



The Relationship Between Monocyte/High-Density Lipoprotein Cholesterol Ratio and Microvascular Complications in Patients with Type 2 Diabetes Mellitus

Tip 2 Diyabetli Hastalarda Monosit/Yüksek Yoğunluklu Lipoprotein Kolesterol Oranı ile Mikrovasküler Komplikasyonlar Arasındaki İlişki

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ABSTRACT

Aim: This study investigates the relationship between the monocyte-to-high-density lipoprotein cholesterol ratio (MHR) and microvascular complications (nephropathy, retinopathy, and neuropathy) in patients with type 2 diabetes mellitus (T2DM). With the increasing global burden of diabetes and its associated complications, identifying simple and accessible biomarkers for early prediction and management is of great importance.

Materials and Methods: The data of 229 T2DM patients who applied to the internal medicine and diabetes outpatient clinics of Haseki Training and Research Hospital between June 1, 2012, and June 1, 2017, were retrospectively analyzed. Demographic, clinical, and laboratory data, including MHR values, were collected. Statistical analyses were performed using IBM Statistical Package for Social Sciences (SPSS) program version 23.0, and a significance level of $p < 0.05$ was considered. The Mann-Whitney U test was used for data that did not show a normal distribution.

Results: Of the 229 patients included in the study, 52.8% were female, and the mean age was 56.7 years. Diabetic retinopathy (DRP) was detected in 28.8% of the patients, diabetic nephropathy (DN) in 34.5%, and diabetic neuropathy in 42.8%. A statistically significant relationship was found between MHR and DRP ($p=0.015$) and between MHR and DN ($p < 0.001$); however, no significant association was found between MHR and neuropathy ($p=0.124$).

Conclusion: Monocyte-to-high-density lipoprotein cholesterol ratio may be a useful and easily calculable marker for predicting diabetic retinopathy and nephropathy in patients with type 2 diabetes. However, no significant relationship was found between MHR and diabetic neuropathy. Further prospective studies are needed to confirm the prognostic value of MHR in clinical practice.

Key words: monocyte-to-HDL cholesterol ratio; type 2 diabetes mellitus; microvascular complications; diabetic nephropathy; diabetic retinopathy; diabetic neuropathy

ÖZET

Amaç: Bu çalışma, tip 2 diabetes mellitus (T2DM) hastalarında monosit/yüksek yoğunluklu lipoprotein kolesterol (HDL) oranı (MHR) ile diyabete bağlı mikrovasküler komplikasyonlar olan nefropati, retinopati ve nöropati arasındaki ilişkiyi araştırmayı amaçlamaktadır. Diyabet ve ilişkili komplikasyonların küresel yükü giderek artarken, erken tahmin ve yönetim için basit ve erişilebilir biyobelirteçlerin belirlenmesi büyük önem taşımaktadır.

Materyal ve Metot: Çalışmada, 1 Haziran 2012 ile 1 Haziran 2017 tarihleri arasında Haseki Eğitim ve Araştırma Hastanesi iç hastalıkları ve diyabet Polikliniklerine başvuran 229 T2DM hastasının verileri retrospektif olarak analiz edildi. Demografik, klinik ve laboratuvar verileri ile MHR değerleri kaydedildi. İstatistiksel analizler IBM Sosyal Bilimlerde İstatistik Paket Programı (SPSS) sürüm 23.0 programı kullanılarak yapıldı; $p < 0,05$ anlamlı kabul edildi. Normal dağılım göstermeyen veriler için Mann-Whitney U testi kullanıldı.

Bulgular: Çalışmaya dâhil edilen 229 hastanın %52,8'i kadındı ve ortalama yaş 56,7 idi. Hastaların %28,8'inde diyabetik retinopati (DRP), %34,5'inde diyabetik nefropati (DN) ve %42,8'inde diyabetik nöropati saptandı. Monocyte-to-high-density lipoprotein kolesterol ile DRP ($p=0,015$) ve DN ($p < 0,001$) arasında istatistiksel olarak anlamlı bir ilişki bulundu. Ancak MHR ile nöropati arasında anlamlı bir ilişki saptanmadı ($p=0,124$).

Sonuç: Tip 2 diyabetli hastalarda MHR, diyabetik retinopatiyi ve nefropatiyi öngörmeye kullanılabilecek pratik ve hesaplanması kolay bir biyobelirteç olabilir. Ancak diyabetik nöropati ile anlamlı bir ilişki gösterilmemiştir. MHR'nin klinik uygulamadaki prognostik değerinin netleşmesi için ileriye dönük, çok merkezli çalışmalara ihtiyaç vardır.

Anahtar kelimeler: monosit/yüksek yoğunluklu lipoprotein kolesterol oranı; tip 2 diyabetes mellitus; mikrovasküler komplikasyonlar; diyabetik nefropati; diyabetik retinopati; diyabetik nöropati

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Introduction

Diabetes mellitus (DM) is a chronic metabolic disease characterized by sustained high blood glucose levels, arising from insufficient insulin secretion or impaired cellular response to insulin. This metabolic imbalance adversely affects the regulation of carbohydrate, lipid, and protein metabolism. Epidemiological estimates suggest that the global burden of diabetes may reach nearly 693 million individuals by 2045 (1,2). Macrovascular and microvascular complications—including diabetic nephropathy, retinopathy, and neuropathy—play a major role in increasing mortality and reducing quality of life among individuals with diabetes. With the growing prevalence of the disease, secondary outcomes such as limb loss and dependence on dialysis significantly intensify both the individual health burden and societal costs. Among these complications, microvascular disorders, in particular, are key drivers of rising healthcare expenditures in many nations (3,4).

Studies have demonstrated that diabetes facilitates the overproduction of reactive oxygen species (ROS). Key contributors to superoxide radical formation include fluctuations in blood glucose levels, endothelial dysfunction, and oxidative damage to pancreatic beta cells (5). Epidemiological evidence indicates a close relationship between inflammatory biomarkers and both the development and progression of type 2 diabetes mellitus (T2DM) and its associated complications. This inflammatory cascade is thought to be initiated by interactions among adipocytes, macrophages, and various immune cells that infiltrate enlarged adipose tissue (6).

Monocytes and macrophages are essential components of the immune system that actively produce and secrete pro-inflammatory and oxidative cytokines. Together with leukocytes and lymphocytes, monocytes play a crucial role in the innate immune response. After differentiating in peripheral tissues, these cells contribute to both the initiation and resolution of inflammation via mechanisms such as phagocytosis, cytokine secretion, reactive oxygen species (ROS) production, and activation of the adaptive immune system. However, an overabundance of monocytes can exacerbate oxidative stress and amplify inflammatory pathways. Elevated monocyte activity has also been linked to platelet activation and endothelial dysfunction, potentially promoting prothrombotic processes (7). In contrast to monocyte-driven inflammation, high-density lipoprotein cholesterol (HDL-C) plays a protective role by mitigating oxidative and inflammatory responses. It

accomplishes this by preventing the oxidation of low-density lipoprotein (LDL) particles and by restricting macrophage migration. Moreover, HDL influences the proliferation and differentiation of progenitor cells, thereby regulating monocyte activation (8).

Oxidative stress disrupts cellular metabolic processes and undermines cellular homeostasis, playing a critical role in the emergence of insulin resistance and beta-cell impairment. These pathological alterations represent a core mechanism underlying the development of vascular complications in diabetic individuals (9). Furthermore, low serum magnesium levels—negatively correlated with HbA1c—may contribute to this vicious metabolic cycle (10). Recent investigations have highlighted the monocyte-to-high-density lipoprotein cholesterol (MHR) ratio—calculated from circulating monocyte and HDL levels—as a novel biomarker indicative of systemic inflammation and oxidative stress. In addition to its diagnostic value, MHR has been proposed as a prognostic tool in diverse clinical contexts. Multiple studies have emphasized its relevance as a surrogate marker primarily associated with inflammation-driven mechanisms (11–13).

The objective of this study is to investigate the relationship between the monocyte-to-HDL cholesterol (MHR) ratio and microvascular complications in patients with T2DM. Through this analysis, we aim to underscore the potential utility of MHR as an accessible and easily calculable biomarker that could support clinicians in risk stratification and therapeutic decision-making.

Materials and Methods

Patients

Before the commencement of the study, ethical clearance was obtained from the institutional ethics committee (Decision No: 516, dated 21.06.2017). Clinical data were retrospectively collected from the electronic health information system and archived records of patients who presented to the internal medicine and diabetes outpatient clinics of Haseki Training and Research Hospital between June 1, 2012, and June 1, 2017.

A total of 229 individuals who met the inclusion criteria were included in the study. Participants were required to be at least 18 years old and have a confirmed diagnosis of T2DM. Patients were excluded if they had gestational or type 1 diabetes, malignancy, recent trauma or surgical intervention within the past three months, end-stage renal disease requiring dialysis, congestive heart failure, use of non-invasive ventilation for

chronic obstructive pulmonary disease (COPD), systemic rheumatologic diseases with organ involvement, or ongoing infectious conditions.

Statistical Analysis

Categorical data were expressed as frequencies and percentages, whereas continuous variables were summarized using descriptive statistics, including mean, standard deviation, median, minimum, and maximum values. As the numerical data did not meet the assumptions of normal distribution, comparisons between two independent groups were performed using the Mann-Whitney U test. All statistical analyses were conducted using IBM Statistical Package for Social Sciences (SPSS) program version 23.0 for Windows,

and a p-value of less than 0.05 was considered statistically significant.

Results

A total of 229 patients were enrolled in the study, of whom 121 (52.8%) were female. The participants had a mean age of 56.7 years, ranging from 36 to 79. The average disease duration was 11.5 years, and the mean age at diagnosis was 45.1 years. Regarding antidiabetic therapy, 16 patients (7%) used insulin exclusively, 86 (37.6%) used oral antidiabetic agents (OAD) alone, and 127 (55.5%) used a combination of insulin and OAD. Detailed demographic and clinical characteristics are presented in Table 1.

The average HbA1c level among the study population was 8.1%, and the mean fasting blood glucose (FBG) concentration was 172.1 mg/dL. A comprehensive overview of the laboratory findings is provided in Table 2. In terms of microvascular complications, diabetic neuropathy was observed in 98 patients (42%), diabetic retinopathy (DRP) in 66 patients (28%), and diabetic nephropathy in 79 patients (34.5%). The median monocyte-to-HDL cholesterol (MHR) ratio was calculated as 0.013. Hematological indices and associated data are detailed in Table 3.

Table 1. Baseline demographic, anthropometric, and clinical characteristics of the study population

	N	%
Gender		
Female	121	52.8
Male	108	47.2
Mean Age \pm SD		56.7 \pm 8.1 (36–79)
Height (cm) \pm SD		163.5 \pm 9.3 (135–190)
Weight (kg) \pm SD		82.8 \pm 15.6 (50–130)
BMI \pm SD		31.0 \pm 5.8 (20.1–55.4)
Duration of Diabetes (years) \pm SD	11.5 \pm 7.4 (1–40)	
Age at Diagnosis \pm SD	45.1 \pm 8.3 (24–72)	
Medication Usage		
Insulin	16	7.0
OAD	86	37.6
Insulin + OAD	127	55.5
Comorbidities		
Hypertension (HT)	133	58.1
Chronic Kidney Disease (CKD)	18	7.9
Asthma	17	7.4
COPD	3	1.3
Hyperlipidemia (HL)	140	61.1
Coronary Artery Disease (CAD)	67	29.3
Congestive Heart Failure (CHF)	5	2.2
Rheumatologic Disease	2	0.9
Family History	161	70.3

BMI: body-mass index; OAD: oral antidiabetic drugs; HT: hypertension; CKD: chronic kidney disease; COPD: chronic obstructive pulmonary disease; HL: hyperlipidemia; CAD: coronary artery disease; CHF: congestive heart failure.

Table 2. Biochemical and hematological parameters of the study population

	Mean \pm SD	Min-Max	Median
HbA1 c (%)	8.1 \pm 1.6	5.4–13.2	7.9
FBG (mg/dL)	172.1 \pm 60.3	56–419	158
Urea (mg/dL)	36.4 \pm 20.7	12.9–208	32.2
Creatinine (mg/dL)	0.84 \pm 0.39	0.34–3.6	0.78
CRP (mg/L)	8.36 \pm 14.02	0.4–118.8	4.04
Albumin (g/dL)	4.19 \pm 0.36	2.9–5.1	4.20
Total Cholesterol (mg/dL)	188.6 \pm 40.0	87–326	186
Triglycerides (mg/dL)	193.7 \pm 106.0	58–754	167
LDL-C (mg/dL)	108.6 \pm 33.6	10–233	109
HDL-C (mg/dL)	43.8 \pm 11.0	7–112	42
WBC ($\times 10^3/\mu\text{L}$)	8.25 \pm 2.08	2.4–16.4	7.96
Neutrophils ($\times 10^3/\mu\text{L}$)	4.77 \pm 1.59	0.82–12.86	4.51
Lymphocytes ($\times 10^3/\mu\text{L}$)	2.62 \pm 0.85	0.64–6.55	2.54
Monocytes ($\times 10^3/\mu\text{L}$)	0.77 \pm 2.38	0.19–36	0.57
HGB (g/dL)	13.3 \pm 1.7	7.4–18.5	13.3
HCT (%)	39.8 \pm 5.1	4.1–52.6	40
PLT ($\times 10^3/\mu\text{L}$)	272057.5 \pm 72405.5	39000–556000	263500
Monocyte/HDL-C ratio	0.018 \pm 0.048	0.000–0.735	0.013

FBG: fasting blood glucose; T. Cholesterol: total cholesterol; TG: triglycerides; LDL-C: low-density lipoprotein cholesterol; HDL-C: high-density lipoprotein cholesterol.

Table 3. Comparison of monocyte-to-HDL cholesterol ratio according to microvascular complications in patients with diabetes

	Monocyte/HDL		P
	Mean \pm SD	Median	
DRP			0.015
Present	0.014 \pm 0.011	0.013	
Absent	0.019 \pm 0.057	0.013	
Neuropathy			0.124
Present	0.015 \pm 0.010	0.013	
Absent	0.020 \pm 0.063	0.013	
Nephropathy			<0.001
Present	0.183 \pm 0.059	0.016	
Absent	0.150 \pm 0.008	0.012	

The analysis demonstrated statistically significant differences in MHR values between individuals with and without diabetic retinopathy ($p=0.015$) and between those with and without diabetic nephropathy ($p < 0.001$). In contrast, no meaningful difference in MHR levels was observed when comparing patients with and without diabetic neuropathy ($p=0.124$).

Discussion

Individuals with diabetes are at increased risk for developing various microvascular complications, including diabetic retinopathy (DR)—a leading cause of vision impairment—diabetic nephropathy (DN), which is the most frequent driver of end-stage renal failure, and diabetic peripheral neuropathy (DPN). These complications play a substantial role in elevating both morbidity and mortality rates in the diabetic population. In 2015, the global prevalence of diabetes was estimated at 415 million cases, and forecasts indicate that this number may escalate by 55%, reaching around 642 million by 2040 (2,4). This suggests that the disease will bring a substantial global financial and humanitarian burden.

Reliable risk prediction models for assessing morbidity and mortality in diabetes should be practical, cost-effective, and clinically applicable. However, real-world data show that even evidence-based treatments such as statins are not sufficiently prescribed or adhered to (14). This highlights the limitations of relying solely on conventional lipid parameters for risk prediction, thereby supporting the evaluation of alternative markers such as MHR. Emerging biomarkers are vital for optimizing disease management. Their inclusion in risk models helps anticipate complications effectively.

A review of existing literature indicates that MHR has emerged as a valuable biomarker in clinical conditions characterized by increased intracellular oxidative stress, such as coronary artery disease and atherosclerosis. It is widely regarded as a surrogate marker reflecting both oxidative burden and endothelial dysfunction. Nevertheless, investigations into the relevance of MHR in diabetes, particularly in relation to microvascular complications, remain relatively scarce. In light of this, our study aimed to examine the relationship between MHR and specific microvascular outcomes—namely retinopathy, nephropathy, and neuropathy—in individuals with T2DM.

Diabetic retinopathy (DR) represents the most common preventable cause of vision loss and blindness among adults. The risk of developing DR rises proportionally with the length of time a person has lived with diabetes (15). Several studies have investigated the association between MHR and diabetic retinopathy. For example, Erdem et al. demonstrated a statistically significant correlation between elevated MHR values and the presence of retinopathy in a sample of 118 patients with diabetes. In a larger cohort of 771 individuals, Tang et al. reported similar findings, reinforcing the potential relevance of MHR in diabetic eye disease (16,17).

In a multicenter study involving 14 different institutions and a total of 2,362 diabetic patients, Ahmet TAŞ and colleagues reported a diabetic retinopathy prevalence rate of 30.5% (18). Within our study population, diabetic retinopathy (DR) was diagnosed in 66 of the 229 participants, corresponding to a prevalence of 28.8%. This rate is consistent with previously published data.

Diabetic nephropathy is the foremost contributor to end-stage renal disease (ESRD) and constitutes a significant public health concern, primarily because of its strong association with increased mortality rates (19). It is estimated that between 30% and 35% of patients with T2DM eventually develop diabetic nephropathy over the course of their illness (20). In our cohort, diabetic nephropathy was diagnosed in 79 out of 229 patients, yielding a prevalence rate of 34.5%. This proportion is largely consistent with data reported in earlier studies. Importantly, Karataş et al. and Xu et al. have also highlighted the potential of the monocyte-to-HDL cholesterol ratio (MHR) as a predictive biomarker for identifying individuals at risk for diabetic nephropathy (21,22). Our results revealed a significant correlation between elevated MHR levels and the occurrence of both diabetic

nephropathy and retinopathy. The shared pathophysiological mechanisms by which chronic hyperglycemia leads to these microvascular complications appear to overlap considerably. Both disorders are strongly associated with oxidative stress and inflammation, which are well-recognized drivers in their pathogenesis (23). This may explain why both complications are similarly associated with MHR.

Diabetic neuropathy, unlike other causes of peripheral nerve injury, can develop during both the clinical and subclinical phases of DM and is defined by damage to peripheral nerves (24). Previous studies have indicated that the prevalence of diabetic neuropathy varies widely, with reported rates ranging from 5% to 60% across different populations (25). In our study, diabetic neuropathy was detected in 98 patients, representing 42.8% of all participants.

In contrast to other microvascular complications, our analysis did not reveal a significant association between MHR and diabetic neuropathy. To the best of our knowledge, only one prior study conducted in Türkiye involving diabetic patients has similarly reported an absence of correlation between MHR and neuropathy (26). The pathogenesis of diabetic neuropathy results from a multifaceted interaction among metabolic, vascular, genetic, immunological, and neurotrophic factors. While metabolic and vascular disturbances are widely regarded as the primary contributors, growing evidence from recent preclinical studies has drawn attention to the potential influence of immune mechanisms and neurotrophic signaling pathways (25,27). Neuroinflammation, a pivotal mechanism in the pathogenesis of diabetic neuropathy, is influenced by systemic inflammatory activity but proceeds via distinct cellular pathways that may diminish the effects of circulating inflammatory mediators (24). The absence of a significant relationship between MHR and neuropathy in our study could be explained by the multifactorial nature of neuropathy, involving diverse mechanisms beyond systemic inflammation.

This study is not without limitations. As a retrospective, single-center analysis with a relatively limited sample size, generalizability may be restricted. Despite careful participant selection, various confounding factors can influence laboratory measurements. Nonetheless, a major strength of the study is the simultaneous evaluation of all major microvascular complications within a uniform patient cohort, allowing for a comprehensive comparative analysis.

Conclusion

In this study, a statistically significant association was observed between MHR and both diabetic nephropathy and retinopathy, whereas no meaningful correlation was found with neuropathy. These findings suggest that MHR—a readily accessible marker derived from routine laboratory parameters—may hold promise as a predictive tool for certain microvascular complications in individuals with T2DM.

The monocyte-to-HDL cholesterol ratio (MHR) is a practical, cost-effective biomarker that can be easily calculated from routine blood tests, making it accessible across diverse clinical settings. Its significant association with diabetic nephropathy and retinopathy highlights its potential for risk stratification, enabling clinicians to identify high-risk patients early and tailor therapeutic interventions accordingly. By integrating MHR into clinical practice, healthcare providers may enhance their ability to predict and manage these complications, ultimately improving patient outcomes.

Future prospective studies are warranted to more clearly define the prognostic significance and practical applicability of MHR in diabetic care.

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