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ORIGINAL ARTICLE – OPEN ACCESS

Monocyte to High-Density Lipoprotein Ratio: A Novel Inflammation Marker Related to Diabetic Retinopathy

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ABSTRACT

Objective: The most common microvascular complication of diabetes is diabetic retinopathy (DR). A new and recently emerged marker of oxidative stress and inflammation is monocyte to high-density lipoprotein cholesterol ratio (MHR). Platelet to lymphocyte ratio (PLR) and neutrophil to lymphocyte ratio (NLR) have also been shown as they are biomarkers of systemic inflammation in various diseases. The present study aims to assess MHR, its predictive value and relations between other inflammation markers in DR patients.

Materials and Methods: Sixty-eight patients with DR, fifty-four DM patients without DR and forty-two control subjects were included in this study. Complete blood count, lipoprotein and uric acid levels were recorded. MHR was calculated.

Results: MHR, NLR and PLR were statistically significantly higher in DR group than DM without DR group (p=0.008, p=0.042, p=0.003, respectively). Then, receiver operating characteristic (ROC) curve analysis was performed and pointed that MHR predicted DR using a cut-off level of 0.0156 with 63% sensitivity and 76% specificity.

Conclusion: In this study, we investigated MHR in DR patients and its relationship with other inflammatory markers, lipoproteins and uric acid. We suggested that an elevated admission of MHR may be of benefit to detect DR and to determine the CVD risk of these patients.

Keywords: Monocyte, high-density lipoprotein cholesterol, diabetic retinopathy, inflammation.

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INTRODUCTION

Diabetes mellitus (DM) is a chronic civilisation disease. There is an increase in the number of patients with diabetes worldwide. This increase causes an increasing number of patients with diabetes complications, too. Diabetic retinopathy (DR) is the most common microvascular complication of diabetes. Globally, DR remains one of the leading reasons for adult blindness (1). There are different studies telling the prevalence of DR: approximately 17% in Asian countries and 33% in the USA (1). DR pathogenesis has not been fully elucidated, but as a widely accepted opinion, oxidative stress and inflammation play important roles. Based on data from epidemiological studies and clinical trials, there are well-accepted risk factors for the development and progression of DR, such as longer duration of diabetes, elevated blood glucose, hyperlipidemia and hypertension (2, 3). However, for DR, these conventional risk factors seem to explain only a portion (3) and other potential risk factors, such as subclinical chronic inflammation, should be evaluated (4–6).

Circulating monocytes lead to inflammation and also prothrombosis by interacting with platelets8and endothelial cells. High-density lipoprotein (HDL) inhibits the macrophages' migration, promotes the cholesterol efflux from macrophages and reduces the oxidation of the low-density lipoprotein (LDL) molecules. Thus, pro-inflammatory and pro-oxidant effects of monocytes are reduced by HDL (7, 8). Emerging evidence suggests that monocyte count to HDL cholesterol ratio (MHR) is a novel potential marker of inflammatory responses. Platelet to lymphocyte ratio (PLR) and neutrophil to lymphocyte ratio (NLR) are named as 'systemic inflammation biomarkers' in recent studies (9, 10). There are studies about the relationship between MHR and cardiovascular problems in chronic kidney disease and studies about MHR evaluation in patients with coronary artery diseases, coronary bypass and coronary angiography (11–14). However, to my knowledge, there is no research evaluating MHR levels in DR patients like ours.

The final metabolite of purine metabolism is uric acid, an oxidative stress marker. DM is a risk factor for cardiovascular diseases, and patients having a high risk of cardiovascular diseases need to be monitored concerning serum uric acid levels. Thus, the present study aimed to evaluate the associations, to our knowledge, for the first time, between DR and the MHR, PLR, NLR, lipoproteins and uric acid levels.

Table 1. Comparison of CSPH parameters between the groups in female participants

	Diabetic retinopathy group	Diabetic group without retinopathy	Control group	p
Number of subjects	68	54	42	–
Age (years)	61.51±11.22	59.30±10.13	63.42±11.83	0.360
WBC (x10^3/mm^3)	8.57±2.04	7.48±1.67	6.80±1.47	[a]0.000
Neutrophil (x10^3/mm^3)	*65.40 (59.80–70.70)	*57.15 (52.70–60.87)	*62.35 (53.77–67.77)	[b]0.000
Lymphocyte (x10^3/mm^3)	*25.10 (20.30–30.30)	*32.0 (29.0–38.10)	*63.0 (54.75–72.25)	[a]0.000
Monocyte (x10^3/mm^3)	6.35±2.37	7.15±1.82	6.95±2.27	0.113
MCV (fL)	84.77±6.70	84.50±5.70	84.51±8.53	0.097
MCH (pg)	27.68±2.38	28.27±2.59	27.64±3.34	0.061
PLT (x10^3/mm^3)	280.26±89.20	263.88±73.26	262.71±76.50	[a]0.042
MPV (fL)	10.30±1.14	10.53±0.97	10.11±1.23	0.17
PDW (fL)	*15.70 (13.10–16.20)	*12.75 (10.90–14.05)	*15.90 (15.40–16.30)	[b]0.000
RDW (fL)	*42.80 (40.70–46.0)	*40.10 (38.40–43.67)	*28.70 (27.37–29.60)	[a]0.002
MHR	0.167±0.03	0.157±0.04	0.141±0.04	[a]0.008
PLR	142.21±68.92	154.56±67.17	114.11±36.91	[b]0.003
NLR	2.84±1.06	2.64±1.03	1.86±0.67	[a]0.000; [b]0.042
Uric acid (mg/dL)	5.85±1.73	5.52±1.54	5.68±1.43	0.53
HbA1c (%)	8.74±1.60	7.97±1.75	–	[b]0.014
TC (mg/dL)	207.53±49.8	197.30±40.59	208.90±78.59	0.52
TG (mg/dL)	188.0±117.45	197.32±112.60	166.39±90.91	0.38
HDL-c (mg/dL)	47.61±10.58	44.60±8.94	48.39±12.88	0.18
LDL-c (mg/dL)	122.30±39.21	124.01±38.52	134.32±69.61	0.45

(One-way ANOVA test was applied. *Kruskal-Wallis test post hoc Mann-Whitney U test; data are median and interquartile range (25%–75%). a: Between control group versus diabetic retinopathy; b: Between diabetic retinopathy group versus diabetic group without retinopathy. P≤0.05, statisticallysignificant. NS: Non-significant

MATERIALS and METHODS

Study Population

In our study, we divided 122 Type 2 DM patients into DR (68 patients) group and non-DR group (54 patients) and also we compared them with 42 control subjects without diabetes and ocular diseases except cataract. Chronic kidney or liver problems, infection, heart failure, cardiovascular disease, cerebrovascular disease, systemic steroid therapy, hormone replacement therapy and gout were the exclusion criteria in this study.

The ethics committee of Erciyes University approved the study protocol (approval number: 2019/839). This study was performed in accordance with the Declaration of Helsinki.

Laboratory Measurements

Complete blood count, uric acid and lipid profile are routinely evaluated in subjects with diabetes. The hematological measurements were obtained using an automated blood cell counter Mindray BC-6800 (Shenzhen Mindray Biomedical Electronics, Nanshan, P.R. China). Lipoprotein and uric acid levels of patients were analyzed by Olympus AU 2700 autoanalyzer (Beckman Coulter Inc, CA, USA).

WBC, neutrophil, lymphocyte, monocyte, hemoglobin, platelet, lipoprotein, HbA1c (only for diabetic patients) and uric acid levels were recorded. Monocyte to HDL ratio (MHR) was calculated as the ratio of the percentage of monocytes divided by high-density lipoprotein (HDL) count. The following reference values were determined for WBC: 4.5–10x10^3/mm^3, neutrophil: 1.5–7.5x10^3/mm^3, lymphocyte: 0.8–3.4x10^3/mm^3, monocyte: 0–0.9x10^3/mm^3, hemoglobin: 12–17 g/dL, platelet: 150–450x10^3/mm^3, total cholesterol (TC): 0–200 mg/dL, HDL–c: 40–60 mg/dL, LDL-c: 0–135 mg/dL, triglyceride (TG): 35–150 mg/dL and uric acid: 2.6–7.2 mg/dL.

Statistical Analyses

SPSS (Statistical Package for Social Sciences Inc., Chicago, IL, USA) 23.0 program was used for statistical analysis. We expressed data as mean±SD or median [interquartile range (25%–75%)] for our continuous variable data. We compared our data of mean values by One-way ANOVA test followed by Tukey's post-hoc test for three groups. We used the Kruskal-Wallis post-hoc Mann-Whitney U test for comparison of median values of data with non-normal distribution for three groups. Spearman correlation analysis was performed to evaluate the correlations between MHR and NLR, PLR, uric acid, WBC, PDW, MPV and lipids levels. To investigate the diagnostic values of MHR, PLR, NLR, WBC and uric acid in patients with DR, we perform the receiver operating characteristic (ROC) curve analysis. P-value <0.05 was accepted as statistically significant.

RESULTS

Baseline characteristics and laboratory findings are listed in Table 1. Mean age of the patients with DR, DM without DR and the

Table 2. Spearman's correlations between MHR and NLR, PLR, uric acid, WBC, PDW, MPV, and lipids levels of DM patients' groups

	DM with DR/ without DR	
MHR	**R**	**P**
NLR	0.034/-0.066	0.781/0.635
PLR	-0.178/-0.186	0.146/0.177
Uric acid	0.174/0.212	0.167/0.124
WBC	-0.077/0.012	0.422/0.932
PDW	-0.278/0.157	[a]0.023/0.256
MPV	-0.105/0.307	0.397/0.024
TC	-0.414/-0.047	[a]<0.001/0.737
TG	-0.139/0.240	0.288/0.084
HDL-c	-0.168/-0.560	0.170/0.000
LDL-c	-0.383/0.125	[a]0.001/0.374

a: P≤0.05, statistically significant. For units, see Table 1

Table 3. Receiver operating characteristics (ROC) curve analysis for MHR, PLR, NLR, WBC and uric acid

			Asymptotic 95% Confidence Interval	
Variables	**AUC**	**P**	**Lower bound**	**Upper bound**
MHR	0.769	<0.001	0.686	0.853
PLR	0.606	0.047	0.505	0.707
NLR	0.732	<0.001	0.640	0.823
WBC	0.646	0.006	0.548	0.745
Uric acid	0.545	0.395	0.442	0.649

AUC: Area under the curve

controls were 61.51±11.22, 59.30±10.13 and 63.42±11.83, respectively. No statistically significant difference was found concerning age (p=0.360). The mean WBC levels of the DR patients were found statistically significantly higher, compared to the mean WBC levels of DM without DR and control group (8.57±2.04x10^3/mm^3, 7.48±1.67x10^3/mm^3 and 6.80±1.47x10^3/mm^3, respectively) (p<0.001). The mean MHR values of DR patients, DM without DR patients and control subjects were 0.167±0.03, 0.157±0.04 and 0.141±0.04, respectively, and the difference between mean MHR values of DR patients and mean MHR values of control subjects was statistically significant (p=0.008) (Table 1, a Between control group versus diabetic retinopathy). The mean PLR values were 142.21±68.92, 154.56±67.17 and 114.11±36.91 and NLR values were 2.84±1.06, 2.64±1.03 and 1.86±0.67 in DR patients, DM without DR patients and control group, respectively and both NLR and PLR levels were statistically significantly higher in DR group. Serum uric acid levels were numerically higher in DR patients group but there is no statistically significant difference concerning uric acid mean values between three groups (Table 1).

To evaluate the correlations between patients' inflammatory markers, such as MHR, NLR, PLR, WBC, PDW, MPV, uric acid levels and also lipoproteins, we performed Spearman's correlation analyses. In DR patients, there were positive but not statistically significant correlations between MHR levels and NLR and uric acid levels (Table 2). Although there was no correlation between MHR, WBC and also uric acid levels in DM without DR patients', there was a positive correlation between MHR levels and MPV levels and a negative correlation between MHR levels and HDL levels (p=0.024, R=0.307 and p<0.001, R=-0.560, respectively) (Table 2). According to a ROC analysis, optimal cut-off points were calculated using the maximum value of Youden's index (sensitivity + specifity-1). The ROC rederived cut-off value for MHR was 0.0156 [AUC:0.769; 95% confidence interval (CI): 0.686-0.853, 63% sensitivity, 76% specificity, p<0.001] (Table 3) (Fig. 1).

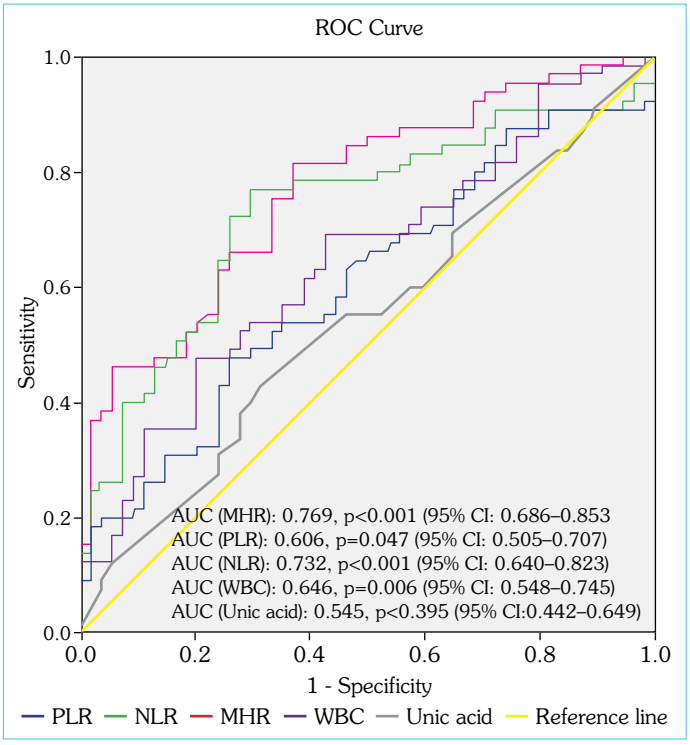

Figure 1. ROC curves for MHR, PLR, NLR, WBC and uric acid. cut-off value for MHR was 0.0156 [AUC:0.769; 95% CI:, 63% sensitivity, 76% specificity, p<0.001]

AUC: Area under the curve; CI: Confidence interval

DISCUSSION

The present study demonstrated that MHR levels are higher in patients with DR compared to patients without DR. Moreover, >0.0156 of MHR levels predicted DR with a sensitivity of 63% and specificity of 76%. MHR correlates with PDW, TC and LDL-c levels, but not correlated with PLR, NLR, WBC and uric acid levels (Table 2). DM is characterized with chronic hyperglycemia that induces oxidative stress, and increased oxidative stress causes the most common microvascular complication of diabetes: DR. Our results suggest that increased MHR, as an inflammatory biomarker, contributes to the progression of chronic inflammation from initiation of diabetes to the progression of diabetic retinopathy. There is one study reported by Karataş et al. (15) evaluating the relationship between MHR and diabetes mellitus and diabetic nephropathy. In

their study, they showed the increased values of MHR in patients with diabetic nephropathy and its correlation with urine albumin to creatinine ratio.

MHR combined the predictive efficacy of two different inflammatory markers, monocyte and HDL, into a single, easily calculable and readily available risk factor. MHR reflects the inflammatory situation. Monocyte has inflammatory and atherosclerotic effects but HDL cholesterol has anti-inflammatory, antioxidant, and antithrombotic effects (16). HDL cholesterol plays a close interaction role with monocytes. HDL interrupts differentiation of monocytes to macrophages, suppresses monocyte activities, prevents monocyte recruitment to the artery wall and inhibits adhesion of molecules to the endothelial surfaces (17). In this study, we revealed that MHR is independently associated with the presence of DR.

The final metabolite of purine metabolism is uric acid and tends to accumulate in humans. Biosynthesis of uric acid is significantly higher amount than taken orally (18). It is almost certain that higher serum levels of uric acid induces endothelial dysfunction and causes hypertension (19). For cardiovascular diseases, it is still under debate whether hyperuricemia is a risk factor or not (19). Additionally, no conclusion has been reached yet for healthy people with only hyperuricemia need to receive treatment or not (18). In the study of Ioachimescu et al. (20), increased levels of serum uric acid was told to be related with the prognosis of patients having a high risk of cardiovascular diseases. In another study reported by Chen et al. (21), higher serum uric acid levels were related with cardiovascular diseases and also with ischemic stroke. Hyperuricemia causes oxidative stress, inflammation and endothelial disfunction, so it is thought to be an independent risk factor for hypertension in a healthy person without a cardiovascular disease risk and patients having a high risk of cardiovascular diseases, like patients with diabetes, need to be monitored concerning serum uric acid levels. Recent studies consider that there is a relation between glucose metabolism and uric acid and uric acid is a serum indicator of glycometabolic disorders (22). Increasing evidence reported that elevated serum uric acid levels were related with glucose metabolic disorders (23) and diabetes (24). In our study, serum uric acid levels were numerically higher in patients group but there was no significant difference between patients and control subjects concerning uric acid levels (Table 1).

There are some limitations to our study. The main limitation is relatively small sample size. Our study enrolment was retrospective and it was a single-center design. Specificity and sensitivity of MHR in detecting DR were relatively low.

In conclusion, we investigated the correlation between MHR and DR patients. Compared to other inflammatory markers, the MHR is a simple, inexpensive and a widely available test. Our study results show the correlations between MHR and lipoproteins and also indicate that elevated levels of MHR are associated with DR. MHR levels may identify patients at higher risk for DR. Further and prospective studies are needed with larger sample size to elucidate the predictive value of MHR in DR patients.

Ethics Committee Approval: The Ethics Committee of Erciyes University approved the study protocol (date: 11.12.2019, number: 2019/839).

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