Invited Commentary

Clinical Use of Optical Coherence Tomography Angiography in Diabetic Retinopathy Treatment
Ready for Showtime?

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Diabetic macular edema (DME) and proliferative diabetic retinopathy (PDR) are the 2 advanced stages of diabetic retinopathy (DR) that are the main causes for visual loss in patients with diabetes. Both DME and PDR can be readily diagnosed with clinical examination and, increasingly, by the noninvasive use of optical coherence tomography. However, another, less commonly recognized cause of visual loss in patients with diabetes is diabetic macular ischemia (DMI) in the absence of DME.[1] The understanding of the natural history, risk factors, and functional outcomes of DMI remains limited. This is partly because of the long-standing need for invasive fluorescein angiography to diagnose DMI, which is characterized by enlargement of foveal avascular zone (FAZ) and retinal capillary loss.[1]

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With the advent of optical coherence tomography-angiography (OCTA), which enables detailed depth-resolved visualization of the retinal capillary layers without the need for dye injection, the interest in studying DMI has been reignited. Importantly, in contrast to fluorescein angiography, which shows mainly alterations in the superficial capillary plexus, OCTA allows the 3 retinal capillary plexuses (superficial, intermediate, and deep) to be evaluated independently. A number of OCTA-based metrics (such as FAZ size and circularity, perifoveal capillary density, retinal vessel area density, vessel length density, and perfusion density) have been reported to be useful in quantifying and monitoring the degree of microvascular damage with increasing severity of DR.[2-4] However, it remains unclear whether these OCTA parameters have significant functional or prognostic implications. Studies correlating FAZ area and visual acuity have yielded discordant conclusions so far.[1,5] This may be because normative data on FAZ is unavailable and the size of FAZ might be influenced by physiological factors other than diabetes, such as age. Furthermore, it is unknown whether important diabetes-associated risk factors, such as duration, hemoglobin A1c level, and systemic comorbidities, may also affect the retinal vascular parameters measured on OCTA. Therefore, further studies are clearly needed to evaluate which of the numerous OCTA-based metrics, if any, have the highest diagnostic or prognostic value for OCTA to be useful in clinical practice.

In this issue of *JAMA Ophthalmology*, Dupas et al[6] evaluated the association between visual acuity and retinal vessel density and FAZ area in 22 eyes of patients with type 1 diabetes with severe nonproliferative DR or PDR without DME. The authors demonstrated reduction in vessel density in all 3 retinal vascular plexuses evaluated in eyes of patients with diabetes, even for those with normal vision. However, eyes of patients with diabetes that have subnormal vision were found to have more pronounced vessel density loss, particularly in the deep capillary plexus (DCP). These results suggest that, among the many parameters that can be evaluated on OCTA, DCP vessel density may have the strongest correlation with functional deficit.

This study adds to several recently published studies that have suggested that alterations in the DCP have stronger correlations with visual acuity than changes within the superficial capillary plexus.[5,7] The mechanism underlying this association remains to be elucidated, because the outer retina, including photoreceptors, is thought to receive most of its blood supply from the choroid. One hypothesis suggests that the DCP may contribute more significantly to the metabolic demands of photoreceptor metabolism in eyes with DMI than previously thought.[5,7,8] This is supported by imaging studies using spectral-domain OCT and adaptive optics scanning laser ophthalmoscopy that have demonstrated areas of photoreceptor disruption in eyes with DCP nonperfusion.

These novel, OCTA-based findings have enhanced our understanding of the pathogenesis of DR and the mechanism of visual loss in ischemia. However, as with all new technologies, the findings will need to be replicated in larger cohorts not limited to patients with type 1 diabetes. Age-specific normative values of the various quantitative parameters will need to be established to facilitate widespread adoption of their assessment in clinical settings. Similarly, the potential influence of other systemic factors (such as duration of diabetes, hemoglobin A_{1c} level, comorbidities such as hypertension or ischemic heart disease, and smoking status) on retinal vascular parameters on OCTA will need to be determined. Finally, enhancement of OCTA hardware and software to improve ease of image capture, reduce artifacts, and increase consistency of interobserver and intraobserver measurements at different points, is clearly needed for OCTA to be a mainstream technology.

Translation of a novel imaging technology, such as OCTA, toward clinical utility is a progressive step-by-step method designed to move the needle. First, studies of the novel technology should show independent information that is not apparent or easily obtained from traditional means (in this case, the ability to assess DMI noninvasively using OCTA). Larger studies including patients with more diverse systemic medical backgrounds will then be needed to robustly demonstrate the functional outcomes of DMI. The progression pattern and prognostic value of OCTA-diagnosed DMI should then be confirmed in prospective clinical studies. Currently, we still do not

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know whether DCP measures of DMI are associated with poor visual acuity as time passes.

Second, the technology should be reproducible; one of the current limitations of OCTA is the variability between studies and instruments. Studies to standardize retinal vascular metrics measurements across different OCTA instruments, similar to previous efforts to standardize retinal thickness measurements using different commercial OCT instruments, will be needed.

Third, the measure should have good sensitivity, specificity and high predictive value. The area under the receiver operating curve should be determined. These statistics are not yet available for OCTA in diagnosing DMI.

Finally, the technology will need incorporation into a treatment regime. Currently, there is no specific therapy for DMI. Thus the value of adding OCTA to the assessment of possible DMI is unclear. However, OCTA will have paved the way for developing such treatment by offering an increasingly reliable imaging modality to quantify ischemia. It is highly likely that these challenges of OCTA in management of DR will be overcome in time. When that point has been reached, these currently subclinical findings may replace clinical assessment, fluorescein angiography, and visual acuity as future treatment end points for potential new therapies to reverse ischemia.

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