

# Vitamin D and Elevated Serum Uric Acid as Novel Predictors and Prognostic Markers for Type 2 Diabetes Mellitus

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## ABSTRACT

**Aim:** To ascertain the active role of uric acid and vitamin D as potential biomarkers for impaired glucose metabolism among people living with type 2 diabetes mellitus (T2DM) in Turkish community. **Subjects and Methods:** This study was based on 680 patients with T2DM and 680 healthy subjects aged between 25 and 70 years, who visited the diabetes and endocrinology department of Istanbul Mega Medipol University Teaching Hospital, Istanbul, Turkey, during January 2016 to April 2018. The investigated biochemical indices included lipid profiles (low-density lipoprotein [LDL], high-density lipoprotein, total cholesterol, and triglyceride [TG]), uric acid, blood pressure (BP), serum creatinine, glycosylated hemoglobin (HbA1c), thyroid-stimulating hormone (TSH), postprandial glucose, and any related comorbidities. **Results:** This study reported significant differences between family history duration of patients with T2DM of  $\leq 5$  and  $> 5$  years when compared to that of control subjects with respect to body mass index (BMI), smoking habit, *sheesha* smoking, income, family history of metabolic syndrome, hypertension, coronary heart disease, and nephropathy. Similarly, significant differences were found between patients with T2DM (with family history T2DM duration of less than 5 years and more than 5 years in contrast to healthy subjects' level of LDL, TG, fasting blood glucose, HbA1c, systolic BP (SBP), bilirubin, albumin, magnesium, potassium, calcium, number of sleeping hours, and TSH. We uncovered the correlation between serum uric acid level with the clinical biochemical indices related to T2DM: serum calcium ( $r = 0.336$ ), magnesium ( $r = 0.272$ ), potassium ( $r = 0.205$ ), HbA1c ( $r = 0.638$ ), fasting blood glucose ( $P = 0.486$ ), bilirubin ( $r = 0.251$ ), albumin ( $r = 0.285$ ), LDL ( $r = 0.322$ ), TG ( $r = 0.434$ ), diastolic BP (DBP) ( $r = 0.392$ ), SBP ( $r = 0.344$ ), BMI ( $r = 0.482$ ), waist circumference (WC) ( $r = 0.366$ ), age ( $r = 0.217$ ), number of sleeping hours ( $r = 0.275$ ), and TSH ( $r = 0.445$ ). Multivariate stepwise logistic regression showed that variables, such as serum vitamin D, uric acid, TSH, HbA1c, DBP, WC, BMI, and SBP, were considered at higher risk as significant ( $P < 0.001$ ) predictors for T2DM. **Conclusion:** The results suggest strong positive correlation between serum uric acid level with BP (SBP and DBP), age, BMI, and WC among patients with T2DM. This study ascertains that an increase in uric acid level may be due to elevated level of HbA1c, metabolic syndrome, diabetes, obesity, and/or hypertension.

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**KEYWORDS:** Biomarker, epidemiology, nephropathy, type 2 diabetes mellitus, uric acid, vitamin D

## INTRODUCTION

Type 2 diabetes mellitus (T2DM) with its comorbidities and mortality poses a significant burden on health-care expenditure. Substantial epidemiological studies suggest the pivotal role of serum uric acid as independent risk factor of cardiovascular disease (CVD), particularly in patients with hypertension and DM.<sup>[1,2]</sup> T2DM is also a prime risk factor for CVD,<sup>[3,4]</sup> which is the leading cause of death in Western countries.<sup>[3-5]</sup> Several modifiable risk factors, for example, diet, physical activity level, and sleep duration, can reduce the incidence of T2DM among at-risk individuals.<sup>[2]</sup> Several prospective studies have documented the impact of elevated serum uric acid level on the development of T2DM, metabolic syndrome,<sup>[2]</sup> hypertension,<sup>[3]</sup> and CVD.<sup>[4]</sup> Similarly, it has been confirmed that serum uric acid is a probable risk factor for developing DM,<sup>[6-8]</sup> metabolic syndrome,<sup>[8,9]</sup> hypertension, stroke,<sup>[9,10]</sup> and CVDs.<sup>[11]</sup> The value of elevated levels of uric acid in serum as risk factor for DM development is still under scrutiny. More recent studies have shown that uric acid levels are higher in subjects with prediabetes and early T2DM than that in healthy controls.<sup>[8,9]</sup> Furthermore, an elevated serum uric acid level was found to increase the chances for developing T2DM in individuals with impaired glucose tolerance.<sup>[10]</sup> An elevated uric acid level, as reported, often precedes the development of obesity,<sup>[9]</sup> hyperinsulinemia,<sup>[10-12]</sup> and diabetes.<sup>[13-15]</sup> In addition, uric acid has been implicated in the initiation of metabolic syndrome<sup>[16]</sup> and hypertension.<sup>[17]</sup>

The aim of the study was to examine the potential role of uric acid as biomarker for impaired glucose metabolism and diabetes in Turkish population.

## SUBJECTS AND METHODS

This study was based on 680 patients with T2DM and 680 healthy subjects aged between 25 and 70 years, who visited the diabetes and endocrinology department of Istanbul Mega Medipol University Teaching Hospital, Istanbul, Turkey, during January 2016 to April 2018.

### Laboratory measurements

People living with T2DM were considered as “case” patients if they had a history of DM and were taking any oral diabetes medications for 3 years.<sup>[18-20]</sup> These “case” subjects were investigated for their lipid profile (total cholesterol, low-density lipoprotein [LDL], high-density lipoprotein [HDL], triglyceride [TG]), glycosylated

hemoglobin (HbA1c), postprandial glucose, blood pressure (BP), serum creatinine, thyroid, and presence of any related medical comorbidities. On the contrary, “healthy” subjects were the ones who were not taking any DM medications and whose HbA1c levels were less than 6.5% and their fasting blood glucose levels were less than 7.0 mmol/L (126 mg/dL), which were confirmed from their medical records.

### Statistical analysis

Student's *t*-test was conducted to reveal if any significant difference exists between mean values of two continuous variables. One-way analysis of variance (ANOVA) was used for comparison of more than two mean values. Fisher's exact test (two-tailed) and chi-square test were used to show differences in proportions of categorical variables between two or more groups. Multivariate logistic regression analysis was used to estimate the associated risk factors for T2DM. Pearson's correlation coefficient test was used between two continuous variables ( $P < 0.05$  was regarded as the cutoff value for significance).

## RESULTS

Sociodemographic and clinical characteristics of investigated cases/patients with T2DM and control subjects are shown in Table 1. The findings showed significant differences between patients with T2DM with less than 5 years and more than 5 years of T2DM history when compared with control subjects with respect to their body mass index (BMI) (kg/m<sup>2</sup>), smoking habit, *sheesha* smoking, income, family history of metabolic syndrome, hypertension, coronary heart disease (CHD), and nephropathy.

Table 2 shows the baseline values of biochemical indices among patients with T2DM versus control subjects. Significant differences were reported between patients with T2DM (with less than 5 years and more than 5 years of T2DM history) when compared to control subjects with respect to the values of their calcium ( $P < 0.001$ ), magnesium ( $P < 0.001$ ), potassium ( $P < 0.001$ ), HbA1c ( $P < 0.001$ ), fasting blood glucose ( $P < 0.001$ ), TG ( $P < 0.001$ ), LDL ( $P = 0.008$ ), bilirubin ( $P = 0.015$ ), systolic BP (SBP) ( $P = 0.009$ ), albumin ( $P < 0.001$ ), number of sleeping hours ( $P < 0.001$ ), and thyroid-stimulating hormone (TSH) ( $P < 0.001$ ).

Table 3 shows a correlation between serum uric acid level with the clinical biochemical indices related to T2DM with serum calcium ( $r = 0.336$ ), magnesium ( $r = 0.272$ ), potassium ( $r = 0.205$ ), fasting blood glucose ( $r = 0.486$ ),

**Table 1: Sociodemographic and clinical characteristics of studied patients with type 2 diabetes mellitus and healthy subjects (n = 1360)**

Variables	Diabetic $\leq 5$ years N = 329, n (%)	Diabetic $> 5$ years N = 351, n (%)	Healthy subjects N = 680, n (%)	P value <sup>a</sup>
Age groups (years)				0.001
<40	87 (26.4)	89 (25.4)	224 (32.9)	
40–49	77 (23.4)	77 (21.9)	190 (27.9)	
50–59	74 (22.5)	79 (22.5)	161 (23.7)	
>60 and above	91 (27.7)	106 (30.2)	105 (15.4)	
Gender				0.077
Male	159 (48.3)	153 (43.6)	347 (51)	
Female	170 (51.7)	198 (56.4)	333 (49)	
BMI (kg/m <sup>2</sup> )				0.001
Normal (<25 kg/m <sup>2</sup> )	98 (29.8)	94 (26.8)	257 (37.9)	
Overweight (29–30 kg/m <sup>2</sup> )	151 (45.9)	152 (43.3)	309 (45.6)	
Obese (>30 kg/m <sup>2</sup> )	80 (24.3)	105 (29.9)	112 (16.5)	
Physical activity 30 min/day				0.538
Yes	84 (25.5)	103 (29.3)	188 (27.6)	
No	245 (74.5)	248 (70.7)	492 (72.4)	
Household income				0.014
Low	102 (31.0)	103 (29.3)	169 (24.9)	
Medium	166 (50.5)	187 (53.4)	340 (50)	
High	61 (18.5)	61 (17.3)	171 (25.1)	
Sheesha smoking				0.019
Never	50 (15.2)	73 (20.8)	96 (14.1)	
Current smoker	279 (84.8)	278 (79.2)	584 (85.9)	
Cigarette smoking				0.010
Never	261 (79.3)	283 (80.6)	524 (77.1)	
Current smoker	52 (15.8)	47 (13.4)	85 (12.5)	
Past smoker	16 (4.9)	21 (6.0)	71 (10.4)	
Family history of hypertension				0.001
Yes	75 (22.8)	59 (16.8)	89 (13.1)	
No	259 (77.2)	292 (83.2)	591 (86.9)	
Metabolic syndrome ATP-III				0.001
Yes	106 (32.2)	124 (35.3)	64 (9.4)	
No	323 (67.8)	227 (64.7)	616 (90.6)	
CHD				0.021
Yes	49 (14.9)	55 (15.7)	70 (10.3)	
No	280 (85.1)	296 (84.3)	610 (89.7)	
Family history of nephropathy				0.001
Yes	42 (12.8)	56 (16.0)	26 (3.8)	
No	287 (87.2)	295 (84.0)	654 (96.2)	

<sup>a</sup>Chi-square test was performed

ATP = Acute thrombocytopenic purpura

TG ( $r = 0.434$ ), HbA1c ( $r = 0.638$ ), LDL ( $r = 0.322$ ), bilirubin ( $r = 0.251$ ), albumin ( $r = 0.285$ ), diastolic BP (DBP) ( $r = 0.392$ ), SBP ( $r = 0.344$ ), BMI ( $r = 0.482$ ), waist circumference (WC) ( $r = 0.366$ ), age ( $r = 0.217$ ), number of sleeping hours ( $r = 0.275$ ), and TSH ( $r = 0.445$ ).

Table 4 shows multivariable stepwise logistic regression analysis of independent predictors for the presence of diabetes. Serum vitamin D (mmol/L) (odds ratio [OR], 3.38, 95% confidence interval [CI], 1.60–5.80;  $P < 0.001$ ), uric acid (mmol/L) (OR, 3.24, 95% CI, 1.84–4.53;  $P < 0.001$ ), TSH (mIU/L) (OR, 3.11, 95% CI, 2.12–4.40;  $P < 0.001$ ),

HbA1c (OR, 2.95, 95% CI, 1.77–4.32;  $P < 0.001$ ), DBP (OR, 2.88, 95% CI, 2.13–3.91;  $P < 0.001$ ), WC (cm) (OR, 2.61, 95% CI, 1.72–4.44;  $P < 0.001$ ), BMI (OR, 2.39, 95% CI, 1.68–4.39;  $P = 0.003$ ), and SBP (mm Hg) (OR, 1.78, 95% CI, 1.30–2.59;  $P = 0.026$ ) were considered at higher risk as predictors for T2DM.

## DISCUSSION

The study reports strong positive correlation between uric acid and HbA1c levels. The current results are confirmative with other reported that correlations

**Table 2: Clinical biochemistry baseline value among type 2 diabetes mellitus and healthy subjects (n = 1360)**

Variables	Diabetic ≤5 years	Diabetic > 5 years	Healthy	P value <sup>a</sup>
	N = 329 Mean ± SD	N = 351 Mean ± SD	N = 680 Mean ± SD	
Age (years)	49.76 ± 14.90	50.57 ± 14.31	46.93 ± 13.43	<0.001
Number of sleeping (hours)	5.90 ± 0.92	5.90 ± 0.92	5.90 ± 0.92	<0.001
BMI (kg/m <sup>2</sup> )	27.32 ± 4.28	27.85 ± 4.86	26.34 ± 4.33	<0.001
Vitamin D (g/dL)	14.89 ± 5.38	15.07 ± 6.01	21.87 ± 4.58	<0.001
Hemoglobin (g/dL)	12.79 ± 2.21	12.65 ± 2.45	13.20 ± 2.68	<0.001
Magnesium (mmol/L)	0.70 ± 0.06	0.79 ± 0.08	0.92 ± 0.09	<0.001
Potassium (mmol/L)	3.55 ± 0.57	3.34 ± 0.50	4.46 ± 0.37	<0.001
Calcium (mmol/L)	1.78 ± 0.80	1.69 ± 0.45	1.94 ± 1.26	0.002
Phosphorous (mmol/L)	1.30 ± 0.57	1.28 ± 0.54	1.20 ± 0.62	0.092
Creatinine (mmol/L)	62.38 ± 29.19	67.25 ± 16.90	63.85 ± 12.33	0.101
Fasting blood glucose (mmol/L)	7.39 ± 1.02	7.29 ± 0.91	6.25 ± 1.42	<0.001
HbA1c (mmol/L)	7.32 ± 0.94	7.94 ± 0.91	5.19 ± 0.25	<0.001
Cholesterol (mmol/L)	4.74 ± 1.09	4.85 ± 1.02	3.22 ± 1.67	<0.001
HDL (mmol/L)	1.60 ± 0.44	1.14 ± 0.39	1.33 ± 0.16	0.483
LDL (mmol/L)	1.87 ± 0.90	1.96 ± 1.00	2.12 ± 0.95	0.008
Albumin (mmol/L)	40.79 ± 11.50	40.30 ± 9.22	36.66 ± 10.38	<0.001
Bilirubin (mmol/L)	8.84 ± 4.28	9.22 ± 5.66	9.88 ± 4.25	0.009
Alkaline phosphate (mmol/L)	81.37 ± 36.52	82.97 ± 39.83	70.61 ± 12.33	<0.001
Triglyceride (mmol/L)	1.97 ± 1.36	1.99 ± 1.35	1.17 ± 0.65	<0.001
Uric acid (mmol/L)	263.81 ± 87.51	272.76 ± 69.23	292.87 ± 78.49	<0.001
TSH serum (mmol/L)	2.70 ± 1.02	2.67 ± 0.97	1.98 ± 1.36	<0.001
SBP (mm Hg)	129.00 ± 15.71	130.10 ± 15.84	126.86 ± 9.25	0.009
DBP (mm Hg)	78.90 ± 10.82	79.95 ± 9.73	75.69 ± 7.41	<0.001

SD = standard deviation

<sup>a</sup>One-way analysis of variance (ANOVA) test was performed**Table 3: Correlations between uric acid, biological and clinical biochemistry, and studied parameters**

Variables	Pearson's correlation (r)	P value <sup>a</sup>
Age (years)	0.217	<0.001
Waist circumference (cm)	0.366	<0.001
BMI (kg/m <sup>2</sup> )	0.482	<0.001
Hemoglobin (g/dL)	0.249	0.025
Magnesium (mmol/L)	0.272	<0.001
Potassium (mmol/L)	0.205	<0.001
Serum calcium level (mmol/L)	0.336	<0.001
Phosphorous (mmol/L)	0.182	0.042
Creatinine (mmol/L)	0.287	<0.001
Fasting blood glucose (mmol/L)	0.486	<0.001
HbA1c (mmol/L)	0.633	<0.001
Cholesterol (mmol/L)	0.341	<0.001
HDL (mmol/L)	0.320	<0.001
LDL (mmol/L)	0.309	<0.001
Albumin (mmol/L)	0.226	0.038
Bilirubin (mmol/L)	0.251	<0.001
Triglyceride (mmol/L)	0.435	<0.001
SBP (mm Hg)	0.344	<0.001
DBP (mm Hg)	0.392	<0.001
TSH (mIU/L)	0.416	<0.001
Number of sleeping hours	0.275	<0.001

<sup>a</sup>Pearson's correlation coefficient test was performed with Student's *t*-test for significance**Table 4: Multivariate stepwise logistic regression analysis of predictors as prognostic marker for type 2 diabetes mellitus**

Independent variables	Adj. OR	95% Confidence interval	P value
Vitamin D deficiency (ng/mL)	3.38	1.60–5.80	<0.001
Uric acid (mmol/L)	3.24	1.84–4.53	<0.001
TSH (mIU/L)	3.11	2.12–4.40	<0.001
HbA1c (mmol/L)	2.95	1.77–4.32	<0.001
DBP (mm Hg)	2.88	2.13–3.91	<0.001
Waist circumference (cm)	2.61	1.72–4.44	<0.001
BMI (kg/m <sup>2</sup> )	2.39	1.68–4.39	0.003
SBP (mm Hg)	1.78	1.30–2.59	0.026

Adj. OR = Adjusted odds ratio for age and gender  
95% Confidence interval means that there is a 95% probability that the confidence interval will contain the true population meanbetween uric acid levels and diabetes, family history of hypertension, metabolic syndrome, CHD, and diabetic nephropathy.<sup>[21,22]</sup>Further, we reported a correlation between uric acid levels and age, BMI (kg/m<sup>2</sup>), continuation of DM, and WC. These reported results are in agreement with

the literature.<sup>[8]</sup> The correlation between uric acid and HbA1c levels can be considered as an important risk factor. While preceding researches reported that uric acid was associated with T2DM, and similarly, we established positive association between these variables.<sup>[3,8-11,15,21,22]</sup>

We also report a positive correlation between a high level of uric acid and DBP–SBP among patients with T2DM. Uric acid levels were correlated with the risk of metabolic syndrome and BP and TSH. The association of uric acid levels and T2DM incidence has been indicated in several other populations,<sup>[13,23,24]</sup> which are consistent with our studies among patients with T2DM.

Furthermore, other scientists<sup>[13,21,22]</sup> reported strong positive relationships between the uric acid level, thyroid diseases, and vitamin D deficiency in patients with T2DM. Finally, the prevention and early detection of elevated level of uric acid in both patients with T2DM and hypertension can provide effective investigative tool in reducing CVD. The result with relation to incident prediabetes is consistent with previous research on this subject using impaired fasting glucose level as an end point. This could indicate that serum uric acid is more closely associated with early-phase rather than late-phase mechanisms that play a role in the development of T2DM.<sup>[13,22]</sup>

Serum uric acid level has been investigated in relation to incident T2DM in individuals with impaired fasting glucose level by Kramer *et al.*,<sup>[21]</sup> who found a significant association after adjusting for various confounders in study population with characteristics similar to ours. It is possible that residual confounding in the previous study could account for this difference. These covariates were particularly impactful in our multivariable-adjusted model.<sup>[13,21,22]</sup>

The strengths of our study include its prospective cohort nature, which minimizes the chance of reverse causation, its long follow-up time, and our ability to adjust for a large set of confounders. However, the study has several limitations to discuss. All data were collected using a standardized protocol with rigorous quality control. First, oral glucose tolerance tests were not performed, so we could not identify participants with impaired glucose tolerance (IGT), another characteristic of prediabetes. It is possible that serum gamma-glutamyltransferase and uric acid may show different associations with IGT than that with impaired fasting glucose. Second, only one time point was recorded for the subjects in this study. Third, possible

selection bias was observed as this is not a study of consecutive patients seen at our institution.

## CONCLUSION

The results suggest a strong positive correlation between serum uric acid level with levels of SBP and DBP, age, BMI, duration of DM, and WC among patients with T2DM. This study ascertains that an increase in uric acid level may be due to elevated level of HbA1c, metabolic syndrome, diabetes, obesity, and/or hypertension.

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## Conflicts of interest

There are no conflicts of interest.

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