Distinguishing Diabetic Macular Edema From Capillary Nonperfusion Using Optical Coherence Tomography Angiography

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BACKGROUND AND OBJECTIVE: To describe the appearance of diabetic macular edema (DME) using optical coherence tomography angiography (OCTA) and distinguish it from capillary nonperfusion.

PATIENTS AND METHODS: Patients with DME were recruited for OCTA imaging. Eyes with confounding retinal diseases were excluded. Using 3 mm × 3 mm OCT angiograms segmented into the superficial and deep inner retinal vascular plexuses, two graders described the appearance of DME and confirmed the diagnosis with structural OCT and fluorescein angiography.

RESULTS: DME was evaluated in 17 eyes of 12 patients. The cystoid spaces in DME appeared completely devoid of flow on the OCT angiograms and were oblong in shape with smooth borders that did not follow the distribution of surrounding capillaries, whereas areas of capillary nonperfusion were a greyer hue and had irregular borders.

CONCLUSIONS: The cystoid spaces in DME can be differentiated from capillary nonperfusion using OCTA. OCTA may help to guide treatment decisions in the future.


INTRODUCTION

In 2014, the Center for Disease Control and Prevention estimated that the number of Americans with diabetes had grown to more than 29 million. In this population, diabetic macular edema (DME) is the most common cause of visual impairment, with an estimated prevalence ranging from 2.7% to 9%. Although the effect of DME can vary from slight blurring of central vision to severe visual loss, effective treatment can improve visual acuity and quality of life. Therefore, it is essential to have tools for identifying DME, monitoring the efficacy of treatments, and improving our understanding of its pathophysiology.

In DME, the highly organized anatomy of the retina is distorted by fluid from a hyperpermeable retinal vasculature. The combination of hyperglycemia, growth factors such as vascular endothelial growth factor (VEGF), and inflammatory cytokines impairs the function of the retinal vasculature and supporting components constituting the blood-retina barrier. Subsequent exudation of fluid and lipids into the retina results in the formation of intraretinal cystoid spaces, subretinal fluid, and thickening of the retina, distorting the normal anatomy of the retina.

Optical coherence tomography (OCT) has become an essential tool in the diagnosis and monitoring of treatment response in DME by providing detailed structural images of retinal pathology, including intraretinal and subretinal fluid. Furthermore, OCT has become an important tool to quantify DME via au
tomated measurements of retinal thickness.\textsuperscript{7,8} Structural OCT B-scans and en face scans are able to gauge the extent of intraretinal cystoid spaces in patients with DME.\textsuperscript{9} However, structural OCT scans provide no information about the retinal vasculature and its relationship to edema.

OCT angiography (OCTA) may complement standard structural OCT in the evaluation of diabetic eyes.\textsuperscript{10,11} OCTA compares the decorrelation signal between sequential OCT B-scans acquired at the same location to create en face angiograms (OCT angiograms) that provide detailed images of the retinal blood flow.\textsuperscript{12-15} OCTA is able to image the retinal microvascular network in three dimensions and detect capillary abnormalities in patients with diabetic retinopathy and other retinal vascular diseases.\textsuperscript{10,11,14} In eyes with DME, OCTA is able to provide a single en face representation that depicts both retinal vasculature and the corresponding structural changes of macular edema; however, it may be difficult to distinguish areas of edema from capillary nonperfusion.

Because of the growing use of OCTA and the prevalence of diabetic eye disease, a description of the characteristics of DME as seen on this platform is necessary. The purpose of this paper is to describe the appearance of DME in OCTA and to distinguish regions of edema from capillary nonperfusion.

**PATIENTS AND METHODS**

This retrospective, observational study was completed in accordance with the tenets of the Declaration of Helsinki and the Health Insurance Portability and Accountability Act of 1996. After approval by the institutional review board of Tufts Medical Center, subjects were recruited from the Retina Service of the New England Eye Center at Tufts Medical Center in Boston between August 2014 and March 2015. After providing written informed consent, each patient was scanned using a commercially available spectral-domain OCT (SD-OCT) device (RTVue XR; Optovue, Fremont, CA) with prototype OCTA software.

Study participants included in this evaluation had DME diagnosed clinically by a retina specialist and confirmed on standard cross-sectional OCT and underwent OCTA imaging at two or more visits. Subjects with concomitant, confounding retinal diagnoses, such as age-related macular degeneration, retinal vascular occlusion, and central serous chorioretinopathy, were excluded. Furthermore, poor quality scans, defined as the inability to delineate the retinal vasculature in at least one-third of the OCT angiogram, were not included in the analysis.

A 3 mm × 3 mm OCTA scan of each eye was evaluated. Scanning at a rate of 70,000 A-scans per second, the system produced volumes of 304 x 304 A-scans. OCT angiograms of the “superficial” inner retinal vasculature, delineated by the internal limiting membrane and the inner plexiform layer, and the “deep” inner retinal vasculature, between the inner plexiform layer and the outer plexiform layer, were automatically segmented by the software. These two inner retinal vascular plexuses were evaluated separately.

In a process of side-by-side open adjudication, two trained readers (TED, ATC) from the Boston Image Reading Center evaluated the 3 mm × 3 mm OCT angiograms. Readers evaluated all visits from each eye as a set; however, they remained masked to treatment sequence and all other patient characteristics.
Figure 2. (A) Fluorescein angiography (FA) intermediate (A1) and late phase (A2) demonstrating multiple leaking microaneurysms causing edema (arrow) in the macula and more peripheral areas of non-perfusion (*). The yellow box is an approximately 3 mm × 3 mm area corresponding to the scan area of the optical coherence tomography angiography (OCTA) images (B). Superficial (B1) and deep (B2) vascular plexuses of the inner retina showing pockets of edema (arrows) seen as oblong areas of flow voids in a similar distribution as the FA. Areas of capillary nonperfusion (*) are apparent as grey irregularly-bordered areas bordered by the surrounding microvasculature. (C) En face structural OCT image of the superficial (C1) and deep (C2) inner retina showing exudates and edema (arrows) in the same distribution. (D) Structural OCT B-scan through the fovea with edema (arrows). Both the en face structural OCT and OCT B-scan were automatically generated and coregistered with the OCTA image during the same acquisition period. (E) OCT retinal thickness map demonstrating thickening in the macula. (F) Color fundus photograph showing areas of intraretinal hemorrhage and hard exudate, and a cotton-wool spot.
For each visit, the readers evaluated OCT angiograms for the presence of DME and described the appearance of intraretinal cystoid spaces. The appearance of the intraretinal fluid was contrasted with the appearance of capillary nonperfusion. Structural OCT images and, when available, fluorescein angiograms (FA) were used to confirm the location and diagnosis of the intraretinal cystoid spaces on the OCT angiograms (Figure 1).

RESULTS

Seventeen eyes of 12 patients with DME were evaluated between August 2014 and March 2015. The average patient age was 63 years (range: 45 to 72 years). There were five women and seven men included in the study. Nine patients were white and three patients were black. Four eyes had DME associated with proliferative diabetic retinopathy (PDR) and 13 eyes had DME associated with nonproliferative DR (NPDR). On average, each eye was imaged using OCTA on three different visits (range: 2 to 6 visits).

Cystoid DME spaces were seen on all OCTA images as oblong areas of complete flow void (showing as black on the OCT angiograms) that did not follow the distribution of the surrounding capillaries. In some instances, it appeared that capillaries would come to an abrupt stop at the border of the DME as if the intraretinal cysts were pushing the vessels to...
the side or masking their presence. In contrast, the areas of capillary nonperfusion were directly bordered by the adjacent capillaries, which were still perfused, thereby creating a highly irregular border. The cystoid spaces had rounded edges, as opposed to the sharper, more irregular borders of capillary nonperfusion. Additionally, the intraretinal cystoid spaces appeared completely black (devoid of signal), whereas areas of capillary nonperfusion were a greyer hue, possibly representing signal noise. Figure 2 illustrates the appearance of DME on OCTA, confirming the locations of the cystoid spaces using FA and structural OCT. The cystoid spaces were much more apparent on the OCT angiograms of the deep inner retinal vasculature than those of the superficial inner retinal vasculature, which is consistent with the location of intraretinal fluid in histopathological studies of DME. Therefore, the segmentation of the deep retinal vascular plexus was more useful in evaluating for presence or absence of DME and for changes in amount of fluid over time. Finally, as cystoid changes are variable over time, the DME tended to increase or

Figure 4. The right eye of a 69-year-old white woman with proliferative diabetic retinopathy. (A) The patient received an intravitreal anti-vascular endothelial growth factor (VEGF) injection in October 2014 for visually compromising diabetic macular edema (DME). The optical coherence tomography angiography (OCTA) images of the superficial (A1) and deep (A2) vascular plexuses of the inner retina demonstrated cystic changes seen as oblong areas of flow voids (arrow). The OCT retinal thickness map (A3) and structural OCT B-scan are consistent with DME. Structural OCT B-scans 1 month (B) and 3 months (C) after the injection showing persistent edema. A second intravitreal anti-VEGF injection was given. (D) Two months after the second injection, the DME is mostly resolved. OCTA of the superficial (D1) and deep (D2) vascular plexuses of the inner retina show only a few small pockets of edema (arrows) and a large region of capillary nonperfusion in the fovea and perifoveal area seen as grey flow voids following the distribution of the surrounding vessels. The OCT retinal thickness map (D3) and structural OCT B-scan appear greatly improved.
decrease in size over time, whereas areas of capillary nonperfusion remained consistent (Figure 3).

During the study period, nine of the 17 eyes received treatment with intravitreal anti-VEGF injection alone, no eyes were treated with laser or other treatment modalities, and eight eyes were followed without treatment. An average of 2.78 injections were given in each treated eye (range: 1 to 7 injections). Nine of the nine eyes (100%) treated with anti-VEGF showed a decrease in DME on OCTA over time (Figures 3 and 4). Untreated eyes showed a variety of changes during the study period. Three of the eight eyes (37.5%) had an increase in fluid, two eyes (25%) demonstrated a decrease in edema, and three eyes (37.5%) remained relatively stable based on the evaluation of the OCT angiograms.

**DISCUSSION**

Diabetic retinopathy is a major cause of blindness in working age individuals, and DME is one of the most readily treatable causes of visual loss.17 Because diabetic retinopathy is a responsible for a significant amount of the industrialized world’s visual burden and tends to occur in the working-age population, the ability to detect and monitor diabetic changes is important.

OCTA is a fast, noninvasive, and inexpensive imaging modality that allows for the evaluation of DME and the retinal microvascular network simultaneously. Each OCTA image set provides both structural and blood flow information in tandem by outputting a volumetric OCT angiogram, 304 corresponding structural OCT B-scans, en face structural OCT scans, and an OCT thickness map all in approximately 6 seconds of scanning time (Figure 2). In this study, the superficial and deep retinal vascular layers on OCTA were segmented using the prototype software. Rounded areas of black flow voids representing intraretinal cystoid spaces were evident, and most apparent in the deep retinal vascular layer on OCTA. The structural OCT B-scans and en face structural OCT that were coregistered with each OCT angiogram could also be used to confirm the locations of the cystoid spaces.

As OCT angiograms show microvascular changes in addition to the structural changes of DME, microaneurysms adjacent to the intraretinal cystoid spaces could be seen (Figure 5). Although currently, most eyes with DME are treated using anti-VEGF, there are patients in whom focal laser still plays a role in treatment of this disease. The ability to noninvasively differentiate which microaneurysms are adjacent to intraretinal fluid may be important in guiding focal laser treatment, which could be targeted to these areas. Further studies are needed to evaluate the use of OCTA in detecting leaking microaneurysms associated with intraretinal cystoid spaces.

OCTA may also be useful in assessing vasculature before and after treatment with anti-VEGF. As demonstrated in Figure 3, areas previously shown to have flow voids due to intraretinal fluid in DME later showed the reappearance of the microvasculature in these regions after treatment. OCTA may be able to determine if vessels are poorly perfused prior to treatment (and, therefore, not visible on OCTA) but then reperfused after anti-VEGF. Alternatively, the fluid may be blocking the ability to see the vessels within the cystoid spaces, or the vessels may be perfused throughout the treatment course but displaced by the pockets of edema then returned to their original position once the fluid resolves. These theories are supported by the appearance of the surrounding vessels appearing to abruptly stop at the rounded edges of the intraretinal cysts. Further studies using OCTA could better elucidate how the vasculature is affected by DME and treatment with anti-VEGF.

One of the major limitations of the OCTA technology used in this study was the accuracy of segmentation. The automated segmentation lines were not always precise especially when major changes to the retinal architecture (ie, DME) were present because...
the software had difficulty detecting the different vascular layers. For the purposes of simply detecting DME, this did not play a major role. However, separating the inner retinal vascular layers to evaluate other changes in DR would be more difficult when DME is present, so this may limit its use when evaluating diabetic eyes as a whole. The OCTA software did allow for manual correction of the segmentation lines, but this is a time-consuming process. Therefore, improvements in the accuracy of automated segmentation would be beneficial.

In summary, we described the appearance of DME on OCTA and differentiated intraretinal fluid-filled spaces from capillary nonperfusion, confirmed using structural OCT and FA. OCTA is a promising tool for the detection and management of DME because it is able to noninvasively detect cystoid changes, as well as the adjacent microvascular abnormalities, including retinal capillary nonperfusion. Using this new imaging modality, DME can be detected and treatment decisions can be made accordingly.

REFERENCES