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Original Article

The Effect of Uric Acid and Bilirubin Levels on Type 2 Diabetes Mellitus Development in Prediabetic Patients

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A R T I C L E I N F O

A B S T R A C T

Background: This study aims to investigate whether or not uric acid and bilirubin have a role in the development of type 2 diabetes mellitus (T2DM) in prediabetic patients.

Methods: 93 patients were included in the study. These patients were diagnosed as being prediabetic using the oral glucose tolerance test, and they also had their serum uric acid and total bilirubin measured during the follow-up application (1 - 5 years).

Results: 17 out of the 93 patients developed T2DM during the study period. The only significant difference between the T2DM group and the non-T2DM group was OGTT 0.min and 120.min (p=0.001 and p=0.007, respectively). Analysis of the relationship between age, sex, HbA1c, uric acid, total bilirubin, direct bilirubin levels and T2DM development showed that none of the aforementioned risk factors were related with diabetes development. In the non-T2DM group, the median total bilirubin level was only found to be higher in the baseline assessment (p=0.042).

Conclusion: It was found that uric acid and bilirubin had no effect on the development of diabetes in the 1-5-year follow-up of prediabetic patients. Randomized-controlled studies of a larger number of patients and sufficient follow-up time are required to provide clearer data on this topic.

Introduction

Diabetes mellitus is a disease of high morbidity and mortality due to its acute and chronic complications. It occurs due to insufficient insulin secretion from the pancreas, or to insulin resistance, and it affects fat, protein, and particularly carbohydrate metabolisms [1]. Due to its complications and growing incidence worldwide, diabetes mellitus has become a major global health problem [2]. As of 2013, there were 382 million diabetic individuals in the world, and this total is estimated to reach 592 million by 2035 [3]. According to predictions made in the 6th Edition of the International Diabetes Federation's Diabetes Atlas, Turkey is expected to become one of ten countries with the highest number of diabetes mellitus patients [4, 5]. Such an increase in the incidence of diabetes signifies the necessary of taking measures to prevent diabetes. The first step that should be taken is to identify relevant

risk factors on diabetes candidates and diabetes development. The presence of impaired fasting glucose, impaired glucose tolerance, or of both, increases the likelihood of contracting diabetes. Either of the above conditions is referred to as prediabetes [6]. Unless necessary precautions are taken, most prediabetic patients are known to go on to develop diabetes mellitus. Insufficient insulin secretion, insulin resistance, visceral obesity, and non-alcoholic fatty liver disease, have all been reported as factors that facilitate the progression of a patient from prediabetes to diabetes mellitus [7]. In recent studies; a history of gestational diabetes, polycystic ovary syndrome, and ethnicity, have all also been reported as significant factors in the progression from prediabetes to diabetes mellitus [8].

In addition to the aforementioned risk factors, oxidative stress is also believed to be a risk factor in the development of diabetes mellitus [9].

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It therefore may be expected that oxidant radicals can contribute to the progression of diabetes mellitus, while antioxidant molecules may reduce the progression. In several studies, uric acid and bilirubin have been shown to behave as antioxidant molecules in certain concentrations, and as oxidant molecules outside of these concentrations [10, 11]. It is not clear how these two molecules are involved in the progression of diabetes mellitus or diabetes development in prediabetic patients. The purpose of this study is to therefore to investigate the effect of uric acid and bilirubin levels on type 2 diabetes mellitus development in prediabetic patients.

Methods

I Study Population

This retrospective study was conducted between 15 January 2018 - 15 March 2018 by examining patients who had applied to the Internal Diseases Clinic of Ankara Numune Training and Research Hospital between 2011 – 2016. Using data taken from the hospital's information system, 93 patients who were diagnosed as being prediabetic, using the oral glucose tolerance test, and who had also had had their serum uric acid and total bilirubin measured during the follow-up application, (1 – 5 years) were included in the study. The exclusion criteria included pregnancy, chronic liver disease, systemic disease (malignancy, rheumatic disease), connective tissue disorder, a history of infection and/or trauma within the previous two weeks, hormone replacement therapy for any reason (thyroid dysfunction, post menopause), evidence of congestive heart failure or known coronary artery disease, acromegaly, and the use of drugs affecting plasma uric acid level. The criteria suggested by the American Diabetes Association were considered in the diagnosis of diabetes – prediabetes [2]. HbA1c was not used as a diagnostic criteria, since it is not standardized in Turkey, and so only patients whose OGTT was performed with 75 gr glucose were included in the study. Medical records, physical examination reports, drug use reports, and information relating to the diagnosis of the patients was obtained using the Fonet Hospital System. The study was performed in accordance with the Helsinki Declaration and patient rights and was approved by the Ethics Board of Ankara Numune Education and Research Hospital on 17.01.2018 by decision no. 1744/2018.

II Laboratory Parameters

The oral glucose tolerance test was performed by taking blood sample for baseline glucose measurement after at least 8 hours of fasting and then having the patient drink 75g of glucose, mixed in 250 – 300 ml water, within 5 minutes. The moment when the patient started to drink the water containing glucose was accepted as the starting point of the test. The blood sample was taken 2 hours later, and this point was accepted as being the 2-hour postprandial. Uric acid was measured by the colorimetric enzymatic and bilirubin spectrophotometric methods using a Hitachi Modular P800 (Roche) autoanalyzer. Glucose was measured by the Beckman Coulter AU 5800 (Beckman Coulter Inc. USA) autoanalyzer using the enzymatic UV hexokinase method. Glycated hemoglobin (HbA1c) was measured using the Arkray ADAMS A1c HA8180 (Arkray Global Business Inc., Kyoto, Japan) automated glycohemoglobin analyzer which utilizes the cation exchange high-performance liquid chromatography method.

III Statistical Analysis

The Statistical Package for Social Sciences (SPSS) for Windows 20 (IBM SPSS Inc., Chicago, USA) was used for statistical assessment. The normal distribution of the data was evaluated using the Kolmogorov-Smirnov test. Numeric variables with normal distribution were presented as mean ± standard deviations, while numeric variables without normal distribution were presented as median (min-max). Categorical variables were presented as numbers and percentages. The comparison between the two groups in terms of numeric variables with normal distribution was made with the student t test, and the comparison between the two groups in terms of numeric variables without normal distribution was made using the Mann Whitney U test. The change in follow-up time by diabetes mellitus development was assessed using the repeated measures of the ANOVA test. Multivariable COX regression analysis was used to identify possible risk factors for diabetes mellitus development, with p< 0.05 being considered significant in statistical analysis.

Results

Table 1 shows details of the demographic, clinical, and laboratory findings of the study population. 17 out of the 93 patients followed throughout the study period developed diabetes mellitus. The remaining 76 patients did not develop diabetes mellitus. The only significant difference between the diabetes mellitus group and the non-diabetes mellitus group was OGTT 0.min and 120.min (*p*=0.001 and *p*=0.007, respectively).The only significant difference between the baseline and 2nd visit assessments of the diabetes mellitus group was in terms of fasting blood glucose (*p*=0.011). No significant difference was observed in terms of other laboratory findings. No significant difference was found between the baseline and the 2nd visit assessments of the non-diabetes mellitus group in terms of laboratory findings (Table 2).The analysis examining the relationship between age, sex, HbA1c, uric acid, total bilirubin, and direct bilirubin levels and diabetes mellitus development showed that none of the aforementioned risk factors was related with diabetes development (Table 3). Table 4 shows the detailed clinical and laboratory findings of the study population by diabetes development and age. The fasting blood glucose was found to be higher in the 2nd visit assessment, compared to the baseline assessment, for patients aged both <65 and ≥65 in the diabetes mellitus group (*p* =0.009 and *p* =0.022, respectively). No significant difference was observed between the groups in terms of other findings. In the non-diabetes mellitus group, the median total bilirubin level was found to be higher in the baseline assessment, compared to the 2nd visit, only for the group aged ≥65 (*p*=0.042). However, significant differences were observed between the baseline assessment and the 2nd visit assessment in terms of other findings for patients aged both <65 and ≥65.

Discussion

While there are other studies investigating the effect of bilirubin on diabetes development in the literature, their number is quite limited. To the best of our knowledge, there is no other study in the literature examining the effect of both uric acid and bilirubin on diabetes development. In certain cases, antioxidants may become pro-oxidant [12]. Uric acid is the most significant marker of plasma antioxidant capacity, and is known to behave as an antioxidant in the early stages of the atherosclerotic process [13]. However, the serum uric acid level

becomes pro-oxidant at values over 6 mg/dl in women, and 6.5 – 7.0 mg/dl in men, in the later stages of the atherosclerotic process, and this paradoxal condition seems to be associated with several environmental factors such as tissue and substrate localization, acidity, oxidant environment, decrease in other local antioxidants, secretion and the presence of oxidant agents and enzymes [14, 15].

When reviewing the literature data, Bohle et al. studied the relationship between uric acid and diabetes with 641 diabetes cases in the original cohort, and 497 cases in the offspring cohort. The researchers found the incidence rates of diabetes per 1000 person-years for serum uric acid levels <5.0, 5.0-5.9, 6.0-6.9, 7.0-7.9 and ≥8.0 mg/dL to be 3.3, 6.1, 8.7, 11.5, and 15.9 in the original cohort, and 2.9, 5.0, 6.6, 8.7, 10.9 in the offspring cohort, respectively. The multivariable relative risks per mg/dL increase in the serum uric acid levels were 1.20 (95% CI, 1.11 to 1.28) for the original cohort, and 1.15 (95% CI, 1.06 to 1.23) for the offspring cohort, and the effect of uric acid did not vary between sexes [16]. Yamada et al. performed a study with 6408 men and 5309 women in which the researchers assigned women and men into 4 groups depending on their uric acid levels (<3.7 mg/dl, 3.7-4.19 mg/dl, 4.20 - 4.79 mg/dl, ≥ 4.8 mg/dl for women). Further analysis, excluding hypertension, alcohol use, smoking , body mass index, and hepatosteatosis, showed that the type 2 diabetes risk was 1.12, 1.49, and 1.85 times higher for other groups when compared to the first group (<3.7 mg/dl), and an increase of 1 mg/dl in the uric acid level increased the diabetes risk by 1.85 times [17]. However, studies also exist in literature which report opposing results. In a prospective cohort study from Japan, Taniguchi et al. assigned 6356 men between the ages of 35-60 into 5 groups depending on their uric acid level (36 -250 µmol/l, 251-290 µmol/l**,** 291-330 µmol/l, 331-370 µmol/l, 371-833 µmol/l). The researchers found that there was no difference between the groups in terms of type 2 diabetes risk [18]. In another study from Japan, 2449 men and 1448 women were examined in 4 groups (1-5.2 mg/dl, 5.3-6.0 mg/dl, 6.1-6.8 mg/dl, 6.9-12.1 mg/dl) and uric acid level was found to have no effect on diabetes development in men. The authors stated that this might be associated with hyperuricuria, which may develop in overt diabetes cases [19].

However, our study showed that uric acid level was not found to be an effective risk factor in prediabetic patients developing diabetes mellitus. It is believed that this finding may be related with the insufficient number of patients, the assessment of uric acid level without using quartiles as in aforementioned studies, and the inclusion of patients with isolated prediabetes (who might have comorbid conditions affecting uric acid level). Based on previous studies, uric acid is believed to show pro-oxidant activity in concentrations higher than about 6 mg/dl. In light of this data, the aforementioned studies report the consensus in literature that elevated concentrations of uric acid lead to a greater risk of diabetes mellitus development. In our study, the average uric acid level was 5.1 mg/dl among prediabetic patients. Considering that this level may have antioxidant or neutral effects, rather than an oxidant effect, this may explain why uric acid was not found to be an effective risk factor for diabetes mellitus development in the prediabetic patient group in our study. Another speculative explanation is that there is no clear idea about the total oxidant and antioxidant molecules that are effective with prediabetic patients. It is possible that uric acid might be an effective risk factor and its effect may have been neutralized by other antioxidant molecules present in the organism.

According to our literature review, the number of studies investigating the relationship between the bilirubin level and diabetes mellitus development is very limited. A review of available studies leads to the idea that bilirubin has a bilateral effect at a cellular level (and while bilirubin has an antioxidant effect at a physiological level, it may cause oxidative damage when it reaches a pathological level) [11].Studies on this topic suggest that bilirubin acts as a physiological antioxidant against atherosclerosis, coronary artery disease, and inflammation in low concentrations; and even bilirubin levels over 8.0 mg/dl (8-10 mg/dl) reduces coronary artery disease by 40% [20]. However, it is stated that higher concentrations of bilirubin may cause an increase in oxidative stress [11]. In a Hong Kong study with 1508 patients where the researchers divided the participants into four quartiles based on serum bilirubin concentrations (2-7 µmol/l, 7-9 µmol/l, 9-12 µmol/l, 12-81 µmol/l), the groups with lower bilirubin concentration were found to have increased cardiovascular disease risk factors and abnormal glucose tolerance, after adjusting for covariates such as age, sex, and smoking [21]. In our study, there was no statistically significant difference between the diabetes group and the non-diabetes group in terms of bilirubin level. The only significant difference was found between the baseline and the second visit bilirubin levels of the patients over the age of 65 in the non-diabetes group. In other words, there was a significant decrease in bilirubin level in the second visit. This finding may be considered as an antioxidant effect preventing diabetes development in prediabetic patients over the age of 65. The reason why we were not able to obtain a finding related to the protective or preventive effect of the bilirubin level against diabetes progression in normal population may be related to factors such as (i) the insufficient number of patients, (ii) insufficient follow-up time, (iii) the insufficient difference between bilirubin levels of the patients, and (iv) the neutralization of bilirubin's oxidative effects by other oxidant and antioxidant molecules present in the organism.

Although it varies depending on the characteristics of the population and the definition of prediabetes, 5 to 10% of prediabetic patients develop diabetes mellitus annually. The annual diabetes incidence is 4-6% for isolated impaired glucose tolerance, 6-9% for isolated impaired fasting glucose, and 15-19% for cases with both conditions [22]. In our study, 17 out of 93 prediabetic patients (18.2%) developed diabetes within 1-5 years, which is similar to the results obtained from other reports in the literature. Our main limitation has been the retrospective design of the study. Therefore, as patient parameters such as height, weight, and body mass index were not recorded, the fact that the relationship between diabetes development and these parameters was not studied is a significant limitation. Other limitations are that the entire population could not be followed-up homogeneously for a sufficient period of time, and uric acid and bilirubin levels could not be measured periodically. A further limitation is that several features could not be assessed, including oxidant and antioxidant molecules other than uric acid and bilirubin, which are believed to have both pro-oxidant and antioxidant effects, and total oxidant and antioxidant levels. This means that their relationship with diabetes progression could not be determined in our study.

In conclusion, no significant differences could be found between the diabetes and the non-diabetes group in terms of uric acid and bilirubin levels in the entire population. The differences that existed between HbA1c levels, uric acid levels, total bilirubin levels, and direct bilirubin levels measured in the first visit, and those that were measured in the

second visit, were not related with diabetes mellitus development. In light of these results, it was found that uric acid and bilirubin had no effect on the development of diabetes in the 1-5-year follow-up of prediabetic patients. Randomized-controlled studies with a higher number of patients and a sufficient follow-up time are required to provide clearer data on this topic.

Table 1: Clinical demographic and laboratory findings of participants according to diabetes mellitus development.

| Variables | All population $n=93$ | Diabetes mellitus | | p |
		Developed $n=17$	Not – Developed $n=76$	
Gender, $n(\%)$				
Female	65 (69.9)	10 (58.8)	55 (72.4)	0.380
Male	28 (30.1)	7 (41.2)	21 (27.6)	
Age (year)	56.0±11.1	58.5±12.8	55.4±10.6	0.299
<65	73 (78.5)	12 (70.6)	61 (80.3)	0.589
≥65	20 (21.5)	5 (29.4)	15 (19.7)	
OAD kullanımı, $n(\%)$				
(-)	75 (80.6)	12 (70.6)	63 (82.9)	0.308
(+)	18 (19.4)	5 (29.4)	13 (17.1)	
Basal examination				
OGTT 0.min (mg/dL)	106.0±9.7	113.1±9.1	104.4±9.2	0.001*
OGTT 120.min (mg/dL)	148.0±31.3	166.2±41.2	143.8±27.4	0.007*
HbA1c (%)	5.8±1.0	6.1±0.6	5.7±1.1	0.320
Uric acid (mg/dL)	5.1 (2.3-10.9)	5.1 (3.8-7.2)	5.1 (2.3-10.9)	0.945
Total bilirubin (mg/dL)	0.5 (0.1-1.4)	0.5 (0.2-1.4)	0.5 (0.1-1.3)	0.822
Direct bilirubin (mg/dL)	0.1 (0.1-1.4)	0.1 (0.1-0.4)	0.1 (0.1-1.4)	0.978
II. visit examination				
FBG (mg/dL)	112.8±28.0	146.6±45.5	105.2±14.2	0.002*
Control FBG (mg/dL)	109.0±13.1	121.0±20.8	107.7±11.6	0.050*
PPG (mg/dL)	133.7±42.8	180.5±53.0	126.2±36.8	0.016*
HbA1c (%)	6.0±0.5	6.8±0.7	5.8±0.4	0.006*
Uric acid (mg/dL)	5.2 (1.5-8.5)	5.0 (3.2-8.4)	5.2 (1.5-8.5)	0.538
Total bilirubin (mg/dL)	0.4 (0.1-1.4)	0.4 (0.2-1.1)	0.4 (0.1-1.4)	0.940
Direct bilirubin (mg/dL)	0.2 (0.1-1.1)	0.1 (0.1-0.4)	0.1 (0.1-1.1)	0.876

Categorical variables were expressed as numbers and percentage, numerical variables were expressed as mean±standard deviation or median (min-max).
*$p < 0.05$ was considered statistically significant.

OAD: Oral Anti-diabetic Drug, OGTT: Oral Glucose Tolerance Test, FBG: Fasting Blood Glucose, PPG: Post Prandial Glucose, HbA1c: Glycosylated Hemoglobin

Table 2: Changes in laboratory findings according to diabetes mellitus development during follow-up.

| Variables | Diabetes Mellitus Developed | | | Diabetes Mellitus Not – Developed | | | Δp |
	Basal	II. visit	p	Basal	II. visit	p	
FBG (mg/dL)	113.1±9.1	146.6±45.5	0.011*	104.4±9.2	105.2±14.2	0.65	<0.001*
HbA1c (%)	6.1±0.6	6.8±0.7	0.589	5.7±1.1	5.8±0.4	0.969	0.386
Uric Acid (mg/dL)	5.1 (3.8-7.2)	5.0 (3.2-8.4)	0.355	5.1 (2.3-10.9)	5.2 (1.5-8.5)	0.088	0.926
Total Bilirubin (mg/dL)	0.5 (0.2-1.4)	0.4 (0.2-1.1)	0.463	0.5 (0.1-1.3)	0.4 (0.1-1.1)	0.082	0.090
Direk Bilirubin (mg/dL)	0.1 (0.1-0.4)	0.1 (0.1-0.4)	0.241	0.1 (0.1-1.4)	0.1 (0.1-1.1)	0.27	0.731

Categorical variables were expressed as numbers and percentage, numerical variables were expressed as mean±standard deviation or median (min-max).
*$p < 0.05$ was considered statistically significant.

OAD: Oral Anti-diabetic Drug, OGTT: Oral Glucose Tolerance Test, FBG: Fasting Blood Glucose, PPG: Post Prandial Glucose, HbA1c: Glycosylated Hemoglobin

Table 3: Possible risk factors for developing diabetes mellitus.

Variables	Univariate		
	HR	**95% CI**	**p**
Gender			
Female	ref		
Male	1.42	0.53-3.84	0.485
Age	1.02	0.97-1.06	0.455
<65	ref		
≥65	1.31	0.45-3.83	0.618
Basal examination			
HbA1c	7.46	0.90-61.93	0.063
Urik acid	1.04	0.74-1.44	0.839
Total bilirubin	0.40	0.06-2.55	0.334
Direct bilirubin	0.10	0.01-20.60	0.170
II. visit examination			
HbA1c	9.06	0.87-94.91	0.066
Uric acid	1.02	0.74-1.40	0.908
Total bilirubin	0.93	0.16-5.44	0.931
Direct bilirubin	0.46	0.01-26.43	0.705
Basal – II. visit examination (Δ)			
ΔHbA1C	1.64	0.21-12.81	0.639
Δ Uric acid	0.96	0.56-1.66	0.891
Δ Total bilirubin	1.71	0.40-7.28	0.467
Δ Direct bilirubin	3.08	0.16-58.1	0.453

HR: Hazard ratio, CI: Confidence Intervale

Table 4: Distribution of laboratory findings during follow-up in patients < 65 and ≥65 years according to diabetes mellitus development.

Age	Variables	Diabetes Mellitus Developed			Diabetes Mellitus Not – Developed			Δp
		Basal	**II. visit**	**p**	**Basal**	**II. visit**	**p**	
<65	FBG	114.8±8.1	147.3±47.2	0.009*	104.4±9.6	104.3±11.6	0.95	<0.001*
	HbA1c	6.3±0.8	6.6±0.8	0.460	5.9±0.4	5.9±0.5	0.996	0.322
	Uric acid	5(3.8-6.5)	4.7(3.4-5.8)	0.302	5.1(2.3-8.3)	5.3(1.5-7.4)	0.605	0.416
	Total bilirubin	0.5(0.3-1.4)	0.4(0.2-0.7)	0.105	0.5(0.1-1.3)	0.4(0.1-1.4)	0.305	0.705
	Direct bilirubin	0.1(0.1-0.4)	0.2(0.1-0.4)	0.160	0.1(0-1.4)	0.1(0-1.1)	0.412	0.806
≥65	AKŞ	109±11	144.8±46.2	0.022*	104.1±7.4	108.9±22	0.980	0.001*
	HbA1c	6.0±0.1	6.5±0.6	0.753	6.1±0.3	5.6±0.8	0.104	0.114
	Uric acid	5.7(4.2-7.2)	5.4(3.2-8.4)	0.850	5(3.2-10.9)	4.8(3.3-8.5)	0.322	0.229
	Total bilirubin	0.6(0.2-0.7)	0.6(0.3-1.1)	0.940	0.7(0.3-1.1)	0.5(0.1-0.9)	0.042*	0.036*
	Direct bilirubin	0.1(0.1-0.3)	0.1(0.1-0.4)	0.912	0.1(0.1-0.8)	0.2(0.1-0.3)	0.088	0.105

Categorical variables were expressed as numbers and percentage, numerical variables were expressed as mean±standard deviation or median (min-max).
*$p < 0.05$ was considered statistically significant.
FBG: Fasting Blood Glucose, HbA1c: Glycosylated Hemoglobin

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