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Association of Monocyte to High-Density Lipoprotein Cholesterol Ratio with Hyperreflective Foci in Patients with Diabetic Macular Edema

Diyabetik Maküler Ödemi Olan Hastalarda Monosit/Yüksek Yoğunluklu Lipoprotein Kolesterol Oranının Hiperreflektif Odaklarla İlişkisi

Ümit Çallı, Neslihan Sevimli

ABSTRACT

Objectives: We aimed to investigate the monocyte/high-density lipoprotein cholesterol (HDL-C) ratio (MHR) in diabetic macular edema (DME) patients with hyperreflective foci (HF) on optical coherence tomography (OCT) and compare them with the results of patients without HF.

Methods: The data were obtained by retrospectively reviewing the data of patients followed up with a diagnosis of diabetes mellitus in the internal medicine clinic and with a diagnosis of DME in our clinic. DME patients who have blood monocyte and HDL-C levels before the treatment of DME in the laboratory archive were included in the study. DME and HF were detected by OCT. The patients with DME were divided into two groups according to the presence of HF observed on OCT. Thirty-five DME patients with HF were included in the study group. Thirty-five DME patients without HF were determined as the control group.

Results: The mean MHR was significantly higher in DME patients with HF (p=0.002). The optimal cutoff value of MHR for HF was 9.72. The area under the receiver operating characteristics curve was 0.681.

Conclusion: The MHR described as a potential biomarker of inflammation was significantly higher in DME patients with HF, suggesting that elevated MHR might be associated with severity of inflammation in DME patients.

Keywords: Biomarker; diabetic macular edema; hyperreflective foci; inflammation.

ÖZET

Amaç: Bu çalışmada, optik koherens tomografide (OKT) hiperreflektif odakları (HO) ve diyabetik maküla ödemi (DMÖ) olan hastalarda monosit/yüksek yoğunluklu lipoprotein kolesterol (HDL-K) oranının (MHR) araştırılması ve sonuçların HO olmayan DMÖ hastalarıyla karşılaştırılması amaçlandı.

Yöntem: Veriler, dahiliye kliniğinde diabetes mellitus ve kliniğimizde DMÖ tanısı ile izlenen hastaların verilerinin geriye dönük olarak incelenmesiyle elde edildi. DMÖ tedavisi öncesi kan monosit ve HDL-K düzeyleri mevcut olan DMÖ hastaları çalışmaya dahil edildi. DMÖ ve HO, OKT ile tespit edildi. DMÖ olan hastalar OKT'de gözlenen HO varlığına göre iki gruba ayrıldı. Çalışma grubuna HO saptanan 35 DMÖ hastası dahil edildi. HO olmayan 35 DMÖ hastası kontrol grubu olarak belirlendi.

Bulgular: HO mevcut olan DMÖ hastalarında ortalama MHR anlamlı olarak daha yüksekti (p=0,002). HO için MHR'nin optimal eşik değeri 9,72 idi. ROC eğrisinin altındaki alan 0,681 idi.

Sonuç: Potansiyel bir inflamasyon biyobelirteç olarak tanımlanan MHR, HO olan DMÖ hastalarında anlamlı olarak daha yüksekti, bu da yüksek MHR'nin DMÖ hastalarında inflamasyonun şiddeti ile ilişkili olabileceğini düşündürdü.

Anahtar sözcükler: Biyobelirteç; diyabetik maküla ödemi; hiperreflektif odaklar; inflamasyon.

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Diabetic macular edema (DME), described as an accumulation of fluid in the macula, is the leading cause of vision loss in diabetic retinopathy (DR) patients and occurs at all stages of DR.[1] Several previous studies have reported that the chronic inflammation occurring as a result of hyperglycemia and dyslipidemia has a key role onset and progression of DR and DME.[2,3] Upregulation of intercellular adhesion molecule-1 caused by chronic hyperglycemia, mediates leukocyte adhesion to the capillary endothelium, leads to breakdown of blood-retinal barrier, and retinal hypo/non-perfusion resulting in DR and DME.[4] It has been also reported that the levels of various inflammatory cytokines and chemokines, such as vascular endothelial growth factor (VEGF), interleukine-6 (IL-6), IL-8, and monocyte chemotactic protein-1 (MCP-1) are higher in vitreous and aqueous humor samples of patients with DME, suggesting a major role of inflammatory process in the appearance of DME.[5]

Optic coherence tomography (OCT) is widely used to detect and classify the types of DME and observe the response to the treatment regimens. OCT also allows to detect hyperreflective foci (HF), which are small, dot-shaped, discrete, focal intraretinal spots with equal, or more reflectivity when compared to the retinal pigment epithelium[6] as we show in Figure 1 in our study. The exact pathogenesis of HF is yet to be defined. Some studies suggested that HF were small, extravasated intraretinal lipid or protein deposits secondary to damage of blood retinal barrier, and that may be the precursor of hard exudates.[7] In another theory, microglia cells which were activated due to chronic retinal inflammation migrate to all retinal layers and turn into HF.[6,8] HF were thought to be associated with severe inflammation, and also they may help customize treatment regimens according to inflammatory profile in DME patients.[9]

Monocytes have a major role in inflammation and take part in vascular inflammatory reaction.[10] In addition, high-density lipoprotein cholesterol (HDL-C) is well known for anti-inflammatory and antioxidant effects and also protects vascular endothelial cells against the unfavorable influences of low-density lipoprotein cholesterol (LDL-C).[11] More recently, the monocyte/HDL-C ratio (MHR) was described as a new potential biomarker of inflammatory reaction in many systemic diseases[12-14] and also diabetic complications in the literature.[15,16] Based on this, the purpose of this study was to evaluate the MHR in DME patients with HF on OCT and compare them with the results of patients without HF.

Methods

The study was approved by the Clinical Research Ethics Committee and was conducted in accordance with the Helsinki Declaration. All patients have been provided with information and their written consent was obtained.

We reviewed records of patients diagnosed with DME who visited our clinic January 2019–December 2020 in this study. The data were composed based on a retrospective scan of the medical records of patients who also had visits to our internal diseases clinic.

DME patients with non-proliferative DR and who have blood monocyte and HDL-C levels before the treatment of DME in the laboratory archive were included in the study. The presence of DME and HF was detected by OCT (Rs. 3000; Nidek Inc., Fremont, CA, USA) and DR stage was detected by fundus fluorescein angiography (Kowa VX-10i, Kowa, Tokyo, Japan). Patients who smoke and who had

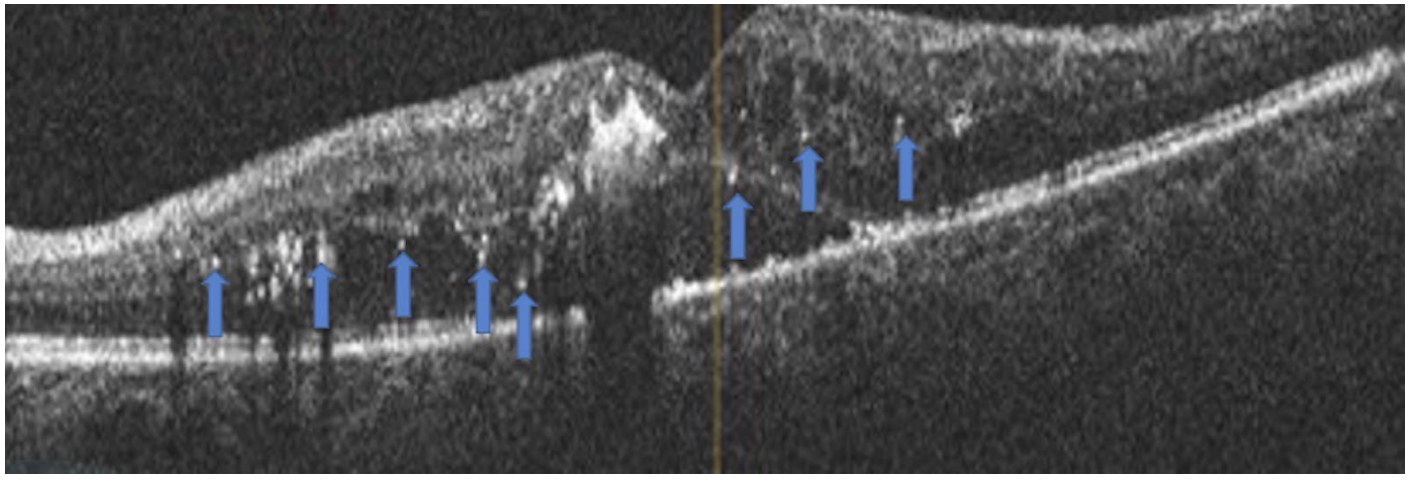

Figure 1. Hyperreflective foci (indicated by blue arrows) on optical coherence tomography.

Table 1. Demographic characteristics and laboratory parameters of two groups

	DME patients without HF	DME patients with HF	p
Age, years	55.2±5.2	56.7±8.5	0.336*
Female/Male	14/21	16/19	0.946†
Diabetes duration, years	12.9±4.7	13.1±5.4	0.922*
HbA1c	9.76±1.2	9.54±1.3	0.874*
DR stage, moderate	13	11	0.672†
Severe	22	24	
CMT (μm)	469±109	484±172	0.625*
HDL (mg/dL)	46.1±8.6	37.9±5.9	<0.001*
Monocyte (×10^9/L)	452.9±87.8	460±115.5	0.767*
MHR	10.1±2.6	12.3±3.7	0.002*

*Independent t-test; †Pearson's Chi-square test. DME: Diabetic macular edema; HF: Hyperreflective foci; HbA1c: Glycated hemoglobin; DR: Diabetic retinopathy; CMT: Central macular thickness; HDL: High-density lipoprotein; MHR: Monocyte count to HDL ratio.

Type 1 DM, proliferative DR, acute inflammation, infectious disease, acute/chronic renal failure, chronic liver diseases, other any microvascular complications of diabetes except DR, coronary artery disease, cerebrovascular disease, connective tissue diseases, other ocular diseases, and history of any surgery within 3 months were excluded from the study.

Age, sex, and ocular examination findings (DR stage according to FFA, central macular thickness (CMT) and presence of HF according to OCT), any chronic/systemic disease, CRP, glycosylated hemoglobin (HbA1c), triglyceride, LDL-C, HDL-C, total cholesterol, serum creatinine (Scr), blood urea nitrogen (BUN) levels, estimated glomerular filtration rate (eGFR), and spot urine albumin to creatinine ratio (UACR) were recorded from the medical and laboratory records. Patients with out of normal levels of CRP, Scr, BUN, UACR, and eGFR were also excluded from the study.

Participants were divided into the following two groups according to the presence of HF: DME patients with HF and DME patients without HF as a control group. Thirty-five DME patients with HF were eligible for the study. Samely, 30 DME patients without HF were determined as a control group.

All statistical analyses of this study were performed with SPSS for Windows 22.0 package program (SPSS Inc., Chicago, IL). The Kolmogorov–Smirnov test was performed to test normality of distribution. Pearson's Chi-square test was used for categorical data analyses. We compared parametric values among groups by independent t-test. We used receiver operating characteristic (ROC) curve analysis to compare the prognostic powers of the MHR for HF. P=0.05 was accepted as statistically significant.

Results

Thirty-five DME patients (16 female and 19 male) who had HF were eligible for the study. Samely, 35 DME patients (14 female and 21 male) without HF were determined as a control group. The mean age of patients was 56.7±8.5 years in the study group and 55.2±5.2 years in the control group. There were not any statistical differences between the two groups in terms of age, gender, HbA1c, DR stage, and CMT as summarized in Table 1.

The monocyte levels were not significantly different between the two groups (460±115.5 and 452.9±87.8, respectively. P=0.767). HDL-C levels were significantly lower in DME patients with HF compared to DME patients without HF (37.9±5.9 vs. 46.1±8.6, p<0.001). The mean MHR was significantly higher in the study group when compared to the control group (12.3±3.7 vs. 10.1±2.6, p=0.002). The optimal cutoff value of MHR for HF was 9.72 with 74.3% sensitivity and 63.2% specificity. The area under the ROC curve was 0.681 as shown in Figure 2.

Discussion

Monocytes are the most important cell types of inflammation because they are responsible for the secretion of pro-inflammatory cytokines.[10] MCP-1, the main chemotactic cytokine for monocytes, is also elevated in the vitreous of DR patients.[4,5] Conversely, HDL-C has anti-inflammatory and antioxidant effects such as inhibiting monocyte accumulation and transmigration of monocytes, and protecting the capillary endothelium due to the increase in the expression of nitric oxide synthase in endothelial cells.[11] More recently, the MHR was described as a new potential biomarker

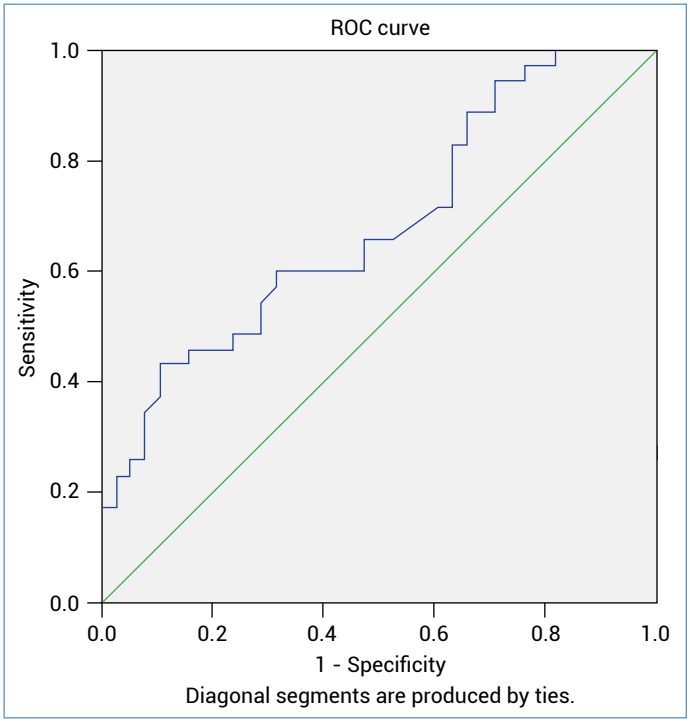

Figure 2. Receiver operating characteristic analysis of monocyte/high-density lipoprotein cholesterol ratio for diabetic macular edema patients with hyperreflective foci.

ROC: Receiver operating characteristic.

of inflammation in many systemic diseases including DM[12-16] and also some ocular disorders such as branch retinal vein occlusion (BRVO), pseudoexfoliation syndrome (PEX), and keratoconus and optic neuritis.[17-20]

In a study by Satırtav et al.,[17] the mean MHR value in patients with BRVO was significantly higher when compared to the healthy subjects (13.4±5.2 and 8.1±2.2, respectively). The area under the ROC curve was 0.862, and the optimal cutoff value of MHR for BRVO was 9.5 with 76% sensitivity and 70.8% specificity. In another study, the mean MHR was significantly higher in patients with PEX than in healthy subjects. The area under the ROC curve was 0.795, and the optimal cutoff value of MHR for PEX was 8.1 with 71.4% sensitivity and 67.7% specificity.[18] The mean MHR (13.7±5 and 9.1±3.7, respectively) was statistically higher in keratoconus patients than the control group in a study conducted by Katipoğlu et al.[19] Koçak et al.[20] reported that the mean MHR value was significantly higher only in the arteritic anterior ischemic optic neuropathy group when compared with the non-arteritic anterior ischemic optic neuropathy and control group. In our study, the mean MHR in DME patients with HF was significantly higher than the MHR value of DME patients without HF (12.3±3.7 vs. 10.1±2.6, p=0.002). The optimal cutoff value of MHR for HF was 9.72 with 74.3% sensitivity and 63.2% specificity. The area under the ROC curve was 0.681.

Numerous studies in the literature evaluated the association of inflammation with different types of DME.[4,21] Investigation of the vitreal concentrations of inflammatory cytokines in the DME patients with HF demonstrated elevated concentrations of VEGF, IL-6, and IL-8.[22] A previous study showed a powerful association between increased concentration of IL-6 and the appearance of HF and hypnotized that inflammatory reactions have a major role in the development of HF.[20] The soluble CD14 levels, a cytokine secreted by monocytes, were higher in aqueous humor of DME patients with HF, suggesting that HF observed on OCT might be associated with severe inflammation.[9]

In this present study, we evaluate the association of the MHR with HF in patients with DME. The mean MHR was significantly higher in the DME patients with HF when compared to DME patients without HF, suggesting that elevated MHR might be associated with severity of inflammation in DME patients. There are some potential limitations of our study. The first limitation is relative small numbers of patients and the retrospective design of the study. The second limitation is the fact that monocyte count was presented as a numeric value which do not show monocyte activation.

Conclusion

Monocyte activation might be critical in the pathogenesis of diabetic complications, DR, and DME. According to the results of the previous studies, high MHR levels could be considered as a new potential biomarker to indicate inflammation in systemic diseases and in ophthalmic disorders. Furthermore, our study has demonstrated that MHR is significantly elevated in DME patients with HF. We concluded that high MHR may be associated with the severity of inflammation in DME patients. The advantages of MHR are simple, easy to calculate, and cost-effective.

Disclosures

Ethics Committee Approval: The study was approved by Fatih Sultan Mehmet Training and Research Hospital Ethics Committee, Date: 13.10.2021, decision number: E-17073117-050.06.99.

Peer-review: Externally peer-reviewed.

Conflict of Interest: None declared.

Authorship Contributions: Concept – Ü.Ç.; Design – Ü.Ç.; Supervision – N.S.; Materials – Ü.Ç.; Data collection &/or processing – Ü.Ç.; Analysis and/or interpretation – N.S.; Literature search – N.S.; Writing – N.S.; Critical review – Ü.Ç.

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