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Original Scientific Paper

SERUM URIC ACID TO HDL CHOLESTEROL RATIO IS ASSOCIATED WITH DIABETIC CONTROL IN NEW ONSET TYPE 2 DIABETIC POPULATION

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SUMMARY – Since uric acid to HDL cholesterol ratio (UHR) is proposed as a novel predictor of metabolic and inflammatory disorders, we aimed to study UHR levels in patients with new onset type 2 diabetes mellitus (T2DM) and compare them to those in healthy controls. Patients with new onset T2DM were enrolled and control subjects were volunteers to participate without any established diseases. Laboratory data including UHR, fasting blood glucose (FBG) and glycated hemoglobin (HbA1c) were compared. The mean UHR of the T2DM and control groups was 16±8% and 10±3%, respectively ($p<0.001$). Moreover, UHR was significantly and positively correlated with HbA1c ($r=0.75$, $p<0.001$), FBG ($r=0.64$, $p<0.001$), waist circumference ($r=0.35$, $p<0.001$), body mass index ($r=0.20$, $p=0.002$) and inversely correlated with glomerular filtration rate ($r=-0.24$, $p<0.001$). High levels of UHR might be associated with increased mean blood glucose levels for a long time, since UHR was correlated with both FBG and HbA1c in patients with new onset T2DM.

Key words: *Type 2 diabetes mellitus; Uric acid to HDL cholesterol ratio; HbA1c; Fasting blood glucose*

Introduction

Type 2 diabetes mellitus (T2DM) is the most common metabolic disorder among humans. It is strongly associated with other metabolic consequences such as obesity, dyslipidemia and metabolic syndrome[1,2].

Uric acid is the end-product of the degradation of dietary and endogenously generated purine nucleotides[3]. About 2/3 to 3/4 of uric acid is excreted by the kidney and the remaining burden is removed from the body by the gastrointestinal tract[4,5]. Higher serum uric acid levels than a threshold of 6.8 mg/dL is referred to as hyperuricemia[6]. Increased serum levels of uric acid reflect a bundle of underlying etiologies including genetic defects in purine metabolism, reduced renal excretion and increased production[7]. The serum uric acid/HDL cholesterol ratio (UHR) has been proposed as a better predictor in metabolic diseases[8,9]. Moreover, UHR has been associated with various conditions[10,11].

In the present retrospective analysis, we aimed to compare serum UHR in patients with new onset T2DM and those recorded in healthy subjects. We also aimed to reveal the possible correlation between UHR and other metabolic indices including glycated hemoglobin (HbA1c), fasting blood glucose (FBG) and body mass index (BMI) levels in newly diagnosed T2DM patients.

Materials and Methods

Ethics statement

Upon approval from the institutional Ethics Committee (No. 2020/80 as of April 7, 2020), subjects diagnosed with T2DM in internal medicine outpatient

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clinics of our institution between January 2018 and January 2020 were enrolled in the study. Data on the participants were retrospectively analyzed. Control group included healthy volunteers visiting our clinic for routine check-up. Exclusion criteria were history of previous use of any antidiabetic agent, use of any medication that may interact with serum levels of uric acid, chronic kidney disease, malignant conditions, pregnancy, and age <18 years.

Study population and study design

Anthropometric measures and physical examination findings were recorded from patient files kept at our clinic. Age, gender, height, weight, waist circumference, systolic and diastolic blood pressure were noted. The BMI was calculated by dividing weight (kg) by the square of height (m^2).

Laboratory data on the study population, serum uric acid, creatinine, blood urea, aspartate and alanine transaminases (AST and ALT), total cholesterol, LDL-cholesterol, HDL-cholesterol, triglycerides, fasting plasma glucose (FPG) and HbA1c levels were noted from institutional computerized database. Estimated glomerular filtration rate (GFR) was calculated by Cockcroft-Gault equation. UHR was obtained by dividing serum uric acid by HDL cholesterol (uric acid/HDL cholesterol). Moreover, white blood cell count (WBC), hemoglobin (Hb), hematocrit (Htc) and platelet count (Plt) were obtained from hemogram test results.

Statistical analyses

Statistical analyses were conducted with SPSS software (SPSS 15.0 for Windows, IBM Co., Chicago, IL, USA). Distribution of variables between the groups was analyzed with Shapiro-Wilk test. Study parameters with normal distribution were expressed as mean ± standard deviation, while parameters without normal distribution were expressed as median (min-max). Comparison of variables with and without normal distribution was done with independent samples t test and Mann Whitney U test, respectively. Correlation between study parameters was revealed with Pearson's correlation test. The level of statistical significance was set at $p<0.05$.

Results

Study population consisted of 238 subjects, i.e., 136 in T2DM group and 102 in control group, mean age 49±9 and 47±7 years, respectively. Age difference between the groups was not statistically significant (p=0.18). There were 79 (58%) men and 57 (42%) women in T2DM group, and 61 (60%) men and 41 (40%) women in control group. Gender was not statistically different between the groups (p=0.79).

Although Hb (p=0.16) and Htc (p=0.17) were not statistically different between the T2DM and control group, systolic (p<0.001) and diastolic (p<0.001) blood pressure (SBP and DBP), BMI (p<0.001), waist circumference (p<0.001), body weight (p<0.001), serum uric acid (p<0.001), creatinine (p=0.002), blood urea (p<0.001), total cholesterol (p<0.001), LDL-cholesterol (p<0.001), triglycerides (p<0.001), AST (p=0.008) and ALT (p=0.01) were significantly higher in T2DM group compared to healthy controls. On the other hand, GFR (p<0.001), WBC (p=0.001), Plt (p<0.001) and HDL cholesterol (p<0.001) levels were significantly lower in T2DM group compared to control group. General characteristics and laboratory data of the T2DM and control groups are summarized in Table 1.

Mean UHR was 16±8% and 10±3% in T2DM and control groups, respectively (p<0.001). Expectedly, FPG (135 (126-514) mg/dL in T2DM group *vs.* 93 (79-99) mg/dL in control group) and HbA1c (8.9±2.3% in T2DM group *vs*. 5.1±0.3% in control group) were significantly higher in diabetic subjects compared to healthy controls (p<0.001 for both FPG and HbA1c).

In Pearson's correlation analysis, UHR was significantly and positively correlated with HbA1c (r=0.75, p<0.001), FPG (r=0.64, p<0.001), waist circumference (r=0.35, p<0.001) and BMI (r=0.20, p=0.002), and inversely correlated with GFR (r=-0.24, p<0.001). Figures 1 and 2 show the UHR correlation with HbA1c and FPG, respectively.

Discussion

Significantly elevated UHR levels in patients with T2DM compared to healthy individuals and strong positive correlation between UHR and HbA1c, and between UHR and FBG were the main findings of the present study.

Serum uric acid levels are associated with various metabolic conditions. Although its serum levels are higher in men compared to women probably due to the estrogen inhibitory effect on the reabsorption of uric acid, the rate of hyperuricemia increases after menopause in female population[12]. Elevated levels of

Table 1. Characteristics and data of the study groups

		T2DM group	Control group	p
Sex	Men, n (%)	79 (58)	61 (60)	0.79
	Women, n (%)	57 (42)	41 (40)	
		Mean ± *SD*		
Age (years)		49±9	47±7	0.18
BMI (kg/m^2)		31±3.9	25±4.3	**<0.001**
UHR (%)		16±8	10±3	**<0.001**
Uric acid (mg/dL)		6.3±1.4	5±0.9	**<0.001**
HbA1c (%)		8.9±2.3	5.1±0.3	**<0.001**
LDL cholesterol (mg/dL)		133±39	110±22	**<0.001**
Triglycerides (mg/dL)		233±150	120±67	**<0.001**
WBC (K/mm^3)		7.7±2.3	8.5±0.7	**0.001**
Hb (g/dL)		14.4±1.7	14.7±0.4	0.16
Htc (%)		43±5	44±1	0.17
Plt (K/mm^3)		271±70	350±27	**<0.001**
		Median (min-max)		
SBP (mm Hg)		135 (90-180)	110 (90-130)	**<0.001**
DBP (mm Hg)		80 (50-100)	70 (50-80)	**<0.001**
Waist circumference (cm)		108 (85-132)	88 (65-108)	**<0.001**
Weight (kg)		85 (58-105)	69 (55-86)	**<0.001**
FPG (mg/dL)		135 (126-514)	93 (79-99)	**<0.001**
Urea (mg/dL)		28 (15-60)	23 (13-49)	**<0.001**
Creatinine (mg/dL)		0.82 (0.56-2.7)	0.75 (0.5-1.1)	**0.002**
Total cholesterol (mg/dL)		223 (119-375)	190 (114-248)	**<0.001**
HDL cholesterol (mg/dL)		45 (21-63)	57 (34-85)	**<0.001**
AST (U/L)		20 (9-86)	17 (9-27)	**0.008**
ALT (U/L)		19 (6-94)	18 (6-40)	**0.01**
GFR (%)		95 (29-117)	112 (109-121)	**<0.001**

T2DM = type 2 diabetes mellitus; SD = standard deviation; BMI = body mass index; UHR = uric acid to HDL cholesterol ratio; HbA1c = glycated hemoglobin; LDL = low-density lipoprotein; WBC = white blood cell count; Hb = hemoglobin; Htc = hematocrit; Plt; platelet; SBP = systolic blood pressure; DBP = diastolic blood pressure; FPG = fasting plasma glucose; HDL = high-density lipoprotein; AST = aspartate transaminase; ALT = alanine transaminase; GFR = glomerular filtration rate

serum uric acid have been suggested to be related with hypertension and T2DM[13]. The risk of new onset diabetes mellitus has been supposed to be significantly correlated with uric acid levels[14]. The risk of developing impaired fasting glucose has been reported to be increased in male subjects with elevated serum uric acid levels[15]. Positive correlation has been suggested to exist between serum uric acid levels and both incident T2DM and impaired fasting glucose[16]. Indeed, it has been shown that 1 mg/dL elevation in serum uric acid increases the risk of T2DM by 6%[17]. Moreover, elevated serum uric acid increases the risk of hypertension too. It has been reported that hypertension risk was increased by 25% in subjects with a serum uric acid level higher than 6.5 mg/dL[18]. Grayson *et al*. found the risk of hypertension to increase by more than 10%

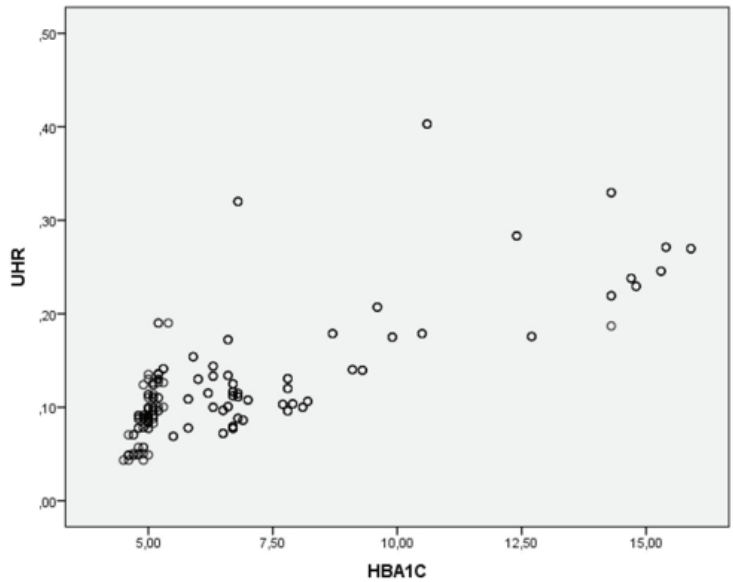

Fig. 1. Correlation between UHR and HbA1c.

UHR = uric acid to HDL cholesterol ratio; HbA1c = glycated hemoglobin

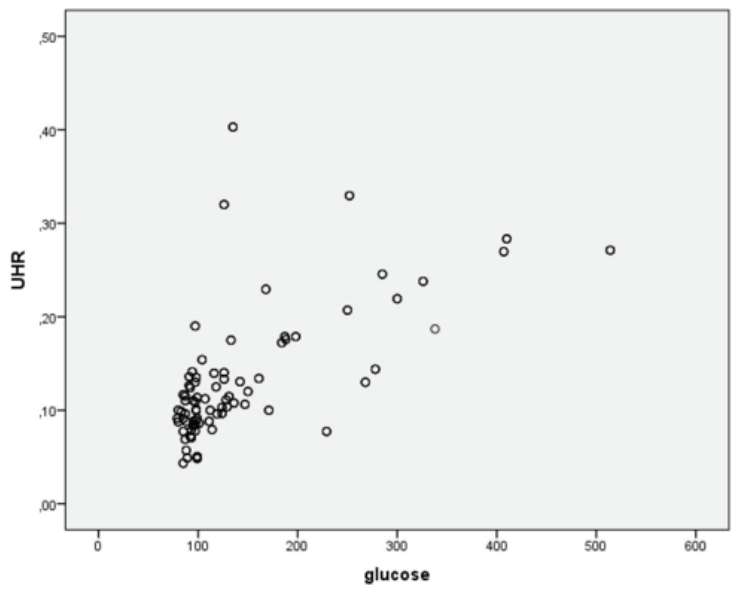

Fig. 2. Correlation between UHR and FBG.

UHR = uric acid to HDL cholesterol ratio; FBG = fasting blood glucose

per 1 mg/dL elevation in serum uric acid levels[19]. Besides these uric acid associations, we report on elevated UHR in new onset type 2 diabetic subjects in the present study.

Decreased HDL cholesterol is also associated with some risks in the general population. Low HDL cholesterol is one of the five components of metabolic syndrome. Besides, decreased HDL cholesterol levels are a well-established independent risk factor for cardiovascular diseases[20]. Madsen *et al*. report that low HDL cholesterol is associated with a high risk of autoimmune disease in individuals from the general pop-

ulation[21]. Lower HDL cholesterol levels have been reported in diabetic subjects compared to controls in the literature[22]. Some authors suggest that HDL cholesterol has suppressing effects on inflammation[23]. Thus, decreased HDL could be a consequence of inflammatory burden. UHR is the ratio between serum uric acid and HDL cholesterol. UHR has been suggested as a better predictor of metabolic syndrome than either of its components, uric acid and HDL cholesterol[8]. Elevated UHR has also been reported in vascular pathologies. Mansiroglu *et al*. showed that patients with coronary artery fistula had increased UHR levels compared to subjects with normal coronary arteries[11]. Furthermore, Zhang *et al*. report that increased UHR could be a marker of non-alcoholic fatty liver disease[10]. Similar to the literature, we found that patients with new onset T2DM had a significantly higher UHR than healthy controls.

Another important result of the present study was a significant positive correlation of UHR with HbA1c, FBG, waist circumference, and BMI. These parameters are indicators of altered metabolism, thus, as a novel inflammatory and metabolic predictor, UHR showed positive correlation with them. Moreover, UHR was negatively correlated with GFR levels. Similarly, significant negative correlation was demonstrated between uric acid levels and GFR in the literature[24].

Elevated UHR is not only an indicator of new onset T2DM. Recent studies have reported high UHR levels in other diseases characterized by chronic, low-grade inflammation such as non-alcoholic fatty liver disease[25], diabetic nephropathy[26], hypertension[27], and Hashimoto's thyroiditis[28]. All of these conditions are characterized with a high burden of inflammation as new onset T2DM is. Therefore, our results are consistent with literature data.

There were several limitations of the present study. Retrospective design could make our results difficult to interpret. A relatively small study population could be considered as another limitation. Single center nature of the work is the third limitation.

In conclusion, elevated UHR levels could predict T2DM in recently diagnosed DM patients, thus, we suggest routine screening of serum uric acid and HDL cholesterol levels to enable UHR measurement, especially in subjects at a high risk of T2DM. Higher levels of UHR might be associated with increased mean blood glucose levels for a long time, since UHR was correlated with both FPG and HbA1c.

References

1. Ogbera AO, Azenabor AO. Hyperuricaemia and the metabolic syndrome in type 2 DM. Diabetol Metab Syndr. 2010;2:24. DOI: 10.1186/1758-5996-2-24.
2. Ogbera A, Azenabor A, Ogundahunsi OA, Ekun AO, Adejumo EN. Cytokines, type 2 DM and the metabolic syndrome. Nig Q J Hosp Med. 2013;23(4):318-22.
3. Mortada I. Hyperuricemia, type 2 diabetes mellitus, and hypertension: an emerging association. Curr Hypertens Rep. 2017;19(9):69. DOI: 10.1007/s11906-017-0770-x.
4. Rock KL, Kataoka H, Lai JJ. Uric acid as a danger signal in gout and its comorbidities. Nat Rev Rheumatol. 2013;9(1):13-23. DOI: 10.1038/nrrheum.2012.143.
5. de Oliveira EP, Burini RC. High plasma uric acid concentration: causes and consequences. Diabetol Metab Syndr. 2012;4:12. DOI: 10.1186/1758-5996-4-12.
6. Terkeltaub R. Update on gout: new therapeutic strategies and options. Nat Rev Rheumatol. 2010;6(1):30-8. DOI: 10.1038/nrrheum.2009.236.
7. Ichida K, Matsuo H, Takada T, Nakayama A, Murakami K, Shimizu T, *et al*. Decreased extra-renal urate excretion is a common cause of hyperuricemia. Nat Commun. 2012;3:764. DOI: 10.1038/ncomms1756.
8. Kocak MZ, Aktas G, Erkus E, Sincer I, Atak B, Duman T. Serum uric acid to HDL-cholesterol ratio is a strong predictor of metabolic syndrome in type 2 diabetes mellitus. Rev Assoc Med Bras. 2019;65(1):9-15. DOI: 10.1590/1806-9282.65.1.9.
9. Aktas G, Kocak MZ, Bilgin S, Atak BM, Duman TT, Kurtkulagi O. Uric acid to HDL cholesterol ratio is a strong predictor of diabetic control in men with type 2 diabetes mellitus. Aging Male. 2019:1-5. DOI: 10.1080/13685538.2019.1678126.
10. Zhang YN, Wang QQ, Chen YS, Shen C, Xu CF. Association between serum uric acid to HDL-cholesterol ratio and nonalcoholic fatty liver disease in lean Chinese adults. Int J Endocrinol. 2020;2020:5953461. DOI: 10.1155/2020/5953461.
11. Mansiroglu AK, Cekici Y, Sincer I, Gunes Y. Serum uric acid and uric acid to HDL-cholesterol ratio in coronary artery fistulas. Ann Med Res. 2019;26(12):2771-5.
12. Hak AE, Choi HK. Menopause, postmenopausal hormone use and serum uric acid levels in US women – the Third National Health and Nutrition Examination Survey. Arthritis Res Ther. 2008;10(5):R116. DOI: 10.1186/ar2519.
13. Kuwabara M. Hyperuricemia, cardiovascular disease, and hypertension. Pulse (Basel). 2016;3(3-4):242-52. DOI: 10.1159/000443769.
14. Krishnan E, Akhras KS, Sharma H, Marynchenko M, Wu EQ, Tawk R, *et al*. Relative and attributable diabetes risk associated with hyperuricemia in US veterans with gout. QJM. 2013;106(8):721-9. DOI: 10.1093/qjmed/hct093.
15. Liu Y, Jin C, Xing A, Liu X, Chen S, Li D, *et al*. Serum uric acid levels and the risk of impaired fasting glucose: a prospective study in adults of north China. PLoS One. 2013;8(12):e84712. DOI: 10.1371/journal.pone.0084712.
16. Jia Z, Zhang X, Kang S, Wu Y. Serum uric acid levels and incidence of impaired fasting glucose and type 2 diabetes mellitus:

a meta-analysis of cohort studies. Diabetes Res Clin Pract. 2013;101(1):88-96. DOI: 10.1016/j.diabres.2013.03.026.

17. Lv Q, Meng XF, He FF, Chen S, Su H, Xiong J, *et al*. High serum uric acid and increased risk of type 2 diabetes: a systemic review and meta-analysis of prospective cohort studies. PLoS One. 2013;8(2):e56864. DOI: 10.1371/journal.pone.0056864.
18. Perlstein TS, Gumieniak O, Williams GH, Sparrow D, Vokonas PS, Gaziano M, *et al*. Uric acid and the development of hypertension: the normative aging study. Hypertension. 2006;48(6):1031-6. DOI: 10.1161/01.HYP.0000248752.08807.4c.
19. Grayson PC, Kim SY, LaValley M, Choi HK. Hyperuricemia and incident hypertension: a systematic review and meta-analysis. Arthritis Care Res (Hoboken). 2011;63(1):102-10. DOI: 10.1002/acr.20344.
20. Reiner Z, Muacevic-Katanec D, Katanec D, Tedeschi-Reiner E. [Low HDL-cholesterol – an important risk factor for cardiovascular diseases]. Lijec Vjesn. 2011;133(3-4):111-6. (in Croatian)
21. Madsen CM, Varbo A, Nordestgaard BG. Low HDL cholesterol and high risk of autoimmune disease: two population-based cohort studies including 117341 individuals. Clin Chem. 2019;65(5):644-52. DOI: 10.1373/clinchem.2018.299636.
22. Canecki-Varžić S, Prpić-Križevac I, Mihaljević S, Bilić-Ćurčić I, Alkhamis T, Wagner J, *et al*. Association between interleukin-10 gene (-1082g/a) polymorphism and type 2 diabetes, diabetes-related traits, and microvascular complications in the Croatian population. Acta Clin Croat. 2018;57(1):71-81. DOI: 10.20471/acc.2018.57.01.08.
23. Welty FK. How do elevated triglycerides and low HDL-cholesterol affect inflammation and atherothrombosis? Curr Cardiol Rep. 2013;15(9):400. DOI: 10.1007/s11886-013-0400-4.
24. Komendarek-Kowalska M. The assessment of renal function in patients with newly diagnosed hypertension – the role of hyperuricemia as a risk factor for chronic kidney disease – preliminary study. Pol Merkur Lekarski. 2017;42(251):193-6.
25. Kosekli MA, Kurtkulagi O, Kahveci G, Taslamacioglu Duman T, Atak Tel BM, Bilgin S, *et al*. The association between serum uric acid to high density lipoprotein-cholesterol ratio and non-alcoholic fatty liver disease: the ABUND study. Rev Assoc Med Bras. 2021;67(4):549-54. DOI: 10.1590/1806-9282.20201005.
26. Aktas G, Yilmaz S, Kantarci DB, Taslamacioglu Duman T, Bilgin S, Balci SB, *et al*. Is serum uric acid-to-HDL cholesterol ratio elevation associated with diabetic kidney injury? Postgrad Med. 2023;135(5):519-23. DOI:10.1080/00325481.2023.2214058.
27. Aktas G, Khalid A, Kurtkulagi O, Taslamacioglu Duman T, Bilgin S, Kahveci G, *et al*. Poorly controlled hypertension is associated with elevated serum uric acid to HDL-cholesterol ratio: a cross-sectional cohort study. Postgrad Med. 2022;134(3):297-302. DOI: 10.1080/00325481.2022.2039007.
28. Kurtkulagi O, Atak Tel BM, Kahveci G, Bilgin S, Taslamacioglu Duman T, Erturk A, *et al.* Hashimoto's thyroiditis is associated with elevated serum uric acid to high density lipoprotein-cholesterol ratio. Rom J Intern Med. 2021;59(4):403-8. DOI: 10.2478/rjim-2021-0023.

Sažetak

OMJER MOKRAĆNE KISELINE I HDL KOLESTEROLA U SERUMU POVEZAN JE S REGULACIJOM ŠEĆERNE BOLESTI U POPULACIJI BOLESNIKA S DIJABETESOM TIP 2

M. A. Kosekli i *G. Aktas*

Omjer mokraćne kiseline i HDL kolesterola (*uric acid to HDL cholesterol ratio*, UHR) predložen je kao novi predskazatelj metaboličkih i upalnih bolesti pa smo odlučili ispitati razine UHR u bolesnika s novonastalim dijabetesom tip 2 (T2DM) i usporediti ih s onima kod zdravih kontrolnih osoba. Uključeni su bolesnici s novonastalim dijabetesom tip 2, a kontrolnu skupini činili su dobrovoljci bez poznatih bolesti. Uspoređeni su rezultati laboratorijskih pretraga uključujući UHR, glukozu u krvi natašte (*fasting blood glucose*, FBG) i glikozilirani hemoglobin (HbA1c). Srednja vrijednost UHR bila je 16±8% u skupini bolesnika s T2DM i 10±3% u kontrolnoj skupini (p<0,001). Štoviše, UHR je značajno pozitivno korelirao s HbA1c (r=0,75, p<0,001), FBG (r=0,64, p<0,001), obujmom struka (r=0,35, p<0,001) i indeksom tjelesne mase (r=0,20, p=0,002), a obrnuto korelirao sa stopom glomerularne filtracije (r=-0,24, p<0,001). Visoke razine UHR mogle bi biti udružene s povišenim razinama glukoze u krvi kroz duže vrijeme, jer je UHR korelirao i s FBG i s HbA1c u bolesnika s novonastalim T2DM.

Ključne riječi: *Dijabetes melitus tip 2; Omjer mokraćne kiseline i HDL kolesterola; HbA1c; Glukoza u krvi natašte*