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Monocyte to HDL ratio as an indicator of subclinical atherosclerosis in diabetic retinopathy

Diyabetik retinopatide subklinik aterosklerozun bir göstergesi olarak monosit /HDL oranı

Seyfullah Kan[1], **Adnan Karaibrahimoğlu**[2]

[1] Suleyman Demirel University, Faculty of Medicine, Department of Endocrinology and Metabolism, Isparta, Turkey.

[2] Suleyman Demirel University, Faculty of Medicine,Department of Biostatistics and Medical Informatics, Isparta, Turkey

ABSTRACT

Aim: Incidence of cardiovascular diseases is gradually increasing in patients with diabetic retinopathy (DR). MHR (Monocyte/HDL ratio), is a novel marker related to cardiovascular and cerebrovascular diseases. The aim of this study was to investigate the relationship between a subclinical atherosclerosis marker, carotid intima media thickness (CIMT), and MHR in diabetic retinopathy patients without an apparent cardiovascular disease.

Material and Method: 106 diabetic patients without an apparent cardiovascular disease and 35 healthy controls matched for age, gender and body mass index (BMI) were included in this study. The patients were separated into four groups which were proliferative diabetic retinopathy (PDR, n=30), nonproliferative diabetic retinopathy (NPDR, n=35), diabetic patients without retinopathy (n=41) and control group (n=35). Anthropometric, biochemical parameters and CIMT were measured. Correlation and regression analysis were done to assess the relation between MHR and CIMT.

Results: MHR was significantly different between groups and significantly higher in PDR group ($p<0.001$). CIMT, a marker for atherosclerosis, significantly differed between groups ($p<0.001$). CIMT levels were significantly higher in PDR while similar values were found in other than groups. In PDR group, a significant correlation was found between MHR and CIMT ($r=0.96$; $p<0.001$). According to binary logistic regression analysis, MHR had a significant effect on CIMT [β=0.206, (%95 CI: 1.004-1.505), p=0.046].

Conclusion: This study showed that in patients with diabetic retinopathy, high levels of MHR which is a non-invasive, simple and inexpensive marker, might be useful for determination of subclinical cardiovascular risk. This study which is the first in literature that investigated the relation between MHR and CIMT in diabetic retinopathy might have a benefit on early detection of cardiac risk in diabetic patients without an apparent cardiovascular disease.

Keywords: Diabetic retinopathy, subclinical atherosclerosis, monocyte to HDL ratio

ÖZ

Amaç: Diyabetik retinopatisi olan hastalarda kardiyovasküler hastalıkların artan sıklığı bilinmektedir. MHO (Monosit/HDL oranı), kardiyovasküler ve serebrovasküler hastalıklarla ilişkisi yeni saptanmış bir belirteçtir. Bu çalışmanın amacı aşikar kardiyovasküler hastalık bulgusu olmayan diyabetik retinopatisi olan hastalarda subklinik ateroskleroz risk göstergesi karotis intima media kalınlığı (KİMK) ile MHO ilşkisini araştırmaktır.

Gereç ve Yöntem: Aşikar kardiyovasküler hastalığı olmayan 106 diyabetik hasta ve 35 yaş, cinsiyet ve BMI (body mass index) ile uyumlu sağlıklı kontrol alındı. Hastalar proliferatif diyabetik retinopati (PDR, n=30), nonproliferatif diyabetik retinopati (NPDR, n=35), retinopati olmayan diyabet hastaları (n=41) ve kontrol grubu (n=35) olmak üzere dört gruba ayrıldı. Antropometrik, biyokimyasal parametreler ve KİMK ölçüldü. MHO ile KİMK arasındaki ilişkiyi değerlendirmek için korelasyon ve regresyon analizi yapıldı.

Bulgular: MHO değerleri gruplar arasında anlamlı farklılığa sahip ve PDR grubunda anlamlı düzeyde daha yüksekti ($p<0.001$). Ateroskleroz göstergesi olan KİMK gruplar arasında anlamlı farklılık gösterdi ($p<0.001$). KİMK değeri PDR grubunda anlamlı düzeyde yüksek iken diğer gruplarda birbirine yakın değerler ölçüldü. PDR grubunda MHO ile KİMK arasında önemli düzeyde anlamlı korelasyon bulundu (r=0,96; $p<0.001$). Binary logistic regression analizinde MHO'nin KİMK üzerine anlamlı etkisi bulunmaktaydı [β=0,206, (%95 CI: 1,004-1,505), p=0,046].

Sonuç: Bu çalışma, yüksek MHO'nın diyabetik retinopatisi olan hastalarda subklinik kardiyovasküler riski belirlemede non-invaziv, basit ve maliyeti düşük bir marker olarak kullanılabileceğini göstermektedir. Diyabetik retinopatide MHO ve KİMK arasındaki ilişkiyi inceleyen literatürdeki ilk çalışma olan bu çalışma, aşikar kardiyovasküler hastalık bulgusu olmayan diyabetik hastalardaki kardiyak riski erken belirlemede fayda sağlayabilir.

Anahtar Kelimeler: Diyabetik retinopati, subklinik ateroskleroz, monosit /HDL oranı

Corresponding Author: Seyfullah Kan, Süleyman Demirel Üniversitesi Tıp Fakültesi, İç Hastalıkları Anabilim Dalı, Endokrinoloji ve Metabolizma Hastalıkları Bilim Dalı, Isparta, Türkiye

E-mail: seyfullahkan76@hotmail.com

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INTRODUCTION

Besides oxidative stress and inflammation, monocyte/HDL cholesterol ratio (MHR) is recently defined as a marker related to negative cardiovascular outcomes (1). In patients with chronic renal disease, it is reported to have a relation with cardiovascular events (2) and in patients with infective endocarditis and normal left ventricular function, it is shown to be related to in-hospital and long term mortality (3).

CIMT is considered an indicator of subclinical atherosclerosis. In many studies, value of CIMT in predicting cardiac and cerebrovascular events has been proven (4,5).

In several studies, diabetic retinopathy has been reported as an independent predictor of all cause mortality and cardiovascular events in patients with type 1 and 2 diabetes (6). Many potential mechanisms including oxidative and glycemic stress, chronic inflammation and defective vascular tissue repair mechanisms are suggested to clarify the pathophysiological relation between diabetic micro- and macroangiopathy (7).

The aim of this study in patients with diabetic retinopathy and without apparent cardiovascular disease is to investigate the relationship between subclinical atherosclerosis risk factors (CIMT) and MHR as well as to assess the value of MHR as a marker in determination of cardiovascular risk.

MATERIAL AND METHOD

Selection of Cases for the Study Population

During the assessment of complications of diabetic patients who admitted to Süleyman Demirel University Endocrinology Clinic, the patients with retinopathy were included in this study. The patients were separated into four groups which were proliferative diabetic retinopathy (PDR, n=30), nonproliferative diabetic retinopathy (NPDR, n=35), diabetes without a retinopathy (n=41) and control group (n=35). Age and BMI values did not differ between groups. MHR sample size was determined due to the MHR data obtained during pilot study. Inter-group effect size was calculated as 0,40 according to mean and variance values. Sample size was calculated as 80, according to 85% potency and 5% error margin. However, to increase potency, more data (141 patients) was included in pre-determined time interval.

The patients with diseases that might cause inflammation (acute infectious diseases, rheumatic diseases, malignancies, etc), pregnancy, chronic renal disease, acute and chronic liver diseases, who were using glucocorticoid and/or nonsteroidal anti-inflammatory drugs, who smoked and who had cardiovascular diseases were excluded.

Anthropometric Measurements and Biochemical Tests

In initial assessment, systolic and diastolic blood pressures were measured in all patients; Body weights and heights were measured and body mass index was calculated (BMI: body weight (kg) /height (cm^2)). From all patients, brachial venous blood samples were taken for biochemical analysis, in the morning, after 12 hours fasting. The blood samples were analyzed for plasma fasting glucose, triglyceride (TG), total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), and high-density lipoprotein cholesterol (HDL-C). All the analyses were performed with Symex XN-1000 hematology analyzer (Sysmex Corporation, Kobe, Japan) according to manufacturer's instruction. MHR was calculated as ratio of monocyte count to HDL level.

Measurement of Carotid İntima-Media Thickness

CIMT was measured in each patient with Shimadzu (2200 X plus, Kyoto, Japan) device using a 7,5-13,5 MHz multifrequency lineer array probe. All ultrasound examinations were performed by the same investigator in a silent environment after the patient rested for 15 minutes. For carotid artery imaging, the patient stayed in supine position. Measurements were done from three different places of 1 cm distal of right and left anterior carotid artery. Mean of right and left carotid artery measurements was calculated and recorded as CIMT.

Statistical Analysis

Statistical analyses were performed by SPSS 20.0 software (IBM Inc., Chicago, IL, USA). Numerical variables were expressed as mean±SD ((median; IQR) where necessary) and the gender was expressed as frequency (percentage) in tables. Continuous variables were checked for normality by Kolmogorov-Smirnov test. Comparison of independent groups was done by One-Way ANOVA with Tukey HSD post-hoc test. The relation between numerical variables was performed by Pearson Correlation Analysis. The sample size was calculated by GPower 3.1.9.2 software. Binary logistic regression model of CIMT was created. In all analyses, $p<0.05$ was considered as statistically significant with 5% type-I error.

Ethical Declaration

This study was approved by Süleyman Demirel University Medical Faculty Ethics Committee. All patients planned to be included have been informed both verbally and written, and an informed consent was taken (Date 05/03/2019, Decision No: 32).

RESULTS

The groups did not differ for demographic features such as age (p=0.79), gender (p= 0.96) and BMI (p= 0.41). MHR calculated according to monocyte and HDL levels was significantly different between groups, and was higher in PDR group ($p<0.001$). In other groups the results were close to each other. CIMT which is an indicator of atherosclerosis significantly differed between groups ($p<.001$). CIMT was

Table 1. Patient demographics and clinical features

	PDR (n=30)	NPDR (n=35)	DM+No DR (n=41)	Control (n=35)	
	Mean±SD (median, IQR)				p
Gender Male N(%)	18 (56.3)	18 (58.1)	19 (57.6)	18 (56.3)	0.991
Female N(%)	14 (43.8)	13 (41.9)	14 (42.4)	14 (43.8)	
Age (yrs)	61.66±5.24	60.51±5.04	61.29±4.85	60.82±4.97	0.798
BMI (kg/m^2)	28.73±1.73	28.42±2.65	29.19±2.69	29.32±2.71	0.413
Body weight (kg)	79.10±5.20	78.34±6.34	79.43±5.95	80.05±5.54	0.661
Height (cm)	165.93±4.65	166.14±4.39	165.14±5.61	165.45±5.72	0.838
SBP (mmHg)	122.16±9.79	122.85±10.72	122.56±10.84	123.0±10.65	0.990
DBP (mmHg)	72.33±6.26	71.71±7.56	71.82±7.56	72.14±7.79	0.937
DM duration (years)	11.53±1.73^{a}	11.14±1.35^{b}	7.29±1.05^{a,b}	N/A	< 0.001*
Neutr (10^9/L)	6.87±0.70 ^{a,b}	5.37±0.29 ^{a,c}	4.42±0.42 ^{b,c}	4.41±0.41 ^{b,c}	< 0.001*
Lymp (10^9/L)	1.89±0.36	1.90±0.39	1.94±0.31	1.93±0.30	0.900
Mono (10^9/L)	725.0±96.26^{a,b,c}	501.42±60.83 ^{a}	503.41±57.68 ^{b}	501.42±60.83 ^{c}	< 0.001*
HDL (mg/dl)	37.63±1.69 ^{a,b,c}	48.20±1.95 ^{a}	48.19±1.90 ^{b}	48.31±2.08 ^{c}	< 0.001*
LDL (mg/dl)	132.80±34.06 ^{a,b}	133.02±28.32 ^{c,d}	111.21±21.18 ^{a,c}	110.48±20.49 ^{b,d}	< 0.001*
Cholesterol (mg/dl)	204.80±32.15	209.85±32.00	196.29±24.78	196.0±23.40	0.105
TG (mg/dl)	197.83±46.56 ^{a,b}	198.68±46.96 ^{c,d}	177.14±20.53 ^{a,c}	178.71±20.92 ^{b,d}	0.010*
Glucose (mg/dl)	182.03±52.78 ^{a,b}	181.0±48.62 ^{c,d}	87.21±9.08 ^{a,c}	87.20±9.63 ^{b,d}	< 0.001*
HbA1C (%)	8.09±1.09 ^{a,b,c}	7.93±1.10 ^{a}	7.21±0,48 ^{b}	5.35±0.31 ^{c}	< 0.001*
CRP (mg/L)	5.53±1.30 ^{a,b}	5.00±1.30 ^{c,d}	2.09±1.01 ^{a,c}	1.88±0,83 ^{b,d}	< 0.001*
CIMT (mm)	0.91±0.04^{a,b,c}	0.63±0.08^{a}	0.62±0.11^{b}	0.63±0.11^{c}	< 0.001*
Fibrinogen (g/L)	534.47±39.12 ^{a,b}	419.72±71.65 ^{c,d}	370.72±53.16 ^{a,c}	361.26±48.06 ^{b,d}	< 0.001*
MHR	19.41±3.47 ^{a,b,c}	10.46±1.65 ^{a}	10.50±1.57 ^{b}	10.44±1.66 ^{c}	< 0.001*
NLR	3.78±0.92 ^{a,b,c}	2.95±0.67 ^{a}	2.35±0.55 ^{b}	2.35±0.53 ^{c}	< 0.001*

*: significant at p< 0.05 level according to One-way ANOVA
a,b,c,d: Same superscript letters denote the significant pairwise groups

significantly high in PDR groups but similar to each other in the remaining groups (**Table 1**).

Correlation coefficients between measurements and MHR values were calculated in each group. In PDR group, there was a highly significant correlation between MHR and CIMT (r=0,96; p<.001). In addition, a low correlation was found with neutrophil (r=0,39) and a moderate correlation, with lymphocyte (r=0,53). A high and positive correlation was found between diabetes duration and MHR (r=0,62; p= 0.002) besides a significant and positive relation, with LDL (r=0.36; p= .034) and glucose (r=0.33; p= 0.047). In NPDR group, a significant relation has existed between MHR and CIMT and only a moderate positive correlation was detected with diabetes duration (R=0.51; p= .013) (**Table 2**).

In the group in which the patients had only diabetes, patients' body weight and BMI were low and positively correlated with MHR. In control group, MHR was not correlated with atherosclerotic parameters (**Figure 1**).

Figure 1. Correlation values between CIMT and MHR in DR groups

Results of CIMT measurement were divided into two groups as median below and above 0.64. The values below 0.64 were considered as reference group and a binary logistic regression model was developed. To overcome the multiple correlation problem, a model was formed with forwarding LR stepwise method and adjustment results were significant (Nagelkerke R^2=0.361; -2LL=138.99 and Hosmer-Lemeshow Chi-square=12.74 (p=.121)). Four factors affected CIMT and all of them positively contributed to the model. Contribution of fibrinogen was significant and MHR, HbA1C, and CRP had obvious contributions (**Table 3**).

DISCUSSION

Standard risk factors of cardiovascular disease (CVD) do not sufficiently explain the high cardiovascular risk in diabetes. Regarding the poor prognosis of CVD in diabetes, detection of novel subclinical atherosclerotic markers such

Table 2. Correlation values between MHR and other biochemical measures in DM and proliferation groups

MHR	PDR		NPDR		DM+No DR		Kontrol	
	r	p	r	p	r	p	r	p
NLR	-0.327	0.078	-0.038	0.827	-0.229	0.150	-0.256	0.138
SBP	-0.131	0.489	0.164	0.348	-0.038	0.815	0.011	0.949
DBP	-0.239	0.204	-0.277	0.107	-0.005	0.974	-0.041	0.813
DM Duration	0.628[R]	0.002*	0.517	0.013*	0.231	0.084	N/A	N/A
NEUT	0.397	0.030*	0.248	0.151	-0.104	0.520	-0.109	0.532
LYMP	0.532	0.002*	0.099	0.573	0.203	0.203	0.221	0.203
MONO	0.999	<0.001*	0.995	**<0.001***	0.992	<0.001*	0.996	<0.001*
HDL	-0.996	<0.001*	-0.991	**<0.001***	-0.988	<0.001*	-0.994	<0.001*
LDL	-0.112	0.556	0.359	**0.034***	-0.193	0.226	-0.257	0.135
CHOLESTEROL	-0.178	0.347	-0.241	0.164	-0.229	0.150	-0.302	0.078
TG	-0.154	0.416	-0.029	0.867	-0.037	0.817	-0.105	0.547
GLUCOSE	0.084	0.661	0.338	0.047*	0.054	0.739	0.059	0.735
HBA1C	-0.039	0.837	-0.236	0.173	-0.108	0.500	-0.083	0.634
CRP	-0.094	0.623	-0.135	0.441	-0.076	0.637	-0.171	0.326
CIMT	0.968	<0.001*	0.233	0.177	0.142	0.376	-0.404	0.016
FIBRINOGEN	-0.234	0.213	-0.155	0.375	-0.003	0.984	0.008	0.962
AGE	0.042	0.826	-0.048	0.786	0.010	0.952	-0.037	0.832
BODY WEIGHT	0.028	0.883	0.183	0.292	0.388	**0.012***	0.411	0.014*
HEIGHT	0.192	0.308	-0.096	0.585	0.004	0.982	0.034	0.848
BMI	-0.135	0.477	0.219	0.205	0.322	**0.040***	0.291	0.089

r: Pearson Correlation Coefficient ; R: Spearman's Rho Correlation Coefficient ; *: 0.05 significance level

Table 3. Binary logistic regression model presenting factors that affect CIMT

Factors	Beta	p	OR	95% CI
Fibrinogen	0.013	< 0.001*	1.013	(1.007-1.019)
MHR	0.206	0.046*	1.229	(1.004-1.505)
Age	0.598	.439		
Gender	0.006	0.936		
HbA1C	0.292	0.037*	1.356	(1.010-1.618)
CRP	0.326	0.032*	1.488	(1.116-1.734)
BMI	0.005	0.941		
NLR	1.837	0.175		

OR: Odds ratio; CI: Confidence interval; *: 0.05 significance level

as coronary artery calcium (CAC) and CIMT for early diagnosis and prevention of CVD in diabetes is important (8). Structural and functional alterations in microvascular circulation are related to cardiac, retinal and renal atherosclerosis (9,10). In type 2 diabetic patients, diabetic retinopathy as a marker of microvascular disease is suggested to be related to subclinical atherosclerosis and CVD (11).

Some previous studies showed that DR had a relation with noninvasive subclinical atherosclerotic measures such as CIMT, carotid plaque and arterial stiffness (12). In Chennai Urban Rural Epidemiology Study (CURES-2), a relation between DR and CIMT was reported (13). Jang-Won Son et al. (12), in Korean newly diagnosed type 2 diabetes patients reported that DR was an independent risk marker for subclinical atherosclerosis. Lian-Xi Li et al. (14) found retinal microvascular abnormalities related to independently increased CIMT in Chinese hospitalized patients. In our study, parallel to other studies, CIMT was high in PDR group.

As important markers for inflammatory response, WBC count and its subtypes are related to CVD (15). As well, platelet/lymphocyte ratio (PLR), monocyte/lymphocyte ratio (MLR) and neutrophil/lymphocyte ratio (NLR) are potential biomarkers of inflammatory response. In many studies, conventional inflammatory markers had positive correlation with PLR and NLR. Besides, in many studies, in especially DM patients, PLR and NLR had predictive effects on acute coronary syndrome (16,17). In addition, only one study has been performed that included MLR in diabetic retinopathy as an immune marker. (18). Our study is the only one in literature investigating the effect of MHR in diabetic retinopathy.

MHR is investigated as a novel inflammatory marker and suggested to be superior to WBC subtypes in patients with cardiovascular and cerebrovascular diseases (19,20). Monocytes are inflammatory reaction markers responsible of release of proinflammatory and prooxidant cytokins (21). Monocytes previously have been shown to be related to diabetic micro-and macrovascular complications (22).

Matsumura et al. (23) reported that monocyte amount was positively correlated with CIMT in T2DM patients. On the other hand, HDL cholesterol can decrease macrophage accumulation, prevents monocyte migration, increases nitric oxide synthase expression in endothelial tissues and has antioxidant and anti-inflammatory effects on endothelial cells (24). MHR seems like a novel and useful marker related to pro-inflammatory and anti-inflammatory processes. In our study, we showed that MHR had a significant role in PDR patients for prediction of subclinical atherosclerosis. In PDR patient group, there was a strong correlation between CIMT and MHR. Therefore, MHR might be considered a good predictor for vascular structural alteration in PDR patients. However, diabetic patients without a complication and nondiabetic patients had a moderate imbalance between pro- and anti-inflammatory mechanisms. This might be because MHR was related to CIMT in PDR group but not in other groups. Previously, Kanbay et al. (2) reported that in chronic renal disease patients, MHR behaved like an independent marker for cardiovascular events. In patients with Behçet disease, MHR was correlated with brachial artery flow-mediated dilatation (FMD) (25). All this evidence suggests that predictive value of MHR for CVD is higher in chronic inflammatory diseases such as complicated diabetes.

In literature, there are two studies that aim to evaluate MHR in ocular diseases. In the first study, Mirza et al. (26) found high MHR values in glaucoma patients. In the second one, MHR level was high in patients with retinal venous occlusion (27). Thus, our study is the first one that investigates the relation between diabetic retinopathy and MHR. In especially PDR patients, MHR might be a promising marker for cardiovascular risk.

As reported in current literature, this study had 4 major results. First of all, MHR and CIMT were significantly higher in proliferative diabetic retinopathy group. Secondly, in PDR patient group, MHR, and a subclinical atherosclerotic marker, CIMT had a very significant correlation. Thirdly, there was a significant positive correlation between classical atherosclerotic risk factor LDL and MHR, in PDR group. And lastly, MHR and diabetes duration were high and positively correlated in both PDR and NPDR groups. There was an increased cardiovascular risk in patients with diabetic retinopathy. In these patients, CIMT was an important non-invasive method to determine subclinical cardiovascular risk (6,11). Also in our study, CIMT was significantly high in PDR group. Studies suggest that NLR could be used as a marker for subclinical CVD (28). Till now, no study has investigated the relationship between diabetic retinopathy and MHR. In our study, MHR was significantly high in PDR group and was significantly correlated with subclinical cardiovascular risk marker, CIMT. According to binary logistic regression analysis, MHR had a significant effect on CIMT [β=0.206, (%95 CI: 1.004-1.505), P=0.046] (Table 3). So, MHR might be used as a non-invasive, simple and inexpensive marker on determination of subclinical cardiovascular risk in patients with diabetic retinopathy.

This study has several limitations. First of all, this is a cross sectional study; The relation between DR and early atherosclerosis is not evaluated as a cause-result relation and prospective studies are required. Secondly, in our study, though a correlation is found between MHR and CIMT, MHR effect on CIMT progression is not examined since it is a cross-sectional study. Therefore, in the future large prospective studies should be planned. Thirdly, oxidative stress, inflammation, and endothelial dysfunction have important role in pathogenesis of DR and subclinical atherosclerosis (29,30). However, in our study, lack of oxidative stress and endothelial dysfunction markers limited the relation between MHR and CIMT in PDR group. However, regression analysis showed that; hyperglycemia, inflammation (CRP, MHR), and coagulation defect (Fibrinogen) responsible for etiopathogenesis of diabetic retinopathy had also an effect on atherosclerosis (Table 3). All of these findings suggest that a common pathophysiological process might be responsible for both retinopathy and atherosclerosis for which endothelial damage might be the reason. Further studies are required to clarify this suggestion.

CONCLUSION

According to these findings and especially to the results of prospective studies, it is concluded that biomarkers of inflammation, endothelial dysfunction and coagulation might help to determine subjects that are under risk for diabetes, diabetic microangiopathy, and CVD. Although disease progression will be slowed down or delayed with most of the interventions used for diabetes treatment, future dilemma is finding new biomarkers as CRP with proven clinical diagnostic and therapeutical value. Increasing burden of diabetes demands such brand approaches.

As a conclusion, this study shows that high MHR is an appropriate and effective method to predict subclinical atherosclerosis and its progression in patients with diabetic retinopathy.

CONFLICT OF INTEREST

No conflict of interest among authors.

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