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Research Article/Araştırma Makalesi

Three non-invasive methods in the evaluation of subclinical cardiovascular disease in patients with diabetic retinopathy: endothelial dysfunction, serum E-selectin level and monocyte to HDL ratio

Diyabetik retinopatili hastalarda subklinik kardiyovasküler hastalığın değerlendirilmesinde üç non-invaziv yöntem: endotel disfonksiyonu, serum E-selektin düzeyi ve monosit/HDL oranı

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ABSTRACT

Aim: Cardiovascular risk has increased in diabetic retinopathy (DR). Brachial artery flow mediated dilation (FMD) is a non-invasive method used to evaluate endothelial dysfunction. Measurement of adhesion molecules such as E-selectin is the indirect method of predicting endothelial dysfunction. Monocyte/HDL ratio (MHR) is a novel marker found to be related with cardiovascular diseases. In this study, in DR patients without an apparent cardiovascular disease, we aimed to investigate the relation between endothelial dysfunction indicators such as MHR, FMD, E-selectin and subclinical atherosclerosis.

Material and Method: In this study, 96 tip 2 diabetic patients without apparent cardiac symptoms and 32 healthy control patients that matched for gender, age and body mass index (BMI) were included. The patients were separated into four groups as; nonproliferative diabetic retinopathy (NPDR, n=31), proliferative diabetic retinopathy (PDR, n=32), diabetic patients without retinopathy (n=33) and control group (n=33). Anthropometric, biochemical values, and FMD were measured. Correlation and regression analysis were done for the relation between MHR and FMD.

Results: MHR was significantly high in the PDR group ($p<0.001$). E-selectin and FMD which are indicators for endothelial dysfunction were significantly different between groups ($p< 0.001$). E-selectin measures were highest in the PDR group, lower in NPDR group, however, it was significantly higher than DM and control groups ($p= 0.026$). Inversely proportional to E-selectin, FMD was significantly higher in control and significantly lower in the PDR group ($p< 0.001$). The univariate logistic regression method was used to determine factors that had an influence on FMD. Glucose, HbA1C, CRP, and MHR had a negative effect.

Conclusion: In patients with DR, MHR levels might be used as a novel non-invasive marker to determine early atherosclerotic risk.

Keywords: Diabetic retinopathy, MHR, FMD, E-selectin

ÖZ

Amaç: Diyabetik retinopatide (DR) kardiyovasküler risk artmıştır. Brakiyal arterin akım aracılı dilatasyonu (FMD), endotel disfonksiyonunu test etmede kullanılan non-invaziv bir yöntemdir. E-selectin gibi adezyon moleküllerinin ölçümü endotel disfonksiyonunu tahmin etmekte kullanılan indirekt ölçüm metodlarıdır. Monosit HDL oranı (MHR) kardiyovasküler hastalıklar ile ilişkisi tanımlanmış yeni bir belirteçtir. Bu çalışmada aşikar kardiyovasküler hastalık bulgusu olmayan DR hastalarında MHR, FMD ve E-selectin gibi endotel disfonksiyonu belirteçlerinin subklinik ateroskleroz ile ilişkisini değerlendirmeyi amaçladık.

Gereç ve Yöntem: Çalışmaya aşikar kardiyak semptomu olmayan 96 tip 2 diyabet hastası ve 32 cinsiyet, yaş ve VKİ (Vücud kitle indeksi) benzer sağlıklı kontrol alındı. . Hastalar nonproliferatif diyabetik retinopati (NPDR, n=31), proliferatif diyabetik retinopati (PDR, n=32), retinopati olmayan diyabet hastaları (n=33) ve kontrol grubu (n=33) olarak dört gruba ayrıldı. Anthropometric, biyokimyasal değerler ve FMD ölçüldü. MHR ile FMD arasındaki ilişki için korelasyon ve regresyon analizi yapıldı.

Bulgular: MHR, PDR grubunda anlamlı yüksekti ($p<0,001$). Endotel disfonksiyon göstergeleri olan E-selectin ve FMD açısından gruplar arasında anlamlı farklılık mevcuttu ($p<0,001$). E-selectin ölçümleri PDR grubunda en yüksek, NPDR grubunda ise daha düşük ancak DM ve kontrol gruplarına göre anlamlı düzeyde daha yüksekti ($p=0,026$). FMD ise e-selectin ile ters orantılı olarak kontrol grubunda anlamlı düzeyde yüksek ve PDR grubunda anlamlı düzeyde düşük bulundu ($p<0,001$). Tekli lojistik regresyon yöntemi ile FMD'yi etkileyen faktörler belirlenmeye çalışıldı. Glukoz, HbA1C, CRP ve MHR'nin etkisi negatif oldu.

Sonuç: DR'si olan hastalarda erken aterosklerotik riski belirlemede yeni non-invaziv bir belirteç olarak MHR düzeylerinin önemli olduğunu söyleyebiliriz.

Anahtar Kelimeler: Diyabetik retinopati, MHR, FMD, E-selectin

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INTRODUCTION

Endothelial cell dysfunction is generally considered the first lesion in atherogenesis and might be reversed with effective therapy (1). Prior to clinical signs of atherosclerosis, cardiovascular risk factors such as smoking, hypertension, hyperlipidemia, diabetes, and obesity might lead to endothelial dysfunction (2). Many researchers proved that inflammation was is an independent risk factor for endothelial dysfunction (3). Measurements of adhesion molecules such as endothelial-derived vascular cell adhesion molecule-1 (VCAM-1) and E-selectin were widely used indirect measurement methods for prediction of endothelial dysfunction level (4).

Diabetic retinopathy (DR) is one of the most frequent and potentially threatening microvascular complications of diabetes mellitus (DM). It is globally the most common cause of preventable vision loss in a population aged 20-74 (5). Many basic and clinical studies have been done to clarify pathophysiological mechanisms underlying DR development, to decrease the prevalence of the disorder, and to determine the risk factors (6). There is a lot of evidence regarding the role of inflammation and endothelial dysfunction on DR pathogenesis (7). Measurement of brachial artery FMD is a simple and noninvasive procedure for early prediction of atherosclerosis development in DR. Using this non-invasive method, cardiovascular problems might be predicted and early preventive interventions might be done at a subclinical phase of the disease.

DR patients are under the risk of cardiovascular diseases (8–10). Therefore, early diagnosis of subclinical atherosclerosis and understanding the development steps are very crucial. MHR is a novel marker with a well-defined relation with cardiovascular diseases (11). In this study, we aimed to evaluate the relation of indicators of endothelial dysfunction like MHR, FMD, and E-selectin with subclinical atherosclerosis in DR patients without an apparent cardiovascular disease (CVD).

MATERIAL AND METHOD

Selection of Cases For The Study

Patients who admitted to diabetes clinics and retinopathy was diagnosed during routine complication examinations was included in this study. The patients with retinopathy were divided into two groups as proliferative diabetic retinopathy (PDR) and nonproliferative diabetic retinopathy (NPDR). Later, four groups were formed which were PDR (n=32), NPDR (n=31), diabetes without retinopathy (n=33) and control group (n=32). There was not any difference between groups regarding BMI and age. MHR sample size was determined by taking into account monocyte and HDL data measured in the pilot study. The intergroup effect size was calculated as 0,47 regarding mean and variance values. The sample size was determined as 28 subjects by 85% potency and 5% error margin. In the targeted period, more patients were included to increase potency and study was completed with 128 subjects. Patients who had an active infection, chronic inflammatory disease or connective tissue disorder, chronic renal disease, acute coronary syndrome, decompensated heart failure, pregnancy, nonsteroidal anti-inflammatory and glucocorticoid drug usage, blood transfusion within several days and hematological diseases (including anemia) were excluded.

Anthropometric Measurements and Biochemical Tests

In an initial visit, systolic and diastolic blood pressures of all patients were recorded. 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 of fasting and stored at-80 C^0 till analysis. 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 the manufacturer's instruction. MHR was calculated as a ratio of monocyte count to HDL level. C reactive protein (CRP) levels were measured with the nephelometry method. Standard methods were used for all other biochemical tests. Serum E-selectin was determined with an ELISA kit (Biovendor Research and Diagnostic Products, Heidelberg, Germany). The interassay coefficient of variation was 6% and the intra-assay coefficient of variation was 5,4%.

Brachial Artery Flow Mediated Dilation (FMD) Measurement

Endothelial dysfunction was evaluated according to a method previously described by Celermajer et al. (12). The patients were evaluated at the supine position after 12 hours fasting, at room temperature ($22C^0$), and after resting for 10 minutes. The arm to be measured was placed properly in extension and immobilized. Measurement of the brachial artery was done at 3-5 cm upper to antecubital fossa with 10 MHZ high resolution ''linear transducer''. After giving the best position, the skin was marked for subsequent measurements. Three consecutive end-diastolic brachial artery inner lumen diameter was measured and the mean value was calculated. After the basal measurement, the cuff was placed and inflated with a pressure higher than systolic value. The cuff was inflated for 3-5 minutes till forearm ischemia; later, deflated and measurements were repeated after 60 seconds. Using an equation, FMD percent as a response to reactive hyperemia was calculated with the formula; FMD (%) = (mean diameter after hyperemic flow-basal brachial artery diameter)X 100/Basal brachial artery diameter.

Statistical Analysis

Statistical analyses were performed by SPSS 20.0 software (IBM Inc., Chicago, IL, USA). Numerical variables were expressed as mean±SD for continuous variables and additionally [median, (Q1-Q3)] for discrete variables, and the

gender was expressed as frequency (percentage) in tables. Continuous variables were checked for normality by Kolmogorov-Smirnov test. A comparison of independent groups was done by One-Way ANOVA with Tukey HSD post-hoc test since the distribution was found to be normal. The relation between numerical variables was performed by Pearson Correlation Analysis. The sample size was calculated by GPower 3.1.9.2 (Kiel Universitaet, Germany) software. Binary logistic regression model of E-selectin and FMD was created. In all analyses, p<0.05 was considered as statistically significant with 5% type-I error.

Ethical Declaration

The approval was obtained from Süleyman Demirel University Ethics Committee prior to the study. All patients planned to be included were informed both verbally and written, and an informed consent was taken from the patients who were decided to be included.

RESULTS

In study groups, demographic features like BMI (*p= 0.266*), age (*p= 0.827*) and gender (*p= 0.917*) were similar. MHR values were significantly different between groups, were higher in the PDR group (*p<0.001*) and were similar in the other groups. NLR significantly differed between groups (*p<0.001*). It was significantly high in both the PDR and NPDR groups, but similar in diabetes (without retinopathy) and the control groups. Endothelial dysfunction indicators, E-selectin and FMD were significantly different between groups (*p<0.001*). In the PDR group, E-selectin values were highest and in NPDR group lower, but significantly higher than diabetes and control groups (*p=0.026*). FMD, contrary to e-selectin, was significantly high in the control group and significantly low in the PDR group (*p<0.001*). FMD levels were similar to each other in NPDR and DM groups (**Table 1**).

In study groups, correlation coefficients between MHR values and other measures and demographic features were calculated (**Table 2**).

In PDR group, there was a positive, significant correlation between MHR and endothelial dysfunction indicator, and a negative, significant correlation with FMD (r=0.91; *p<0.001* and r=-0.92; *p<0.001,* respectively). In NPDR group, MHR and diabetes duration, LDL, Glucose, HbA1C and E-selectin were positive and moderately correlated. However, between FMD and MHR, there was a low and negative correlation (r=-0.37; *p=0.039*) (**Figure 1-3**).

For FMD, which is one of the best indicators of endothelial dysfunction, two groups were formed according to 10% ratio. Values under 10% were reference group; factors that affected FMD were investigated with univariate logistic regression method. According to a model formed with a forward LR stepwise method to overcome multiple connection problem; goodness of fit results were found to be signifi-

Table 1. Demographical and clinical characteristics of groups

	PDR (n=32)	NPDR (n=31)	DM+NoDR (n=33)	Control (n=32)	
	mean±SD (median, IQR)				p
Age (yr)	60.75±5.45 (60.5; 7.50)	60.35±5.07 (62.0; 9.0)	61.39±4.47 (62.0; 7.0)	60.40±4.93 (61.0; 9.25)	.827
BMI (Kg/m^2)	28.56±2.48	28.62±2.48	29.30±2.87	29.58±2.59	.266
Weight (Kg)	78.68±5.16	78.93±5.6	79.63±6.5	80.96±4.2	.348
Height (cm)	166.03±4.80	166.19±4.45	165.03±5.70	165.73±5.21	.818
SBP(mmHg)	122.50±9.91	123.06±9.97	122.42±11.25	123.28±10.82	.984
DBP(mmHg)	72.81±6.34	72,25±7.28	71.27±7.61	72.34±7.23	.988
DM duration(yr)	11.53±1.68a (11.0; 2.75)	10.80±1.64b (11.0; 2.0)	7.33±1.10a, b (7.0; 1.0)	N/A	< .001*
HDL-C (mg/dl)	38.90±2.96 a,b,c	48.29±1.98 a	48.09±1.77 b	48.28±2.01 c	< .001*
LDL-C (mg/dl)	131.90±33.23a,b	132.96±28.77 c,d	111.12±22.00 a,c	113.62±17.96 b,d	< .001*
Cholesterol (mg/dl)	205.37±29.87	209.38±32.06	195.48±26.28	193.31±24.45	.140
TG (mg/dl)	202.03±46.95 a,b	190.61±42,15 c,d	174.81±21.39 a,c	177.96±21.96 b,d	.008*
Glucose (mg/dl)	189.03±52.71 a,b	171.70±52.44 c,d	87.66±8.92 a,c	86.93±9.68 b,d	< .001*
HbA1C (%)	8.12±1.09 a,b	7.95±1.13 c,d	7.20±0.57 a,c	5.34±0.32 b,d	< .001*
CRP (mg/dl)	5.34±1.35 a,b	4.74±1.65c,d	2.12±1.08 a,c	1.96±0.82 b,d	< .001*
Fibrinogen (g/L)	508.48±81.96 a,b	414.98±72.77 c,d	381.23±52.20 a,c	365.82±47.76 b,d	< .001*
E-selectin (ng/mL)	161.16±27.75 a,b	123.95±194.96c	94.51±16.99a,c	98.01±21.21b	.026*
FMD (%)	6.23±0.76a,b,c	9.08±1.41a,d	9.40±1.53b,e	11.55±1.52c,d,e	< .001*
MHR	18.35±3.77 a,b,c	10.34±1.69 a	10.60±1.48 b	10.46±1.64 c	< .001*
NLR	3.72±0.97a,b,c	2.84±0.65 a	2.28±0.47 b	2.37±0.54 c	< .001*

Table 2. Correlation between MHR and other measurements in proliferation and DM groups

MHR	PDR		NPDR		DM+No DR		Control	
	r	p	r	p	r	p	r	P
NLR	-.189	.299	-.286	.119	-.023	.898	-.266	.142
SBP (mmHg)	-.190	.298	.233	.207	-.123	.496	-.062	.736
DBP (mmHg)	-.284	.115	-.183	.324	-.023	.901	-.154	.401
DM Duration(Years)	.553R	.002*	.477R	.007*	.192R	.284	N/A	N/A
HDL-C (mg/dl)	-.886	<.001*	-.981	<.001*	-.988	<.001*	-.990	<.001*
LDL-C (mg/dl)	-.028	.881	.418	.019*	-.210	.240	-.265	.142
Cholesterol (mg/dl)	-.183	.317	-.334	.066	-.108	.550	-.308	.086
TG (mg/dl)	-.250	.167	-.179	.335	-.011	.950	-.149	.414
Glucose(mg/dl)	.557	.001*	.069	.707	.110	.542	.137	.455
HbA1C (%)	.421	.018*	.182	.318	.134	.458	-.074	.688
CRP (mg/dl)	.027	.885	-.334	.067	-.080	.660	-.207	.256
E-Selectin (ng/ml)	.912	<.001*	.463	.007*	-.080	.667	-.058	.754
FMD (%)	-.928	<.001*	-.372	.039*	-.042	.817	-.320	.075
Age (Year)	.211	.247	-.045	.809	.115	.524	-.042	.819
Weight (Kg)	.192	.293	.300	.101	.362	.024	.567	.001
Height (cm)	.035	.848	-.100	.591	-.098	.586	-.002	.992
BMI (Kg/m²)	.170	.353	.318	.081	.406	.019*	.349	.052

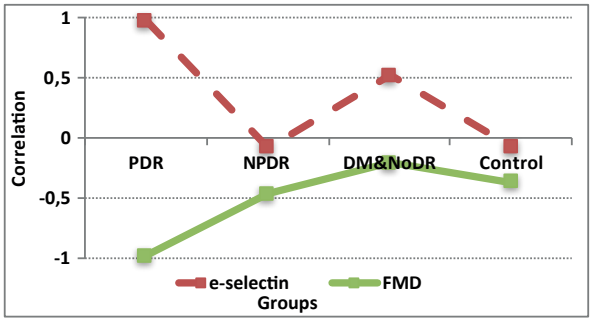

Figure 1. Correlation between MHR and endothelial indicators

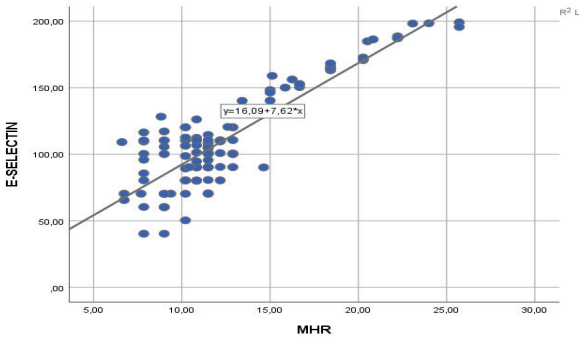

Figure 2. Correlation between MHR and E-selectin (For all patients, n=128)

cant (Nagelkerke R^2=0.445;-2LL=111.71 and Hosmer-Lemeshow Chi-square=5.606 (p= 0.691)). Glucose, HbA1C, CRP and MHR had a significant contribution to the model. Effects of glucose, HbA1C, CRP and MHR were negative. For MHR, since OR was .695 (.545-.886) (when converted

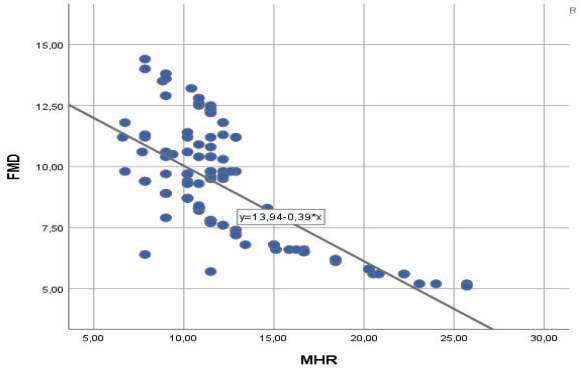

Figure 3. Correlation between MHR and FMD (For all patients, n=128)

positive risk ratio OR=1.48 (1.83-1.12)) elevation observed in MHR level was considered to cause a 0.48 unite decrease in FMD (**Table 3**).

Table 3. Binary logistic regression model of factors affecting FMD

Variables	Beta	p	OR	95% CI
Fibrinogen	.006	.170		
MHR	-.365	.003*	.695	.545-.886
Glucose	-.015	.047*	.982	.924-.999
Gender (Male)	.021	.884		
HbA1C	-.959	<.001*	.383	.226-.651
CRP	-.432	.027*	.649	.442-.953
BMI	-.031	.742		
NLR	-.298	.468		

DISCUSSION

In the DM, the most important factor in the development of microvascular angiopathy is a high blood glucose (13). As well, factors such as obesity, hypertension, smoking, and hyperlipidemia might lead to microangiopathy. In macroangiopathy, factors other than high blood glucose that leads to microangiopathy are more prominent. These risk factors are inflammation and endothelial dysfunction. After discovering the significance of endothelial dysfunction in the development of micro-and macroangiopathy, studies have focused on this issue (14). In diabetes, DR is considered as a mortality marker for cardiovascular system diseases (10). DR is thought to be related with to role of inflammation and endothelial dysfunction markers responsible for DR etiopathogenesis and the effect of MHR, a novel inflammation marker, on the detection of subclinical cardiovascular risk.

The main results of our study were as follows: MHR level was significantly high in proliferative diabetic retinopathy (PDR) group. E-selectin level was significantly high in both PDR and nonproliferative diabetic retinopathy (NPDR) groups. FMD was significantly low in PDR group, contrary to E-selectin. A new finding of our study was that inflammation marker MHR was significantly high in the PDR group and a positive correlation was found between MHR and diabetes duration, HbA1C, and E-selectin; however, a negative correlation was found between MHR and FMD. Also, according to regression analysis, MHR, HbA1C, and CRP were variables that affected FMD. This especially suggested that inflammation and hyperglycemia had a role on endothelial dysfunction. Our results showed that DR might actually be related to vasodilator endothelial dysfunction evaluated by FMD. This provides indirect evidence that NO synthesis is reduced in type 2 diabetic patients with DR.

Recently, two prospective studies on relation between DR and cardiovascular events were published. In the first report, EURODIAB group showed that cardiovascular disease risk was higher in type 2 diabetics with DR (9). On the other hand, in Valpolicella Heart Diabetes Study (VHDS), the relation initially observed was not confirmed after adjusting several classical risk factors including arterial hypertension (16). Our study is noteworthy for cardiovascular risk assessment, since blood pressure values were not different between groups. In both studies mentioned above the relation between HbA1C and DR was apparent. In our study, HbA1C was significantly high in the retinopathy group. Besides regression analysis showed that; HbA1C was the variable that affected FMD. Therefore, we want to draw attention to the effect of hyperglycemia on endothelial dysfunction and retinopathy. The aggravation of endothelial dysfunction in PDR patients suggests that risk of atherosclerosis and future adverse cardiac events have increased in this patient group (16,17).

It was shown that inflammation contributed to many cardiovascular events and was related to various clinical statuses of coronary artery disease. Turhan et al. found that in slow coronary flow patients with normal angiographic coronary arteries, adhesion molecule levels that were markers of endothelial activation or inflammation were increased (18). Also in our study, adhesion molecule, E-selectin level was significantly high in retinopathy patients and especially in PDR group. This showed that cardiac risk was elevated in PDR patients. Studies have revealed an increased mortality risk in PDR patients (17). In Wisconsin Epidemiologic Study of Diabetic Retinopathy (WESDR) study, survival rate was 72% in elderly patients without a retinopathy and 52% in PDR patients. Also, in another study, patients over 50 had a high stroke rate that showed a strong correlation with retinopathy severity (16,18). In WESDR study, PDR was related to cardiovascular disease and mortality in all age groups (17). Vascular inflammation was the cornerstone of atherosclerotic lesion formation and progression (19). In our study, in accordance with the abovementioned studies, we showed that PDR patients had a high MHR, had a continuous low grade inflammation and thus, had a high future risk of cardiovascular event development. Besides, in our study, we found a negative relation between MHR and FMD; and a positive relation between E-selectin. This suggested the existence of common pathophysiological pathways between inflammation, endothelial dysfunction, and atherosclerosis.

Recent studies showed that there was a relation between MHR and coronary atherosclerosis (11,20,21). Both experimental and clinical studies proved the role of inflammation on development of atherosclerosis (3). Active inflammatory processes that include leucocytes and adhesion molecules play role in the development of vascular pathology that triggers atherosclerosis (22). In type 2 diabetes, chronic inflammatory disorders and dyslipidemia significantly contribute to the development of atherosclerotic cardiovascular disease. MHR is a novel and simple marker that is positively related to inflammatory and oxidative stress conditions. So, it might be used to determine cardiovascular risk in type 2 diabetes (23). Previously, Kanbay et al. reported that MHR was an independent marker for cardiovascular events in patients with chronic renal disease and was elevated in accordance with decrease in GFR (24). Also in some studies, in type 2 diabetic patients, a significant relation was observed between MHR and CIMT (23). In non-diabetic conditions, the imbalance between pro-and anti-inflammatory events is generally moderate. Therefore, any relation can not be shown between MHR and CIMT (23). We, in our study, detected a high MHR in PDR patient group with poorly controlled diabetes and found a correlation between MHR and endothelial dysfunction markers, FMD and E-selectin. However, we did not found this relation between diabetes and control group. Current data show that, in type 2 diabetes, systemic endothelial dysfunction was related to DR and vascular abnormalities in retinal arterioles.

Our study had several limitations. First of all, it included a small patient group and was a single center study. Secondly, we used a single MHR value for analysis; serial alterations were not assessed; and besides, we did not eva-

luate the MHR effect on FMD progression. Lastly, we did not follow up with the patients for negative cardiovascular outcomes.

CONCLUSION

Endothelial dysfunction and inflammation are responsible for vascular complications in DM. In healthy patients endothelium regulates the complex balance that protects vascular homeostasis and normal artery function. Impairment of endothelial function is known to be the early pathological process underlying the development of subsequent cardiovascular disease, including atherosclerosis and coronary heart disease. In addition, it is important to detect the increased risk of CVD in these individuals due to the rising global outbreak of type 2 DM, and to detect this risk early in the endothelial dysfunction stage without any apparent clinical symptoms.

In addition to the accumulation of macrophages and high levels of inflammatory cytokines in atherosclerotic plaques, the plasma concentration of various inflammatory markers also increases in cardiovascular disease. Therefore, it is important to identify new inflammatory markers to identify and predict non-invasive individuals at risk for future CVD. In patients with DR, we might suggest that MHR, E-selectin and FMD levels are important to determine atherosclerotic risk. The results of such a study might have significant practical outcomes that point to the need for a more careful cardiovascular care in diabetic patients with microvascular complications.

CONFLICT INTEREST

No conflict of interest among authors

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