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ORIGINAL ARTICLE

Assessment of the relationship between serum uric acid levels and oxidative stress markers in patients with uncomplicated type 2 diabetes mellitus

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ABSTRACT

Objective: Type 2 Diabetes Mellitus is a worldwide health issue characterized by hyperglycemia due to defects in insulin secretion, insulin action, or both, and is associated with significant negative health outcomes. Oxidative stress plays a crucial role in the onset, progression, and complications of this disorder. Elevated serum uric acid level is an independent predictor of vascular complications in diabetic patients, and hyperuricemia may contribute to oxidative stress. The objective of this study is to examine the correlation between increased serum uric acid levels and the markers of oxidative stress, including ischemia-modified albumin (IMA), total oxidant status (TOC), and total antioxidant capacity (TAC), in type 2 diabetic patients who don't have vascular complications.

Materials and Methods: A total of 73 individuals were enrolled in the study including 20 type 2 diabetic patients with high serum uric acid levels (> 6.5 mg/dl), 21 type 2 diabetic patients with normal serum uric acid levels (< 6.5 mg/dl), and 32 healthy individuals. Ischemia-modified albumin, total oxidant status, and total antioxidant status levels were compared between patient groups and the control group

Results: As a result of this study, there was no significant association between serum uric acid levels and ischemia-modified albumin, total oxidant status, and total antioxidant status levels in type 2 diabetic patients.

Conclusions: This study concluded that high serum uric acid levels do not directly affect oxidative stress in type 2 diabetic patients without vascular complications.

Keywords: diabetes mellitus, uric acid, ischemia-modified albumin, total oxidant status, total antioxidant status.

INTRODUCTION

Increased advanced glycosylation end products due to activation of the polyol; hexosamine pathway and protein kinase c activation induced by hyperglycemia is the main pathophysiological mechanism responsible for the complications of type 2 diabetes mellitus (type 2 DM) [1]. In this way, oxidative stress increases, tissue damage occurs and chronic complications of diabetes emerge [2,3].

On the other hand, high serum uric acid levels are also known to be an independent risk factor for vascular complications and mortality in type 2 DM [4]. Each 1 mg/dL increase in serum uric acid level has been reported to increase the risk of developing type 2 DM by 20% [5].

Even though uric acid is considered an antioxidant molecule, it is also known that antioxidant molecules play a role as prooxidants in certain situations [6]. At the beginning of the atherosclerotic process, uric acid acts as an antioxidant molecule. In contrast, when the atherosclerotic process progresses and serum uric acid levels increase, uric acid acts as an oxidant molecule [7]. During the production of uric acid, xanthine formation from hypoxanthine, uric acid formation from xanthine, and one superoxide radical is formed in both steps.

In the presence of oxidative stress, hypoxia, acidosis, and ischemia, a change occurs in the N-terminal region of albumin, which is the binding site for divalent metals such as copper, nickel, and cobalt. This modified form of albumin is known as ischemia-modified albumin (IMA). The metal binding rate of the N-terminal part decreases due to this molecular change. Studies are showing that IMA levels are high in patients with type 2 diabetes, which may be related to a chronic hypoxic state triggered by hyperglycemia and oxidative stress, endothelial dysfunction, and chronic inflammation [8,9].

The level of oxidative stress in the whole body is shown by total oxidant capacity (TOC). For this reason, it is more valuable than assessing oxidant radicals separately [10,11]. In the human body, oxidant and antioxidant systems are normally in balance. In the presence of oxidative stress, the oxidant-antioxidant balance in the body is known to shift towards the oxidant side. Increased oxidative stress is recognized as a contributor to the pathogenesis of insulin resistance and type 2 DM. In the literature, studies indicate that total antioxidant capacity (TAC) decreases in diabetic patients in direct correlation with this mechanism [10]. It is also known that TAC levels are low in prediabetic patients [11]. In diabetic patients with complications, the TAC level is lower than in uncomplicated diabetic patients [12].

This study aims to evaluate the potential relationship between serum uric acid levels and markers of oxidative status, specifically IMA, TOC, and TAC, in patients with type 2 DM without microvascular and macrovascular complications.

MATERIALS and METHODS

The study was designed as a single-center, case-controlled cohort study. A total of 73 participants, including 21 patients with type 2 DM with normal uric acid levels, 20 patients with type 2 DM with increased uric acid levels, and 32 healthy individuals between the ages of 30-70 years, who applied to the Internal Medicine outpatient clinic of Ufuk University Faculty of Medicine Dr. Rıdvan Ege Hospital, were included in the study.

Patients' demographic characteristics, anamnesis, and physical examination findings were recorded. Fasting plasma glucose (FPG), blood urea nitrogen (BUN), creatinine, uric acid, complete blood count, lipid profile, HbA1c, fasting insulin level, C- Reactive Protein (CRP), albumin/creatinine in spot urine were measured. Additionally, a 12-lead electrocardiogram (ECG) was performed for each subject, and ophthalmologic evaluations were carried out.

Anthropometric measurements of the participants were recorded. Body mass index (BMI) was calculated using the formula weight/(height)^2 (kg/m^2). Type 2 DM was diagnosed according to the American Diabetes Association (ADA) criteria [13]. Patients previously diagnosed with diabetes and receiving diabetes treatment were also included in the study.

Patients were evaluated for microvascular and macrovascular complications. Nephropathy was assessed by measuring the albumin-to-

creatinine ratio in spot urine samples. A spot urine albumin/creatinine ratio < 30 mg/day was considered an absence of diabetic nephropathy. The glomerular filtration rate was calculated using the CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration) formula based on serum creatinine measurements [14]. For diabetic retinopathy, past ophthalmologic examinations were reviewed from the patient files. Neuropathy was assessed through patient history, clinical findings, and neurological examination. Clinical findings, ECG data, cardiologic examination, and test results of the patients were evaluated after questioning about cardiovascular risk factors for the presence of coronary heart disease (CHD). Diabetic foot, peripheral arterial disease (PAD), and cerebrovascular accident (CVA) were evaluated by anamnesis, clinical findings, and patient follow-up notes.

Patients were divided into two groups based on their serum uric acid levels: those with levels of 6.5 mg/dL or above were classified as the high uric acid group, while those with levels below 6.5 mg/dL were classified as the normal uric acid group. Control group individuals were selected from hospital employees and patients' relatives who applied to our department and agreed to participate in the study, who had no disease, and whose routine laboratory values were within the normal range. The cut-off value for IMA was determined by measuring IMA levels in the healthy control group, and IMA levels were assessed in comparison to this cut-off value. Ten milliliters (ml) of venous blood samples were obtained from patients with patients with type 2 DM for IMA, TOC, and TAC levels at the Endocrinology and Metabolism Department of Ufuk University Dr. Rıdvan Ege Hospital. The serum of 10 ml of blood was separated and stored at -80°C until the day of the study. On the day of the study, all samples were brought to room temperature, and the study was completed on the same day and the results were evaluated.

Hypertension, known history of CHD, decompensated heart failure, chronic liver, and kidney disease, diabetic nephropathy, retinopathy, neuropathy, history of transient ischemic attack or ischemic CVA, acute and chronic infection (those with significantly increased CRP levels and those with laboratory and physical examination findings in favor of infection), vitamin and antioxidant use, history of PAH, any diagnosed malignant disease and paraproteinemia, pregnant and lactating females, diuretic drug users, those aged <30 and >70 years, and those who refused to give informed consent were excluded.

Biochemical evaluation methods

Plasma fasting glucose levels were determined by Hexokinase/G-6-PDH (Glucose 6 Phosphate Dehydrogenase) method and serum total cholesterol, low-density lipoprotein (LDL), high-density lipoprotein (HDL), triglyceride (TG), BUN, and uric acid levels were determined colorimetrically. Fasting insulin levels were determined by chemiluminescent microparticle immunoassay (CMIA). HbA1c level was measured by high-performance liquid chromatography (HPLC). Serum creatinine was evaluated by the kinetic alkaline picrate method. CRP was measured by the immunoturbidimetric method. In spot urine, albumin was measured turbidimetrically, and creatinine was measured by kinetic alkaline picrate technology.

Ischemia-modified albumin, the complex formed by cobalt (II) not bound to albumin with dithioerythritol was measured by colorimetric method at 470 nm with a spectrophotometer. Results were given in Absorbance unit (ABSU). TOC was measured with a spectrophotometer at 530 nm and the results were calculated as micromol/L. TAC was measured with a spectrophotometer at 660 nm and the results were calculated as mmol/L.

Statistical analysis

The IBM SPSS Statistics 20.0 software was used for statistical analysis of the data. Continuous data were presented as mean ± standard deviation, and median (minimum-maximum value); discrete data were presented as frequency and percentage. Shapiro Wilk's test was used to evaluate whether there was a normal distribution among the variables. For normally distributed groups, comparisons were made using the t-test for independent samples, whereas the Mann-Whitney U test was used for non-normally distributed groups. The Chi-square test was used to compare the percentage data between groups. The Kruskal-Wallis test was used to compare IMA levels among three groups of diabetic patients. The correlations between the variables were analyzed with Spearman's correlation coefficient. In the study, $p<0.05$ was considered statistically significant.

Ethical approval

This study (21012015-1) was approved in terms of medical ethics by the Ufuk University Faculty of Medicine Dr. Rıdvan Ege Hospital Non-Interventional Clinical Research Ethics Committee and was conducted by the Declaration of Helsinki. The informed consent form was obtained from each patient participating in the study.

RESULTS

Comparison of diabetic groups with high and normal uric acid levels

A total of 41 subjects, including 20 (10 F/10 M) diabetic patients with high uric acid levels and 21 (10 F/11 M) diabetic patients with normal uric acid levels, with a mean age of 60.9±7.1 years and BMI of 27.9±2.9 kg/m^2, were included in the study. Detailed comparisons of the groups concerning demographic, clinical, and biochemical variables are shown in Table 1. It was found that patients were homogeneously distributed in terms of age, gender, and BMI in both groups. The BUN level of diabetic patients in the group with high uric acid levels was statistically significantly higher than that of diabetic patients with normal uric acid levels (p=0.034). No statistically significant difference was found between other biochemical parameters between both groups.

The correlation between variables was evaluated using Spearman's correlation coefficient for a sample of 41 patients with type 2 DM, a statistically significant correlation was found between the HbA1c levels and BMI (p<0.001, r=0.71). A significant correlation was also found between HbA1c - CRP (p=0.041, r=0.54) and BMI - CRP (p=0.046, r=0.48) levels. A statistically significant negative correlation was found between HDL-HbA1c (p=0.025, r=-0.57).

Ischemia-modified albumin levels of diabetics and healthy individuals with normal and high uric acid levels

IMA levels in 41 diabetic patients (21 patients with normal uric acid/20 patients with increased uric acid) and 32 healthy controls were evaluated. As shown in Table 2, a detailed comparison of the groups based on IMA levels revealed no significant differences (p=0.332).

Table 1. Comparison of diabetic groups with high and normal uric acid levels

	Diabetics with high uric acid (n:20)	Diabetics with normal uric acid (n:21)	P value
Age (years)	61.3±7.1	60.5±7.2	0.715
F/M (n, %)	10/10 (50.0/50.0)	10/11 (48.8/51.2)	0.896
BMI (kg/m^2)	27.3±2.5	28.5±3.2	0.191
Uric acid (mg/dL)	7.7 (9/6.8) ‡	4.9 (6.4/2.9) ‡	< 0.001
FPG (mg/dL)	149 (253/98) ‡	195.1 (358/104) ‡	0.213
HbA1c (%)	7.16±1.34	7.65±1.97	0.359
Total cholesterol (mg/dL)	204.9±62.5	194±43.6	0.518
LDL (mg/dL)	123.7±43.9	115.4±35.8	0.514
HDL (mg/dL)	37.8±7	42.4±11.9	0.142
Triglycerides (mg/dL)	200.5±115.7	191±118	0.817
BUN (mg/dL)	18.2±4.8	15±4.6	0.034
Creatinine (mg/dL)	0.96±0.18	0.86±0.17	0.076
Spot urine alb/cre (mg/day)	14.3±7.9	13.9±6.4	0.867
Hb (g/dL)	14.9±1.8	15.5±1.5	0.566
CRP (mg/L)	4±2.6	3.2±2.3	0.317
IMA (ABSU)	0.38±0.16	0.40±0.16	0.846

*F/M: Female/Male, BMI: Body mass index, FPG: Fasting plasma glucose, HbA1c: Glycated hemoglobin, LDL: Low-density lipoprotein, HDL: High-density lipoprotein, BUN: Blood urea nitrogen, Hb: Hemoglobin, Alb/cre: Albumin/creatinine ratio, CRP: C-Reactive protein, IMA: Ischemia modified albumin, ±: Standard deviation, ‡: Min. – Max. values

Table 2. Ischemia-modified albumin (IMA) levels of diabetics and healthy individuals with normal and high uric acid levels

	Diabetics with high uric acid (n:20)	Diabetics with normal uric acid (n:21)	Healthy individuals (n:32)	P value
Age (years)	61.3±7.1	60.5±7.2	68±7	
F/M (n, %)	10/10 (50.0/50.0)	10/11 (48.8/51.2)	12/20 (37.5/62.5)	
IMA (ABSU)	0.38±0.16	0.40±0.16	0.37±0.08	(p=0.332)

* F/M: Female/Male, IMA: Ischemia modified albumin, ABSU: absorbance-unit

Comparison of TOC and TAC levels in diabetic groups with high and normal uric acid levels

In all diabetic patients, the mean TOC level was 46.2±45 µmol/L, which was higher than the reference values as expected. Comparing the diabetic groups among themselves, the mean TOC level in the high uric acid group was higher than the TOC level in the normal uric acid group (49.5±45.5 µmol/L, 43±45.4 µmol/L respectively). However, this height is not statistically significant (p=0.655). A mean TAC value of 3.0±0.5 mmol/L was observed in all diabetic patients, which was higher than the reference values. A comparison of diabetic groups according to TAC levels revealed no significant relationship between those with high uric acid levels and those with normal uric acid levels (3.1±0.4 mmol/L, 3.0±0.5 mmol/L respectively) (p=0.461).

DISCUSSION

Hyperuricemia has been associated with hypertension, atherosclerotic cardiovascular disease, chronic kidney disease, and metabolic syndrome [4,15,16].

Metabolic abnormalities in type 2 DM are thought to alter uric acid metabolism, prompting numerous studies to explore this correlation. Animal studies suggest that uric acid may impair insulin resistance by decreasing nitric oxide bioavailability, potentially contributing to diabetes development [17].

However, whether serum uric acid is an independent risk factor for type 2 DM remains unclear. Some studies link serum uric acid levels with carotid atherosclerosis in type 2 DM patients, while others report no significant correlation [16,18]. A Mendelian randomized study by Sluijs et al., found no relationship between serum uric acid levels and diabetes risk, nor did uric acid-lowering treatments affect diabetes development [19]. Nevertheless, other research consistently demonstrates a linear relationship between high uric acid levels and diabetes complications. A meta-analysis by Xu et al., reported that a 1 mg/dl increase in serum uric acid levels raises the risk of vascular complications by 18% and mortality by 9% [4]. Serum uric acid is also considered a risk factor for diabetic nephropathy and is associated with various diabetes complications, suggesting that it should be closely monitored in patients with type 2 DM [20].

This study evaluated the impact of elevated uric acid on IMA, TOC, and TAC levels which are used as indicators of oxidative stress in individuals with type 2 DM. To evaluate the independent effect of uric acid, we excluded patients with type 2 DM who had developed either microvascular or macrovascular complications. Considering the evidence from studies showing a positive relationship between HbA1c levels and uric acid levels [20,21], we formed two groups with statistically similar HbA1c values in our study. Based on the evidence from the literature indicating a positive association between BMI, obesity, and uric acid [22,23], we established groups with similar BMI levels.

To ensure accurate efficacy evaluation and mitigate the confounding effect of uric acid, we excluded patients with elevated CRP levels. While the study included patients with normal CRP levels, our analysis of CRP levels across all groups identified a significant correlation between CRP levels and BMI-HbA1c, as reported in the literature. Gender is another important issue when evaluating uric acid levels [24]. It is higher in males than in females. A possible explanation is that increased renal clearance of urate in females, compared to males, may be attributed to higher estrogen levels [16]. In females, the renal proximal tubular urate transporter is inhibited by estrogenic compounds. Consequently, uric acid levels and pools are typically lower in females than in males until menopause. This

difference is evidenced by the increased incidence of gout observed in males over the age of 30 and in females over the age of 50. To control for the effects of age and gender in our study, we matched the groups to ensure no significant differences in age and gender distribution.

Since studies are showing that uric acid plays a pro-oxidant role when the uric acid level exceeds > 6.5 - 7 mg/dL in males and > 6 mg/dL in females [6,22], we classified type 2 DM patients with uric acid levels> 6.5 mg/dL as a uric acid high group.

This study demonstrated that IMA, TOC, and TAC levels did not differ significantly between patients with type 2 DM who had elevated serum uric acid levels and those with normal uric acid levels.

The pioneering study by Piwowar et al., on IMA levels in patients with type 2 DM, demonstrated elevated IMA levels compared to healthy individuals [25]. Their research identified a significant correlation between IMA levels and HbA1c while showing a weak correlation between IMA levels, blood pressure, and LDL. Piwowar et al., were the first to report that elevated IMA levels in diabetic patients may originate from non-cardiac sources, highlighting that chronic hypoxia-induced by hyperglycemia and oxidative stress can modify the albumin molecule in the plasma of these patients [25]. El-Eshmawy et al. also observed a significant increase in IMA levels in prediabetic individuals compared to healthy controls [26].

Although our study showed higher IMA levels in type 2 DM patients relative to the control group, this difference was not statistically significant. This result is supported by the findings of Dahiya et al., who similarly reported no significant difference in IMA levels between 60 newly diagnosed type 2 DM patients without vascular complications and 30 healthy controls [27]. In line with the results of our study, the study by Ma et al., also reported no significant difference in IMA levels between individuals with type 2 DM without peripheral arterial disease (PAD) and the healthy control group. [28]. Although ischemia-modified albumin is a proven cardiac marker, its role in type 2 DM without vascular complications has not yet been reported [27].

When comparing the results of existing studies with our findings, it can be concluded that IMA levels are significantly elevated in patients with type 2 DM who have complications compared to healthy individuals; however, this difference is not observed in patients with type 2 DM who do not have complications. This discrepancy may be attributed to the fact that oxidative stress, ischemia, vascular endothelial damage, and chronic hypoxia are significantly more pronounced in patients with type 2 DM who have complications compared to those without complications, potentially leading to a significant increase in IMA levels. Besides, in most of the studies that found high levels of IMA in patients with type 2 DM, burayı high sensitive C-reactive protein (hs-CRP) level and IMA were found to be correlated. Kaefer et al., reported that hs-CRP levels were also significantly higher in diabetic patients with high IMA levels [29], but the patient group in our study was selected from patients with normal CRP levels. This may be a factor in the fact that the IMA level was not found to be significantly high. IMA was mainly associated with CRP, a marker of inflammation, rather than diabetes itself in uncomplicated diabetic patients, as in the studies mentioned above [29]. In our study, the high uric acid level did not affect this condition.

According to the results of this study, we found that the mean TOC level was higher than the reference values in all patients with type 2 DM. Numerous studies have indicated that TOC levels are elevated in patients with type 2 DM [30,31]. The findings of our study are consistent with these observations. In the comparison of the study groups with each other, although the TOC level was higher in the group with higher uric acid, this increase was not significant.

In this study, TAC levels were higher than reference values across all patients with type 2 DM, which reflects a contrast with diverse findings in existing literature. This observation is consistent with the study by Savu et al., where increased TAC levels were reported in type 2 DM patients without vascular complications [31]. The body tries to keep the oxidant/antioxidant system in balance. Oxidative stress induces an increase in the activity of antioxidant mechanisms. However, once oxidative stress reaches a threshold level, these antioxidant defenses become inadequate and depleted, leading to a decline in TAC levels [19]. Considering the study results, it is suggested that since the study group consisted of type 2 DM patients without

vascular complications, the level of oxidative stress was likely manageable by antioxidant mechanisms, which could explain the high TAC levels recorded. The comparison of TAC levels across different serum uric acid levels did not reveal any significant differences. When the results related to TOC-TAC were evaluated together, the effect of uric acid level alone on oxidant/antioxidant balance in patients with type 2 DM without vascular complications was not strong enough to make a significant difference. However, the fact that both systems are active indicates that uncomplicated diabetic individuals still have adequate antioxidant capacity to respond to the oxidative response.

The study's strengths lie in its focus on patients with type 2 DM without microvascular or macrovascular complications, offering insights into the early stages of the disease and the role of uric acid in oxidative stress. Additionally, including diabetic patients with varying uric acid levels and healthy controls, it establishes a comparative framework for understanding oxidative markers.

Also, this study has several limitations to consider. Firstly, the small sample size (41 diabetic patients and 32 healthy controls) limits the statistical power to detect significant differences or subtle correlations. Secondly, as a cross-sectional study, it only provides a snapshot of serum uric acid levels and oxidative markers, restricting the ability to infer causal relationships or long-term effects in type 2 DM. Lastly, being a single-center study is also a major limitation.

In conclusion, we did not find a direct correlation between increased serum uric acid level alone and IMA - TOC - TAC in our study. These results imply that increased serum uric acid levels alone do not influence oxidative stress in patients with uncomplicated type 2 diabetes. The study's findings demonstrate that uncomplicated diabetic patients can augment their TAC capacity to sustain antioxidant defenses. Thus, uric acid should not be considered a marker of oxidative stress or a protective factor against oxidative stress in individuals with uncomplicated type 2 DM. Nevertheless, future research should aim to provide a more comprehensive understanding of how serum uric acid levels influence the oxidant/antioxidant balance in patients with type 2 DM. Long-term studies are also needed to follow diabetic patients without complications and to explore the relationships between uric acid, IMA, TOC, and TAC as complications progress.

Author contribution

Study conception and design: EKK, TC, and IE; data collection: EKK; analysis and interpretation of results: EKK, IE; draft manuscript preparation: EKK, IE. All authors reviewed the results and approved the final version of the manuscript.

Ethical approval

The study was approved by the Ethics Committee of Ufuk University Faculty of Medicine Dr. Rıdvan Ege Hospital (Protocol no: 21012015-1).

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Conflict of interest

The authors declare that there is no conflict of interest.

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