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The relationship between uric acid variability and cardiovascular risk factors in patients with diabetes

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ABSTRACT

Aim: This study aimed to evaluate the relationship between uric acid variability and cardiovascular risk factors, primarily albuminuria and blood lipids, in patients with diabetes.

Material and Method: Data from 174 patients with diabetes whose biochemical parameters were examined at least once a year were collected over the course of five years of regular follow-up. The five-year averages and standard deviations of each parameter for each person were calculated. The adjusted standard deviation for each parameter was considered as a measure of individual variability. The patients were divided into two groups according to the median of the mean uric acid and the median of the adjusted standard deviation of uric acid.

Results: Between low and high uric acid variability groups, while there was no statistically significant difference for the mean values of following parameters, there was a difference in the variability of glucose (p=0.010), HbA1c (p=0.016), total cholesterol (p=0.008), and low-density lipoprotein-cholesterol (p=0.002). Moreover, there was difference in mean albuminuria (p= 0.019), albuminuria variability (p=0.040), mean triglyceride (p=0.011), triglyceride variability (p=0.018), and mean high-density lipoprotein-cholesterol cholesterol (p=0.008).

Conclusion: Clinicians should pay attention to uric acid variability in addition to basal uric acid levels since it is associated with albuminuria, an atherogenic lipid profile, renal functions, and the variability of these parameters, independent of HbA1c and glucose levels.

Keywords: Uric acid, diabetes mellitus, albuminuria, dyslipidemia, cardiovascular disease

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INTRODUCTION

Despite improvements in cardiovascular disease (CVD) mortality rates, the incidence of obesity, metabolic syndrome, and diabetes mellitus (DM) continues to rise. It is estimated that DM prevalence, worldwide, will be 643 million by 2030 and 783 million by 2045 (1). CVD is the primary cause of death in adults with DM, and traditional cardiovascular (CV) risk factors do not account for a major portion of the disease burden in patients with DM.

Elevated blood uric acid (UA) levels have been linked to several diseases that are recognized to be associated with CVD, including obesity, insulin resistance, metabolic syndrome, DM, hypertension, and renal disease (2-7). There is a close association between UA levels and CV risk factors (2-7) and reports state that UA is an independent risk factor for CVD (8,9). But the cause and effect relationship between UA and CVD has not been fully proven. Moreover, some studies have reported that there is a U-shaped association between UA and CVD, (10,11) while other studies have found no association (12,13) between them. While arguments over the association between UA levels and CVD continue, data on the relationship of UA variability with CVD, mortality, and CV risk factors, have begun to be published in the last decade (14-18). Thus, in addition to the variability of HbA1c, lipid parameters, and blood pressure, which have been taken into account in recent years, the metabolic effects of uric acid variability are now being investigated.

Epidemiologic researches suggest that elevated serum UA concentrations are risk factor for the development of renal disease, DM, and related complications. But, differences in the methodologies used in the studies

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and the fact that UA levels are easily affected by drugs, hemodynamic variability, and variable renal functions, make the conclusions of these researches unsatisfactory. There for, a study evaluating the relationship of long-term mean UA values and UA variability rather than basal/cross-sectional serum UA values with CV risk factors, can offer a different viewpoint. In this study, we aimed to reveal the association of UA variability with albuminuria and CV risk factors with single center outpatient clinic data. The association of UA variability with the variability of these CV risk factors were also evaluated.

MATERIAL AND METHOD

The study was carried out with the permission of Erzincan Binali Yıldırım University, School of Medicine, Non-invasive Clinical Researches Ethics Committee (Date: 28.01.2021, Decision No: 30/06). All procedures were carried out in accordance with ethical rules and the principles of the Declaration of Helsinki.

Patients

Patients with a diagnosis of Type 2 Diabetes, who were followed up in our outpatient clinic for 5 years and who admitted at least once a year were included in the study. Within the five-year period examined; patients older than 80 years of age, younger than 18 years of age, patients with end-stage renal disease, patients with pregnancy, patients undergoing major surgery, or hospitalized for any reason were excluded from the study.

Using the archive system of our hospital, 174 patients with DM admitted to the Endocrinology Outpatient Clinic regularly for five years, whose glucose, HbA1c, albuminuria, UA, lipid profile, urea, creatinine, glomerular filtration rate (GFR), and albumin levels were studied at least once a year, were enrolled in the study. Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Assessment of Variability

The gender, age, height, and weight of the patients were recorded. Glucose, HbA1c, albuminuria, UA, lipid profile, urea, creatinine, albumin levels, and GFR of the patients for each admission were recorded. Five-year averages and standard deviations (SD) of each parameter were calculated for each person. The calculated standard deviation value of the parameters was used as an indicator of variability. Because the number of separate visits (n) might impact the SD, the SD values were divided by [n/(n-1)]0.5 to compute adjusted SD and minimize any effect of distinct measurements on the calculated results (19). The adjusted SD for each parameter was considered to be the measure of "variability" for each patient. Then, the calculated mean and adjusted SD of the parameters were evaluated for each person. The patients were separated into two groups based on the median of "mean UA values" and the median of the "adjusted SD of the UA values (UA variability)".

Statistical Analysis

Statistical Package for Social Sciences for Windows, v. 15.0 (SPSS, Chicago, IL, USA) was used to conduct the statistical analyses. For each variable (for every 5-year average value and 5 year adjusted SD of each parameter), descriptive statistics were established. The mean and SD were used to express the normally distributed data. For variables without a normal distribution, the median and minimum-maximum values were used. Student's t-test was used to compare data that had a normal distribution. The Mann-Whitney U test was used to compare continuous data with the asymmetric distribution. The Pearson correlation coefficient and Spearman's rho were used to investigate the relationships between the variables (for data that were not normally distributed).

RESULTS

Retrospective data of 174 patients with diabetes, 98 of whom were female (56.3%) and 76 of whom were male (43.7%), were included in the study. The mean age of the patients was 57.2±14.0 years. The five-year average of HbA1c was found to be 8.4±1.4%. Body mass index (BMI) was found to be 30.0±5.5 kg/m². **Table 1** shows the baseline characteristics and laboratory data of the patients based on the adjusted SD of UA levels. While there were no significant differences between the two groups according to sex distribution, age, mean glucose, mean HbA1c, mean total cholesterol (TC), mean low-density lipoprotein-cholesterol (LDL-C), adjusted SD of high-density lipoprotein-cholesterol (HDL-C), and adjusted SD of albumin, there were statistically significant differences between groups for the following variables: BMI, adjusted SD of glucose, adjusted SD of HbA1c, mean albuminuria, adjusted SD of albuminuria, mean UA, adjusted SD of TC, adjusted SD of LDL-C, mean triglyceride (TG), adjusted SD of TG, mean HDL-C, adjusted SD of urea, mean creatinine, adjusted SD of creatinine, mean estimated GFR (eGFR), adjusted SD of eGFR, and mean albumin.

The correlations between UA variability and several other parameters were tested using bivariate correlation analysis. As shown in **Table 2**, the adjusted SD of UA was significantly correlated with BMI, adjusted SD of glucose, mean HbA1c, adjusted SD of HbA1c, mean albuminuria, adjusted SD of albuminuria, adjusted SD of TC, adjusted SD of LDL-C, mean TG, adjusted SD of HDL-C, adjusted SD of urea, mean creatinine, adjusted SD of creatinine, mean eGFR, adjusted SD of eGFR, mean albumin, and adjusted SD of albumin.

Table 1. Demographic, clinic, and laboratory features of the study groups according to uric acid variability

Parameters	Group 1 Patients with low uric acid variability (Adj. SD of UA <0.584)≠ n= 87	Group 2 Patients with high uric acid variability (Adj. SD of UA ≥0.584)≠ n= 87	P value
Sex (f/m)	51/36	47/40	0.541*
Age (years)	58 (49.75-65.25)	60 (55-67)	0.077**
BMI (kg/m²)	28.4±5.1	31.5±5.5	0.006***
Mean Glucose (mg/dL)	180±52	185±55	0.536***
Adj. SD of Glucose	57.83±34.89	74.06±46.26	0.010***
Mean HbA1c (%)	7.97 (7.28-9.35)	8.47 (7.26-9.50)	0.429**
Adj. SD of HbA1c	0.92 (0.60-1.29)	1.23 (0.80-1.81)	0.016**
Mean Albuminuria (mg/g)	17.93 (9.18-35.93)	25.94 (8.93-145.98)	0.019**
Adj. SD of Albuminuria	11.90 (5.50-24.60	19.80 (5.40-139.70)	0.040**
Mean Uric Acid (mg/dL)	4.7±1.2	5.4±1.1	<0.001***
Adj. SD of Uric Acid	0.42 (0.32-0.48)	0.84 (0.70-1.08)	-
Mean Total Cholesterol (mg/dL)	205 (175-235)	200 (179-226)	0.866**
Adj. SD of Total Cholesterol	23.03 (15.08-28.29)	24.42 (18.87-35.95)	0.008**
Mean LDL-Cholesterol (mg/dL)	118 (99-146)	119 (101-135)	0.347**
Adj. SD of LDL-Cholesterol	19.35 (14.32-24.26)	23.80 (15.71-31.78)	0.002**
Mean TG (mg/dL)	144.67 (111.52-200.14)	179.79 (134.51-245.48)	0.011**
Adj. SD of TG	40.72 (26.64-59.75)	52.74 (33.71-76.28)	0.018**
Mean HDL-Cholesterol (mg/dL)	46.53 (40.50-55.04)	42.99 (39.67-48.18)	0.008**
Adj. SD of HDL-Cholesterol	4.67 (3.42-6.09)	4.89 (3.79-6.53)	0.289**
Mean Urea (mg/dL)	30.89 (25.43-36.52)	31.85 (27.92-42.42)	0.062**
Adj. SD of Urea	5.41 (3.91-6.99)	6.37 (4.77-12.36)	0.001**
Mean Creatinine (mg/dL)	0.85 (0.73-0.99)	0.90 (0.77-1.05)	0.036**
Adj. SD of Creatinine	0.09 (0.073-0.12)	0.12 (0.09-0.19)	0.001**
Mean eGFR mL/min/1.73 m²	85.69 (74.03-94.21)	80.61 (66.40-86.98)	0.014**
Adj. SD of eGFR	6.67 (5.39-8.46)	7.48 (6.01-10.26)	0.005**
Mean Albumin (g/dL)	4.25 (4.11-4.40)	4.15 (3.98-4.32)	0.007**
Adj. SD of Albumin	0.26 (0.18-0.34)	0.27 (0.21-0.37)	0.189**

≠ The variability was determined with the adjusted SD. Considering the median of the adjusted SD value of Uric Acid, the patients were divided into 2 groups as patients with low and high uric acid variability. Sex, age, and anthropometric indices were recorded at the initial evaluation. The parameters presented with the term "Adjusted SD" represent the 5-year variability of the parameters. The parameters presented with the term "Mean" represent the 5-year average of the parameters. * Chi-Square Test, ** Mann-Whitney U test [Continuous variables without anormal distribution presented as; median (IQR)] *** Student's t-test Test (Continuous variables without normal distribution presented as; mean ± standard deviation). BMI: Body Mass Index, HbA1c: Glycosylated Hemoglobin, LDL- Cholesterol: Low-Density Lipoprotein Cholesterol, HDL- Cholesterol: High-Density Lipoprotein Cholesterol, TG: Triglyceride, eGFR: Estimated Glomerular Filtration Rate, Adj. SD: Adjusted Standard Deviation/Variability.

Table 2. Bivariate correlation results between uric acid variability (Adjusted SD of Uric Acid) and other significant parameters in diabetic patients

Parameters	Correlation Coefficient (rs)	P value	Parameters	Correlation Coefficient (rs)	P value
BMI (kg/m²)	0.326	0.001	Adj. SD of HDL-Cholesterol	0.203	0.007
Adj. SD of Glucose	0.238	0.002	Adj. SD of Urea	0.374	<0.001
Mean HbA1c (%)	0.151	0.047	Mean Creatinine (mg/dL)	0.174	0.021
Adj. SD of HbA1c	0.249	0.001	Adj. SD of Creatinine	0.418	<0.001
Mean Albuminuria (mg/g)	0.250	0.001	Mean eGFR mL/min/1.73 m²	-0.215	0.004
Adj. SD of Albuminuria	0.259	0.001	Adj. SD of eGFR	0.212	0.005
Adj. SD of Total Cholesterol	0.209	0.006	Mean Albumin (g/dL)	-0.236	0.002
Adj. SD of LDL-Cholesterol	0.241	0.001	Adj. SD of Albumin	0.195	0.010
Mean TG (mg/dL)	0.149	0.049	-	-	-

The parameters presented with the term "Adjusted SD" represent the 5-year variability of the parameters. The parameters presented with the term "Mean" represent the 5-year average of the parameters. BMI: Body Mass Index, HbA1c: Glycosylated Hemoglobin, LDL- Cholesterol: Low-Density Lipoprotein Cholesterol, HDL- Cholesterol: High-Density Lipoprotein Cholesterol, TG: Triglyceride, eGFR: Estimated Glomerular Filtration Rate, Adj. SD: Adjusted Standard Deviation/Variability.

When patients were divided into two groups based on the median of mean UA levels (Group 1 – mean UA <6 mg/dL and Group 2 – mean UA levels ≥ 6 mg/dL), for the following variables, there were statistically significant differences between the groups: age, mean albuminuria, adjusted SD of albuminuria, adjusted SD of UA, adjusted SD of LDL-C, mean urea, adjusted SD of urea, mean creatinine, adjusted SD of creatinine, and mean GFR (**Table 3**).

Table 3. Demographic, clinic, and laboratory features of the study groups according to 5 year mean uric acid levels

Parameters	Group 1 Mean Uric Acid <6 mg/dL n= 87	Group 2 Mean Uric Acid ≥6 mg/dL n= 87	P-value
Sex (f/m)	75/56	23/20	0.666*
Age (years)	58 (51-65)	62 (54.5-70)	0.004**
BMI (kg/m²)	29.55±5.61	31.01±5.12	0.233***
Mean Glukoz (mg/dL)	186.86±55.11	172.50±48.15	0.106***
Adj. SD of Glukoz	67.40±41.24	61.53±43.09	0.436***
Mean HbA1c (%)	8.34 (7.38-9.53)	7.9 (7.17-9.02)	0.138**
Adj. SD of HbA1c	1.03 (0.64-1.44)	1.07 (0.70-1.57)	0.987**
Mean Albuminuria (mg/g)	18.10 (8.48-43.08)	61.21 (9.93-272.77)	0.004**
Adj. SD of Albuminuria	11.84 (5.31-29.33)	39.43 (6.21-214.53)	0.018**
Mean Uric Acid (mg/dL)	4.52±0.87	6.70±0.61	-
Adj. SD of Uric Acid	0.54 (0.42-0.81)	0.77 (0.55-1.08)	0.007**
Mean Total Cholesterol (mg/dL)	198.5 (178.47-226.41)	206.57 (177.50-233.25)	0.382**
Adj. SD of Total Cholesterol	23.26 (16.35-30.08)	24.53 (16.88-36.71)	0.090**
Mean LDL-Cholesterol (mg/dL)	118.75 (99.6-138.41)	119.75 (100.91-151.12)	0.587**
Adj. SD of LDL-Cholesterol	20.82 (14.93-25.83)	24.40 (15.27-32.36)	0.036**
Mean TG (mg/dL)	159.43 (115.78-239.57)	180.92 (130.58-229.14)	0.050**
Adj. SD of TG	43.74 (31.72-67.98)	52.35 (30.39-71.66)	0.239**
Mean HDL-Cholesterol (mg/dL)	44.62 (40.27-51.77)	42.22 (39.36-48.03)	0.100**
Adj. SD of HDL-Cholesterol	4.92 (3.57-6.34)	4.62 (3.81-5.60)	0.699**
Mean Urea (mg/dL)	30.72 (26.05-35.13)	42.15 (30.61-51.16)	<0.001**
Adj. SD of Urea	5.93 (4.44-7.36)	7.78 (4.61-15.81)	0.004**
Mean Creatinine (mg/dL)	0.85 (0.74-0.95)	1.04 (0.86-1.23)	<0.001**
Adj. SD of Creatinine	0.10 (0.08-0.13)	0.13 (0.08-0.19)	0.004**
Mean GFR mL/min/1.73 m²	85.29 (75.81-93.37)	71.15 (50.63-82.33)	<0.001**
Adj. SD of GFR	7.38 (5.74-9.58)	7.10 (5.72-7.97)	0.379**
Mean Albumin (g/dL)	4.2 (4.05-4.34)	4.15 (4.03-4.34)	0.664**
Adj. SD of Albumin	0.26 (0.20-0.36)	0.26 (0.22-0.34)	0.807**

Sex, age, and anthropometric indices were recorded at the initial evaluation. The parameters presented with the term "Adjusted SD" represent the 5-year variability of the parameters. The parameters presented with the term "Mean" represent the 5-year average of the parameters. * Chi-Square Test, ** Mann-Whitney U test [Continuous variables without anormal distribution presented as; median (IQR)], *** Student's t-test Test (Continuous variables without normal distribution presented as; mean ± standard deviation). BMI: Body Mass Index, HbA1c: Glycosylated Hemoglobin, LDL- Cholesterol: Low-Density Lipoprotein Cholesterol, HDL- Cholesterol: High-Density Lipoprotein Cholesterol, TG: Triglyceride, eGFR: Estimated Glomerular Filtration Rate, Adj. SD: Adjusted Standard Deviation/Variability.

DISCUSSION

Since the results of the Diabetic Control and Complications Trial were published in the early 1990s, the question of glucose fluctuation as a factor in diabetic complications has been debated (20). Following the definition of glucose variability as a target in DM, the term variability is frequently used negatively when referring to human pathologies. The importance of variations in diverse biological processes has attracted the interest of researchers in the field of metabolic disorders during the last decade. For some biological parameters, it seems imperative to always keep them within a very tight narrow range. For example, blood pressure variability has been reported to be associated with CV morbidity and mortality in different studies (21-23). Other studies have reported that glucose and blood pressure variability may be an independent risk factor for albuminuria progression and reduction in GFR in type 2 DM patients (18, 24, 25). Research has also revealed that body weight variability is associated with coronary events and CV deaths (26, 27). The variability of UA is another factor that researchers have recently begun to investigate.

According to the studies, high serum UA levels are strongly associated with obesity, insulin resistance, metabolic syndrome, DM, essential hypertension, and kidney disease (2-7). Additionally, some studies have argued that high serum UA level is an independent risk factor for CV mortality and all-cause mortality (8, 9). According to some reports, the correlation between hyperuricemia and CVD, for which a cause-effect relationship cannot be established, is found to be particularly strong, especially in individuals at high risk for CVD (28). Conversely other studies have reported that UA has no connection with all-cause and CV death after adjusting for other CV risk factors (12, 13).

While it is still unclear whether UA is an independent predictor of all-cause mortality or whether UA plays a significant role in the development of all-cause mortality, the studies mentioned above stated that UA levels consist of a basal single measurement that can be influenced by many factors, including drugs, diet, and renal functions in daily life, and that its variability should be assessed

to make long-term predictions. In this respect, it is important that the mean uric acid value of 5 years was used in our study and that the mean uric acid value was found to be associated with some of cardiovascular risk factors such as albuminuria.

In our study, uric acid variability was evaluated in addition to 5-year mean UA. Only a few research have investigated the effect of UA variability on clinical outcomes. In their community cohort analysis, Wang et al. (14) discovered that increased UA variability was related to increased all-cause mortality. Additionally they reported that UA variability was an independent risk factor for all-cause mortality. Grossman et al. (15) reported that UA variability was linked with all-cause mortality in men. Lim et al. (17) reported that UA variability was significantly linked with the increased incidence of major adverse cardiac events in patients receiving percutaneous coronary intervention. Ceriello et al. (18) proposed that HbA1c, blood pressure, lipid, and UA variability may have varying degrees of effect on the development of albuminuria and other components of diabetic kidney disease in DM patients. In the present study, UA variability was found to be associated with some of the metabolic syndrome parameters. After the HbA1c and glucose levels were equalized in both groups, the variability of UA was associated with the variability of glucose and HbA1c. Interestingly, while there was no difference in the LDL-C and TC levels in the low and high UA variability groups, a significant difference was found between the groups in terms of LDL-C and TC variability. A significant difference was also found between the groups with low and high UA variability in terms of albuminuria and albuminuria variability, which are indicators of CV risk. These findings revealed that the variability of uric acid was closely related to the variability of the lipid profile and glucose regulation indicators among the groups with equalized fasting blood glucose, HbA1c, gender and age values. In our detailed literature review, no study was found that revealed the relationship between uric acid variability and the variability of other risk factors. Interestingly, UA variability was statistically associated with more metabolic risk factors than the 5-year mean UA.

In our study, in accordance with the literature, the variability of UA was found to be associated with triglyceride and blood glucose regulation indicators. The significant relationship between UA variability and triglyceride, HbA1c, glucose variability was interpreted as that these parameters sometimes increase and decrease together, and thus their variability is related.

There is also literature information that can explain the link between UA variability and CVD risk factors. One study identified UA as an inflammatory molecule that promotes oxidative stress (29). Clinical observations showed the fluctuations in UA levels may trigger, exacerbate, and prolong the inflammatory process in gout (17). A rise in UA levels has been shown to enhance the crystallization rate of UA, triggering an immunological and inflammatory response (30). Consequently, variations in the UA levels may be associated with increased oxidative stress, which can contribute to increased CV risk. Another hypothesis is related to UA's anti-oxidant properties. Fluctuating UA levels may represent a compensatory mechanism to counteract oxidative stress, and may reflect CV disease risk factors. Additionally, UA variability is most likely correlated with the variability of CV risk factors, such as hypertension, DM, dyslipidemia, and renal failure (14-18). Therefore, it is suggested that UA variability reflects the development of other CV risk factors rather than stable hyperuricemia (15). Furthermore, in publications evaluating UA variability, patients with higher UA variability used more diuretics and more UA-lowering medications, and they had a lower eGFR and more comorbidities, indicating a high-risk category (17). Another interpretation of these results might be that the variability of UA probably reflects the variability of the quality and efficacy of treatment. Additional large-scale research concentrating on UA variability is required to better understand these issues.

Our research has some limitations as well as some strengths that should be highlighted. First and foremost, this is a retrospective study. Because of the nature of the retrospective analysis, the therapeutic significance of our investigation may be restricted. Another limitation of our study is that it only included a small number of patients. Furthermore, due to the retrospective nature of the study, we were unable to examine the medications taken by the patients or the changes in the drugs they were prescribed. However, we believe the strengths of this study include the length of the patient follow-up period (five years) and the measurement of UA variability and the variability of the other parameters.

CONCLUSION

This study demonstrated that UA variability is related to albuminuria, the atherogenic lipid profile, renal functions, and the variability of these parameters, irrespective of HbA1c and glucose levels. Thus, clinicians should consider uric acid variability in addition to basal UA levels. The therapeutic significance of UA variability and the use of more stable homogeneous metrics to represent UA variation must be examined.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Erzincan Binali Yıldırım University, School of Medicine, Non-invasive Clinical Researches Ethics Ethics Committee (Date: 28.01.2021, Decision No: 03/06).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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