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Original Article

Association of uric acid, atherogenic index of plasma and albuminuria in diabetes mellitus

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Abstract: Background: The associations of serum uric acid (UA), atherogenic index of plasma (AIP) and albuminuria with cardiovascular disease have been shown. Several studies focused on association of serum UA and dyslipidemia, serum UA and renal impairment, dyslipidemia and renal impairment. However, to date, in literature, there have been no studies demonstrating the relationship between these parameters in diabetic patients together. Aims: We aimed to investigate the association between serum UA, albuminuria and AIP in diabetic patients. Methods: This was a retrospective study involving data of 645 diabetic patients. The patients were separated into groups according to their serum uric acid and AIP levels. The quantitative urine albumin/creatinine ratio in morning spot urine samples were used for standard albuminuria determination. Serum uric acid levels under 6 mg/dL were considered as normal. AIP was calculated as the logarithmically transformed ratio of triglyceride to high density lipoprotein cholesterol. Results: AIP and albuminuria levels were high in high serum UA group compared to normal UA group. Uric acid and albuminuria tended to increase with increasing AIP. Correlation analysis showed that albuminuria, AIP and UA were significantly correlated with each other. Additionally, in binary logistic regression analysis, AIP was found to be independently associated with high UA levels. Conclusions: Present study reveals that serum UA, AIP and albuminuria are closely related. Physicians should be aware that patients with concomitant hyperuricemia, albuminuria and high AIP are at increased risk of developing cardiovascular disease. Our study confirms that there is a need for larger prospective studies to determine the mechanisms underlying the association of serum UA, AIP and albuminuria.

Keywords: Uric acid, atherogenic index of plasma, albuminuria

Introduction

Uric acid (UA) is the final product of purine catabolism. High serum UA levels are associated with obesity, dyslipidemia, hypertension and impaired glucose metabolism [1-4], which contributes to development of vascular diseases as stroke, coronary artery diseases and hypertension. During the last decade, there has been renewed interest in association of uric acid and cardiovascular disease (CVD), and high UA levels are designated as a risk factor, except traditional risk factors [5, 6].

Dyslipidemia, a traditional risk factor for CVD, simply can be determined by measurement of plasma lipid and lipoprotein levels. However defining dyslipidemia with these classical methods has several shortcomings such as the ability to estimate particle sizes and lipoprotein subclasses. In the last two decades, studies have demonstrated that a mathematical relationship between plasma triglyceride (TG) and high density lipoprotein cholesterol (HDL-C) levels can be successfully used as an additional index for assessment of CVD risk [7]. Atherogenic index of plasma (AIP) is calculated as log (TG/HDL-C) and it has been designated as a predictor of atherosclerosis [8, 9] and surrogate of small low-density lipoprotein particle size [7-9].

Diabetic nephropathy (DN), the leading cause of end stage renal failure worldwide, contributes to patient morbidity, mortality and increases nation's health care costs [10]. Diabetic and non-diabetic patients with albuminuria have increased cardiovascular mortality [11, 12].

Accumulating data reveal that inflammation, endothelial dysfunction and procoagulant imbalance are associated with nephropathy, retinopathy, and cardiovascular disease in Diabetes Mellitus (DM) [13-15]. The association of serum UA levels and dyslipidemia with inflammation and endothelial dysfunction are also shown [16, 17]. However, the putative association between serum UA levels, AIP and albuminuria is not clear.

The aim of this study was to determine the association between serum UA concentration, AIP and albuminuria in diabetic patients. We expect that the results of this study will help us to figure out probable link with endothelial dysfunction, inflammation and these parameters in diabetic patients.

Methods

Study design, data collection and procedures

This study was performed retrospectively by using Mengucek Gazi Training and Research Hospital database. The data of patients with diabetes admitted to endocrinology and internal medicine clinics in 2013-2014 were screened. Results of the simultaneously performed; serum creatinine, urine creatinine, urine albumin, serum UA (Spectrophotometric analysis, Beckman Coulter Inc. kits and LH 2000 analyzer, Lismeehan, O'Callaghan's Mills, Ireland), Hemoglobin A1c (HbA1c) (High-performance liquid chromatography, Adams A1c HA-8160, Arkray, Japan), total cholesterol (TC), HDL-C and plasma TG concentrations (Oxidize-based technique, Beckman Coulter AU 2700 plus, Missima, Japan), thyroid stimulating hormone (TSH) (Chemiluminescence assay, UniCel DXi 800 imunoassay system, Beckman Coulter, Fullerton CA, USA) undertaken at least after ten hour fasting in the morning were recorded.

Patients who are under 18, patients using medications for hypertension, hyperuricemia, and dyslipidemia were excluded from the evaluation. In case the patients applied for more than once, only the initial tests were recorded. The data of 645 patients who met the criteria were included in the study.

AIP was calculated as the logarithmically transformed ratio of TG to HDL-C [log (TG/HDL-C)] measured in mmol/L. Consistent with previously published epidemiological data and based on AIP, subjects were grouped into three groups: the low (< 0.11), the intermediate (0.11-0.21) and the increased (> 0.21) risk [18]. The quantitative urine albumin/creatinine ratio in morning spot urine samples were used for standard albuminuria determination. Low-density lipoprotein cholesterol (LDL-C) was calculated by Friedewald formula. Serum UA levels under 6 mg/dL were considered as normal.

Statistical analysis

Statistical analyses were carried out using the Statistical Package for Social Sciences, Windows version 15.0 (SPSS, Chicago, IL, USA). Descriptive statistics for each variable were determined. Normality of the data distribution was assessed with the Kolmogorov-Smirnov test. Results for continuous variables were demonstrated as mean ± standard deviation. Results for continuous variables without normal distribution were demonstrated as median [inter quartile range (IQR)]. Statistical significant differences between the groups were determined by chi-square test for categorical variables. For continuous variables, nonparametric statistics (Mann-Whitney or Kruskal-Wallis), and parametric statistics (t test, ANOVA analysis) were all used, as appropriate. Associations between the variables were explored using the Spearman's rho (for data that was not normally distributed). Binary logistic regression analysis was also performed to define variables associated with serum UA. A *P* value less than 0.05 was considered significant.

Results

The data of 645 patients' [300 female (46.5%) and 345 male (53.5%)] were included in the study. The mean age of the study patients was 59.49 ± 12.63 years. The HbA1c of 279 (43.3%) patients were below 7% and 366 (56.7%) patients had uncontrolled diabetes. Albuminuria values of 72.9% of the patients (n = 470) were within normal limits while 27.1% of the patients (n = 175) had albuminuria level above 30 mg/g cr.

Table 1. Demographic, clinic and laboratory features of the subjects according to uric acid levels

Parameters	Diabetic patients with normal uric acid values (Uric Acid < 6 mg/dL) (n = 410)	Diabetic patients with high uric acid values (Uric Acid ≥ 6 mg/dL) (n = 235)	*P* value
Female/Male (n/n)*	180/230	120/115	> 0.05
Age (years)**	59 (51-67)	60 (54-69)	> 0.05
Creatinine (mg/dL)**	0.85 (0.77-0.94)	0.86 (0.75-1.03)	> 0.05
Total cholesterol (mg/dL)***	198.48 ± 43.83	208.78 ± 58.42	0.019
Triglyceride (mg/dL)**	155.0 (107.0-217.8)	171.0 (129.3-226.5)	0.001
LDL- cholesterol (mg/dL)**	117.0 (91.0-142.8)	115.0 (94.3-142.3)	> 0.05
HDL- cholesterol (mg/dL)**	44.5 (38.0-53.0)	44.0 (39.0-52.0)	> 0.05
AIP***	0.18 ± 0.30	0.25 ± 0.27	0.003
Uric Acid (mg/dL)**	4.8 (4.2-5.4)	6.8 (6.3-7.3)	< 0.001
Albuminuria (mg/gr Cr)**	8.77 (3.42-27.03)	10.02 (3.75-46.93)	0.027
HbA1c (%)**	7.5 (6.2-9.1)	7.1 (6.3-7.9)	> 0.05
TSH (U/mL)**	1.33 (0.85-1.86)	1.29 (0.81-2.4)	> 0.05

*Chi-square test, **Mann-Whitney U test [Median (IQR)], ***Independent sample *t* test (Mean ± SD). AIP: Atherogenic Index of Plasma, HbA1c: Glycosylated Hemoglobin, TSH: Thyroid Stimulating Hormone.

Table 2. Demographic, clinic and laboratory features of the subjects according to AIP risk groups

Parameters	Low Risk (AIP < 0.11) (n = 229)	Intermediate Risk (AIP = 0.11-0.21) (n = 88)	Increased Risk (AIP > 0.21) (n = 328)	*P* value
Female/Male (n/n)*	127/102	48/40	125/203	< 0.001
Age (years)**	60 (52-69)	61 (54-70)	59 (51-66)	> 0.05
Creatinine (mg/dL)**	0.83 (0.76-0.92)	0.83 (0.76-0.92)	0.88 (0.79-1.02)	< 0.001
Uric Acid (mg/dL)***	5.3 ± 1.4	5.4 ± 1.3	5.8 ± 1.4	< 0.001
Albuminuria (mg/gr Cr)**	7.05 (3.10-19.60)	8.21 (2.88-36.08)	12.65 (4.20-59.71)	< 0.001
HbA1c (%)**	6.9 (5.9-8.2)	7.3 (6.1-8.9)	7.5 (5.7-9.3)	< 0.001
TSH (U/mL)**	1.25 (0.85-1.81)	1.42 (0.92-2.04)	1.36 (0.79-1.97)	> 0.05

* Chi-square test, **Kruskal Wallis Test [Median (IQR)], ***Oneway ANOVA Test (Mean ± SD). AIP: Atherogenic Index of Plasma, HbA1c: Glycosylated Hemoglobin, TSH: Thyroid Stimulating Hormone.

Baseline characteristics and laboratory data of patients according to serum UA levels are given in **Table 1**. Briefly, while there were no significant differences between groups according to the sex distribution, age, serum creatinine, LDL-C, HDL-C, HbA1c and TSH levels, there were statistically significant differences with respect to the following variables between groups, TC, TG, AIP and albuminuria.

When patients were separated into three groups according to AIP levels [group 1; the low risk group (AIP < 0.11), group 2; the intermediate risk group (AIP = 0.11-0.21) and group 3; the increased risk group (AIP > 0.21)]; while there were no significant differences between the groups according to the age and TSH, there were statistically significant differences between groups according to the following variables; serum UA, albuminuria, serum creatinine and HbA1c (**Table 2**). To our regret, sex distribution between these three groups could not be statistically equalized to avoid the deterioration of sex distribution between high and normal serum UA groups.

The correlation between serum UA, albuminuria and AIP were tested using bivariate correlation analysis. Positive correlation between serum UA and AIP (r_s = 0.154, P < 0.001), serum UA and albuminuria (r_s = 0.108, P = 0.006), AIP and albuminuria (r_s = 0.176, P < 0.001) were determined.

Binary logistic regression analysis was also performed to define the variables associated with serum UA (**Table 3**). Age, sex, creatinine, TC, LDL-C, HDL-C, TG, albuminuria, HbA1c, TSH and AIP levels were included in this model. AIP and HbA1c levels were found to be independently associated with serum UA levels.

Table 3. Binary logistic regression of high serum uric acid

Parameters	Odds Ratio	95% C.I.		*P* value
		Lower	Upper	
Age	1.007	0.991	1.022	> 0.05
Sex (male-1)	1.334	0.900	1.977	> 0.05
Creatinine (mg/dL)	1.410	0.683	2.913	> 0.05
Total cholesterol (mg/dL)	0.978	0.910	1.051	> 0.05
HDL- cholesterol (mg/dL)	1.058	0.978	1.144	> 0.05
LDL- cholesterol (mg/dL)	1.022	0.952	1.098	> 0.05
Triglyceride (mg/dL)	0.997	0.981	1.013	> 0.05
Albuminuria (mg/gr Cr)	1.001	1.000	1.001	> 0.05
HbA1c (%)	0.893	0.805	0.990	0.031
TSH (U/mL)	0.996	0.939	1.057	> 0.05
AIP	53.433	2.880	991.475	0.008

AIP: Atherogenic Index of Plasma, HbA1c: Glycosylated Hemoglobin, TSH: Thyroid Stimulating Hormone.

Discussion

There are four main findings of the present study. First, AIP level was found to be higher in high serum UA group compared to normal UA group. Second, albuminuria level was found to be higher in the high serum UA group compared to the normal serum UA group. Third, although sex distribution could not be equalized because of the reason mentioned above, in low, intermediate and increased AIP risk groups; UA and albuminuria levels were increased in parallel to AIP increase. Finally, AIP was found to be independent predictor of hyperuricemia in diabetic patients.

Multiple studies have shown that serum UA levels are associated with risk factors for CVD and CVD [1-6]. The strong relation with serum UA and dyslipidemia as the other components of metabolic syndrome has been demonstrated by several studies [1-4, 19-21]. To explain the relationship between hyperuricemia and risk factors for CVD, many reasons have been suggested. Reduced renal clearance or increased proximal tubular reabsorption of UA due to the insulin resistance and increased insulin levels, increased leptin levels and increased fructose consumption which is closely associated with obesity have been proposed as possible causes [22-28].

Baliarsingh et al. reported serum UA is positively associated with AIP in healthy, middle aged men [2]. Authors declare that the association of AIP and serum UA which they determined can be explained with hypertriglyceridemia and decreased HDL-C reported in population with high UA in the literature [20, 21, 29, 30]. Additionally some studies proposed that hypertriglyceridemia reduces renal excretion of UA and decrease in triglyceride levels is accompanied with increased urinary UA level [29, 31, 32]. Furthermore, the association of insulin resistance with hypertriglyceridemia and low HDL-C has been well defined [33]. These scenarios reveal that UA and AIP might be different components of a same phenotype as a result of insulin resistance.

Both diabetes and chronic kidney disease are associated with varied aspects of dyslipidemia; hypertriglyceridemia, lower high-density lipoprotein, and higher small, dense low-density lipoprotein [34-36]. Moreover, association of dyslipidemia and albuminuria is determined [17, 20, 34]. Dyslipidemia associated glomerular atherosclerosis, glomerulosclerosis and tubulointerstitial fibrosis are the suggested factors that play role in development of albuminuria and DN [17]. On the other hand, the fact that the high UA and albuminuria plays role in the deterioration in renal function has been also demonstrated [20, 37-41]. However, the effects of improvement of the lipid profile or reduction of UA levels on albuminuria is controversial and beneficial results have not been clearly demonstrated [17, 42-48]. In this perspective authors believe that the positive relationship between these three parameters cannot be explained as a cause and effect relationship and these three risk factors might be different aspects of a high risk phenotype. Additionally, the demonstration of high UA heritability in twins and the proven association of UA with metabolic syndrome also in children who are less likely to be influenced by unfavorable factors such as atherosclerosis and age related risks support that the underlying pathogenic mechanisms are associated with the high risk phenotype [4, 49, 50].

Our study has some limitations. First, our study is limited by its retrospective nature. The process of retrospective data collection may leave out some variables. A prospective study with

more detailed data collection could bring more accurate results. Second, since it involves one single institution, it may not represent the general population. Finally, we cannot determine a cause and effect relationship due to the cross-sectional nature of our study. Despite the difficulties in using retrospective study results, the strength of our study is relatively the large cohort of diabetic patients. Additionally, our study confirms that there is a need for larger prospective studies to determine the mechanisms underlying the association of serum UA, AIP and albuminuria that contributes to the occurrence of CVD.

In conclusion, present study showed that higher serum UA levels were associated with increased AIP and increased albuminuria. From a practical standpoint, physicians should be aware that patients with concomitant hyperuricemia, albuminuria and high AIP are at an increased risk of developing CVD. These factors are the combination of independent risk factors to contribute to the development of CVD.

Disclosure of conflict of interest

None.

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