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Optical Coherence Tomography Angiography of DME and Its Association with Anti-VEGF Treatment Response

Junyeop Lee, MD, PhD,[1] *Byung Gil Moon, MD,*[2,3] *Ah Ran Cho, MD,*[2,3] *Young Hee Yoon, MD, PhD*[2,3]

Purpose: To investigate the structural integrity of the superficial capillary plexuses (SCPs) and deep capillary plexuses (DCPs) using optical coherence tomography (OCT) angiography (OCTA) in patients with diabetic macular edema (DME) and its association with the response to anti–vascular endothelial growth factor (VEGF) treatment.

Design: Retrospective, case-control study.

Participants: We included 51 DME eyes with a poor response to anti-VEGF agents and 32 age-matched DME eyes with a good response to anti-VEGF treatment, along with 20 fellow eyes without DME from the cases and controls.

Methods: The medical records, including OCTA and spectral-domain OCT (SD OCT), were reviewed and compared between the groups. En face OCTA images of the SCP and DCP were obtained for each eye. An anti-VEGF responder was defined by a reduction of more than 50 μm in central retinal thickness after 3 consecutive anti-VEGF treatments. A poor responder was defined by a reduction of less than 50 μm or an increase in central retinal thickness after 3 monthly injections.

Main Outcome Measures: We measured the vascular density and foveal avascular zone (FAZ) area and counted the number of microaneurysms in each layer. The SD OCT images were compared with OCTA findings.

Results: Compared with non-DME eyes, DME eyes had a lower vascular density ($P < 0.001$) and larger FAZ area ($P < 0.001$) in the DCP and more microaneurysms ($P < 0.001$) in both layers. Although there was no significant difference in the SCP between anti-VEGF responders and poor responders, poor responders tended to show greater damage and more microaneurysms in the DCP ($P < 0.001$) and a larger FAZ area ($P < 0.001$). The topographic location of the disrupted synaptic portion of the outer plexiform layer (OPL) in SD OCT exactly corresponded to the nonflow area of the DCP in OCTA.

Conclusions: Compared with DME eyes that responded to anti-VEGF treatment, poor responders show significant damage to the integrity of the DCP, but not the SCP. The degree of OPL disruption in SD OCT corresponds well with the extent of DCP loss in DME eyes. The extent of DCP loss and the corresponding OPL disruption could be useful predictors of responsiveness to anti-VEGF treatment. *Ophthalmology 2016;123:2368-2375*

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Diabetic macular edema (DME), a major cause of visual impairment in diabetic patients, affects up to 21 million of the 93 million patients with diabetic retinopathy (DR) worldwide.[1] The retinal swelling in DME is caused by breakdown of the blood–retinal barrier and leaking microaneurysms. Because vascular endothelial growth factor (VEGF) is the primary factor for retinal vascular hyperpermeability, anti-VEGF agents are used as the primary therapy for DME, effectively improving macular edema and vision in most patients.[2] In contrast, in the case of anti-VEGF–resistant DME, which suggests chronic inflammation, corticosteroids are an alternative treatment option.[3] Because the cost of anti-VEGF agents is a major burden for patients with DME,[4] it is necessary to identify factors in baseline examinations that can predict the treatment response to anti-VEGF agents.

Fluorescein angiography (FA) is an important diagnostic tool for investigating leaking microaneurysms and pooling patterns in DME. However, FA cannot visualize the precise structure of deep retinal layers where most microaneurysms and hyperpermeable retinal capillaries are located.[5] Because spectral-domain (SD) optical coherence tomography (OCT) provides cross-sectional images of the deep retinal layer, several studies have categorized different patterns of DME according to the combination of FA and OCT findings.[6–9] These studies have performed morphologic analyses and speculated about the pathogenesis of DME, but none of these earlier reports evaluated the association with the treatment response.

Optical coherence tomography angiography (OCTA), a recently developed procedure, enables closer observation of

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the blood flow of each retinal capillary layer.[10] Abnormalities in capillary flow density and microaneurysms from the deep capillary layer have been demonstrated in patients with DR, aspects that could not be evaluated with FA and OCT.[11–14] Because the diabetic vascular change occurs primarily in the deep retinal layer, we hypothesized that the integrity of the deep capillary plexus (DCP) might be associated with the pathogenesis and treatment response of DME. We also investigated baseline SD OCT findings associated with the response of DME to anti-VEGF treatment.

Methods

Patients

This retrospective case-control study included 55 patients with type 2 diabetes who were diagnosed with DR using FA and underwent comprehensive ophthalmologic examinations, including SD OCT and OCTA, in the Department of Ophthalmology at Asan Medical Center, Seoul, Korea. The clinical severity of DR in each patient was classified using the International Clinical Diabetic Retinopathy and Diabetic Macular Edema Severity Scale.[15] Eyes with any stage of DR were included in this study. We included treatment-naïve eyes and eyes that received previous anti-VEGF or panretinal photocoagulation treatments more than 6 months before the baseline. We defined DME as a central retinal thickness greater than 300 μm. The cases were DME eyes that poorly responded to anti-VEGF agents, and the controls were age-matched DME eyes with a good response to anti-VEGF agents. A response to anti-VEGF agents was defined as a reduction of more than 50 μm in central retinal thickness after 3 consecutive anti-VEGF injections. A poor response to anti-VEGF agents was defined as no reduction, a reduction less than 50 μm, or an increase in central retinal thickness after 3 consecutive monthly anti-VEGF injections compared with the initial value observed 4 months previously.

We allowed a 1-week variation for every monthly dosing interval. Optical coherence tomography angiography was performed within 2 months of the last consecutive injection of anti-VEGF agent. We selected 20 DR eyes with no history of DME from among the fellow eyes of 55 case and control patients. These non-DME eyes were defined by any visible microaneurysm on FA but no evidence of DME on SD OCT. The anti-VEGF agents used in this study included bevacizumab (76 eyes), ranibizumab (4 eyes), and aflibercept (3 eyes). We did not include any patients with a history of a vitrectomy, other retinal vascular diseases, severe cataracts, or DME previously treated with intravitreal or periocular corticosteroids. Eyes that could not be scanned using SD OCT or with poor OCTA images with a signal strength index <40 due to media opacity or significant motion artifact resulting from poor patient cooperation also were excluded from the study. We evaluated the baseline systemic characteristics of patients, including diabetic duration, presence of hypertension, and glycosylated hemoglobin, within the preceding 3 months. This study was approved by the Institutional Review Board and Ethics Committee of Asan Medical Center.

Optical Coherence Tomography and Optical Coherence Tomography Angiography

We performed SD OCT (Spectralis; Heidelberg Engineering, Heidelberg, Germany) at every visit including the baseline examination. A custom $20^\circ \times 20^\circ$ volume acquisition protocol was used to obtain a set of high-speed scans from each eye. With this protocol, 25 horizontal and central vertical cross-sectional B-scan images were obtained, each composed of 512 A-scans. To improve image quality, 25 to 30 frames were averaged for each B-scan. Of the 25 B-scan images obtained, 1 image with the maximum height of the largest intraretinal cyst was exported to analyze the optical density ratio (ODR). We analyzed the central retinal thickness in the standard 9-area Early Treatment of Diabetic Retinopathy Study grid and total macular volume.

For the OCTA, AngioVue (Optovue Inc., Fremont, CA) was used to obtain split-spectrum amplitude-decorrelation angiography as previously described by Spaide et al.[10] The scanning area was captured in 3×3-mm sections and was centered on the fovea. Optical coherence tomography angiography was performed after the eyes were classified as anti-VEGF responders or poor responders to anti-VEGF treatment. Although there are multiple retinal capillary planes that communicate through the vertical branches in the retina, we simply measured the superficial capillary plexus (SCP) in the ganglion cell layer and the DCP beneath the inner plexiform layer (IPL). We used auto-segmentation software as follows: The en face image was segmented with an inner boundary 15 μm beneath the IPL, and the outer boundary was set at 70 μm beneath the IPL to obtain images of the DCP. In the case of incorrect segmentation, we manually adjusted the boundary between the SCP and the DCP. Multilayer-involving large intraretinal cysts frequently caused errors in the accurate detection of IPL, which is the reference layer for dividing the SCP and DCP. If the border between the SCP and DCP was not located within the range of the IPL, we defined this as an inaccurate segmentation. Although the auto-segmentation set the retinal thickness of the DCP at 55 μm by default, we manually adjusted the offset values of the inner and outer border of the DCP so that the segmentation lines covered the full thickness of the inner nuclear layer and outer plexiform layer (OPL). If the segmentation error with an irregularly wavy border was not resolved by this manual extension of the DCP range, we used the flatten band tools and moved the outer border into the outer nuclear layer to accurately measure the DCP. In addition, we obtained images of the total capillary plexus (TCP) to determine the entire retinal thickness via the flattening and manual extension of the SCP outer border.

Image Analysis and Statistical Analysis

To quantify the OCTA images, we measured the vascular flow density and foveal avascular zone (FAZ) area and counted the number of microaneurysms in each layer (Fig S1, available at www.aaojournal.org). Saccular capillary ends and fusiform dilation 2-fold thicker than the capillary diameter were defined as microaneurysms in this study. The number of microaneurysms in a 3×3-mm area of each vascular layer was manually counted by 2 retinal specialists (J.L. and B.G.M.). The FAZ area was defined as an avascular central area, and the border of the FAZ was manually drawn by 2 retinal specialists (J.L. and B.G.M.) who were blind to all clinical information. These specialists started with the raw images, did their own segmentation correction, and then analyzed the images. The intraclass correlation coefficient was used to determine the interobserver agreement for the manually counted number of microaneurysms and measured FAZ area. Interobserver agreement, in terms of the manual measurements of microaneurysms and FAZ area, was satisfactory (intraclass correlation coefficients of 0.913 and 0.934, respectively). The FAZ area and vascular flow density of images from a 3×3-mm area of each vascular layer were calculated after conversion of the images to 8-bit grayscale images using ImageJ software, as previously described.[16]

In SD OCT images, we measured the ODR of the largest intraretinal cyst to the vitreous humor using ImageJ 1.48 software (National Institutes of Health, Bethesda, MD) as previously described but with minor modifications.[17] The entire intraretinal