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EVALUATION OF MONOCYTE TO HIGH-DENSITY LIPOPROTEIN CHOLESTEROL RATIO AS A PREDICTIVE MARKER OF DIABETES MELLITUS SEVERITY IN OLDER PATIENTS

MONOSİT/YÜKSEK YOĞUNLUKLU LİPOPROTEİN KOLESTEROL ORANININ YAŞLI HASTALARDA DİYABETİN ŞİDDETİNİN PREDİKTİF BİR BELİRTECİ OLARAK DEĞERLENDİRİLMESİ

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ABSTRACT

Objective: Diabetes mellitus (DM) is a disease characterized by chronic hyperglycemia and inflammation, the frequency of which increases with age. The monocyte to high-density lipoprotein cholesterol ratio (MHR) is a recently emerging inflammatory biomarker associated with various diseases. We aimed to investigate the utility of the MHR as a clinically useful inflammation-based marker in determining the severity of DM in older patients.

Material and Method: We designed our study in a retrospective, cross-sectional structure. The participants were assessed for eligibility from the population aged over 60 years of diabetic patients who were admitted to the Istanbul Medipol University Hospital endocrinology outpatient clinic between September 1st 2022, and March 1st, 2023. Data were collected from electronic medical records. Age, gender, and laboratory findings were recorded.

Result: Overall, 148 older participants (70 females, 78 males, mean age 69.17±5.74 years) were included in the analysis. MHR, white blood cell, neutrophil, lymphocyte, and monocyte counts were higher, while high-density lipoprotein cholesterol (HDL-C) levels were lower in patients with inadequate glycemic control (HbA1c≥7%) (p<0.001, for both of them). There was a moderately

ÖZET

Amaç: Diabetes mellitus (DM), sıklığı yaşla birlikte artan, kronik hiperglisemi ve inflamasyon ile karakterize bir hastalıktır. Monosit/yüksek yoğunluklu lipoprotein kolesterol oranı (MHR), çeşitli hastalıklarla ilişkili, son zamanlarda ortaya çıkan inflamatuar bir biyobelirteçtir. Yaşlı hastalarda DM'nin ciddiyetini belirlemede inflamasyona dayalı bir belirteç olan MHR'nin kullanımının faydasını araştırmayı amaçladık.

Gereç ve Yöntem: Çalışmamızı retrospektif, kesitsel bir yapıda tasarladık. Araştırmanın populasyonu oluşturmak için, 01 Eylül 2022 - 01 Mart 2023 tarihleri arasında İstanbul Medipol Üniversitesi Hastanesi endokrinoloji polikliniğine başvuran 60 yaş üstü diyabetik hastalar uygunluk açısından değerlendirildi. Veriler elektronik tıbbi kayıtlardan toplandı. Yaş, cinsiyet ve laboratuvar bulguları kaydedildi.

Bulgular: Toplam 148 yaşlı katılımcı (70 kadın, 78 erkek, ortalama yaş 69,17±5,74 yıl) analize dahil edildi. Yetersiz glisemik kontrolü olan hastalarda (HbA1c ≥%7) MHR, lökosit, nötrofil, lenfosit, monosit sayıları daha yüksek iken, yüksek yoğunluklu lipoprotein kolesterol (HDL-C) düzeyleri daha düşük saptandı (p<0,001, her ikisi için de). HbA1c ve MHR arasında orta derecede güçlü bir korelasyon vardı (r=0,611, p<0,001). Düşük HDL-K ((OR=0,88, (%95

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strong correlation between HbA1c and MHR (r=0.611, p<0.001). Lower HDL-C ((OR=0.88, (95% CI:0.82–0.94), p< 0.001) (Model 1)) and higher MHR ((OR:1.45, 95% CI:1.27-1.65, p<0.001) (Model 4)) were independently associated with increased HbA1c.

Conclusion: HDL-C and MHR were independent factors in predicting an increased HbA1c in older diabetic patients. Lower HDL-C levels had a more significant role in the severity of predicting increased HbA1c compared to the monocyte counts.

Keywords: Monocyte to high-density lipoprotein cholesterol ratio, inflammation, diabetes mellitus, HbA1c, older patient

CI:0,82-0,94), p<0,001) (Model 1)) ve yüksek MHR ((OR:1,45, %95 CI:1,27-1,65, p<0,001) (Model 4)) bağımsız olarak yüksek HbA1c değerleri ile ilişkili bulundu.

Sonuç: HDL-c ve MHR, diyabetik yaşlı hastalarda artmış HbA1c' yi öngörmede bağımsız faktörlerdi. Düşük HDL kolesterol düzeyleri, monosit sayılarına kıyasla artmış HbA1c'yi öngörme şiddetinde daha anlamlı bir role sahipti.

Anahtar Kelimeler: Monosit/yüksek yoğunluklu lipoprotein oranı, inflamasyon, diabetes mellitus, HbA1c, yaşlı hasta

INTRODUCTION

As a result of the prolonged average life expectancy worldwide, the world population is aging. As a natural consequence of extending life, comorbidities are increasing rapidly and becoming a challenge for older adults (1). Diabetes mellitus (DM) is a chronic metabolic disorder that threatens human health all over the world, and its frequency increases with age. This insidious disease is characterized by chronic hyperglycemia, multi-organ dysfunction, and systemic complications, the main causes of increased diabetes-related morbidity and mortality rates. The prevalence of DM between 20-79 years of age is estimated to be 10.5% (536.6 million people) in 2021, increasing to 12.2% (783.2 million) in 2045. The highest prevalence of diabetes was between the ages of 75 and 79 (2). It is emerging as a public health problem, especially in developing countries (3). Diabetes is a disease that requires early intervention, not only because it negatively affects public health but also because managing diabetes and its complications is responsible for the significant increase in healthcare costs (4). Inadequate glycemic control is an important factor affecting the health status of the patients, causing mortality (5). Chronic hyperglycemia related to end-stage organ dysfunctions. (6). Therefore, pathological knowledge about factors in the development and homeostasis of the disease is critical for preventing and controlling it.

The pathophysiology of DM is complex and multifactorial. There are non-modifiable risk factors, including aging and genetic predispositions, and modifiable risk factors, such as physical exercise, diet, and smoking, as a determinant of blood glucose regulation (7). However, inflammation is the main pathological event in the development of DM and its associated complications (8). In particular, these inflammatory biomarkers, secreted from adipocytes, are associated with DM incidence and progression, as well as significant complications and cardiovascular events (9, 10).

Diabetes mellitus is a metabolic disorder whose etiopathogenesis is based on chronic inflammation. It has been associated with various peptide hormones synthesized in many tissues, complete blood count parameters, and their ratios. Monocytes interact mainly with platelets and endothelial cells, causing the exacerbation of the inflammatory and pro-thrombotic pathways (11). Furthermore, high-density lipoprotein cholesterol (HDL-C) particles are dynamically modified by altering lipid and protein content, both structurally and functionally, in response to physiological, pathological, and acute inflammatory conditions. Unlike monocytes with inflammatory and pro-oxidant effects, HDL-C protects endothelial cells from inflammation and oxidative stress by controlling monocyte activation and the migration of macrophages. Although HDL-C has an anti-inflammatory effect in healthy individuals, in case of severe inflammation, the components of HDL-C change, turning it into a dysfunctional, pro-inflammatory particle that cannot perform its normal anti-inflammatory, atheroprotective, and anti-oxidative functions (12). Based on this information, researchers have investigated a new marker of systemic inflammatory response, the monocyte to HDL-C ratio (MHR), obtained by dividing the monocyte count by the HDL-C value. Previous studies have demonstrated that both a high monocyte count and a low HDL-C level are associated with inflammation and oxidative stress. MHR is a useful parameter in predicting patients' clinical course and prognosis in various inflammatory and cardiovascular diseases (12-14). However, to our knowledge, no studies have investigated the utility of the MHR as a clinically useful inflammation-based marker in determining the severity of DM in older patients. In light of the current information, this study was planned to explore whether MHR is a predictive marker for assessing the severity of diabetes in the older diabetic patient group.

MATERIALS and METHODS

We designed our study in a retrospective, cross-sectional structure. The participants were assessed for eligibility from the population aged over 60 of previously diagnosed diabetic patients who were admitted to the Istanbul Medipol University Hospital endocrinology outpatient clinic between September 1st 2022, and March 1st

2023. The diagnosis of diabetes mellitus was identified according to the American Diabetes Association criteria: fasting plasma glucose≥126 mg/dL, or randomly plasma glucose≥200 mg/dL with suspected diabetes-related symptoms, or 2nd-hour plasma glucose ≥200 mg/dL with 75 g oral glucose tolerance test, or HbA1C value ≥%6.5. Some exclusion criteria were determined for the study. Patients with a clinical diagnosis of malignancy, inflammatory disease, autoimmune disease, anemia, hematologic disease, severe complications of type 2 diabetes, hepatic and renal failure, steroid usage, and receiving lipid-lowering therapy were excluded. After exclusion, a total of 148 participants were analyzed. Data were collected from electronic medical records. Age, gender, and laboratory finding were recorded. Evaluated venous blood parameters were taken in the morning after all participants had fasted for 8-10 hours. The complete blood count, fasting plasma glucose, and biochemistry parameters, including lipids, were assessed. Given that the current guidelines from the American Diabetes Association and Association of Clinical Endocrinologists recommends an HbA1c level of <7.0% as the treatment goal for older adults with intact cognitive and functional status, we divided into two categories the patients according to HbA1c values (below and above 7%) and examined. MHR was calculated by monocyte counts ($\times 10^9$/l)/HDL-C (mg/dL). Informed consent was obtained from all participants. Ethical committee approval for this study was obtained from the ethics committee of Istanbul Medipol University Hospital (Date: 20.03.2023, No: 265).

Statistical analysis

Statistical Package (SPSS for Windows, version 21.0; IBM Corp. Armonk, NY, USA) was used for data analysis. Descriptive statistics were given as mean and standard deviation (SD) for continuous variables, counts and percentages for categorical variables, and median and Interquartile range (IQR) for do not have normal distribution variables. The chi-square test was performed for categorical variables. The groups were compared by Student's t-test when the data was with a normal distribution and by The Mann–Whitney U-test when the data has a non-normal distribution. A Pearson correlation analysis was performed for Hba1c, age and associated laboratory parameters. Values determined to interpret the correlation's power were, for values of r, 0.00-0.29 is regarded as weak, 0.30-0.69 as moderate, 0.70-0.99 as strong, and 1.00 as a perfect linear relationship. Logistic regression analysis was applied to determine the factors related to the HbA1c level. Values of $p<0.05$ were accepted as statistically significant.

RESULTS

Overall, 148 older participants (70 females, 78 males) were analyzed. The mean age of patients was 69.17±5.74. Patients were divided into groups according to their HbA1c values.

The baseline clinical characteristics and laboratory findings of the patients according to the HbA1c value are given in Table 1. The mean white blood cell (WBC), neutrophil, lymphocyte, and monocyte counts were significantly higher in patients with inadequate glycemic control (HbA1c ≥7%) ($p<0.001$, for both of them). Moreover, the mean eosinophil, basophil, and mean platelet volume (MPV) values significantly differed between groups ($p=0.027$, 0.002, 0.002, 0.015, respectively).

Within the biochemistry parameters, glucose was significantly higher, as expected in patients with inadequate glycemic control ($p<0.001$). HDL levels were lower ($p<0.001$), and creatinine were higher ($p=0.004$) in patients with HbA1c≥7%. Monocyte to HDL-C ratio was higher in patients with the T2DM inadequately controlled ($p<0.001$).

The correlation analysis between HbA1c, MHR, and associated laboratory parameters is given in Table 2. There was a moderate correlation between HbA1c and MHR ($r=0.611$, $p<0.001$), HbA1c and monocyte counts ($r=0.458$, $p<0.001$). A negative correlation was found between Hba1c and HDL-C ($r=-0.624$, $p<0.001$). MHR was correlated with glucose, creatinine, WBC, hemoglobin, neutrophil, lymphocyte, monocyte, basophil, and platelet counts. A negative correlation was found between MHR and HDL-C ($r=-0.868$, $p<0.001$), MHR and total cholesterol ($r=-0.162$, $p=0.049$) levels.

Moreover, we performed multivariate regression analysis to predict an increased HbA1c in older diabetic patients in Table 3. We found that lower HDL-C was independently associated with increased HbA1c in all models (OR=0.88, (95% CI:0.82–0.94), $p<0.001$) (Model 1), (OR=0.87, (95% CI:0.82–0.93), $p<0.001$) (Model 2), (OR=0.84, (95% CI:0.80–0.89), $p<0.001$) (Model 3). Neutrophil (OR:1.60, 95% CI:1.09-2.33, p:0.017) and lymphocyte (OR:2.47, 95% CI:1.01-6.04, p:0.047) were independently related to predicting factors for an increased HbA1c in older diabetic patients, in Model 3. When MHR was included in the model, only MHR remained to be an independent determinant of predicting an increased HbA1c (OR:1.45, 95% CI:1.27-1.65, $p<0.001$) (Model 4).

DISCUSSION

This study demonstrated a strong association and moderately strong correlation between MHR and HbA1c in older diabetic patients. In other words, older adults with poorly controlled diabetes, revealed a higher MHR than patients with controlled diabetes.

White blood cells (WBC), additionally, leukocyte subtypes were detected to be robustly associated with HbA1c levels. Moreover, monocyte, WBC, neutrophil, lymphocyte, eosinophil, and basophil counts were higher in T2DM

Table 1: The clinical characteristics and laboratory findings of the patients according to the Hba1c value

Characteristics	Hba1c < 7 (n=73)	Hba1c ≥ 7 (n=75)	P value
Age (years), mean±SD	68.86±5.62	69.47±5.79	0.520
Gender, n (%)			
Female	40 (55%)	30 (40%)	
Male	33 (45%)	45 (60%)	0.071
Hemoglobin (g/dL), mean±SD	13.28±1.45	13.70±1.24	0.062
WBC (10^9/L), mean±SD	6.22±1.63	7.78±1.74	**<0.001**
Neutrophil (10^9/L), mean±SD	3.69±1.38	4.71±1.40	**<0.001**
Lymphocyte (10^9/L), mean±SD	1.97±0.48	2.34±0.54	**<0.001**
Monocyte (10^9/L), mean±SD	0.37±0.11	0.53±0.11	**<0.001**
Eosinophil (10^9/L), mean±SD	0.16±0.10	0.20±0.14	**0.027**
Basophil (10^9/L), mean±SD	0.03±0.02	0.04±0.02	**0.002**
Platelet (10^9/L), mean±SD	259.92±61.74	280.55±65.46	0.076
MPV (fL), mean±SD	10.46±1.21	10.02±0.95	**0.015**
Glucose (mg/dL), mean±SD	99.82±23.31	136.72±45.70	**<0.001**
Urea (mg/dL), mean±SD	27.11±8.19	28.44±5.82	0.256
Creatinine (mg/dL), mean±SD	0.75±0.14	0.82±0.14	**0.004**
ALT (U/L), median (IQR 25-75)	17.00 (13.00-25.50)	20.00 (17.00-36.00)	0.052
AST (U/L), median (IQR 25-75)	17.00 (14.00-20.50)	21.00 (16.00-23.00)	0.186
Total Cholesterol (mg/dL), mean±SD	199.64±42.44	197.08±47.24	0.729
HDL-C (mg/dL), mean±SD	50.40±6.89	38.26±8.53	**<0.001**
LDL-C (mg/dL), mean±SD	121.97±36.99	125.41±41.79	0.597
Triglycerides (mg/dL), median (IQR 25-75)	98.00 (65.70-122.00)	102.00 (68.00-170.00)	0.088
MHR, median (IQR 25-75)	6.84 (5.71-8.21)	14.32 (10.70-18.10)	**<0.001**

WBC: White blood count, MPV: Mean Platelet Volume, ALT: Alanine aminotransferase, AST: Aspartate aminotransferase, HDL-C: High-density lipoprotein cholesterol, LDL-c: Low-density lipoprotein-cholesterol, MHR: Monocyt-to-HDL cholesterol ratio, SD: Standard deviation, IQR: Interquartile range, Significant p values are bolded. P<0.05 was considered statistically significant

patients with poor glycemic control than in controlled diabetes. In addition, WBC, neutrophil, lymphocyte, and monocyte counts were correlated with increased HbA1c levels. Based on all the scientific data mentioned above, we hypothesized that full blood count parameters indices as a practical way of evaluating diabetes regulation and complication risk in older diabetic patients.

Many of the components in the blood cell are related to the inflammatory process. Circulating monocytes affect platelets and endothelial cells, causing aggravation, thrombosis, and inflammation. In atherosclerosis, low density lipoprotein cholesterol (LDL-C) is captured by macrophages leaving circulating monocytes, thereby forming plaques. The circulating monocytes are decisive in new plaque formation and atherosclerosis progression (11, 15). Therefore, monocytes are essential in managing diabetes and coping with its complications (16). Some studies have highlighted these associations, especially with diabetic micro and macrovascular complications (17-20). HDL-C prevents macrophage migration and LDL-C oxidation and blocks the effects of monocytes. HDL-C promotes Cholesterol efflux from macrophages, inactivates vascular adhesion in endothelial cells, and prevents the development of atherosclerosis; thus, it has an anti-inflammatory effect (21). In our study, HDL-C levels were lower and negatively correlated in our diabetic patients with inappropriate glycemic control. Higher monocyte counts and lower HDL-C levels are signs of inflammation. Moreover, it is well-known that diabetes is a part of inflammation (22).

MHR is a novel and valuable inflammatory biomarker with a routine blood test. MHR has been identified as a reliable marker for cardiovascular diseases (23). In patients with diabetic nephropathy, MHR was found to be a convenient predictive biomarker by detecting simple blood tests (13, 14). Chen WJ et al. suggested that a higher

Table 2: Correlation analysis between Hba1c, MHR and associated laboratory parameters

	Hba1c		MHR	
	r	p	r	p
Age	0.007	0.936	0.141	0.087
Glucose	**0.634**	**<0.001**	**0.469**	**<0.001**
Urea	0.149	0.070	0.043	0.607
Creatinine	**0.229**	**0.005**	**0.277**	**0.001**
ALT	0.066	0.428	0.002	0.979
AST	0.146	0.076	0.013	0.871
Total Cholesterol	-0.088	0.288	**-0.162**	**0.049**
Triglycerides	0.114	0.167	0.061	0.463
HDL-C	**-0.624**	**<0.001**	**-0.868**	**<0.001**
LDL-C	-0.067	0.419	-0.115	0.164
WBC	**0.298**	**<0.001**	**0.478**	**<0.001**
Hemoglobin	0.047	0.569	**0.194**	**0.018**
Neutrophil	**0.228**	**0.005**	**0.392**	**<0.001**
Lymphocyte	**0.290**	**<0.001**	**0.350**	**<0.001**
Monocyte	**0.458**	**<0.001**	**0.891**	**<0.001**
Eosinophil	0.098	0.234	0.102	0.216
Basophil	0.136	0.099	**0.217**	**0.008**
Platelet	0.082	0.321	**0.209**	**0.011**
MPV	**-0.191**	**0.020**	**-0.268**	**0.001**
MHR	**0.611**	**<0.001**	-	-

ALT: Alanine aminotransferase, AST: Aspartate aminotransferase, HDL-C: High-density lipoprotein cholesterol, LDL-C: Low-density lipoprotein-cholesterol, Wbc: White blood count, MPV: Mean Platelet Volume, MHR: Monocyt-to-HDL cholesterol ratio. Significant p values are bolded. P<0.05 was considered statistically significant

MHR value is influential in prescribing the existence and progression of carotid atherosclerosis in diabetic patients (24). A study found that WBC, neutrophil, and lymphocyte counts were higher in diabetic patients with inadequate control and correlated with cardio-metabolic risk factors (25). You S et al. revealed that MHR was associated with an increased risk of disability or death at discharge in patients with acute cerebrovascular events (26). Another study found MHR to significantly predict high thrombus burden in patients with acute coronary syndrome (27). MHR represents independent variables for predicting patients with cardiovascular risk factors such as diabetes mellitus, hypertension, dyslipidemia, and older age (28).

In this study, a significant correlation was found between higher MHR values with the increase of values in many of the components in the blood cells, including WBC, neutrophil, lymphocyte, monocyte, basophil, hemoglobin, and platelet. We found that HDL-C and MHR were independent factors for predicting an increased HbA1c in older diabetic patients. Conspicuously lower HDL-C was independently associated with higher Hba1c values in all models. Furthermore, in Models 1 and 2, we performed the regression analysis to determine whether HDL-C or monocyte was the predictor of increased HbA1c in older diabetic patients. We showed that lower HDL-C had a more significant role in the severity of predicting increased HbA1c.

We conducted the study in a single center with a relatively small sample, which can be considered the major limitation of our study. Another limitation is the lack of adequate assessment of the effect of exercise and smoking on HDL-C value due to the study's retrospective nature. However, this study may inspire future studies in which the impact of exercise and smoking will also be evaluated. Although the cause-and-effect relationship can not be inferred from the study, it is noteworthy that we focused on the value of interesting blood cell parameters predicting increased HbA1c in older diabetic patients.

Table 3: Multivariate regression analysis for predicting an increased HbA1c in older diabetic patients

	Odds Ratio (95% CI)	p-value
Model 1		
HDL-C	**0.88 (0.82-0.94)**	**<0.001**
Neutrophil	1.37 (0.91-2.07)	0.131
Lymphocyte	1.74 (0.69-4.38)	0.237
Monocyte	143.43 (0.80-25602.11)	0.060
Mean platelet volume	0.96 (0.62-1.50)	0.871
Model 2		
HDL-C	**0.87 (0.82-0.93)**	**<0.001**
Neutrophil	1.37 (0.91-2.06)	0.133
Lymphocyte	1.75 (0.70-4.39)	0.234
Monocyte	143.43 (0.87-26014.76)	0.057
Model 3		
HDL-C	**0.84 (0.80-0.89)**	**<0.001**
Neutrophil	**1.60 (1.09-2.33)**	**0.017**
Lymphocyte	**2.47 (1.01-6.04)**	**0.047**
Model 4		
MHR	**1.45 (1.27-1.65)**	**<0.001**
Neutrophil	1.25 (0.85-1.83)	0.255
Lymphocyte	1.59 (0.69-3.68)	0.277

HDL-C: High-density lipoprotein cholesterol, MHR: Monocyt-to-HDL cholesterol ratio. Significant p values are bolded. p<0.05 was considered statistically significant.

CONCLUSION

A strong association and moderately strong correlation were detected between increased MHR values and HbA1c levels, as well as an increase in various components of blood cells, including WBC, neutrophil, lymphocyte, monocyte, basophil, hemoglobin, and platelet in older patient with poorly controlled DM. HDL-C and MHR were identified as independent factors for predicting increased HbA1c in older diabetic patients. Lower levels of HDL-C played a more significant role in predicting the severity of increased HbA1c compared to monocyte counts. In conclusion, MHR can help predict the severity of diabetes in older patients. Therefore, this parameter can serve as a clinically useful and potentially predictive inflammation-based marker for identifying patients with uncontrolled blood glucose who are at higher risk of complications related to DM.

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Ethics Committee Approval: This study was approved by Istanbul Medipol University Non-Interventional Clinical Research Ethics Committee (Date: 20.03.2023, No: 265).

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