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Research Article

Assessment of Serum Uric Acid Levels and Their Relationship with Serum Lipid Parameters in Prediabetic Patients

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Abstract

Objectives: Serum uric acid has been implicated in the pathogenesis of metabolic syndrome; however, its association with cardiometabolic risk in prediabetes remains unclear. This study aimed to evaluate the relationship between uric acid levels and cardiometabolic risk factors in prediabetic individuals compared with normoglycemic subjects.

Methods: A total of 329 patients (155 normoglycemic, 174 prediabetic; aged 31–59 years) were included. Prediabetes was defined according to American Diabetes Association criteria (impaired fasting glucose [IFG] or impaired glucose tolerance. [IGT]). Serum uric acid (UA), lipid parameters (total cholesterol [TC], triglycerides [TG], high-density lipoprotein cholesterol [HDL-C], low-density lipoprotein cholesterol [LDL-C]), and atherogenic index of plasma (AIP; log[TG/HDL-C]) were assessed. Patients were categorized according to uric acid levels (<5.4, 5.4–6.4, and >6.4 mg/dL).

Results: Prediabetic patients had significantly higher uric acid levels than normoglycemic individuals ($p<0.001$). Uric acid levels differed significantly across groups and were positively correlated with age, TC, LDL-C, and AIP, and negatively correlated with HDL-C in prediabetic subjects ($p<0.001$).

Conclusion: Elevated uric acid levels are associated with adverse lipid profiles and increased cardiometabolic risk in prediabetes and may serve as a predictor of diabetes development.

Keywords: Glucose tolerance, prediabetic, uric acid

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Diabetes mellitus (DM) is a metabolic disease characterized by chronic hyperglycemia resulting from decreased insulin secretion, impaired insulin action, or both.[1] Early recognition of diabetes and the implementation of appropriate preventive measures, particularly during the prediabetic stage, are of great importance for slowing disease progression and preventing complications.

Prediabetes, defined as impaired fasting glucose (IFG) and/or impaired glucose tolerance (IGT), is an important risk factor for the development of type 2 diabetes and cardiovascular diseases.[1,2] A significant proportion of individuals with prediabetes develop overt diabetes in subsequent years, and these individuals show a predisposition to cardiovascular complications similar to patients with diabetes.[3]

Uric acid is the final product of purine metabolism, and elevated serum levels have been associated with various diseases. Recent studies have suggested that hyperuricemia may be related to metabolic syndrome, hypertension, diabetes, and dyslipidemia.[4–6] However, the relationship between serum uric acid levels and prediabetes, particular-

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ly their association with cardiovascular risk factors in prediabetic individuals, has not yet been fully clarified.[7]

In addition to classical lipid parameters used in cardiovascular risk assessment, the atherogenic index of plasma (AIP), calculated from the triglycerides (TG) to high-density lipoprotein cholesterol (HDL-C) ratio, has emerged as an important biomarker in recent years.[8]

The aim of this study was to evaluate the relationship between serum uric acid levels and cardiovascular risk factors, such as serum lipid levels and AIP in prediabetic individuals, compared with individuals with normal glucose tolerance.

Methods

This study was based on the retrospective evaluation of medical records of 329 patients (181 women and 148 men), aged between 31 and 59 years, who were admitted to the Internal Medicine outpatient clinics of Istanbul Training and Research Hospital between December 1, 2012, and December 1, 2014, had an indication for an oral glucose tolerance test (OGTT) (Table 5), and underwent a 2-hour OGTT with 75 g glucose.

Inclusion Criteria

1. Patients admitted to the Internal Medicine outpatient clinics of Istanbul Training and Research Hospital
2. Patients with an indication for OGTT who underwent a 2-hour OGTT with 75 g glucose
3. Patients with fasting plasma glucose ≥ 100 mg/dL and <126 mg/dL and/or 2-hour plasma glucose during OGTT ≥ 140 mg/dL and <200 mg/dL

Exclusion Criteria

1. Fasting plasma glucose ≥ 126 mg/dL and/or 2-hour plasma glucose ≥ 200 mg/dL
2. Known diagnosis of diabetes mellitus
3. Pregnant women
4. Serum creatinine > 1.3 mg/dL

Patient Classification

Patient groups were classified as follows:

- Individuals with normal fasting and 2-hour plasma glucose levels were classified as normoglycemic.
- Patients with fasting plasma glucose between 100–125 mg/dL were classified as having impaired fasting glucose (IFG).
- Patients with 2-hour plasma glucose between 140–199 mg/dL were classified as having impaired glucose tolerance (IGT).

Patients with HbA1c levels above 6.4% and serum creatinine levels > 1.3 mg/dL were excluded from the study.

Serum uric acid, total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), HDL-C, and plasma TG levels of all patients were recorded. These parameters were obtained from measurements performed in the hospital's biochemistry laboratory.

After comparing uric acid levels among the three groups (normoglycemic, IFG, and IGT), normoglycemic and prediabetic subjects were further divided into three subgroups according to serum uric acid levels:

- Uric acid <5.4 mg/dL
- 5.4 mg/dL ≤ Uric acid ≤ 6.4 mg/dL
- Uric acid > 6.4 mg/dL

The lipid profiles of these three groups were compared separately in normoglycemic and prediabetic subjects.

To assess cardiovascular risk, plasma lipid profiles and the atherogenic index of plasma (AIP) were evaluated. AIP was calculated using the following formula:

AIP=log (plasma TG / HDL-C)

Statistical Analysis

Statistical analyses were performed using SPSS version 15.0 for Windows (Armonk, New York: IBM Corp.). Descriptive statistics were presented as numbers and percentages for categorical variables, and as mean, standard deviation, minimum, and maximum values for numerical variables. Comparisons among more than two groups were performed using one-way ANOVA when normal distribution was satisfied, and the Kruskal–Wallis test when it was not. Subgroup analyses were performed using the Tukey test for parametric tests and the Mann–Whitney U test with Bonferroni correction for nonparametric tests. Comparisons between two independent groups were performed using Student's t-test when normal distribution was satisfied, and the Mann–Whitney U test otherwise. Categorical variables were compared using chi-square analysis. When assumptions were not satisfied, Monte Carlo simulation was applied. Relationships between numerical variables were evaluated using Spearman correlation analysis, since parametric assumptions were not met. Factors determining numerical variables were evaluated using linear regression analysis with the backward elimination method. The statistical significance level was accepted as $p<0.05$. This retrospective study was approved by the Istanbul Training and Research Hospital Clinical Research Ethics Committee (decision number: 595, approval date: January 23, 2015). The study was conducted in accordance with the Declaration of Helsinki.

Results

A total of 329 patients were included in the study: 155 normoglycemic patients (72 men and 83 women) with a mean age of 41.2±6.4 years, 97 prediabetic patients with IFG (39 men and 58 women) with a mean age of 43.1±6.1 years, and 77 prediabetic patients with IGT (37 men and 40 women) with a mean age of 45.6±6.1 years (Fig. 1).

The difference in mean age among the groups was statistically significant (p<0.001). Pairwise comparisons also demonstrated statistically significant differences between all groups (normoglycemic vs. IFG, p=0.009; normoglycemic vs. IGT, p<0.001; IFG vs. IGT, p=0.004). The highest mean age was observed in the IGT group, followed by the IFG group and the normoglycemic group.

There was no statistically significant difference in sex distribution among the groups (p=0.516).

Significant differences were observed in mean uric acid levels and their distribution across groups (HDL-C, p=0.027; all other comparisons, p<0.001). Mean uric acid levels were significantly higher in prediabetic patients with IFG and IGT compared with normoglycemic individuals. However, no statistically significant difference was observed between the two prediabetic groups (Table 1).

There was a statistically significant difference in uric acid categories among the groups (p<0.001). In the normoglycemic group, only one patient had a uric acid level above 6.4 mg/dL, while 70.3% of patients had uric acid levels below 5.4 mg/dL.

In the normoglycemic group, uric acid levels showed a statistically significant positive correlation with age, TC, and LDL-C (p=0.001, p<0.001, and p=0.001, respectively). However, no statistically significant association was observed between uric acid levels and TG, HDL-C, or AIP (p=0.609, p=0.331, and p=0.645, respectively).

In the prediabetic group, uric acid levels were positively correlated with age, TC, TG, LDL-C, and AIP, and negatively correlated with HDL-C, all of which were statistically significant (p<0.001 for all comparisons) (Fig. 2, 3).

Among normoglycemic patients, those with uric acid levels

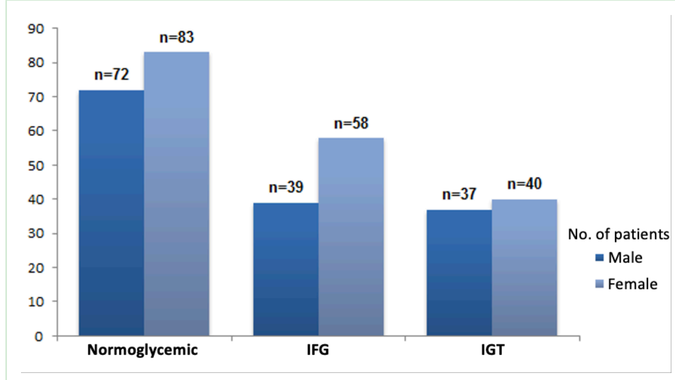

Figure 1. Number of patients in the study groups.

IFG: Impaired fasting glucose; IGT: Impaired glucose tolerance.

between 5.4–6.4 mg/dL had significantly higher mean values of age, TC, TG, LDL-C, and AIP compared with patients whose uric acid levels were below 5.4 mg/dL (p=0.004, p<0.001, p=0.019, p<0.001, p=0.001, and p=0.009, respectively). However, no statistically significant difference was observed in mean HDL-C levels (p=0.170).

In prediabetic patients, significant differences were observed among uric acid groups in terms of age, TC, TG, LDL-C, HDL-C, and AIP levels (p<0.001 for all comparisons). These differences were statistically significant between all groups except for HDL-C levels between the groups with uric acid levels below 5.4 mg/dL and those with levels between 5.4–6.4 mg/dL (Tables 2 and 3).

In the model constructed to evaluate the factors determining serum uric acid levels (sex, age, TC, TG, LDL-C, HDL-C, and AIP), age, TC, HDL-C, and AIP were identified as the most significant predictors in the normoglycemic group, whereas age, LDL-C, AIP, and sex were identified as the most significant predictors in the prediabetic group (Table 4).

When prediabetic male and female patients were grouped separately according to uric acid levels, statistically signif-

Table 1. Mean values and distributions of gender, age, and uric acid levels in Normoglycemic, IFG and IGT groups

	Normoglycemic	IFG	IGT	p
Age (years)	41.2±6.4 (31-59)	43.1±6.1 (31-59)	45.6±6.1 (32-59)	**<0.001**
Gender				
Male	72 (46.5)	39 (40.2)	37 (48.1)	0.516
Female	83 (53.5)	58 (59.8)	40 (51.9)	
Uric Acid(mg/dL)	4.8±0.9 (2.6-6.6)	5.6±1.1 (2.6-7.1)	5.9±1.0 (3.6-8)	**<0.001**
<5.4	109 (70.3)	40 (41.2)	23 (29.9)	**<0.001**
5.4-6.4	45 (29.0)	25 (25.8)	27 (35.1)	
>6.4	1 (0.6)	32 (33.0)	27 (35.1)	

IFG: Impaired fasting glucose; IGT: Impaired glucose tolerance.

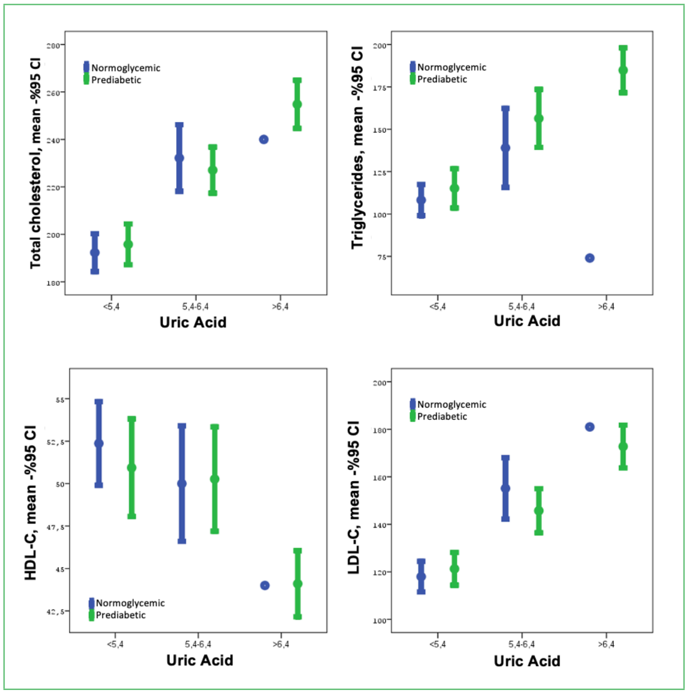

Figure 2. Mean values and confidence intervals of total cholesterol, triglycerides, HDL-C, and LDL-C according to uric acid categories in normoglycemic and prediabetic groups.

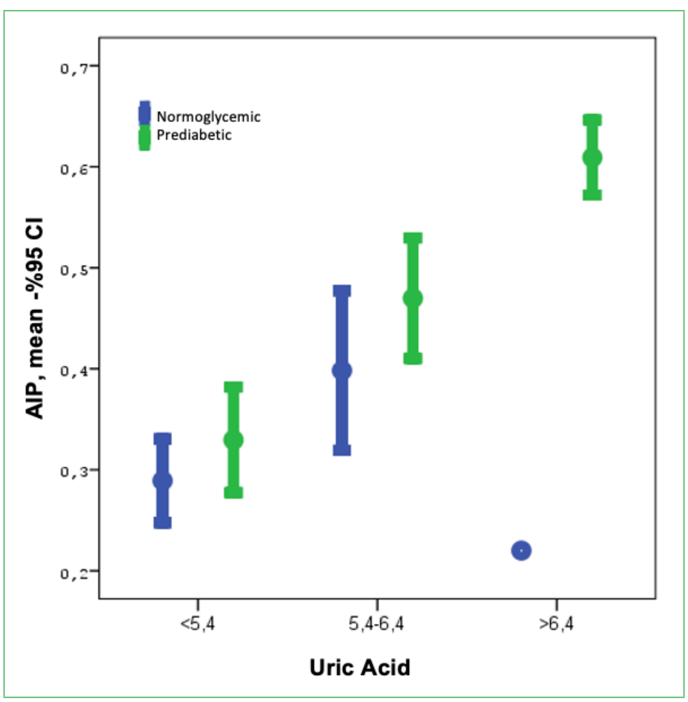

Figure 3. Mean AIP values and confidence intervals according to uric acid categories in normoglycemic and prediabetic groups.

icant differences were observed across almost all parameters.

Among prediabetic male patients, significant differences were found between uric acid groups for all parameters (age, p=0.008; HDL-C, p=0.015; all other parameters, p<0.001).

Similarly, among prediabetic female patients, significant differences were observed among the three uric acid groups for all parameters (HDL-C, p=0.022; all other parameters, p<0.001) (Table 5).

Discussion

Prediabetes, defined as impaired fasting glucose and/or impaired glucose tolerance.[1], is an important risk factor for the development of overt diabetes and cardiovascular disease (CVD).[1,9] Prediabetic individuals are at an increased risk of cardiovascular disease and mortality compared with normoglycemic individuals; in most cases, prediabetic patients remain clinically asymptomatic.[10]

This retrospective study was conducted to evaluate serum uric acid levels and their relationship with serum lipid parameters in individuals with prediabetes and those with normal glucose tolerance. In our study population, the proportion of prediabetic patients was 52.8%. This rate differs from the 28.7% prevalence reported in the TURDEP-II study conducted by Satman et al.[11] This discrepancy may be explained by the fact that our study population consisted only of patients who had an indication for an OGTT, particularly individuals with a family history of diabetes or suspected metabolic syndrome.

The pathophysiological relationship between elevated uric acid levels and prediabetes has not yet been fully clarified. Hyperuricemia is most commonly caused by reduced renal excretion of uric acid, and it has been shown to correlate with the severity of insulin resistance.[12] In addition, insulin resistance is associated with reduced nitric oxide levels, and increased uric acid levels have been shown to reduce nitric oxide availability.[13] Elevated insulin levels may impair renal tubular function, thereby decreasing uric acid excretion.[14] Diets rich in fructose are also known to increase uric acid production. Another study demonstrated that fructose-induced hyperuricemia may impair glucose tolerance and contribute to the development of metabolic syndrome.[15]

One of the studies investigating the association between uric acid levels and the risk of prediabetes and diabetes was conducted in China. In this study, individuals with higher baseline uric acid levels had a significantly increased risk of developing diabetes during a 9-year follow-up period.[16] Similarly, a study conducted by Dehghan et al.[17] in 2008 demonstrated that the future risk of diabetes was correlated with serum uric acid levels. In our study, serum uric acid levels were also significantly higher in the prediabetic group compared with the normoglycemic group. Consistent with previous studies, our findings suggest that serum

Table 2. Distribution of mean age, lipid parameters, and AIP values according to uric acid categories in normoglycemic and prediabetic groups

	Normoglycemic				Prediabetic			
	Uric acid				Uric Acid			
	<5.4	5.4-6.4	>6.4*	p	<5.4	5.4-6.4	>6.4	p
Age(years)	40.0±5.4	44.0±7.4	56.0	**0.004**	41.1±5.0	43.0±4.9	48.6±6.0	**<0.001**
TC (mg/dL)	192.3±42.1	232.2±46.7	240.0	**<0.001**	195.8±34.1	227.1±3.8	254.8±38.9	**<0.001**
Triglycerides (mg/dL)	108.2±48.3	139.0±77.6	74.0	**0.019**	115.1±46.1	156.4±6.5	184.8±50.7	**<0.001**
HDL-C (mg/dL)	52.4±13.0	50.0±11.3	44.0	0.170	50.9±11.4	50.3±11.0	44.1±7.5	**<0.001**
LDL-C (mg/dL)	118.0±33.9	155.1±43.0	181.0	**<0.001**	121.3±27.3	145.7±33.3	172.8±34.6	**<0.001**
AIP	0.29±0.22	0.40±0.26	0.22	**0.009**	0.33±0.21	0.47±0.21	0.61±0.14	**<0.001**

*Excluded from statistical analysis due to inclusion of only one patient. TC: Total cholesterol; TG: Triglycerides; HDL-C: High-density lipoprotein cholesterol; LDL-C: Low-density lipoprotein cholesterol; AIP: Atherogenic index of plasma.

Table 3. Spearman correlation coefficients (ρ) between uric acid levels and age, lipid parameters, and AIP in normoglycemic and prediabetic patients

	Uric acid			
	Normoglycemic		Prediabetic	
	Rho	p	rho	p
Age (years)	0.260	**0.001**	0.540	**<0.001**
TC (mg/dL)	0.376	**<0.001**	0.639	**<0.001**
TG (mg/dL)	0.041	0.609	0.590	**<0.001**
HDL-C (mg/dL)	-0.079	0.331	-0.244	**<0.001**
LDL-C (mg/dL)	0.425	**<0.001**	0.635	**<0.001**
AIP	0.037	0.645	0.581	**<0.001**

TC: Total cholesterol; TG: Triglycerides; HDL-C: High-density lipoprotein cholesterol; LDL-C: Low-density lipoprotein cholesterol; AIP: Atherogenic index of plasma.

uric acid levels are associated with prediabetes and may serve as a potential predictor for its development.

Chen et al.[18] reported a negative correlation between HDL-C and uric acid levels. The probable mechanism underlying this relationship is the association between insulin resistance and decreased HDL-C levels. In our study, when patient groups were compared according to uric acid levels, the group with the highest uric acid levels had the lowest HDL-C values, while the group with the lowest uric acid levels had the highest HDL-C values. However, in individuals with normal glucose tolerance, no significant differences were observed between groups in terms of HDL-C levels.

In a study conducted by Agamah et al.[19], individuals with elevated uric acid levels were found to have higher total cholesterol levels compared with individuals with lower uric acid levels. Another study by Akbas et al.[20] conducted in diabetic patients demonstrated that total cholesterol

Table 4. Results of multivariate linear regression analysis (backward method) for determining uric acid levels in normoglycemic and prediabetic patients

	B	Beta	p
Normoglycemic			
Intercept	0.469		
Age	0.037	0.262	**<0.001**
TC	0.010	0.513	**<0.001**
HDL-C	-0.027	-0.372	**0.001**
AIP	-0.831	-0.220	**0.028**
Prediabetic			
Intercept	-0.336		
Age	0.033	0.198	**<0.001**
LDL-C	0.010	0.352	**<0.001**
AIP	1.300	0.280	**<0.001**
Sex	-0.366	-0.176	**0.001**

Normoglycemic R: 0.337 Prediabetic R:0.617 Model: sex, age, TC, TG, LDL-C, HDL-C, AIP, TC: Total cholesterol; TG: Triglycerides; HDL-C: High-density lipoprotein cholesterol; LDL-C: Low-density lipoprotein cholesterol; AIP: Atherogenic index of plasma.

levels were significantly higher in patients with uric acid levels above 6 mg/dL compared with those with lower levels. Similarly, in our study, prediabetic patients with uric acid levels above 6.4 mg/dL had higher total cholesterol levels compared with those with uric acid levels between 5.4–6.4 mg/dL and those with levels below 5.4 mg/dL. A similar pattern was also observed among normoglycemic individuals, where higher uric acid levels were associated with higher total cholesterol levels.

One explanation for the relationship between hyperuricemia and elevated plasma triglyceride levels is that the synthesis

Table 5. Mean age, lipid parameters, and AIP values according to uric acid categories in male and female prediabetic patients

	Uric acid			p
Male	<5.4 (n=15)	5.4-6.4 (n=18)	>6.4 (n=43)	
Age (years)	42.6±4.8	44.4±5.7	47.9±6.1	**0.008**
TC (mg/dL)	198.1±39.6	231.4±36.0	259.8±34.2	**<0.001**
TG (mg/dL)	118.2±37.4	143.7±46.7	189.7±51.5	**<0.001**
HDL-C (mg/dL)	52.2±11.5	51.9±15.1	44.5±6.8	**0.015**
LDL-C (mg/dL)	122.0±30.4	151.0±26.2	176.7±31.5	**<0.001**
AIP	0.34±0.16	0.43±0.25	0.62±0.15	**<0.001**
Female	<5.4 (n=48)	5.4-6.4 (n=34)	>6.4 (n=16)	
Age (years)	40.7±5.0	42.2±4.3	50,5±5,5	**<0.001**
TC (mg/dL)	195.0±32.7	224.7±34.5	241.4±48.2	**<0.001**
TG (mg/dL)	114.2±48.8	163.1±67.8	171.9±47.7	**<0.001**
HDL-C (mg/dL)	50.5±11.5	49.4±8.3	43.1±9.1	**0.022**
LDL-C (mg/dL)	121.0±26.7	142.9±36.6	162.2±40.9	**<0.001**
AIP	0.3±0.2	0.5±0.2	0.6±0.1	**<0.001**

TC: Total cholesterol; TG: Triglycerides; HDL-C: High-density lipoprotein cholesterol; LDL-C: Low-density lipoprotein cholesterol; AIP: Atherogenic index of plasma.

of fatty acids and triglycerides requires large amounts of NADPH, which also promotes hepatic purine synthesis and consequently uric acid production. Nakagawa et al.[21] suggested that uric acid may be associated either with excess triglyceride production or decreased triglyceride clearance. Another study reported that reduced activity of lipoprotein lipase (LPL), which is responsible for the lipolysis of both triglycerides and LDL-C, may lead to increased serum lipid levels in patients with hyperuricemia.[22]

In a study conducted by Shelmadine et al.[23], allopurinol was administered to 12 patients with end-stage renal disease to reduce uric acid levels, and its effects on metabolic syndrome parameters were evaluated. The study demonstrated an average decrease of 3.53 mg/dL in uric acid levels and 14.00 mg/dL in LDL-C levels. Similarly, in our study, higher TG and LDL-C levels were observed in parallel with increasing uric acid levels in prediabetic individuals.

In the study conducted by Soğut et al.[24], a TG/HDL-C ratio greater than 3.69 was found to be significantly associated with the risk of atherosclerosis, with 82.5% sensitivity and 58.1% specificity. In another study conducted by Lippi et al.[25] in 2010, hyperuricemic individuals had higher AIP values compared with individuals with normal uric acid levels. Similarly, in our study, patients with higher uric acid levels also had significantly higher AIP values compared with those with lower uric acid levels.

Another noteworthy finding in our study was that only 18.3% of normoglycemic individuals with uric acid levels below 5.4 mg/dL were classified in the low-risk group. This may be explained by the fact that many of these patients had a family history of diabetes or a higher body mass index, despite having normal uric acid levels and glucose tolerance.

Considering the high sensitivity of AIP in predicting ischemic heart disease risk, our findings suggest that uric acid may represent an important risk factor for ischemic cardiovascular disease.

Study Limitations

The primary limitation of our study is that the available data were obtained solely from laboratory records. It was not possible to determine whether patients were receiving medications that could influence laboratory parameters such as uric acid, glucose, HbA1c, or lipid levels. In addition, the absence of important clinical data such as family history, body mass index, smoking and alcohol history, and blood pressure measurements limited the scope of our analysis.

Conclusion

In this study evaluating laboratory data from 329 individuals with prediabetes and normal glucose tolerance, our findings were generally consistent with previous studies reported in the literature.

First, the observation that serum uric acid levels were higher in prediabetic individuals compared with normoglycemic individuals supports the hypothesis that uric acid may serve as a strong positive predictor for diabetes risk.

When prediabetic individuals were grouped according to uric acid levels, uric acid was found to be positively associated with TC, LDL-C, TG, and AIP levels, and negatively associated with HDL-C levels.

The strong relationship observed between uric acid and cardiovascular risk factors suggests that uric acid may represent an important risk factor that should be monitored and controlled in the early stages among prediabetic individuals.

Nevertheless, larger, prospective, well-designed studies are needed to better understand the interaction between serum uric acid levels and cardiovascular risk in prediabetic patients.

Disclosures

Ethics Committee Approval: This retrospective study was approved by the İstanbul Training and Research Hospital Clinical Research Ethics Committee (approval number: 595, approval date: 23 January 2015).

Informed Consent: Informed consent was waived due to the retrospective design of the study.

Conflict of Interest: The authors declare no conflict of interest.

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Author Contributions: Concept: İÇ, HP; Methodology: İÇ; Data collection and/or Processing: İÇ; Analysis and/or Interpretation: İÇ; Literature Review: İÇ; Writer: İÇ; Critical Review HP.

Peer-review: Externally peer-reviewed

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