Abant Tıp Dergisi

Abant Medical Journal

Abant Med J 2023;12(2):131-139, doi:10.47493/abantmedj.1341855

The Role of Uric Acid to HDL Cholesterol Ratio in Predicting Myocardial Ischemia in Myocardial Perfusion Scintigraphy in Diabetic Patients

Diyabetli Hastalarda Miyokard Perfüzyon Sintigrafisinde Miyokard İskemisini Öngörmede Ürik Asit-HDL Kolesterol Oranının Rolü

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Geliş Tarihi (*Received*): 12.08.2023 **Kabul Tarihi (*Accepted*):** 23.08.2023 **Yayın Tarihi (*Published*):** 31.08.2023

Abstract

Objective: Diabetes Mellitus (DM) is a significant risk factor for cardiovascular diseases, particularly myocardial ischemia. Both diabetes mellitus type 2 and cardiovascular conditions are characterized by a high burden of inflammation. The uric Acid to High-Density Lipoprotein cholesterol ratio (UHR) has been suggested as a novel marker of metabolic and inflammatory diseases. Hence, this study investigated the predictive role of the Uric Acid to High-Density Lipoprotein cholesterol ratio (UHR) in myocardial ischemia detected by Myocardial Perfusion Scintigraphy (MPS) in diabetic patients.

Materials and Methods: This study included patients who underwent MPS between January 2022 and March 2023 at the Nuclear Medicine Department of Abant Izzet Baysal University Hospital. Based on the MPS results, the participants were divided into normal perfusion and myocardial ischemia. Variables such as age, sex, leukocyte count, hemoglobin, hematocrit, platelet count, serum uric acid, urea, creatinine, total cholesterol, LDL-cholesterol, HDL-cholesterol, triglyceride, transaminase, blood fasting glucose, C-reactive protein, and serum albumin were recorded and compared between the groups.

Results: Among the 73 diabetic patients, 37 had myocardial ischemia, and 36 had normal MPS. Serum uric acid levels were higher in the ischemic group (6.3 ± 1.5 mg/dL) than in the normal group (5.1 ± 1.8 mg/dL) ($p<0.05$). The UHR in the ischemic group was significantly higher (0.15 ± 0.05) than that in the normal MPS group (0.11 ± 0.04). Serum UHR was significantly positively correlated with myocardial ischemia ($r=0.36$, $p=0.002$). With a cut-off value of ≥ 0.11, UHR exhibited 76% sensitivity and 58% specificity in detecting myocardial ischemia ($p<0.05$).

Conclusion: High UHR is an independent predictor and diagnostic tool for myocardial ischemia in patients with diabetes and coronary artery disease. Routine use of UHR as an independent predictive marker is recommended for diabetic patients with myocardial ischemia who undergo MPS.

Keywords: Uric Acid to High-Density Lipoprotein cholesterol ratio (UHR), Myocardial Ischemia, Myocardial Perfusion Scintigraphy, Diabetes Mellitus, Biomarkers

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Öz

Amaç: Diabetes Mellitus (DM) başta miyokardiyal iskemi olmak üzere kardiyovasküler hastalıklar için önemli bir risk faktörüdür. Hem diabetes mellitus tip 2 hem de kardiyovasküler durumlar, yüksek bir inflamatuar yük ile karakterizedir. Ürik Asit -Yüksek Yoğunluklu Lipoprotein kolesterol oranı (UHR), metabolik ve enflamatuar hastalıkların yeni bir belirteci olarak önerilmiştir. Bu nedenle, bu çalışma diyabetik hastalarda Miyokard Perfüzyon Sintigrafisi (MPS) ile saptanan miyokard iskemisinde Ürik Asidin Yüksek Yoğunluklu Lipoprotein kolesterol oranının (UHR) öngörmedeki rolünü araştırmıştır.

Gereç ve Yöntemler: Bu çalışmaya Ocak 2022 ile Mart 2023 tarihleri arasında Abant İzzet Baysal Üniversitesi Hastanesi Nükleer Tıp Anabilim Dalı'nda MPS uygulanan hastalar dahil edildi. MPS sonuçlarına göre katılımcılar normal perfüzyon ve miyokard iskemisi olarak iki gruba ayrıldı. Gruplar arasında yaş, cinsiyet, lökosit sayısı, hemoglobin, hematokrit, trombosit sayısı, serum ürik asit, üre, kreatinin, total kolesterol, LDL-kolesterol, HDL-kolesterol, trigliserit, transaminaz, kan açlık glikozu, C-reaktif protein ve serum albümini gibi değişkenler kaydedildi ve karşılaştırıldı.

Bulgular: Diyabetli 73 hastanın 37'sinde miyokardiyal iskemi, 36'sında normal MPS mevcuttu. Serum ürik asit düzeyleri iskemik grupta (6,3 ± 1,5 mg/dL) normal gruba (5,1 ± 1,8 mg/dL) göre daha yüksekti ($p<0,05$). İskemik gruptaki UHR, normal MPS grubundakinden (0,11 ± 0,04) anlamlı derecede yüksekti (0,15 ± 0,05). Serum UHR, miyokard iskemisi ile anlamlı olarak pozitif korelasyon gösterdi ($r=0,36$, $p=0,002$)). Cut off değeri ≥ 0,11 olan UHR, miyokard iskemisini saptamada %76 duyarlılık ve %58 özgüllük sergiledi ($p<0,05$).

Sonuç: Yüksek UHR, diyabetli ve koroner arter hastalığı olan hastalarda miyokard iskemisi için bağımsız bir prediktör ve tanı aracıdır.

Anahtar Kelimeler: Ürik Asit/Yüksek Yoğunluklu Lipoprotein kolesterol oranı (UHO), Miyokardiyal İskemi, Miyokard Perfüzyon Sintigrafisi, Diabetes Mellitus, Biyobelirteçler

Atıf/Cite as: Afşin H. The Role of Uric Acid to HDL Cholesterol Ratio in Predicting Myocardial Ischemia in Myocardial Perfusion Scintigraphy in Diabetic Patients. Abant Med J. 2023; 12(2): 6-7. doi:10.47493/abantmedj.1341855

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Introduction

Diabetes Mellitus (DM) may affect carbohydrate metabolism, resulting in chronic hyperglycemia, which is associated with abnormalities in protein, lipid, and carbohydrate metabolisms. This condition is a key driver of crucial atherosclerosis, a significant cause of cardiovascular diseases. Altered lipid metabolism, a characteristic of atherosclerosis, intensifies cardiovascular risk, while chronic inflammation forms the fundamental link between DM and atherosclerosis, an inflammatory disorder of the arterial wall that can lead to serious health deterioration and even death (1).

Chronic hyperglycemia, a characteristic of DM, contributes to long-term dysfunction and damage to several organs. The complications associated with diabetes pose significant health risks, including retinopathy, nephropathy, peripheral neuropathy, and cardiovascular symptoms. Diabetic patients exhibit more atherosclerosis-related cardiovascular, peripheral arterial, and cerebrovascular diseases than the general population (2).

Coronary artery disease (CAD) is a significant cause of global mortality and morbidity, with over 90% of myocardial ischemia cases caused by coronary artery obstruction. Multiple factors contribute to the development of atherosclerosis, leading to CAD, including dyslipidemia, hypercoagulability, endothelial dysfunction, oxidative stress, inflammation, and infection (3).

Diabetes mellitus (DM) is a significant risk factor for CAD. The diagnostic methods include stress electrocardiography, stress echocardiography, and Gated and MPS SPECT to evaluate myocardial ischemia due to suspected CAD (4). Atherosclerosis involves lipid accumulation in arteries, leading to macrophage infiltration and the formation of cholesterol-rich foam cells (5).

Diabetes increases the risk, progression rate, and severity of CAD. Diabetic patients without previous myocardial infarction (MI) exhibit an MI risk similar to non-diabetic patients with an earlier history of MI (6).

High-Density Lipoprotein (HDL) cholesterol plays a pivotal role in cardiovascular diseases, as it transports excess cholesterol to the liver. It also supports vascular endothelial cells and reduces oxidative reactions in blood. Hyperuricemia can predict cardiovascular mortality and morbidity, causing gout, insulin resistance, high blood pressure, and deterioration of renal function. Uric acid is the final product of purine metabolism, and its increase leads to vascular endothelial dysfunction and stimulates oxidative stress (7).

Uric acid and HDL cholesterol disorders are important risk factors for CAD. Previous studies have reported that the Uric Acid to High-Density Lipoprotein cholesterol ratio (UHR) is associated with hypertension, liver steatosis, cardiovascular mortality, and thyroiditis. Some studies have revealed that high uric acid and low HDL cholesterol levels can cause endothelial oxidative damage and insulin resistance, leading to the deterioration of the cardiovascular system. Serum UHR is emerging as a novel superior biomarker for interpreting inflammatory and anti-inflammatory substances and the severity of CAD (8).

Both diabetes mellitus type 2 and cardiovascular conditions are characterized by a high burden of inflammation. The uric Acid to High-Density Lipoprotein cholesterol ratio (UHR) is suggested as a novel marker of metabolic and inflammatory diseases. The study significantly contributes to refining the diagnostic protocols for myocardial ischemia, particularly in the diabetic patient population. Our ultimate goal was to enhance early detection and subsequent management of myocardial ischemia, thereby improving patient outcomes.

The central aim of our study was to investigate the potential role of UHR in predicting myocardial ischemia in MPS. This ratio is gaining recognition as an emergent biomarker in cardiovascular health, and we intend to examine its effectiveness and predictive power in a specific clinical context.

Materials and Methods

Design and Setting

This study examined patients with diabetes who underwent MPS between January 2022 and March 2023 at the Nuclear Medicine Department of Abant Izzet Baysal University Hospital. Comprehensive patient demographics and laboratory data were obtained from institutional databases and individual patient files. Based on the MPS results, patients were divided into CAD and normal groups. Based on our MPS results, the subjects were systematically categorized into two groups: those exhibiting myocardial ischemia and those with normal perfusion. A wide range of parameters was recorded for each participant, including age, sex, blood leukocyte count (WBC), hemoglobin, hematocrit, platelet count, serum uric acid, blood urea, creatinine, total cholesterol, Low Density Lipoprotein (LDL)-cholesterol, HDL-cholesterol, triglycerides, aspartate, and alanine transaminase, fasting blood glucose, C-reactive protein, and serum albumin. A comparative analysis was performed between the myocardial ischemia and normal perfusion groups.

Inclusion/Exclusion Criteria

The eligibility criteria for the study were carefully defined. The study did not include patients presenting with active infections or inflammatory diseases, pregnant women, cancer patients, and individuals younger than 18 years.

Ethics Approval

We obtained informed consent from all participants, and the research protocol was approved by the local Ethics Committee of Abant Izzet Baysal University (Approval Number: 2023/101, Date: 11.04.2023).

Myocardial Perfusion Scintigraphy Imaging and Application Protocol

The MPS imaging procedures were carefully delineated. Stress perfusion alone was deemed sufficient for patients with normal perfusion no resting study was required. However, patients with abnormal perfusion during the stress study underwent a resting separate survey, typically the following day. Resting research was conducted within a week, depending on the patient's or department's circumstances. Exercise stress tests were performed using the Modified Bruce Protocol. Upon reaching the target heart rate (220-age) x 0.85, an intravenous injection of 20 mCi Tc99m-Sestamibi was administered, and the patient was asked to continue exercising for an additional minute. Imaging commenced 30-45 minutes post-exercise.

Patients who could not perform exercise stress tests for neurological or orthopedic reasons or non-diagnostic exercise tests were subjected to pharmacological stress tests using adenosine. Adenosine was intravenously administered at 140 µg/kg/min over six minutes. At the end of the third minute, at peak coronary hyperemia, a 20 mCi Tc99m-Sestamibi intravenous injection was administered, and the adenosine injection continued until the end of the sixth minute. İmaging began 30-45 minutes after adenosine injection.

Patients were administered milk and chocolate after stress (exercise or adenosine) and rest radiopharmaceutical injections to enhance cardiac imaging and reduce abdominal activity. The remaining stress images were deemed unnecessary for patients with normal perfusion. However, patients with suspected perfusion defects or hypoperfusion in stress images were administered a 20 mCi Tc99m-Sestamibi IV injection at rest, followed by rest imaging after 30-45 minutes. MPS is a less invasive method than coronary angiography for detecting coronary vascular diseases.

Radiophamaceuticals given for MPS imaging and their doses, adenosine dose and duration as well as procedures were performed according to the Turkish Nuclear Medicine Association Myocardial Perfusion SPECT Procedure Guideline published in 2020 (9).

MPS imaging was performed using a high-resolution dual-headed gamma camera (Siemens Symbia, Germany) covering a 180° angle between the 45° right anterior oblique view and the 45° left posterior oblique view. Images were acquired in a 64 × 64 matrix at 3° intervals with 60 projections. Each image had

a duration of 18 s, and a 20% energy window centered on the 140 keV Tc 99m photon peak was utilized. Patients were placed supine with their arms raised and immobile during image acquisition.

Statistical Analyses

All statistical analyses were performed using the SPSS software package (SPSS 20.0, IBM Corp., Armonk, NY, USA). The normality of the data was assessed using the Kolmogorov-Smirnov test. Variables that followed a normal distribution were expressed as means and standard deviations, and differences between groups were evaluated using an independent sample t-test. Non-normally distributed variables were presented as medians and interquartile ranges (IQR), and comparisons between groups were made using the Mann-Whitney U test.

The interrelationships between the study parameters were examined using Pearson's correlation test. Receiver operating characteristic (ROC) curve analysis was used to ascertain the sensitivity and specificity of UHR for detecting myocardial ischemia. The area under the curve (AUC) and 95% confidence interval (CI) values were calculated during the ROC analyses. The level of statistical significance was set at a p-value less than 0.05.

Results

The study population comprised 73 patients, 37 in the myocardial ischemia group and 36 in the normal MPS group. The median ages of the normal MPS and ischemia groups were 68 (39-81) years and 68 (41-82) years, respectively (p=0.41). There were 24 women and 12 men in the normal MPS group and 14 women and 23 men in the myocardial ischemia group (p=0.01) (Table 1).

No statistical differences between normal MPS and myocardial ischemia were reported in terms of WBC (p=0.13), Hb (p=0.28), Htc (p=0.78), Plt (p=0.68), total cholesterol (p:0.06), triglyceride (p=0.56), AST (p=0.98), ALT (p=0.84), GGT (p=0.37), fasting glucose (p=0.19), urea (p=0.30), creatinine (p=0.11), albumin (p=0.52), and CRP (p=0.67) levels (Table 1).

Serum uric acid levels of the diabetic patients with normal MPS and myocardial ischemia were 5.1 ± 1.8 mg/dL and 6.3 ± 1.5 mg/dL, respectively. The serum uric acid level of the ischemic diabetic subjects was higher than that of the diabetic patients with normal MPS (p=0.004). LDL cholesterol levels in diabetic patients with normal MPS and myocardial ischemia were 121 ± 35 mg/dL and 100 ± 39 mg/dL, respectively. LDL cholesterol levels were lower in ischemic diabetic subjects than in diabetic patients with normal MPS (p=0.02) (Table 1).

The mean UHR of diabetic patients with myocardial ischemia was 0.15 ±0.05 and was higher than that in the normal MPS group (0.11 ± 0.04). The difference between ischemia and normal MPS groups was statistically significant (p=0.001) (Table 1).

Serum UHR was significantly positively correlated with myocardial ischemia in patients with diabetes (r=0.36, p=0.002).

A UHR level higher than 0.11 have 76% sensitivity and 58% specificity in detecting myocardial ischemia in diabetic patients [AUC (Area under curve):0.71, p=0.002, 95% CI (confidence interval):0.59-0.83] (Figure 1).

Discussion

Our investigation revealed several key findings: (I) UHR can be positively associated with myocardial ischemia in diabetic patients, (II) an elevated UHR level significantly correlates with the onset of myocardial ischemia in individuals with type 2 diabetes mellitus, and (III) high UHR levels exhibit high sensitivity and moderate specificity for the detection of myocardial ischemia. This study represents a pioneering effort to elucidate the connection between elevated UHR levels and myocardial ischemia in diabetic patients who underwent MPS.

Table 1.

Laboratory and Demographic Data of Diabetic Patients According to MPS Results

	Normal Myocardial Perfusion	Myocardial Ischemia	p value
Gender			**0.01**
Male	12 (33%)	23 (62%)	
Female	24 (67%)	14 (38%)	
	Median (min-max)	**Median (min-max)**	
Age (years)	68 (39-81)	68 (41-82)	0.41
WBC (k/mm³)	6.99 (4-11)	7.21 (5-11)	0.13
Urea (mg/dL)	32 (15-110)	41 (19-82)	0.30
Creatinine (mg/dL)	0.86 (0.63-2.69)	1.01 (0.57-3.07)	0.11
HDL Chol.(mg/dL)	48.60 (29-77)	41.80 (23-85)	0.28
Triglyceride (mg/dL)	155 (34-416)	133 (63-378)	0.56
ALT (U/L)	16 (11-49)	15 (9-48)	0.84
GGT (U/L)	22.30 (13-74)	26 (11-98)	0.37
CRP (mg/dL)	1.36 (0.1-15.1)	1.05 (0.1-57.5)	0.67
Albumin (g/dL)	4.1(3.8-5.3)	4.3 (2.4-5.1)	0.52
Fasting Glucose (mg/dL)	128 (77-287)	117(74-564)	0.19
	Mean ± SD	**Mean ± SD**	
UHR	0.11±0.04	0.15±0.05	**0.001**
Hb (g/dL)	13.1±1.3	15.7±1.5	0.28
Htc (%)	40.2±3.7	40.5±6	0.78
Plt (k/mm³)	254±83.5	246.8±65.6	0.68
Uric acid (mg/dL)	5.1±1.8	6.3±1.5	**0.004**
Total Cholesterol (mg/dL)	198±44.2	177.9±46.5	0.06
LDL Chol. (mg/dL)	121±35	100.±39	**0.02**
AST (U/L)	19.9±6.5	19.8±5.4	0.98

WBC: White Blood Cells, HDL: High-Density Lipoprotein, ALT: Alanine Transaminase, GGT: Gamma-Glutamyl Transferase, CRP: C-Reactive Protein, UHR: Uric Acid to HDL Ratio, Hb: Hemoglobin, Htc: Hematocrit, Plt: Platelets, LDL: Low-Density Lipoprotein.

Elevated UHR has been implicated in inflammatory and metabolic disorders, including Hashimoto thyroiditis, type 2 diabetes mellitus, metabolic syndrome, and non-alcoholic fatty liver disease. Elevated UHR has also emerged as a potential biomarker for diabetic nephropathy in type 2 diabetes mellitus, which triggers chronic and low-grade inflammation. Our findings resonate with these observations, corroborating that myocardial ischemia triggered by chronic inflammation in patients with diabetes is significantly associated with high UHR (10).

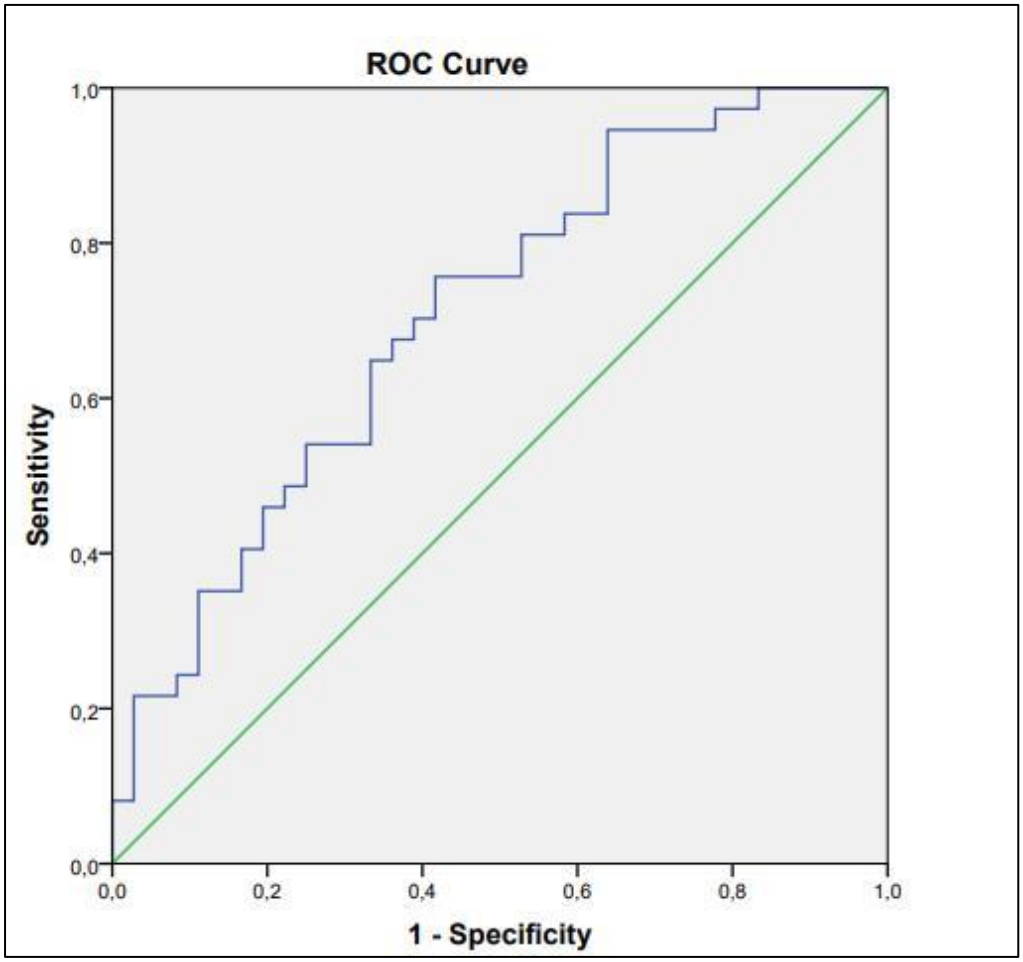

Figure1. ROC curve analysis of UHR in predicting myocardial ischemia, AUC of UHR for ischemia in diabetics: 0.71% 95 CI: 0.59-0.83; p<0.002; ROC: Receiver operating characteristics, AUC: Area under the curve, UHR: Uric Acid to HDL Ratio, CI: Confidence interval.

Furthermore, high uric acid levels have been implicated in many inflammatory conditions such as type 2 diabetes mellitus, metabolic syndrome, obesity, gout, and autoimmune thyroiditis (14,18,19). Kurtkulağı et al. delineated a substantial positive correlation between UHR and thyroid-stimulating hormone (TSH) and an inverse correlation with free T4 (FT4). The investigators underscored that elevated UHR is a robust and practical marker of Hashimoto's thyroiditis, an autoimmune disease in which chronic inflammation is instrumental in its clinical course (11). A high UHR could enhance the diagnostic utility of other markers for Hashimoto's thyroiditis. Our results are congruent with these findings, particularly in light of the substantial correlation between myocardial ischemia precipitated by persistent low-grade inflammation and increased UHR in our diabetic cohort.

Elevated serum uric acid levels are often associated with cardiovascular diseases, diabetes, hypertension, chronic kidney disease, and metabolic syndrome. Hyperuricemia is an independent risk factor for diabetes and positively correlates with diabetes-related complications. HDL cholesterol plays an integral role in cardiovascular health and metabolic syndrome, with the components of the metabolic syndrome being low HDL cholesterol, dyslipidemia, hypertriglyceridemia, hypertension, and impaired glucose tolerance. Notably, patients with diabetes exhibit decreased high-density lipoprotein (HDL) cholesterol levels. UHR, encompassing both uric acid and HDL cholesterol, is a robust indicator of metabolic deterioration, as shown in our study. The findings of this study underscore the significance of UHR as a diagnostic marker for diabetes and related metabolic disorders (12).

Type 2 diabetes mellitus and its consequential complications are often linked to inflammatory biomarkers such as neuregulin-4 (Nrg-4) and adipokines secreted by brown adipose tissue. Xuan et al. revealed a correlation between UHR and both macrovascular and microvascular complications of diabetes mellitus, in addition to a relationship between UHR and diabetic retinopathy, particularly in men and postmenopausal women. They advocated for monitoring and managing elevated UHR during diabetes follow-up, emphasizing its importance in preventing and mitigating diabetes-associated vascular complications. These results corroborate our findings, which showed a pronounced positive correlation between increased UHR and myocardial ischemia in diabetic patients with persistent inflammation (12).

Emerging studies have highlighted the predictive value of high UHR for inflammation in conditions such as metabolic syndrome (13), type 2 diabetes mellitus (14), non-alcoholic fatty liver disease, and liver steatosis (15). These insights underscore the potential utility of UHR as a predictive marker for diverse health conditions, supporting the findings of this study.

Uric acid, a product of purine catabolism, is primarily excreted through urine. Antigen cells exhibit sensitivity to uric acid owing to endogenous pro-inflammatory signaling; therefore, increased uric acid levels may induce inflammation. Conversely, a reduction in uric acid levels is related to a decrease in the overall inflammatory burden. Elevated uric acid levels have been associated with chronic low-level inflammatory conditions such as obesity, metabolic syndrome, and type 2 diabetes mellitus. Moreover, uric acid levels have been linked to glycated hemoglobin (HbA1c) levels and regulation of diabetes mellitus. Kosekli and colleagues suggested that high UHR levels could indicate hepatic steatosis in healthy individuals, proposing that UHR levels could be used for diagnostic and monitoring purposes in individuals with liver steatosis (15). Our findings resonate with these insights, suggesting that elevated UHR levels in patients with diabetes may potentially serve as a predictor of myocardial ischemia.

A recent large-scale population study highlighted a positive association between elevated UHR levels and reduced Glomerular Filtration Rate (GFR), which indicates a risk of chronic kidney disease. UHR is a sensitive and specific marker of kidney function. These findings and those of our research showed a consistent relationship between elevated UHR levels and the prediction of myocardial ischemia in MPS for diabetic patients (16).

Uric acid is a potential biomarker of diabetic nephropathy. An investigation by Kocak et al. showed that elevated uric acid levels correspond with the severity of diabetic kidney disease in patients with diabetes. These insights resonate with our findings, which indicate a correlation between high UHR levels and myocardial ischemia in patients (17).

HDL cholesterol has gained attention as an essential risk factor for cardiovascular diseases because it safeguards the vascular endothelium by promoting oxidative reactions in the bloodstream. Some studies have suggested a possible association between inflammatory conditions, such as diabetes mellitus, metabolic syndrome, various cancers, and low HDL cholesterol levels. Our study reaffirms this, as we observed that a decrease in HDL cholesterol tends to amplify UHR levels, further validating the use of UHR as a meaningful biomarker for predicting myocardial ischemia in patients with diabetes (20,21).

This is the first study to demonstrate the relationship between UHR and myocardial ischemia detected using MPS. While this study was rigorous in its approach, and the implications could potentially be significant, there were several limitations to note.

1. Sample size and selection bias: The study was conducted in a single hospital, and the sample size may not be sufficiently large to generalize the findings. The patients in this study may not represent the complete spectrum of patients with diabetes, leading to potential selection bias.

2. Cross-sectional design: Given that this was a cross-sectional study, it offers only a snapshot of the UA/HDL ratio and myocardial ischemia at a specific point in time. This design cannot capture the dynamic nature of these markers and the progression of myocardial ischemia.

3. Lack of a control group: Although the study compared patients with normal perfusion to those with myocardial ischemia, it did not include a non-diabetic control group. This omission restricts our ability to explore the role of diabetes in observed relationships.

4. Exclusion of confounding factors: While the study attempted to control for various confounding factors, there could be other unaccounted variables, such as lifestyle, dietary habits, and medication adherence, that could influence both UHR and myocardial ischemia.

5. Measurement error: There is always the potential for mistakes in measuring biochemical markers and interpreting MPS images, which could introduce bias into the study findings.

6. Reliance on existing data: This study utilized patient records and an institutional data-collection database. These records may contain inaccurate or missing information, affecting the results.

Future studies addressing these limitations may further increase our understanding of the role of UHR in predicting myocardial ischemia in MPS patients.

Conclusions

Based on the results of our study, we confirmed that high UHR serves as a crucial independent predictor and diagnostic tool for myocardial ischemia in patients with diabetes and CAD. UHR's ease of obtaining and cost-effectiveness of UHR significantly contributes to its potential as a routine diagnostic measure. We suggest that UHR can be routinely used as an independent predictive marker, particularly in diabetic patients suspected of having ischemia, who are candidates for MPS. These findings highlight the value of UHR in clinical practice for diagnosing CAD, thereby contributing to proactive treatment strategies and improving patient outcomes.

Ethics Committee Approval: The study was approved by the Ethics Committee of Bolu Abant Izzet Baysal University (date: 11.04.2023 and approval number: 2023/101).

Informed Consent: Written consent was obtained from the participants.

Conflict of Interest: Author declared no conflict of interest.

Financial Disclosure: Author declared no financial support.

Acknowledgment: We would like to thank all the Bolu Training and Research Hospital researchers.

Author Contributions: Idea/Concept: H.A.; Design: H.A.; Materials: H.A.; Data Collection/Processing: H.A.; Analysis/Interpretation: H.A.; Literature Review: H.A.; Drafting/Writing: H.A.; Critical Review: H.A. The author has accepted responsibility for the entire content of this manuscript and approved its submission.

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