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ORIGINAL ARTICLE

Uric acid to HDL cholesterol ratio is a strong predictor of diabetic control in men with type 2 diabetes mellitus

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ABSTRACT

Aim: Despite it has some disadvantages, the most important marker of diabetic control is glycated hemoglobin (HbA1c). Uric acid to HDL cholesterol ratio (UHR) is a promising marker in metabolic syndrome. We aimed to compare UHR levels of well and poorly controlled type 2 diabetic male subjects, as well as healthy men, and to observe its correlation with other metabolic parameters.

Methods: Male patients with T2DM that showed up in outpatient internal medicine clinics of our hospital were enrolled to the study. Diabetic subjects divided into two groups according to the level of HbA1c: well-controlled T2DM group (HbA1c $< 7\%$) and poorly controlled T2DM group (HbA1c $\geq 7\%$). Third group was consisted of healthy subjects without any chronic diseases. UHR levels of the groups were compared.

Results: The UHR levels of well and poorly controlled diabetics and control subjects were 12%±5%, 17%±6% and 9%±3%, respectively ($p<.001$). The UHR was significantly and inversely correlated with GFR and was significantly and positively correlated with waist circumference, body weight, body mass index, serum creatinine, fasting plasma glucose (FPG) and HbA1c levels.

Conclusion: UHR could serve as a promising predictor of diabetic control in men with T2DM, since it has significant association with HbA1c and FPG levels.

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KEYWORDS
Uric acid to HDL cholesterol ratio; type 2 diabetes mellitus; HbA1c; fasting plasma glucose

Introduction

Type 2 diabetes mellitus (T2DM) is an important metabolic condition that causes both microvascular and macrovascular complications, and well control of the T2DM is associated with reduced diabetes-related morbidity and mortality [1]. To date, the best marker of diabetic control is glycated hemoglobin (HbA1c) [2]. Despite its role in determination of diabetic control level will not be substituted with another marker in near future, lack of reflection of daily change in glucose regulation is still an important insufficiency of HbA1c in follow-up of diabetic patient [3].

Uric acid is a product of purine metabolism and associated with worse metabolic conditions and kidney disease in higher serum levels [4]. Type 2 diabetic subjects tend to have greater uric acid levels [5]. Decreased serum levels of HDL cholesterol are proposed to be related to worse metabolic status and reduced HDL cholesterol is even a marker of metabolic syndrome [6]. A combination of these two metabolic parameters is uric acid to HDL cholesterol ratio (UHR) which is a more useful predictor of metabolic deterioration. UHR was suggested as better predictor of metabolic syndrome than every other markers of this syndrome [7].

We aimed to compare UHR levels of well and poorly controlled type 2 diabetic male subjects, as well as healthy men, and to observe its correlation with other metabolic parameters in the present retrospective study.

Methods

After obtaining approval of institutional board, male patients with type 2 diabetes mellitus that showed up in outpatient internal medicine clinics of our hospital between January 2018 and July 2019 were enrolled in the study. Diabetic subjects were divided into two groups according to the level of HbA1c: well-controlled T2DM group (HbA1c $< 7\%$) and poorly controlled T2DM group (HbA1c $\geq 7\%$). Healthy subjects that showed up for a routine checkup were enrolled in the study as

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control group. Subjects with malignant conditions, patients receiving thiazides, furosemide, acetyl salicylic acid or lipid-lowering drugs were excluded.

Age, height, weight, waist circumference, duration of diabetes mellitus, systolic and diastolic blood pressures were recorded from the patient files. Body mass index (BMI) is calculated with division of weight (in kg) by square of height (in meters). Arithmetic mean of blood pressure that was measured in consecutive two clinic visits in both arms was used as blood pressure measures.

Fasting plasma glucose (FPG), blood urea, serum creatinine, total cholesterol, LDL cholesterol, HDL cholesterol, triglyceride, serum uric acid, glomerular filtration rate (GFR) and HbA1c were obtained from the institutional database and recorded. UHR is calculated with division of serum uric acid by HDL cholesterol.

Data were analyzed by SPSS software (SPSS 15.0; IBM Inc., Chicago, IL, USA). Distribution of the variables in study groups was conducted by Kolmogorov–Smirnov test. Homogenously distributed variables were expressed as mean ± standard deviation and compared with one-way ANOVA test. Non-homogenously distributed variables were expressed as median (minimum–maximum) and compared with Kruskal–Wallis test. Receiver operative characteristics (ROC) were analyzed to determine cutoff values of UHR in predicting poor control of T2DM. A Pearson's analysis was used to find out correlation between UHR, HbA1c, FPG, BMI, waist circumference, body weight, creatinine and GFR levels. The p values lower than .05 were considered statistically significant.

Results

After exclusion of subjects that not fit for the inclusion criteria, a total of 159 patients were enrolled to the study (42 in well-controlled T2DM group, 82 in poorly controlled T2DM group and 35 in control group). Mean age of the subjects in well- and poorly controlled diabetics and control subjects were 55 ± 9 years, 58 ± 10 years and 50 ± 10 years, respectively ($p<.001$). *Post hoc* Tukey test revealed that there was no significant age difference between well-controlled T2DM and poorly controlled T2DM groups ($p=.21$) and between well-controlled T2DM and control groups ($p=.06$); thus, statistical significance in age of study groups was caused by the difference between poorly controlled T2DM and control groups ($p<.001$).

Systolic and diastolic blood pressures ($p<.001$ for both), waist circumference ($p<.001$), body weight ($p<.001$) and BMI ($p=.002$) were significantly different between study groups, which *post hoc* Tukey test revealed those differences were caused by the differences between control subjects and well-controlled diabetics and between control subjects and poorly controlled diabetics.

Fasting plasma glucose ($p<.001$), blood urea ($p=.001$), uric acid ($p<.001$), total cholesterol ($p<.001$), LDL cholesterol ($p=.003$) and triglyceride ($p<.001$) were significantly different between study groups, which *post hoc* Tukey test revealed those differences were caused by the differences between poorly controlled diabetics and well-controlled diabetics and between poorly controlled diabetics and control subjects.

Serum creatinine ($p<.001$), HDL cholesterol ($p<.001$), HbA1c ($p<.001$) and GFR ($p<.001$) were significantly different between study groups, which *post hoc* Tukey test revealed those differences were consequences of the differences of each study groups in binary comparison. Table 1 shows general characteristics and laboratory data of the study groups.

Table 1. General characteristics and laboratory data of the study population.

	Well-controlled T2DM	Poorly controlled T2DM	Control group	p
	Mean ± standard deviation			
Age (years)	55 ± 9	58 ± 10	50 ± 10	<.001
Waist circumference (cm)	106 ± 10	108 ± 12	89 ± 11	<.001
UHR (%)	12 ± 5	17 ± 6	9 ± 3	<.001
Creatinine (mg/dL)	0.88 ± 0.13	0.98 ± 0.26	0.71 ± 0.1	<.001
Triglyceride (mg/dL)	152 ± 86	234 ± 56	114 ± 34	<.001
Blood urea (mg/dL)	29.2 ± 8	34.3 ± 12	26.2 ± 9	.001
Uric acid (mg/dL)	5.1 ± 1.3	6.3 ± 1.6	4.9 ± 0.8	<.001
		Median (Min–Max)		
SBP (mmHg)	130 (110–180)	140 (90–180)	110 (90–130)	<.001
DBP (mmHg)	85 (70–100)	80 (50–105)	70 (60–80)	<.001
Body mass index (kg/m^2)	29.2 (22.3–40.4)	29.4 (21.6–49.4)	27.7 (18.3–33.8)	.002
Body weight (kg)	85 (63–117)	85.5 (63–136)	71 (55–86)	<.001
Total cholesterol (mg/dL)	177 (92–249)	211 (119–290)	190 (147–248)	<.001
LDL cholesterol (mg/dL)	93 (42–165)	124 (49–192)	110 (84–155)	.003
HDL cholesterol (mg/dL)	46 (27–61)	39 (21–58)	56 (34–85)	<.001
HbA1c (%)	6.7 (5.9–6.9)	10 (7–15.9)	5.5 (5.2–5.8)	<.001
Fasting plasma glucose (mg/dL)	119 (85–219)	193 (72–514)	95 (79–99)	<.001
GFR (%)	95 (42–114)	80 (25–117)	105 (95–111)	<.001

Table 2. Correlation of UHR with study parameters.

	HbA1c	FPG	Waist circumference	BMI	Serum creatinine	Weight	GFR
UHR							
r	0.59	0.46	0.34	0.21	0.37	0.25	−0.31
p	<.001	<.001	<.001	.007	<.001	.001	<.001

The UHR levels of well and poorly controlled diabetics and control subjects were 12%±5%, 17%±6% and 9%±3%, respectively. The UHR difference between study groups was statistically significant ($p<.001$). *Post hoc* Tukey test revealed that the UHR levels of well-controlled T2DM and control groups were not statistically different ($p=.08$); however, the UHR levels of well- and poorly controlled diabetics ($p<.001$) and UHR levels of poorly controlled diabetics and control subjects ($p<.001$) were statistically different.

A Pearson's correlation analysis revealed that UHR was significantly and positively correlated with waist circumference ($r=0.34$, $p<.001$), body weight ($r=0.25$, $p=.001$), BMI ($r=0.21$, $p=.007$), serum creatinine ($r=0.37$, $p<.001$), fasting plasma glucose ($r=0.46$, $p<.001$) and HbA1c ($r=0.59$, $p<.001$) levels. On the other hand, UHR was significantly and inversely correlated with GFR ($r=-0.31$, $p<.001$). Table 2 shows the correlation of UHR with other study parameters.

In ROC analysis, a UHR level greater than 11.7% had 78% sensitivity and 60% specificity in predicting poor diabetic control (AUC:0.74, $p<.001$, 95% CI:0.65–0.83). Figure 1 shows the ROC curve of UHR in predicting poor diabetic control.

Discussion

Striking results of this study are (a) UHR of subjects with poorly controlled T2DM was increased compared to the UHR of healthy controls and to the patients with well-controlled T2DM, (b) UHR was positively correlated with other metabolic factors including HbA1c and FPG and (c) UHR has significant sensitivity and specificity in predicting worse diabetic control in men with T2DM.

Increased UHR in elderly men with T2DM is caused by either increased serum uric acid, decreased serum HDL cholesterol or both. Male subjects with metabolic diseases tend to have lower testosterone levels [8–10]. Decreased insulin sensitivity is linked to low testosterone; moreover, lower levels of testosterone have been reported in men with type 2 diabetes mellitus and hyperlipidemia [11,12]. Not only T2DM, but also prediabetes condition was reported to be more common in subjects with low testosterone levels [13]. In another study in the literature, authors showed that testosterone prevents progression of prediabetes to T2DM [14]. Moreover, testosterone treatment may improve glucose and lipid metabolism and body measures, such as waist circumference and BMI in male subjects with metabolic disorders [15]. Since T2DM was associated with lower testosterone levels in men, erectile dysfunction is a more common concern in men with T2DM and low serum testosterone [16]. Obesity, dyslipidemia and metabolic disorders are associated with low serum testosterone [10]. Since serum testosterone gradually decreases by aging in men [17], increased UHR in poorly controlled type 2 diabetics in this study could be caused by advanced age of this group compared to well-controlled diabetic men and healthy controls.

Uric acid is the end product of purine metabolism and eliminated by renal excretion; thus, elevated uric acid levels are consequence of either increased production or decreased excretion [10]. The prevalence of increased serum uric acid levels is ranged between 10% and 25% in the literature [18–20]. Hyperuricemia not only has deleterious effects on joints and kidneys but also has close relationship with metabolic disorders [21]. Obesity, hyperlipidemia and T2DM are all characterized with increased levels of serum uric acid and may cause a lowering in serum testosterone [10]. Furthermore, testosterone replacement treatment improves metabolic measures in obese subjects [22]. Indeed, production of testosterone was reported to be reduced in patients with gout and gouty arthritis [23]. Insulin resistance, which is a feature of T2DM, was suggested to be related to hyperuricemia [24,25]. Moreover, elevated serum uric acid levels in men with T2DM were suggestive of gonad hypofunction [10]. Therefore, increased uric acid levels could induce elevated UHR levels in poorly controlled diabetic men compared to healthy controls and to men with well-controlled T2DM.

Poorly controlled diabetic men were significantly older than well-controlled T2DM subjects and healthy controls in this study. There could be numerous explanations for poorly control in aging male population. Testosterone levels are low in male subjects with metabolic syndrome, T2DM and cardiovascular diseases [26–28]. Androgen deprivation therapy in men with prostate cancer increases the risk of diabetes mellitus [29]. Moreover, all-cause mortality was increased in men with reduced testosterone levels [30].

Retrospective design and relatively small study cohort are two limitations of this study. However, it is the first report in the literature that showed significant

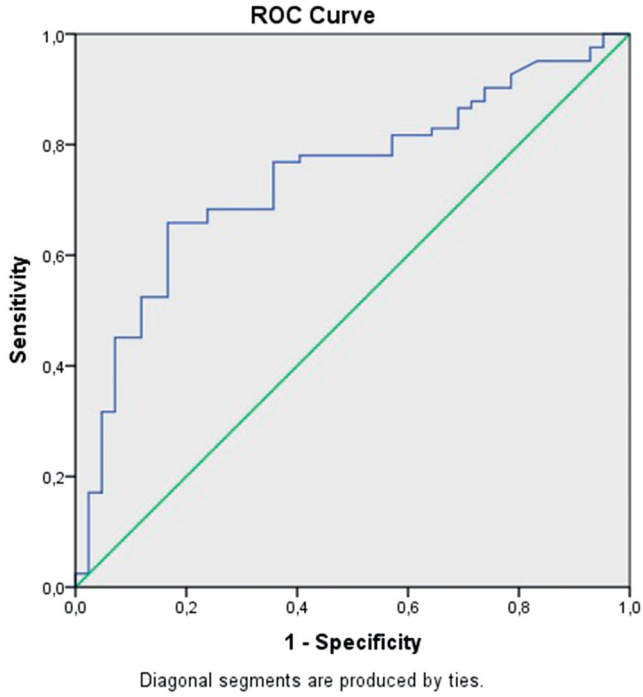

Figure 1. ROC curve of UHR in predicting poor diabetic control.

correlation between UHR and metabolic parameters in men with T2DM.

In conclusion, UHR could serve as a promising predictor of diabetic control in men with T2DM, since it has significant association with HbA1c and FPG levels.

Disclosure statement

No potential conflict of interest was reported by the authors.

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