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ORIGINAL ARTICLE

Vascular indexes of choroidal layers in diabetic macular edema

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Abstract

Purpose: This study aimed to investigate the presence of choroidal vascular parameters, which have a predictive value for diabetic macular edema (DME) development, in eyes with non-proliferative diabetic retinopathy (NPDR).

Methods: 148 eyes of 120 patients were included in the study. Eyes with an untreated mild-to-moderate NPDR stage were divided into 2 groups as those with and without DME. The diabetic retinopathy (DR) group was created from the eyes of patients diagnosed with diabetes mellitus without DR. Choroidal layers were segmented using the enhanced depth imaging mode of spectral domain optical coherence tomography. Choroidal vascular indexes (CVI) of the full-thickness choroid, sattler-choriocapillaris layer, and Haller's layer were calculated separately.

Results: Full-thickness CVI values of the choroid were 65.2±3.1% in the DR-group, 64.2±3.4% in the DME-group, and 64.8±3.08% in the DME+ group (P = 0.318). The CVI values in the Sattler-choriocapillaris complex were 71.3±4.5% in the DR-group, 70.9±5.9% in the DME-group, and 71.7±5.2% in the DME+ group (P = 0.746). The CVI values in the Haller layer were 61.6±4.1% in the DR-group, 60.3±3.7% in the DME-group, and 61.1±3.1% in the DME+ group (P = 0.252).

Conclusion: There was no significant difference between NPDR eyes with and without DME and eyes without DR in terms of CVI. These results may suggest that DME develops due to retinal vascular factors rather than choroidal vascular factors.

Keywords: Choroidal sublayers; choroidal vascularity index; diabetic macular edema; spectral domain optical coherence tomography.

Diabetic retinopathy (DR) is the most common microvascular complication of diabetes mellitus (DM).[1,2] Diabetic macular edema (DME), which can be seen in all stages of DR, is the most common cause of vision loss in these patients.[3] It is known that not only the retina but also the choroid is affected by DM. This condition is defined as diabetic choroidopathy (DC). Microaneurysms, enlargements and occlusions in choroidal vessels, dropout areas in the choriocapillaris, an increase in vascular tortuosity, and neovascularization are pathologies that can be seen in DC.[4,5]

The nutrition of the retinal pigment epithelium (RPE) and outer retinal tissues is provided by the choroid. It is thought that hypoxia occurs in these tissues as a result of DC, and vascular endothelial growth factor secretion increases, so that both the inner and outer blood-retina barrier deteri-

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orates, DR gets worse, and DME occurs.[6,7] In addition, it has been recently reported that choroidopathy develops before retinopathy and that some structural changes in the choroid may have predictive value for DR progression.[8,9]

The choroidal vascularity index (CVI) is a relatively new parameter used to determine the vascular status of the choroid. Images taken by the enhanced depth imaging (EDI) mode of spectral domain optical coherence tomography (SD-OCT) are used for the calculation. Through these images, the stromal area (SA), showing the structural part of the choroid, and the luminal area (LA), showing the vascular part, can be measured separately with the binarization method in the ImageJ program (version 1.53j, National Institutes of Health, Bethesda, MD, USA). CVI is the ratio of LA to total choroidal area (TCA).[10,11]

It has been reported that CVI is lower in DR compared to healthy control groups and even decreases as the DR stage progresses.[12,13] However, there are limited studies on CVI change in the presence of concomitant DME.[14]

The choroidal vascular structure consists of the innermost choriocapillaris layer consisting of small vessels, the middle Sattler layer consisting of larger arteries, and the outermost Haller layer consisting of larger veins.[7] Sim et al. showed that segmentation of these layers of the choroid can be performed reliably and reproducibly with SD-OCT in EDI mode.[15]

In our study, the vascular indexes of the choroidal layers will be examined separately on EDI-OCT images in untreated mild-to-moderate non-proliferative diabetic retinopathy (NPDR) patients. The presence of choroidal vascular parameters, which have a predictive value for DME development, will be investigated in patients with same-stage DR.

Materials and Methods

Ethical Approval

This prospective study was approved by the Institutional Ethics Committee of University of the Health Sciences, Izmir Bozyaka Education and Research Hospital, according to the Declaration of Helsinki (Reference Number: 2023/10, Date: January 25, 2023). Written informed consent was obtained from all the participants.

Study Subjects

Between October 2022 and June 2023, patients with a diagnosis of DM who were referred to the retina unit for DR evaluation from the internal medicine clinic of our hospital were examined. By consulting with the internal medicine specialist who referred the patient to our clinic, those diagnosed with Type 1 DM were excluded from the study. Only those with Type 2 DM were included in the study. Patients were classified as with DR and without DR. DR staging and the presence of DME were determined according to early treatment DR study criteria.[16] Eyes with an untreated mild-to-moderate NPDR stage were divided into 2 groups as those with and without DME. The DR-group was formed from patients without DR and matched with those with NPDR in terms of age and gender. Each patient was enrolled in only one group. Patients with both eyes in the NPDR stage and one eye without DME and the other eye with DME were included in the DME + group. Patients who did not have DR in one eye and had NPDR in the other eye were included in one of the NPDR groups according to their DME status. Thus, 148 eyes of 120 patients were included in the study. 51 eyes of 44 patients constituted the DME-group, 53 eyes of 46 patients constituted the DME+ group, and 44 eyes of 30 patients constituted the DR-group. Both eyes of 14 patients and one eye of the remaining 16 patients were added to the DR-group. The other eyes of these 16 patients could not be included in the study due to exclusion criteria.

Those with different retinal diseases, those with uveitis, glaucoma, intraocular hemorrhage, and ocular trauma histories, those who had surgery other than cataract surgery, those who had cataract surgery in the last 6 months, those who had media opacity such as cataract, a corneal scar, those with an axial length (AL) shorter than 21 mm and longer than 26 mm, and eyes whose choroid could not be evaluated in a healthy way due to dense exudations even with DME were excluded from the study.

Two experienced retina specialists performed the full ophthalmic examination. AL was measured using optical biometry (IOLMaster 500, Carl Zeiss Meditec, Dublin, CA). SD-OCT measurements were made in EDI mod (Spectralis, Heidelberg Engineering, Heidelberg, Germany). Fundus fluorescein angiography was performed in all DR patients. Patients with macular ischemia or neovascularization were excluded from the study. The medical records of all patients were reviewed. Duration of DM, treatments used, additional systemic diseases, and HbA1c values were questioned. Arterial blood pressure was measured. Those with uncontrolled hypertension were also excluded from the study.

DME Classification on OCT

DME was divided into 3 groups according to SD-OCT images.[17] The first group was diffuse retinal thickening type, which is characterized by sponge-like diffuse retinal thickening and decreased intra-retinal reflectivity; the second

group was cystoid macular edema (CME), which is characterized by intraretinal cysts in the macular region; and the third group was serous retinal detachment (SRD), which is characterized by fluid accumulation under the retina. Eyes with more than one edema type were grouped into the dominant edema type.

OCT Image Acquisition and CVI Assessment

All OCT measurements were performed by the same experienced technician with the SD-OCT device following pupil dilation at the same time interval (between 09:00 and 11:00 A.M.). Measurements were performed in EDI mode. Macular OCT images were acquired using horizontal scans centered on the central foveal region. The central choroidal thickness (CCT) was measured manually from the outer portion of the RPE to the inner surface of the sclera at the subfoveal area. Only high-quality scans (>25 Q) were evaluated. The obtained raw OCT data were evaluated with an image processing program for further analysis.

The ImageJ software (version 1.53j, National Institutes of Health, Bethesda, MD, USA) was used for binarization as described by Agrawal et al.[11] For segmentation, we applied the protocol previously described by Sim et al.[15] Using the segmented lines tool in ImageJ, the RPE-Bruch's membrane interface, the outer boundary of the sattler's layer, and the choroid-sclera interface were determined manually in all images. These lines divided the choroid into two layers: The inner and outer. Because the choriocapillaris layer is very thin, it was not evaluated separately from the Sattler's layer in SD-OCT images. It formed the inner choroidal layer as the choriocapillaris-Sattler's layer complex.[18] The outer choroidal layer was formed by Haller's layer. The outer boundary of the Sattler's layer (the boundary between Sattler's and Haller's layers) was determined according to the vessel diameters. Since the smallest vessel diameter in the Haller's layer was previously reported to be 100 micrometers, the Haller's layer was determined accordingly.[19]

Binarization was performed using the Niblack auto-local threshold method.[10,11] The choroidal region within a total of 6 mm, 3 mm nasal, and 3 mm temporal to the foveal center was added to the region of interest (ROI) manager, and TCA was calculated. Then, dark areas representing vascular structures in TCA were identified. These areas were calculated as LA by the ROI manager. SA was calculated by subtracting LA from TCA. Submacular CVI was calculated as the ratio of LA to TCA (Fig. 1). Three researchers in the study group made all these measurements separately (OA, MGT, and MG). A statistical analysis was performed based on the average of three measurements.

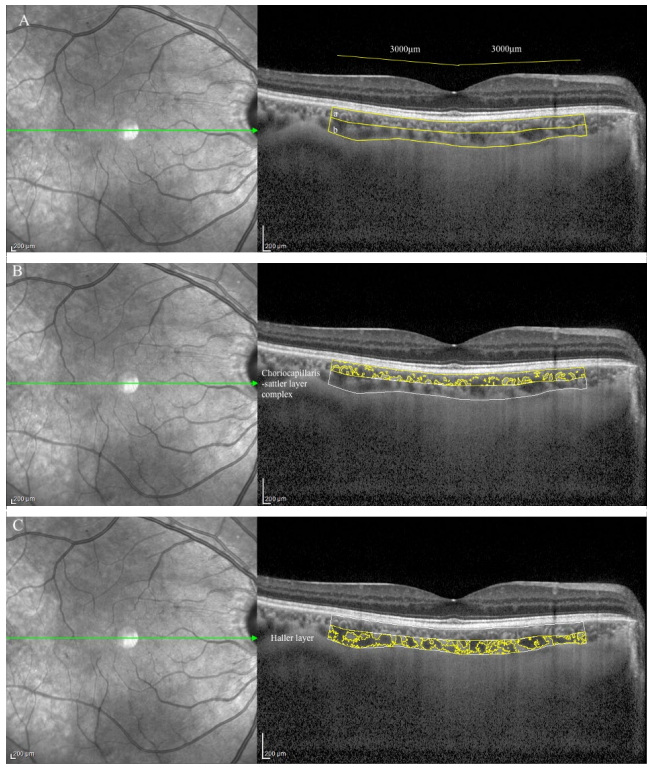

Fig. 1. Choriocapillaris-Sattler's layer complex **(a)**. Haller's layer **(b)**. Choroidal vascularity index measurements from the same image using ImageJ software **(c)**.

Statistical Analysis

Statistical analysis was performed with the Statistical Package for the Social Sciences V.26.0 (SPSS, Chicago, Illinois, USA). Among the three groups, continuous descriptive data were analyzed by ANOVA, and categorical data were analyzed by the Pearson Chi-square test. They were given as the mean and standard deviation. A P-value of 0.05 or less was considered statistically significant in our analysis.

Results

The mean BCVA was measured as 0.29±0.18 logMAR in the DR-group, 0.26±0.14 logMAR in the DME-group, and 0.84±0.22 logMAR in the DME+ group (ANOVA, $P < 0.001$). The disease duration of the 3 groups was similar (ANOVA, $P = 0.087$). HbA1c levels were 6.9±0.5% in the DR-group, 8.7±1.4% in the DME-group, and 9±1.4% in the DME+ group (ANOVA, $P < 0.001$). The mean central macular thickness was 355.3±137.5 µm in the DME+ group, 238.4±29.4 µm in the DR-group, and 246.7±27.1 µm in the DME-group (ANOVA, $P < 0.001$). The CCT was measured at 319.6±55.9 µm in the DR-group, 303.7±56.4 µm in the DME-group, and 298±46.9 µm in the DME+ group (ANOVA, $P = 0.126$). The clinical and demographic characteristics of the patients are shown in Table 1.

Table 1. The clinical and demographic characteristics of patients

	DR– (n=30)	DME– (n=44)	DME + (n=46)	P-value
Age (years)	59.6±7.7	59.1±6.8	60.1±7.3	0.811
Sex (Female/Male)	15/15	24/20	22/24	0.824
BCVA (logMAR)	0.29±0.18	0.26±0.14	0.84±0.22	p<0.001
IOP (mm/Hg)	16.1±3.3	15.8±3.2	15.8±3.2	0.681
AL (mm)	23.4±0.9	23.7±0.7	23.3±0.8	0.060
DM duration (years)	8.2±3	9.7±4	10.1±3.8	0.087
HbA1c (%)	6.9±0.5	8.7±1.4	9±1.4	p<0.001
HT (+ / -)	11/19	20/24	25/21	0.315
Lens status Phakic/Pseudophakic)	36/8	39/12	38/15	0.510
CMT (µm)	238.4±29.4	246.7±27.1	355.3±137.5	p<0.001
CCT (µm)	319.6±55.9	303.7±56.4	298±46.9	0.126

DR: Diabetic retinopathy; DME: Diabetic macular edema; BCVA: Best corrected visual acuity; logMAR: Logarithm of the minimal angle of resolution; IOP: Intraocular pressure; AL: Axial Length; DM: Diabetes mellitus; HbA1c: Hemoglobin A1c; HT: Hypertension; CMT: Central macular thickness; CCT: Central choroidal thickness. A P value <0.05 is considered as significant (ANOVA test for continuous; Chi square test for categorical parameters was used.)

Full-thickness CVI values of the choroid in the submacular area were 65.2±3.1% in the DR-group, 64.2±3.4% in the DME-group, and 64.8±3.08% in the DME+ group (P = 0.318). CVI values in the Sattler layer-choriocapillaris complex were 71.3±4.5% in the DR-group, 70.9±5.9% in the DME-group, and 71.7±5.2% in the DME+ group (P = 0.746). CVI values in the Haller layer were 61.6±4.1% in the DR-group, 60.3±3.7% in the DME-group, and 61.1±3.1% in the DME+ group (P = 0.252) (Table 2).

In the DME+ group, 9 eyes had SRD, 19 had CME, and 25 had diffuse retinal thickening. CVI values were compared according to edema type in all 3 regions. Full-thickness choroidal CVI values were calculated as 63.8±3.1% in patients with SRD, 64.6±2.9% in patients with CME, and 65.2±3.1% in patients with diffuse retinal thickening (ANOVA, P = 0.524). Sattler-choriocapillaris complex CVI values were 69.6±3.6% in patients with SRD, 72.09±5.6% in patients with CME, and 72.3±5.5% in patients with diffuse retinal thickening (ANOVA, P = 0.409). Haller layer CVI values were calculated as 60.5±2.9% in patients with SRD, 61.1±3.3% in patients with CME, and 61.3±3.1% in patients with diffuse retinal thickening (ANOVA, P = 0.785) (Table 3).

Discussion

In this study, we tried to determine the choroidal vascular parameter that may be a precursor for the development of DME. Thus, we planned to identify the patients who will develop DME early, to protect the vision of these patients with

Table 2. Choroidal vascular index values of the groups

CVI %	DR– (n=44)	DME– (n=51)	DME+ (n=53)	P-value
Full thickness choroid CVI%	65.21±3.17	64.23±3.4	64.8±3.08	0.318
Sattler-Choriocapillaris Complex CVI%	71.36±4.52	70.97±5.98	71.77±5.28	0.746
Haller layer CVI%	61.64±4.19	60.39±3.77	61.17±3.12	0.252

CVI: Choroidal vascularity index; DR: Diabetic retinopathy; DME: Diabetic macular edema; A P value <0.05 is considered as significant (ANOVA test is used).

Table 3. Choroidal vascular index values according to edema type

CVI %	SRD (n=9)	CME (n=19)	Diffuse retinal thickening (n=25)	P-value
Full-thickness choroid CVI%	63.88±3.17	64.68±2.97	65.23±3.17	0.524
Sattler-Choriocapillaris Complex CVI%	69.61±3.62	72.09±5.61	72.3±5.5	0.409
Haller layer CVI%	60.53±2.95	61.18±3.34	61.39±3.11	0.785

CVI: Choroidal vascularity index; SRD: Serous retinal detachment; CME: Cystoid macular edema; A P value <0.05 is considered as significant (ANOVA test is used).

early treatment, and to reduce the treatment costs. For this purpose, the vascular indexes of the choroid in the submacular area, the separate Haller layer, and the Sattler-choriocapillaris complex were calculated using the binarization technique using EDI-OCT images. There was no difference between the CVI values of eyes with and without DME and eyes without DR. In addition, similar CVI values were observed in all three edema types in patients with DME.

DR and DME are the leading causes of blindness in the working-age group (24–70 years) in developed countries.[20] Therefore, early diagnosis and treatment are extremely important. Despite advances in technology, the pathophysiological features of DR are not fully understood. Recently, DC has been thought to be a precursor to DR.[8,9] Cao et al. observed choriocapillary degeneration without retinopathy in 10 diabetic eyes, which they evaluated as postmortem. They stated that low vision in diabetic patients without DR may be related to this choroidopathy.[21] For these reasons, it is important to evaluate the choroid non-invasively in the early period. CT, which can be evaluated with EDI-OCT images, is the most studied parameter in this regard. However, there is no consensus regarding CT change in DR eyes according to both the DR stage and the presence of DME.[22] These different results are thought to be due to the effects of CT on ocular and systemic factors. CVI is not affected by these factors. Therefore, it can provide more stable and reliable measurements compared to CT.[11,12]

CVI is known to decrease in DR.[12,13] Tan et al. compared 38 diabetic patients with a healthy control group and observed that the CVI was significantly reduced in DM patients.[12] Kim et al. compared eyes with DM but without DR and eyes with DR at different stages with a healthy control group. They reported that all groups had lower CVI values than the control group.[13] They observed that CVI decreased as the DR stage progressed. They also did not detect a significant CVI difference between eyes with and without DME. In addition to these studies, there are also studies examining the choroidal layers separately in the presence of DR. In their patients followed for 2 years, Kung et al. observed that eyes with a thicker Haller layer and a larger choroidal area at baseline were associated with increased DR progression. When they made a subgroup analysis, they reported that this progression was more pronounced in patients with mild NPDR and without DR, compared to patients with moderate and severe NPDR.[9] Foo et al., on the other hand, reported that the CVI values of the Haller layer in the macular region of DM patients decreased and the CVI values of the Sattler layer decreased as the disease duration increased. They stated that this may be due to the effect of first the large choroidal veins (Haller's layer) and then the medium-sized arterioles (Sattler's layer) and choriocapillaris in DC. They thought that the CVI value of the Haller layer could be used as a marker for the development of DR in newly diagnosed patients.[8]

As can be seen, choroidal parameters, which have predictive value for the development and progression of DR, are intensively investigated. Studies to determine choroidal parameters that have predictive value in terms of DME development are more limited. Nagaoka et al. evaluated the subfoveal choroidal blood flow of 108 eyes with laser Doppler flowmetry. They observed that in NPDR patients, those with DME had significantly lower subfoveal choroidal blood flow than those without DME.[6] We think that our results are different from this study, since only the blood flow of the superficial choriocapillaris layer of the choroid was evaluated with laser Doppler flowmetry. In the EDI-OCT images, we used in our study the choriocapillaris layer cannot be evaluated separately. It was studied as a Sattler-choriocapillaris complex with the underlying Sattler layer. In addition, the CVI of not only the subfoveal but also the entire submacular area was evaluated in our study.

Gupta et al. compared 82 eyes, all with DME but at different stages of DR, with 86 healthy eyes. They reported that CVI was significantly lower in the group with DME and DR compared to the control group. They also observed that CVI decreased as the DR stage progressed, uncorrelated with CT. They also reported that the CT in eyes with SRD was significantly thicker than other edema types. However, they did not detect a significant difference in CVI values according to edema type.[14] Since DME was found in all DR patients in this study, it can be thought that the decrease in CVI may be related to the progression in the DR stage rather than the presence of DME, as reported by Kim et al.[13] In our study, only mild-to-moderate NPDR patients were evaluated, and CVI changes that could be seen due to the difference in DR stage were prevented. Thus, only the structural change in the choroidal layers due to DME was tried to be determined.

The first limitation of our study was that it was conducted with a small number of patients. The second was the use of SD-OCT. Instead, more reliable results could have been obtained with the use of a swept-source OCT device, which is not available in our clinic but provides more detailed imaging of the deep tissues and choroid. The third was the absence of a control group of healthy individuals. Fourth, we did not determine the lower and upper HbA1c values as inclusion criteria. The examination of untreated

NPDR patients was one of the strengths of our study. The other is that, as far as we know, it is the first study in which choroidal vascular changes that may be a precursor to the development of DME were tried to be determined.

Conclusion

No significant difference was found between NPDR eyes with and without DME and eyes without DR in terms of CVI. This finding suggests that DME develops due to retinal factors rather than choroidal factors. Further studies with a larger sample size are required to determine the exact correlation between DME and choroidal vascular layers.

Ethics Committee Approval: This prospective study was approved by the Institutional Ethics Committee of University of the Health Sciences, Izmir Bozyaka Education and Research Hospital, according to the Declaration of Helsinki (Reference Number: 2023/10, Date: January 25, 2023). Written informed consent was obtained from all the participants.

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