2017; 11: 438-446.
3) Xu XH, Ding DF, Yong HJ, Dong CL, You N, Ye XL, Pan ML, Ma JH, You Q, Lu YB. Resveratrol transcriptionally regulates miRNA-18a-5p expression ameliorating diabetic nephropathy via increasing autophagy. Eur Rev Med Pharmacol Sci 2017; 21: 4952-4965.
4) Wang C, Ma S, Deng B, Lu J, Shen W, Jin B, Shi H, Ding F. The predictive value of the product of contrast medium volume and urinary albumin/creatinine ratio in contrast-induced acute kidney injury. Ren Fail 2017; 39: 555-560.
5) Hasanato RM. Diagnostic efficacy of random albumin creatinine ratio for detection of micro and macro-albuminuria in type 2 diabetes mellitus. Saudi Med J 2016; 37: 268-273.
6) Park JI, Baek H, Kim BR, Jung HH. Comparison of urine dipstick and albumin:creatinine ratio for chronic kidney disease screening: a population-based study. PLoS One 2017; 12: e171106.
7) Spaggiari E, Faure G, Dreux S, Czerkiewicz I, Stirnemann JJ, Guimiot F, Heidet L, Favre R, Salomon LJ, Oury JF, Ville Y, Muller F. Sequential fetal serum beta2-microglobulin to predict postnatal renal function in bilateral or low urinary tract obstruction. Ultrasound Obstet Gynecol 2017; 49: 617-622.
8) Okuno S, Ishimura E, Kohno K, Fujino-Katoh Y, Maeno Y, Yamakawa T, Inaba M, Nishizawa Y. Serum beta2-microglobulin level is a significant predictor of mortality in maintenance haemodialysis patients. Nephrol Dial Transplant 2009; 24: 571-577.
9) Kountouras J, Polyzos SA, Katsinelos P, Zeglinas C, Artemaki F, Tzivras D, Vardaka E, Gavalas E, Romiopoulos I, Simeonidou C, Grigoriadis N, Kountouras C, Dardiotis E, Deretzi G. Cardio-cerebrovascular disease and Helicobacter pylori-related metabolic syndrome: we consider eradication therapy as a potential cardio-cerebrovascular prevention strategy. Int J Cardiol 2017; 229: 17-18.
10) Wang J, Qin T, Chen J, Li Y, Wang L, Huang H, Li J. Hyperuricemia and risk of incident hypertension: a systematic review and meta-analysis of observational studies. PLoS One 2014; 9: e114259.
11) Komendarek-Kowalska M. The assessment of renal function in patients with newly diagnosed hypertension-the role of hyperuricemia as a risk factor for chronic kidney disease--preliminary study. Pol Merkur Lekarski 2017; 42: 193-196.
12) Mortada I. Hyperuricemia, type 2 diabetes mellitus, and hypertension: an emerging association. Curr Hypertens Rep 2017; 19: 69.
13) Petreski T, Bevc S, Ekart R, Hojs R. Hyperuricemia and long-term survival in patients with chronic kidney disease undergoing hemodialysis. Clin Nephrol 2017; 88: 69-72.
14) Komendarek-Kowalska M. The assessment of renal function in patients with newly diagnosed hypertension – the role of hyperuricemia as a risk factor for chronic kidney disease – preliminary study. Pol Merkur Lekarski 2017; 42: 193-196.
15) Gul A, Harford A, Zager P. Mendelian randomization to establish the causality of uric acid with diabetic nephropathy in type 1 diabetics. Kidney Int 2017; 91: 1005-1007.

16) Agha A, Bashir K, Anwar E. Use of losartan in reducing microalbuminuria in normotensive patients with type-2 diabetes mellitus. Nepal Med Coll J 2007; 9: 79-83.

17) Haller H, Ji L, Stahl K, Bertram A, Menne J. Molecular mechanisms and treatment strategies in diabetic nephropathy: new avenues for calcium dobesilate-free radical scavenger and growth factor inhibition. Biomed Res Int 2017; 2017: 1909258.

18) Shao YX, Xu XX, Wang K, Qi XM, Wu YG. Paeoniflorin attenuates incipient diabetic nephropathy in streptozotocin-induced mice by the suppression of the toll-like receptor-2 signaling pathway. Drug Des Devel Ther 2017; 11: 3221-3233.