Research Article

Evaluation of the relationship between serum uric acid level and proteinuria in patients with type 2 diabetes

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Abstract

Introduction: Diabetes mellitus and diabetic nephropathy are the most common causes of end-stage renal disease (ESRD) in developed countries, accounting for about 30% of these cases. Up to 40% of patients with type 2 diabetes with micro albumin uria progress to overt nephropathy and develop ESRD after one to two decades. Albumin uria is the most important indicator of diabetic nephropathy and its progression. Also, hyperuricemia has been suggested as a risk factor for kidney damage, this study was designed to determine the relationship between serum uric acid level and proteinuria in patients with type 2 diabetes.

Materials and methods: In this descriptive-analytical and cross-sectional study, data collection was performed among patients with type 2 diabetes referred to the diabetic Center in Gorgan from the years 2015 to 2018. The data collection tool was a two-part questionnaire including demographic and anthropometric characteristics and information about the disease. Serum levels of Uric Acid, Blood Urea Nitrogen (BUN), Creatinine (Cr), Fasting Blood Sugar (FBS) and Hemoglobin A1C (HbA1C) were measured in all patients. 24-hour urine collection was performed for proteinuria, albuminuria, urinary volume, and Cr volume. Patients' GFR was also calculated using the CKD-EPI formula. Patients were re-evaluated 1 year after the initial evaluation in terms of measured factors and the relationship between serum uric acid and albuminuria, proteinuria, kidney function, and other serum factors were evaluated.

Results: Among 823 diabetic patients that were referred to the nephrology center in this study, 90 patients were included. 34 (37.8%) of these patients were men. The age range of patients was between 32 years to 70 years with a mean of 56.31 and a standard deviation of 7.84 years. According to the Pearson correlation coefficient, a direct correlation was observed between uric acid with proteinuria and creatinine levels, and an inverse correlation was observed between uric acid and GFR. But we didn't find any correlation between uric acid and microalbuminuria.

Conclusion: According to the results of this study, the relationship between uric acid level and the severity of nephropathy (based on proteinuria) is proven. It seems that maintaining serum uric acid levels in patients with type 2 diabetes within the normal range and treatment with serum uric acid-lowering drugs may be possible to reduce the progression of diabetic nephropathy and proteinuria.

Introduction

Diabetes mellitus refers to a heterogeneous group of metabolic diseases that are associated with chronic hyper-glycemia and impaired metabolism of carbohydrates, lipids, and proteins. This condition is caused by a disorder in the secretion of insulin, insulin function, or both. In the United States, diabetes mellitus is the sixth leading cause of death from disease, accounting for 18% of all deaths in people over the age of 25 and is the leading cause of ESRD, new cases of blindness, and non-traumatic lower limb amputations [1,2].

Diabetic nephropathy is the most common cause of ESRD in developed countries, accounting for about 30% - 40% of these cases [3,4]. The prevalence of diabetic nephropathy in Iran is 20% of type 2 diabetics and 75% of type 1 diabetics

in 20 years and the incidence of this complication increases in proportion to the duration of the disease. In people with type 2 diabetes, there is less progression to ESRD than in people with type 1 diabetes (20% *vs.* 75% after 20 years) [3]. Initially, renal blood flow is increased in these patients, leading to glomerular hypertrophy, renal enlargement, mesenchymal matrix expansion and glomerular basement membrane thickening, leading to glomerulosclerosis. Subsequently, glomerular filtration becomes normal and intraglomerular pressure increases, and 5 years to 15 years after the diagnosis of diabetes, microalbuminuria develops (20 micrograms per minute to 200 micrograms per minute; 30 mg to 300 mg in 24 hours). Without any intervention, approximately 80% of patients with type 1 diabetes with microalbuminuria progress to overt nephropathy after 10 years to 15 years, eventually 50% after 10 years, and 75% after 20 years become ESRD [5,6]. 20% - 40% of type 2 diabetic patients with microalbuminuria progress to overt nephropathy and 20% of them develop the end-stage renal disease (ESRD) after 20 years [7-9]. Proteinuria screening should be performed annually in all patients, starting immediately after the diagnosis of type 2 diabetes and 5 years after the diagnosis of patients with type 1 diabetes. The simplest method of microalbuminuria screening is to measure the albumin-to-creatinine ratio in random spot urine samples. This measurement is largely consistent with the 24-hour urine protein estimate [9,10]. Information about nephropathy in developing countries is very limited. Available data between 1971 and 2002 showed that the prevalence of nephropathy at different stages of the disease was between 26% - 75% [11-14]. Early treatment and attention to the quality of life prevent the progression of microalbuminuria to macroalbuminuria and eventually ESRD. Therefore, screening patients as soon as possible in the microalbuminuria stage is very important [15,16].

Uric acid is the end product of purine metabolism. Purine is produced in the human body and is a weak acid with a pKa of 5.57 to 10.3. Naturally, two-thirds of urate, the ionized form of uric acid, is excreted by the kidneys and the rest by bile and secretions in the stomach and intestines. Serum urate concentrations vary with age and sex. The average serum urate level in non-menopausal women is lower than in adult men, but increases after menopause and reaches almost the same level in men [17].

Hyperuricemia may be associated with pre-glomerular vascular injury, increased glomerular blood pressure, and decreased renal perfusion, and may cause interstitial fibrosis [18-20]. In patients with type 2 diabetes, hyperuricemia, peripheral arterial disease, hypertension, hypertriglyceridemia, higher HbA1C, higher albuminuria, lower glomerular filtration rate (GFR), and early onset or faster progression of diabetic nephropathy have been reported as a risk factor of kidney dysfunction [21,22]. One study reported that hyperuricemia, independent of blood pressure control, causes glomerular hypertrophy [23,24]. In one study in hypertensive mice, allopurinol reduced renal damage by reducing uric acid [24] and in another animal model, mild hyperuricemia showed increased glomerular pressure and thickening of the afferent arteries and accelerates the progression of kidney disease [25]. In a 7-year study of 21,475 people, the risk of developing kidney disease nearly doubled with an increase in uric acid levels from 7 mg/dL to 8.9 mg/dL. This study showed that hyperuricemia is a risk factor for kidney disease [26].

African Americans and Hispanics with diabetes have a higher incidence of early chronic kidney disease than whites, which is significantly associated with urinary albumin excretion or CRP [27].

Adequate studies have not been performed on uric acid levels and ethnic differences and their association with proteinuria. Therefore, considering that albuminuria is the most important indicator of diabetic nephropathy and its progression and hyperuricemia has been proposed as a risk factor for renal injury, this study was designed to determine the relationship between serum uric acid level and proteinuria in patients with type 2 diabetes.

Materials and methods

In this descriptive-analytical and cross-sectional study, patients with type 2 diabetes who were referred to the Diabetes Control Center in Gorgan from 2015 to 2018 to be evaluated for diabetic nephropathy were selected to participate in the study. After obtaining informed written consent, eligible patients were included in the study. Sampling was performed by available and non-random methods among patients with type 2 diabetes. The data collection tool was a two-part questionnaire including demographic and anthropometric characteristics such as age, gender, ethnicity, BMI, systolic and diastolic blood pressure, and information about the disease like the duration of diabetes and how to control diabetes. Initially, serum levels of Uric Acid, BUN, Cr, FBS and HbA1c were measured for all patients. 24-hour urine collection was performed for microalbuminuria, proteinuria, urine volume, and creatinine. The patient's blood pressure was measured and recorded using a standard hand-held sphygmomanometer in a sitting position and after resting twice at intervals of at least 6 hours. Patients' GFR was also calculated using the CKD-EPI formula as follows;

GFR = [175 × Serum Cr $^{-1.154}$ × age $^{-0.203}$ × 1.212 (if patient is black) × 0.742 (if female)] (Use Serum Cr in mg/dL for this formula)

Patients were re-evaluated up to 1 year after the initial examination in terms of measured factors and changes in serum levels of Uric Acid and other factors and its relationship with proteinuria, kidney function and other serum factors were evaluated.

To describe the quantitatively symmetric traits of mean and standard deviation and the quantitatively asymmetric traits of the middle (first and third quarters) were reported. To analyze the data, first, the normality of data distribution was checked using the Shapiro-Wilk test. If the data distribution was normal, the Pearson correlation coefficient was used to determine the relationship between variables, otherwise, the Spearman correlation coefficient was used. A linear regression model was also used to determine how the relationship between variables. R software version 4.0.2 was used for data analysis. The significance level was equal to 0.05.

Inclusion criteria were type 2 diabetes and informed consent to participate in the study.

Exclusion criteria also were renal impairment or renal insufficiency (serum Creatinine greater than or equal to 1.4 mg/dL), congenital renal malformations, use of nephrotoxic drugs, treatment with diuretics and uric acid-lowering drugs, Urinary tract infection, fever and congestive heart failure (CHF).

Ethical considerations

The study was performed after obtaining permission from the Vice Chancellor for Research and Technology of Golestan University of Medical Sciences, coordination with the treating physician, and obtaining patient consent, and all information was kept confidential with the researcher. No intervention was made for patients. Other cases are in accordance with the standards of the Golestan University of Medical Sciences.

Implementing limitations of the plan and the method of reducing or solving them: Lack of cooperation and proper follow-up of patients can be largely solved by providing the necessary explanations and guiding the patients.

Results

In this study, 90 patients with type 2 diabetes were studied, of which 34 (37.8%) were male. The age range of patients was between 32 years to 70 years with a mean of 56.31 and a standard deviation of 7.84 years (Table 1).

According to the Pearson correlation coefficient, a direct correlation was observed between uric acid and excretory protein (R = 0.738, p - value < 0.0001) and creatinine (R = 0.494, p - value < 0.0001) levels, but an inverse correlation was observed between GFR and uric acid (R = -0.385, p - value < 0.0001) and the relationship between hoops was examined from one year and confirmed the preliminary results Tables 2,3.

As shown in Table 4, age, weight, and BMI were not statistically different between the groups. For example, in proteinuria, we have two groups of less than 150 mg and more than 150 mg. These two groups do not have statistically

significant differences in terms of age and gender BMI Table 5.

By controlling protein levels, the mean uric acid increased by 2,515 units per unit increase in creatinine, which is significant (Regression coefficient = 2.515, p - value = 0.001) Table 6.

Table 1: Frequency (%) or mean ± standard deviation or median (1st quarter, 3rd quarter).

Gender	Male	34 (37.8%)
	Female	56 (62.2%)
Ethnicity	Fars	66 (73.3%)
	Turkmen	15 (16.7%)
	Sistani	4 (4.4%)
	Baloch	3 (3.3%)
	Other	2 (2.2%)
Type of treatment	Oral	60 (66.7%)
	Insulin	25 (27.8%)
	Oral and Insulin	5 (5.6%)
Age		56.31 ± 7.84
BMI		30.23 ± 4.19
Systolic pressure		137.86 ± 25.08
Diastolic pressure		77.36 ± 12.53
Duration of disease		8.28 ± 5.18
Cr 1		0.89 ± 0.21
FBS 1		142.98 ± 37.36
BUN 1		19.96 ± 8.88
HbA1c 1		7.45 ± 1.40
Pro Uria 1		385.03 ± 650.688
Uric Acid 1		5.04 ± 2.11
GFR 1		79.44 ± 23.17
Cr 2		0.95 ± 0.33
FBS 2		149.33 ± 45.24
BUN 2		13.0 (22.0, 27.7)
HbA1c 2		8.09 ± 1.71
Pro Uria 2		432.78 ± 774.01
Uric Acid 2		5.14 ± 1.87
GFR 2		75.88 ± 24.38

Description: Frequency (%) was reported for qualitative variables. For quantitatively symmetric variables, the mean ± standard deviation was reported and for quantitatively asymmetric variables was the Median (1st quarter, 3rd quarter).
Group 1: Initial evaluation of patients, Group 2: Secondary evaluation of patients.

Table 2: Correlation coefficient of Pearson and Uric Acid, Creatinine and GFR.

	Pearson correlation	Sig. (2-tailed)
Pro Uria 1 - Uric Acid 1	0.738	< 0.001
Pro Uria 2 - Uric Acid 2	0.491	< 0.001
GFR 1 - Uric Acid 1	-0.385	< 0.001
GFR 2 - Uric Acid 2	-0.368	< 0.001
Cr 1 - Uric Acid 1	0.494	< 0.001
Cr 2 - Uric Acid 2	0.351	0.001

Description: Group 1: Initial evaluation of patients, Group 2: Secondary evaluation of patients.

Table 3: T - test to compare the mean of Uric Acid in the levels of the following variables.

		Group 1			Group 2		
		N	Mean	p - value	N	Mean	p - value
Pro uria	Less than 150	37	3.97	< 0.001	39	4.16	< 0.001
	More than 150	53	5.79		51	5.88	
GFR	Less than 90	64	5.44	< 0.001	67	5.42	0.053
	More than 90	26	4.07		22	4.30	

Description: The results indicate that the mean of uric acid 1 in proteinuria group 1 is more than 150 than less than 150, which according to the Mann-Whitney test, this difference is statistically significant. Also, the mean of uric acid 1 in proteinuria group 1 is more than 90 compared to less than 90, which according to the Mann-Whitney test, this difference is statistically significant.

Table 4: Adjusting for age, sex, and BMI among the groups compared in Table 3.

		Group 1 (*p* - value)			Group 2 (*p* - value)		
		age	gender	BMI	age	gender	BMI
Pro uria	Less than 150	0.157	0.536	0.869	0.059	0.525	0.241
	More than 150						
GFR	Less than 90	0.546	0.217	0.841	0.054	0.209	0.481

Table 5: The effect of study variables on Uric Acid in the first and second periods using simple linear regression of one variable.

Variable	First round		Second round	
	(Confidence interval) Coefficient	Signify	(Confidence interval) Coefficient	Signify
Gender (male *vs.* female)	0.315 (-0.598, 1.229)	0.494	0.321 (-0.491, 1.133)	0.434
Age	-0.011 (-0.068, 0.046)	0.704	-0.001 (-0.052, 0.049)	0.957
BMI	0.015 (-0.091, 0.121)	0.779	-0.005 (-0.100, 0.089)	0.909
Systolic pressure	0.002 (-0.016, 0.020)	0.843	0.002 (-0.014, 0.018)	0.792
Diastolic pressure	-0.012 (-0.047, 0.024)	0.511	-0.008 (-0.040, 0.024)	0.611
Duration of the disease	-0.010 (-0.096, 0.076)	0.818	0.001 (-0.076, 0.078)	0.977
Cr	4.930 (3.091, 6.768)	< 0.001	1.971 (0.857, 3.085)	0.001
FBS	0.003 (-0.009, 0.015)	0.576	0.003 (-0.005, 0.012)	0.436
BUN	-0.014 (-0.064, 0.036)	0.581	0.014 (0.005, 0.023)	0.003
HbA1C	-0.157 (-0.473, 0.160)	0.328	0.030 (-0.202, 0.262)	0.797
Pro uria	0.002 (0.002, 0.003)	< 0.001	0.001 (0.001, 0.002)	< 0.001
GFR	-0.035 (-0.053, -0.017)	< 0.001	-0.028 (-0.043, -0.013)	< 0.001

Table 6: The effect of study variables on Uric Acid in the first and second periods using multiple simple linear regression by the Backward method.

Variable	First round		Second round	
	(Confidence interval) Coefficient	Signify	(Confidence interval) Coefficient	Signify
Cr	2.515 (1.063, 3.967)	0.001	-	-
Pro uria	0.002 (0.002, 0.003)	< 0.001	0.001 (0.001, 0.002)	< 0.001
GFR	-	-	-0.017 (-0.032, -0.002)	0.025

Discussion

The overall aim of this study was to determine the relationship between serum uric acid and proteinuria in patients with type 2 diabetes. Patients, in addition to examining this relationship, in terms of items and factors that may be related to uric acid levels such as; age, gender, body mass index, blood pressure, duration of diabetes, fasting blood sugar, and how to control diabetes were examined. Studies on the relationship between uric acid and proteinuria are few [28], but more studies on the role of uric acid and the progression of renal failure have been performed.

In this study, 90 patients with type 2 diabetes who were referred to the Diabetes Control Center in Gorgan from 2015 to 2017 were selected and entered to participate in the study. The results showed that creatinine levels in male patients were significantly higher than in female patients after one year. On the other hand, changes in Creatinine, BUN, HbA1C, systolic, and diastolic blood pressure levels were statistically significant in all patients. in addition, changes in uric acid levels and changes in proteinuria levels separately were not statistically significant (*p* = 0.190 and *p* = 0.470). In this study, there is a statistically significant relationship between Creatinine, BUN, and Proteinuria levels with Uric

Acid levels after one year, while other variables do not show this relationship. Accordingly, the study by Tanaka, et al. [29] showed that elevated serum uric acid levels were within the normal range (greater than 6.3 mg/dL for men and greater than 5.1 mg/dL for women) in the onset of overt nephropathy increased the risk of decreased renal function in patients with type 2 diabetes. Momeni, et al. [30] also showed in a study that serum uric acid levels were associated with 24-hour urinary protein content, insulin intake and duration of diabetes. Another cross-sectional study found that compared to the microalbuminuria group, the level of serum uric acid was high in macroalbuminuric diabetic patients [31]. Likewise, Naseri, et al. conducted a study and concluded that Serum uric acid significantly predicted proteinuria in both genders [32].

Yun-Ju Lai, et al. [33] conducted a study and concluded that Serum uric acid was significantly associated with an increased risk of incident albuminuria. In addition, Lin Hou, et al. [34] conducted a study and concluded that serum uric acid level was independently associated with diabetic retinopathy and albuminuria in patients with type 2 Diabetes mellitus. Liang, et al. [35] showed that hyperuricemia was significantly associated with the severities of both DR and albuminuria. In line with our findings, Biyik, et al. [36] indicated that uric acid and proteinuria are closely related. In addition, Hayashino, et al. [37] reported that elevated uric acid levels are associated with a subsequent risk of progression, but not development, of albuminuria in patients with type 2 diabetes. Chonchol, et al. [38] found that levels above the normal range of uric acid in the serum of non-diabetics were associated with decreased GFR. In a study by Iseki, et al. [39] in Japan, people with uric acid levels above 8 mg/dL had a 2.9% risk of kidney failure in men and 10 times more in women than people with uric acid levels less than 5 mg/dL. Ficociello, et al. [40] showed that serum uric acid level is associated with the development of diabetic nephropathy in patients with type 1 diabetes. Similar results were obtained in the study of Hovind, et al. [41]. Gemeka, et al. [40] in a 1-year follow-up of 55 patients with type 2 diabetes concluded that the progression of diabetic nephropathy is faster in patients with higher serum uric acid levels. As in the present study, a study by tseng, et al. in patients with type 2 diabetes showed that uric acid in patients with type 2 diabetes was related to urinary albumin excretion [42].

The conclusion was that according to the findings of the study, the concentration of serum uric acid in patients with type 2 diabetes indicates the amount of protein excretion in the urine, so increasing serum uric acid may play a role in the development of diabetic nephropathy.

Conclusion

According to the results of this study and previous studies, the relationship between uric acid levels and the severity of nephropathy (based on proteinuria) is proven. Also, based

on the results of other studies on the role of hyperuricemia in endothelial vascular injury and exacerbation of renal failure, it seems that maintaining serum uric acid levels in patients with type 2 diabetes within the normal range and treatment with serum uric acid-lowering drugs may be possible. Slow the progression of diabetic nephropathy and reduce proteinuria in patients.

Suggestion

Because in our study it was not possible to measure urinary albumin, 24-hour urine protein was evaluated. It is recommended that studies be performed on a larger sample size by measuring 24-hour urine albumin.

Authors' contributions

SA and MC did the definition of intellectual content, data collection, and data analysis.

SA proposed the study concept, did study design, manuscript preparation, Manuscript editing, and manuscript review. MF and MD helped us with data collection and data acquisition.

Ethical statement: The study complies with the ethical considerations of the 1975 Declaration of Helsinki.

Acknowledgment

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