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CLINICAL STUDY

A novel marker for prediabetic conditions: Uric acid-to-HDL cholesterol ratio

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ABSTRACT
OBJECTIVES: The objective of this study was to identify a parameter that can facilitate the diagnosis of prediabetes and predict the likelihood of its development in individuals at high risk.
METHODS: In this retrospective study, the study population was selected from Bolu Abant Izzet Baysal University Hospital's patients. Participants were divided into two groups, prediabetes and healthy group. We excluded individuals with certain conditions or taking certain medications. The study compared the ratios of uric acid to high-density lipoprotein (HDL) between the two groups and identified the optimal point of differentiation.
RESULTS: The study analyzed data from 228 individuals, including 125 with prediabetes and 103 healthy controls. Those with prediabetes had a significantly higher median UHR (0.13 (0.07–0.24) %) compared to healthy individuals (0.09 (0.05–0.16) %) ($p < 0.001$). Higher UHR values were associated with a greater risk of prediabetes. A UHR cut-off points greater than 0.11 % had a sensitivity of 74 % and specificity of 69 % in detecting prediabetes.
CONCLUSION: The study provides evidence that UHR can serve as a practical and valuable diagnostic and screening tool for prediabetes *(Tab. 2, Fig. 1, Ref. 23)*. Text in PDF *www.elis.sk*
KEY WORDS: serum uric acid, HDL cholesterol, UHR, prediabetes.

Introduction

Prediabetes is considered a condition that occurs prior to type 2 diabetes mellitus. It is associated with insulin resistance (1). If untreated, many people with prediabetes develop overt type 2 diabetes. Since it has close relationship with deteriorated glucose metabolism, inflammation is involved in pathogenesis of prediabetes (2). Chronic, low grade and continuous inflammatory burden has been noted not only in prediabetes but also in type 2 diabetes mellitus.

Recent works have reported significant association between inflammatory markers and metabolic/inflammatory diseases. One of those markers is the uric acid/HDL cholesterol ratio (UHR), which has been introduced as a novel metabolic and inflammatory indicator. Associations between UHR and metabolic conditions, such as metabolic syndrome (3, 4), type 2 diabetes mellitus (5), and hepatosteatosis (6) have been reported. Moreover, it is also associated with inflammatory conditions including hypertension (7), chronic complications of diabetes mellitus (8), and cardiovascular diseases (9). Furthermore, recent studies have suggested that UHR has predictive (10), and prognostic (11) roles in patients with heart conditions. However, to the best of our knowledge there are no reports in the literature that studied UHR in prediabetic states.

In the present study we aimed to investigate UHR levels of prediabetes patients and to compare them with those of healthy individuals. We also aimed to find out whether UHR was correlated with other metabolic and inflammatory markers in this population.

Methods

Study population

After obtaining ethical approval from local ethics committee (approval number: 2023/38), we retrospectively analyzed data of subjects diagnosed with prediabetes (either impaired fasting glucose or impaired glucose tolerance) between February 2019 and February 2023. The data of the patients were obtained from patients' files and institutional database. The control subjects were volunteers who visited outpatient clinics of our institution for a routine check-up and were considered as healthy according to their examination and laboratory results. The patients with overt diabetes mellitus, pregnancy, cancer, under 18 years of age, chronic kidney disease, and, on medications that alter serum uric acid (i.e., thiazides) or serum HDL levels (statins or other hypolipidemic drugs) were excluded.

Age, gender, weight, height, waist circumference, systolic and diastolic blood pressures, and heart rate data of the participants were recorded. Laboratory parameters such as fasting blood glucose, glycated hemoglobin (HbA1c), serum uric acid, serum lipids (total

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cholesterol, LDL cholesterol, HDL cholesterol and triglyceride), serum creatinine, glomerular filtration rate (GFR), C reactive protein (CRP), serum albumin, aspartate aminotransferase (AST), alanine aminotransferase (ALT), white blood cell (WBC) count, hemoglobin, hematocrit, and, platelets count were collected. Body mass index (BMI) is calculated by division of weight (kg) by the square of height (meters). UHR was obtained by division of serum uric acid by the HDL cholesterol levels in serum. General characteristics and laboratory data of the prediabetes and control group were compared.

Statistical analyses

Statistical analyses were performed with statistics software (SPSS 16.0 for Windows, IBM Co. Chicago, IL, USA). The analysis of the variables whether they fit into normal distribution was conducted with Kolmogorov–Smirnov test. The variables with homogeneous distribution were expressed as mean ± SD and compared by independent samples t-test. Mann–Whitney U test was used for comparisons of non-homogeneous variables and these parameters were expressed as median (min, max). Categorical variables were expressed as numbers and, percentage, and compared by Chi-square test. Correlations between UHR and other parameters were conducted by Pearson's correlation analysis test. The sensitivity and specificity of UHR in detection of prediabetes were analyzed by ROC Analyze. p values lower than 0.05 were considered as statistically significant.

Tab. 1. General characteristics of participants.

	Prediabetic patients (n = 125)	Control group (n = 103)	p
	X^2		
Gender			0.27
Men (n (%))	54 (43.2%)	52 (50.5%)	
Women (n (%))	71 (56.8%)	51 (49.5%)	
	Mean±SD		
Age (years)	42±12	41±13	0.29
Weight (kg)	83±14.6	74.7±15.5	**< 0.001**
Waist circumference (cm)	100.6±2.1	89.4±2.1	**0.001**
Height (m)	1.65±0.08	1.67±0.07	0.081
BMI (kg/m^2)	31±6	26±5.2	**< 0.001**
	Median (Min–Max)		
SBP (mmHg)	125 (100–460)	125 (91–150)	0.405
DBP (mmHg)	80 (60–110)	78 (56–98)	0.103
Waist circumference (cm)	100 (61–135)	90 (64–114)	**< 0.001**

Tab. 2. Biochemical markers of the participants.

	Prediabetic patients (n = 125)	Control group (n = 103)	p
	Mean±SD		
Total cholesterol (mg/dL)	210±41	176.3±30.3	**< 0.001**
LDL cholesterol (mg/dL)	127.6±26.3	102±28.7	**< 0.001**
Triglyceride (mg/dL)	192.3±215.3	120±92.2	**0.002**
Hemoglobin (g/dL)	13.7±1.5	14.4±1.6	**0.002**
Hematocrit (%)	42.7±4.6	45.1±4.8	**< 0.001**
	Median (Min–Max)		
HbA1c (mmol/L)	5.9 (5.7–6.4)	5.4 (4.9–5.6)	**< 0.001**
Fasting Blood Glucose (mg/dL)	103 (77–123)	90 (73–104)	**< 0.001**
Serum uric acid (mg/dL)	5.6 (3.5–9.5)	4.6 (3.1–9.5)	**< 0.001**
Urea (mg/dL)	30 (15–51)	26 (9–49)	
Creatinine (mg/dL)	0.79 (0.7–1.1)	0.82 (0.6–1.17)	0.478
GFR (ml/min)	93.8 (53.5–115)	110 (62–131)	**< 0.001**
HDL cholesterol (mg/dL)	45 (21.5–71)	52 (38–73)	**< 0.001**
CRP (mg/dL)	3.5 (0.1–62)	2.6 (0.1–21)	0.112
Serum protein (g/L)	73.5 (62.5–150)	76 (66.5–83.5)	**< 0.001**
Serum albumin (g/L)	44 (38.5–118.6)	46.5 (41.5–51)	**< 0.001**
AST (U/L)	16 (11–64)	20 (13–243)	**0.001**
ALT (U/L)	18 (8–75)	15 (9–58)	0.806

Results

Our population consisted of 228 participants. Out of them, 125 subjects were prediabetes and 103 people were healthy ones. The mean age of prediabetes and control groups was 42 ± 12 years and, 41 ± 13 years, respectively (p = 0.29). 52 subjects (50.5 %) of the control group were men while 54 (43 %) of prediabetes subjects were men (p = 0.27).

The differences of prediabetes and control groups were insignificant in terms of height (p = 0.08), SBP (p = 0.41), DBP (p = 0.1), creatinine (p = 0.48), CRP (p = 0.11), and ALT (p = 0.8) levels. In addition, weight (p < 0.001), BMI (p < 0.001), LDL cholesterol (p < 0.001), total cholesterol (p < 0.001), triglycerides (p = 0.002), hemoglobin (p = 0.002), hematocrit (p < 0.001), waist circumference (p < 0.001), HbA1c (p < 0.001), FBG (p < 0.001), uric acid (p < 0.001), HDL cholesterol (p < 0.001), total protein, (p < 0.001), albumin (p < 0.001), AST (p = 0.001), WBC (p = 0.01), and platelet (p = 0.001) levels were significantly different between prediabetes and control groups. Table 1 shows general characteristics and Table 2 shows the laboratory data of prediabetes and control subjects.

Median UHR of the prediabetic subjects was 0.13 (0.07-0w.24)% and was significantly higher than the UHR of the control subjects (0.09 (0.05–0.16) %) (p < 0.001).

Serum UHR was significantly and positively correlated with BMI (r = 0.38, p < 0.001), body weight (r = 0.45, p < 0.001), waist circumference (r = 0.57, p < 0.001), HbA1c (r = 0.62, p < 0.001), and fasting blood glucose (r = 0.42, p < 0.001). In addition, there was a strong negative correlation between UHR and GFR levels (r = –0.36, p < 0.001).

The sensitivity and specificity of UHR (higher than 0,11%) in detecting prediabetes were 74% and 69%, respectively (AUC: 0.79, p < 0.001, 95% CI: 0.73-0.84). Figure 1 shows the ROC curve of the UHR in detecting prediabetes.

In multivariate analysis considering UHR, body weight, BMI, waist circumference, CRP, HbA1c and fasting blood glucose levels, we revealed that

UHR was an independent risk factor for prediabetes ($p < 0.001$, OR: 5.5, 95% CI: 4.41–6.83).

Discussion

The present study showed for the first time in literature that serum UHR can point out the presence of prediabetes. It is possible to summarize the interesting results of our study as follows: (a) UHR levels of the prediabetes patients are significantly higher than the UHR levels of the healthy controls, (b) UHR levels have significant correlation with metabolic markers such as fasting blood glucose and HbA1c, (c) indicators of adiposity and obesity, such as weight, BMI and waist circumference, have significant correlation with UHR levels, and (d) UHR has high sensitivity and specificity in detecting patients with prediabetes.

Type 2 diabetes mellitus is associated with chronic, low-grade inflammation. Studies in literature reported increased levels of inflammatory markers in diabetic patients. For instance, strong correlation between hyperglycemia and inflammatory predictors has been noted (12). Pro-inflammatory cytokines further deteriorate pancreatic beta cell structure and contribute to insulin resistance in diabetic subjects (13). Significant correlation between cytokines and metabolic parameters, such as fasting glucose and HbA1c, supports this statement (14). Not only overt type 2 diabetes mellitus but also related conditions are associated with inflammatory burden. For example, cytokines have been reported to be associated with an insulin resistant state in pregnancy (15). Another example in this manner is obesity. Increased levels of inflammatory markers have been reported in obese subjects (16). Prediabetic syndromes are also associated with deteriorated glucose metabolism and high levels of fasting insulin. A study in literature found that subjects with hyperinsulinemia have 2 to 7 folds increased risk of developing prediabetes compared to subjects with normal insulin levels (17). These data suggest that similar metabolic mechanisms and similar inflammatory pathways may be triggered in both type 2 diabetes mellitus and prediabetes. Indeed, serum C-reactive protein (CRP), a widely used inflammatory predictor has been suggested to be associated with prediabetes (18). Moreover, inflammatory mediators including CRP, interleukin-4 and interleukin 10 levels are elevated in both prediabetes and type 2 DM (19). UHR is also considered a metabolic and inflammatory marker and increased UHR levels were reported in type 2 DM (5), and other inflammatory conditions (3, 20). The results of the present study showed increased UHR levels in prediabetic patients compared to healthy controls, which is in accordance with the data in literature.

Recent reports revealed correlations between UHR and other metabolic and inflammatory markers. Serum UHR was positively correlated with serum thyrotropin and inversely correlated with free thyroxine levels in subjects with Hashimoto's Thyroiditis (20). The results of the ABUND study were remarkable of UHR's significantly positive correlations with waist circumference, hip circumference, body weight and even serum transaminases (6). In addition, Zhang et al reported that a unit elevation in UHR increases the risk of non-alcoholic fatty liver disease by 17 % (21). UHR was also correlated with the risk of cardiovascular disease in type 2 diabetic patients by a 28 % increased risk per a unit elevation (8). In addition, a unit increase in UHR increases the risk of chronic kidney disease by 78 % in diabetic population (8). Furthermore, both systolic and diastolic blood pressures of patients with hypertension were reported to be significantly correlated with serum UHR (7). The risk of poor blood pressure control was increased 7.3 times per a unit increase in UHR (7). Similarly, we reported significant positive correlations of UHR with BMI, body weight, waist circumference, HbA1c and fasting blood glucose. Additionally, we revealed inverse correlation between UHR and GFR. We also reported that a unit increase in UHR increased prediabetes risk 5.5 folds. These results are consistent with literature knowledge.

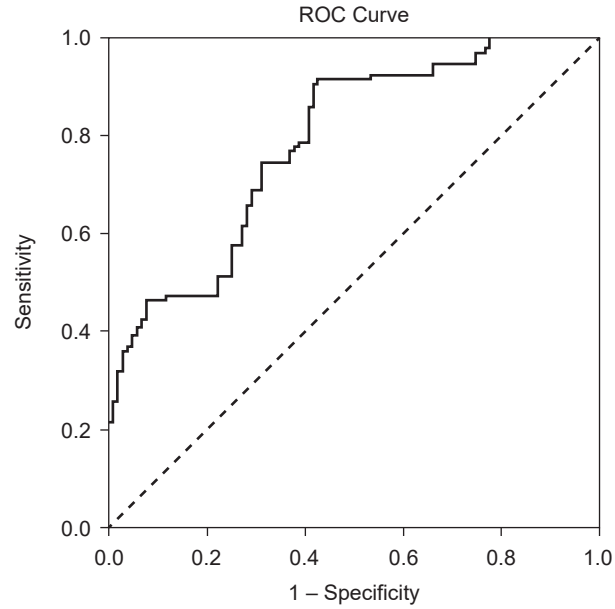

Fig. 1. ROC curve of UHR in detecting prediabetes.

Prediabetes is considered as a state before development of overt type 2 diabetes mellitus (22). Progress to the T2DM can be delayed or halted by appropriate interventions and measures in this state (23). Therefore, establishing prediabetes diagnosis as soon as possible has crucial importance. Two prediabetes syndromes; impaired fasting glucose (IFG) and impaired glucose tolerance (IGT) are associated with high glucose levels that cannot be considered normal but still not high enough to establish the diagnosis of diabetes mellitus. Fasting blood glucose levels between 100 mg/dL and 125 mg/dL are considered as impaired fasting glucose. Making IGT diagnosis requires an oral glucose tolerance test (OGTT) with ingestion of 75 g of glucose and the diagnosis is based on the 2nd hour glucose level which should be between 140–199 mg/dL. Significant association between UHR and prediabetes may overcome the diagnostic issues, especially regarding IGT, since necessity of OGTT may be eliminated with the introduction of UHR for the diagnosis of prediabetes in clinical practice. Because, calculation of UHR is an easy and inexpensive tool, which can be repeated as necessary.

There are several limitations of the present work. These include retrospective and single center nature of our work which cannot judge causal relationship between UHR and prediabetes and needs to be confirmed by longitudinal studies. Another limitation is the relatively small study population. However, our study is the first in the literature that found association between UHR and prediabetes and revealed UHR as an independent risk factor of this medical condition.

Conclusions

In conclusion, we suggest evaluation of UHR in subjects suspected with prediabetes. Due to inexpensive and easy to assess nature, UHR measurement can provide additional diagnostic value in prediabetic population.

Learning points

- Increased serum levels of UHR may yield diagnostic advantage in patients with prediabetes.
- Assessment of UHR is easier and inexpensive in diagnosis of prediabetes.

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