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ORIGINAL ARTICLE

The Relationship Between Uric Acid/HDL Ratio and Monocyte/HDL Ratio and Glycemic Control in Male Type 2 Diabetic Patients

Erkek Tip 2 Diyabetik Hastalarda Ürik Asit/HDL Oranı ve Monosit/HDL Oranı ile Glisemik Kontrol Arasındaki İlişki

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ABSTRACT

Background: Type 2 diabetes mellitus (T2DM) is a major health problem worldwide. As glycemic control worsens, the risk of both microvascular and macrovascular complications increases. The aim of this study is to investigate the relationship between blood glucose regulation and two different parameters: uric acid/HDL ratio (UHR) and monocyte/HDL ratio (MHR) in male subjects with type 2 diabetes.
Methods: In this retrospective study, a total of 166 male patients diagnosed with type 2 diabetes and 83 healthy adult men as a control cohort were included. Diabetic male participants were equally divided into two subgroups: the group with uncontrolled blood glucose (HbA1c levels exceeding 7, n=83) and the group with good glycemic control (HbA1c levels at or below 7, n=83). Our analysis included assessment of several serum markers, including triglyceride, high-density lipoprotein (HDL), uric acid, low-density lipoprotein (LDL), neutrophil, lymphocyte, monocyte, white blood cell, hemoglobin and platelet levels. In addition, uric acid/HDL ratio, body mass index and monocyte/HDL ratio were compared.
Results: Creatinine levels were normal in all study participants and ages were similar in the groups. Triglyceride levels were significantly higher in diabetic patients compared to the healthy group (P<0.001). In contrast, diabetic patients had lower HDL levels than healthy subjects (P=0.002). Serum uric acid levels were lower in the blood glucose unregulated group than in the blood glucose well-regulated group and healthy subjects (P<0.001). UHR was lower in the blood glucose unregulated group compared to the blood glucose well-regulated group and healthy subjects (P=0.003). White blood cell, neutrophil and lymphocyte counts were higher in diabetic patients than in the healthy group (P<0.001, P<0.001, P=0.002). Platelet count and MHR values were higher in the blood glucose-unregulated group compared to the blood glucose-regulated group and healthy subjects (P=0.007).
Conclusion: Increased MHR and decreased UHR levels are associated with uncontrolled blood glucose regulation in male patients with type 2 diabetes.

Keywords: Type 2 diabetes mellitus, Uric acid/HDL ratio, Monocyte/HDL ratio, HbA1C

ÖZ

Amaç: Tip 2 diabetes mellitus (T2DM) dünya çapında önemli bir sağlık sorunudur Glisemik kontrol kötüleştikçe, hem mikrovasküler hem de makrovasküler komplikasyon riski artar. Bu çalışmada amacımız, tip 2 diyabet tanısı almış erkek bireylerde kan şekeri regülasyonu ile iki farklı parametre arasındaki ilişkiyi araştırmaktır: ürik asit/HDL oranı (UHR) ve monosit/HDL oranı (MHR).
Yöntem: Bu retrospektif araştırmada, tip 2 diyabet tanısı konmuş toplam 166 erkek hasta ve kontrol kohortu olarak 83 sağlıklı yetişkin erkek çalışmaya dahil edilmiştir. Diyabetik erkek katılımcılar eşit olarak iki alt gruba ayrıldı: kan şekeri kontrol altında olmayan grup (7'yi aşan HbA1c seviyeleri, n=83) ve iyi glisemik kontrolü olan grup (7 veya altında HbA1c seviyeleri, n=83). Analizimiz, yüksek yoğunluklu lipoprotein (HDL), trigliserit , düşük yoğunluklu lipoprotein (LDL), ürik asit, nötrofil, lenfosit, monosit, beyaz kan hücresi, hemoglobin ve trombosit seviyeleri dahil olmak üzere çeşitli serum belirteçlerinin değerlendirilmesini kapsamıştır. Ayrıca, UHR, vücut kitle indeksi ve MHR karşılaştırılmıştır.
Bulgular: Çalışma kapsamında tüm katılımcıların kreatinin düzeyleri normaldi. gruplarda yaşlar benzerdi. Trigliserid düzeyleri diyabetik hastalarda sağlıklı grubuna kıyasla belirgin şekilde yüksekti (P<0.001). Buna karşılık, diyabetik hastaların HDL seviyeleri sağlıklı bireylerden daha düşüktü (P=0.002). Serum ürik asit düzeyleri, kan şekeri düzenlenmemiş grupta, kan şekeri iyi düzenlenmiş gruptan ve sağlıklı bireylerden daha düşüktü. (P<0.001). Kan şekeri düzenlenmemiş grupta, kan şekeri iyi düzenlenmiş gruba ve sağlıklı bireylere kıyasla UHR daha düşüktü (P=0.003). Beyaz kan hücreleri, nötrofil ve lenfosit sayıları diyabetik hastalarda sağlıklı gruptan yüksek bulundu (P<0.001, P<0.001 ve P=0.002). Trombosit sayısı ve MHR değerleri kan şekeri regüle olmayan grupta kan şekeri regüle edilen gruba ve sağlıklı bireylere kıyasla daha yüksek bulunmuştur (P=0.007).
Sonuç: Tip 2 diyabetli erkek hastalarda artmış MHR ve azalmış UHR düzeyleri kontrolsüz kan şekeri regülasyonu ile ilişkilidir.

Anahtar Kelimeler: Tip 2 diabetes mellitus, ürik asit/HDL oranı, Monosit /HDL oranı, HbA1C.

Introduction

Type 2 diabetes mellitus (T2DM) poses a formidable global health challenge, with complications arising in both the microvascular and macrovascular domains as glycemic control worsens. Hemoglobin A1c (HbA1c) continues to serve as the primary retrospective marker to assess glycemic management, but the inability to monitor daily blood glucose fluctuations remains a persistent concern (1, 2). High-density lipoprotein (HDL) acts by reducing proinflammatory responses triggered by monocytes, effectively restricting monocyte proliferation, activation and migration, and plays a role in the anti-oxidant mechanism. In contrast, reduced levels of HDL in the bloodstream imply a worsening metabolic profile and are a component of the metabolic syndrome

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(3, 4). Uric acid, a product of purine metabolism, acts as an endogenous antioxidant, but its elevation often accompanies renal disorders. Patients with T2DM often have elevated levels of uric acid. (4). Elevated uric acid is associated with hypertension, chronic kidney disease and cardiovascular disease in diabetes (5-7). There are also studies showing that low serum urate levels are associated with poor glycemic control (8, 9).

The uric acid/HDL ratio(UHR) is emerging as a parameter closely linked to the metabolic syndrome, with a body of research highlighting its predictive potential (3, 10).

Monocytes and macrophages play crucial roles in damage to pancreatic islet cells, islet inflammation and impaired insulin signaling in T2DM. In addition, the interaction between lipid metabolism and hematopoiesis is also of interest. (11, 12). The monocyte/HDL-cholesterol ratio (MHR) has been proposed as an indicator of ongoing low-grade metabolic inflammation and has been suggested in subsequent studies to be used as a marker for cardiovascular disease and chronic kidney disease(13, 14). In a study on MHR in DM, it was found higher in nephropathic patients(15).

The aim of this study was to examine the correlation between the uric acid/HDL ratio, monocyte/HDL ratio, and glycemic control in male patients diagnosed with T2DM, and compare these results with those of the control group.

Material And Methods

Study Design

This study retrospectively examined a group of 166 male patients diagnosed with diabetes at a single center. These individuals were enrolled after their visits to the Internal Medicine outpatient clinic at City Training and Research Hospital from January 1, 2021, to June 1, 2022. For comparative analysis, an additional 83 healthy adult males were included as a control cohort. The diabetic male patients were then evenly distributed into two groups: those with less-than-ideal glycemic control (HbA1c levels surpassing 7) and those with commendable glycemic control (HbA1c levels at or below 7). Only men were included in the study to eliminate possible gender-related differences in blood parameters, including uric acid, monocyte and lipid parameters. In addition, only male gender was included in the study in order to reduce the difference between male and female gender in the effect of hormones such as testosterone and estrogen on lipid profile and uric acid.

Exclusion criteria were applied to individuals with malignancies, those using furosemide, thiazide, acetylsalicylic acid, losartan group drugs, cholesterol-lowering drugs, patients with other autoimmune disorders, patients with coronary artery disease, chronic kidney disease or gout. The control group excluded diabetes mellitus by conducting a 75-gram oral glucose tolerance test following the diagnostic guidelines established by the American Diabetes Association. All patients included in the study and those in the control group were selected from individuals whose BUN, creatinine and GFR values were within normal limits to avoid affecting uric acid values.

Patient records provided essential demographic details, weight measurements, and height data. The body mass index (BMI) of all diabetic patients and the control group was calculated. Data regarding biochemical parameters were extracted from the hospital's comprehensive database. The uric acid/HDL ratio was derived by dividing the uric acid value by the HDL cholesterol value for all participants, including those in the control group. The monocyte/HDL ratio was established by dividing the count of monocytes by the HDL level, which was measured through a complete blood count analysis.

Blood studies were conducted using the Abbott Architect 16200 autoanalyzer (Abbott Inc., Princeton, NJ, USA) following a mandatory fasting period of at least 8 hours. As per the classification outlined by the World Health Organization, patients were further stratified into categories of normal weight (BMI < 24.99), overweight (BMI between 25 and 29.99), and obese (BMI > 30).

Statistical analysis

To evaluate the data, various statistical tests were applied. The normality of variables was examined using the Shapiro-Wilk test. For normally distributed variables, descriptive statistics were presented as mean± standard deviation, and group comparisons were performed using the One-Way Analysis of Variance (ANOVA) test for the three independent groups. Non-normally distributed variables were presented as median (minimum-maximum) values and Kruskal Wallis H test was used for comparisons between three independent groups. Categorical variables were presented as frequencies and percentages, and comparisons between groups were assessed using the Pearson chi-square test. Additionally, Pearson's correlation analysis was employed to explore associations between UHR, MHR, FBS, and HbA1c.

All statistical analyses were performed using the IBM SPSS Statistics 22.0 software, with the significance level set at a=0.05.

Ethics statement

The study was conducted in accordance with the Helsinki principles, and approval was obtained from the Mersin University Ethics Committee on 06.07.2022, numbered 2022/455.

Results

All participants in this investigation consisted exclusively of males, with diabetes durations ranging from 1 to 30 years. No statistically significant disparity in age was evident across the groups (P = 0.073). Additionally, all participants displayed blood creatinine levels within the normal range.

In the comparison between diabetic patients and

the control group, triglyceride levels were significantly higher (P < 0.001) while LDL levels did not show a significant difference (P = 0.095). In contrast, the control group exhibited higher HDL levels than the diabetic patients (P = 0.002).

White blood cell (P < 0.001), neutrophil (P < 0.001) and lymphocyte counts (P = 0.002) were all higher in diabetic patients compared to the control group. No significant difference was found between the three groups in terms of monocyte count (P=0.123). The platelet count was significantly higher in the group with poor glycemic control compared to both healthy subjects and the group with good glycemic control (P = 0.007).

Serum uric acid levels were lower in the poorly glycemic controlled diabetic group compared to the control group and the well glycemic controlled diabetic group (P < 0.001).

Table 1. Demographic, clinical data and statistical analysis results of the groups

Parameters *Mean±SD **Median(-min-max)	Group 1 Control group (n=83)	Group 2 Well-controlled T2DM (n=83)	Group 3 Poorly controlled T2DM (n=83)	Test	P value
Age (years) **	51(29-75)	56(33-70)	55(29-70)	5.246	0.073
T2 DM duration**	0	4(1-18)	6(1-30)	3.014	0.083
Fasting blood sugar (mg/dL) **	92(50-99)	123(11-172)	213(105-394)	194.34	<000.1
HbA1c (%)**	5.5(4.6-6.2)	6.7(5.5-7)	9.6(7.5-14.6)	212,22	<000.1
Total cholesterol(mg/dL)*	185.05±33.734	186.16±36.72	201.65±46.41	4.618	0.011
Triglyceride (mg/dL) **	128(94-258)	186(49-500)	208(72-762)	35.02	<000.1
HDL-C (mg/dL) **	47(29-75)	43(27-89)	41(23-72)	12.41	0.002
LDL-C(mg/dL) *	110.14±29.366	100.6±28.73	109.82±37.33	2.372	0.095
Uric acid (mg/dL) **	5.2(3.4-9.2)	5(2.2-8.5)	4.1(2.4-8)	31.17	<000.1
WBC $\cdot 10^3$ cells/IL**	6.6(4.5-11)	7.4(2.24-13)	8.5(4.8-14)	26.84	<000.1
Hemoglobin (g/dL) **	14.8(12.6-17)	14.4(12-17)	15(11-17)	2.747	0.253
Platelet count (k/mm3) **	224(155-395)	228(154-379)	249(150-500)	9.805	0.007
Neutrophil count $\cdot 10^3$ **	3.8(2.1-7.8)	4.3(2.5-9.7)	4.9(2-9)	23.67	<000.1
Lymphocyte count $\cdot 10^3$**	2(1-3.41)	2.4(1.07-3.6)	2.3(0.9-4.9)	12.17	0.002
Monocytes- count $\cdot 10^3$ **	0.40(0.14-2.31)	0.41(0.14-0.96)	0.45(0.23-0.81)	4.194	0.123
BMI (kg/m^2)**	26.23(17.51-51.78)	26.98(18.59-38.82)	26.98(18.93-38.75)	3.137	0.208
UHR**	0.12(0.05-0.28)	0.12(0.03-0.24)	0.10(0.04-0.21)	11.97	0.003
MHR**	0.0090(0.0027-0.0436)	0.0092(0.0033-0.0255)	0.0109(0.0047-0.0352)	9.818	0.007

UHR levels for well- and poorly-controlled diabetic patients and control subjects were at 12%, 10%, and 12%, respectively. UHR was lower in the poorly glycemic-controlled diabetic group compared to healthy subjects and the well-glycemic-controlled diabetic group (P = 0.003). Subsequent post hoc Tukey testing revealed no significant difference in UHR levels between well-controlled T2DM and control groups (p = 0.801). Nevertheless, UHR levels showed significant variation between well and poorly controlled diabetic patients (p = 0.006) and between poorly controlled diabetic patients and control subjects (p = 0.006).

As for MHR levels in well- and poorly-controlled diabetic patients and control subjects, they measured at % 0.90, %0.92, and %1.09, respectively. These differences in MHR among the study groups also held statistical significance (p = 0.007). Post hoc Tukey analysis revealed no statistically significant difference in MHR levels between well-controlled T2DM and control groups (p = 0.199). The MHR level was significantly higher in poorly controlled diabetic patients than in the well-controlled group (p = 0.027) and the control group (p = 0.027). Please refer to Table 1 for a comprehensive breakdown of demographic, clinical data, and detailed statistical analysis results.

Spearman's correlation analysis showed a significant weak negative correlation between UHR and fasting blood glucose (r = -0.147, p = 0.02) and HbA1c (r = -0.152, p = 0.016). Conversely, MHR showed a significant weakly positive correlation with fasting blood glucose (r = 0.128, p = 0.044) and HbA1c (r = 0.217, p = 0.001). A detailed presentation of the statistical results is given in Table 2.

Table 2. Correlation of UHR and MHR with various parameters

		UHR	MHR
Fasting blood glucose	r	-0.147	0.128
	p	0.02	0.044
Hba1c	r	-0.152	0.217
	p	0.016	0.01
Body mass index	r	0.99	0.133
	p	0.120	0.074

Discussion

In the literature, study results regarding uric acid levels in diabetic individuals are contradictory. Uric acid, aside from its association with gout, has been linked to cardiovascular diseases, metabolic syndrome and T2DM in various studies (16, 17). Moreover, soluble uric acid has been implicated in vascular endothelial dysfunction, cell senescence and heightened levels of free oxygen radicals(18-20). Hyperuricemia shows a positive correlation with diabetes mellitus, hypertension and chronic kidney disease while paradoxically offering some protection against neurodegenerative diseases(21-25). However, one study is the first to provide evidence that hypouricemia is associated with decreased kidney function in men (26). A previous study reported that serum uric acid levels were lower in individuals with diabetes, and this association was greater among men(8). In another study, uric acid levels were found lower in type 1 diabetic individuals with poor glycemic control than in well-controlled type 1 diabetic individuals and control group (9). In our study, uric acid levels were lower in the diabetic male group with uncontrolled

blood glucose than in healthy male individuals and well-regulated diabetic male patients. We think that the results in our study may be due to the uricosuric effect of hyperglycemia in the diabetes group with poor glycemic control. In addition, the age difference between healthy subjects and diabetic patients and the difference in creatinine levels between the groups in a previous study conducted only with male subjects may have affected the results (25). Our study revealed no significant difference in age and creatinine levels between the groups.

Low levels of HDL are not only indicative of poor metabolic status but also a component of metabolic syndrome(3). In previous studies, HDL levels were low in diabetics(27, 28). In our study, we observed that HDL levels were significantly lower in the diabetes group with poor glycemic control than in both the diabetes group with good glycemic control and the control group. These results were similar to the literature.

The UHR serves as a parameter associated with impaired metabolic status. A previous study indicated that the UHR was higher in patients with impaired glycemic control compared to those with good glycemic control. (25). In several studies, UHR was found higher in individuals with diabetic metabolic syndrome compared to those without metabolic syndrome (10, 29). Another study showed increased UHR in those with diabetic kidney damage compared to those without(30). In the previous study, UHR was significantly positively correlated with poor glycemic control in diabetic male subjects (25). In our study, on the contrary, a weak negative correlation was observed between UHR and blood glucose and HbA1C. Therefore, it can be said that UHR decreases as blood glucose regulation worsens. However, due to the low correlation, other factors that may have an effect should not be ignored.

Investigations into the interaction between lipid metabolism and hematopoiesis have revealed that HDL attenuates monocyte-induced proinflammatory effects by inhibiting monocyte proliferation, activation and migration (11, 12, 31). MHR has emerged as a potential marker of low-grade metabolic inflammation; subsequent studies suggest its use as a marker of inflammation in cardiovascular disease and chronic kidney disease (14, 32, 33). MHR has been investigated in diabetic complications in previous studies. In several studies, MHR was found higher in individuals with diabetic nephropathy and retinopathy than in those without nephropathy and retinopathy. (34, 35) . One study reported higher MHR in those with diabetic metabolic syndrome than in those without(36). In a previous study, it was determined that MHR was higher in diabetic patients compared to the control group (37). In our study, a significant difference was detected between the control group and the poorly glycemic controlled diabetes group in terms of MHR, whereas no difference was observed between the control group and the well glycemic controlled diabetes group. In our study, MHR showed a significant weak positive correlation with fasting blood glucose and HbA1c ($r = 0.128$, $p = 0.044$; $r = 0.217$, $p = 0.001$). These results are similar to the literature, but in previous studies, MHR was positively associated with diabetic complications. In our study, diabetic complications were excluded. This study is the first study in the literature to evaluate MHR without diabetic complications. However, only male diabetic individuals were included in the study, which was a limitation of the study.

Multiple studies conducted on healthy individuals have established connections between uric acid levels and serum triglycerides (28, 38). In another study, uric acid was also found to have a significant positive correlation with triglycerides and a negative correlation with HDL in diabetic patients(39) . In our study, a low level significant positive correlation was found between triglyceride level and uric acid ($r=0.262$, $p<0.001$). These results are similar to the literature.

Our study has several important limitations. The first one is the retrospective design of the study. The other is that only male individuals were included to eliminate the effect of gender on the parameters. The third is the small number of the study population.

Conclusion

In conclusion, high MHR and low UHR and low serum uric acid level are associated with impaired blood glucose regulation in diabetic male subjects. Impaired blood glucose regulation is also known to lead to diabetic complications if prolonged. Therefore, diabetic male individuals with high MHR and low UHR levels should be considered to have unregulated blood glucose and should be evaluated for more effective blood glucose regulation therapies. Further prospective studies are needed to provide additional information to these findings.

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