Invited Commentary

Optical Coherence Tomography Angiography, Artificial Intelligence, and the Missing Capillaries

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The earliest stages of diabetic retinopathy (DR) are clinically characterized by the presence of microaneurysms. However, it is well established that diabetes is histopathologically characterized by capillary loss long before microaneurysms appear and long after microaneurysms disappear. The juxtaposition of these facts may lead one to wonder why the clinical staging of an ischemic disease has been limited to semiquantitative assessments of perfused vascular features, such as number of microaneurysms, dot-blot hemorrhages, intraretinal microvascular anomalies, and neovascularization. The short answer is that the tools necessary to clinically detect and quantify impaired capillary perfusion have been lacking until now.

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Yang et al[1] have elegantly woven together advances in the application of optical coherence tomography angiography (OCTA) imaging with artificial intelligence (AI)–based analytical methods to demonstrate an association between subclinical diabetic macular ischemia and several key clinical outcomes, such as visual acuity loss, development of diabetic macular edema, and DR progression. Several cross-sectional OCTA studies have previously demonstrated decreased capillary density measures even in patients with minimal or no clinical DR.[2] AI-based methods have been developed to quantify these subclinical changes, an otherwise impractical task for human graders to perform at scale.[3] These subclinical changes are not limited to DR and have been demonstrated in the contralateral eyes of persons with unilateral retinal vascular occlusions[4] as well as eyes with radiation retinopathy,[5] sickle cell disease,[6] and even in asymptomatic persons with genetic risk for vascular cognitive impairment.[7]

These advances have put a spotlight on the limitations in detection and quantification of early retinal ischemia, especially in diabetic macular ischemia. The primary limitation has been invasive fluorescein angiography (FA) that is only indicated in relatively advanced disease (eg, proliferative diabetic retinopathy). Even under the best of circumstances, FA has poor sensitivity for detection of small regions of capillary nonperfusion. Such regions have been repeatedly illustrated by OCTA in early stages of nonproliferative diabetic retinopathy.[2] In their retrospective cohort study of 386 eyes of 202 persons with type 2 diabetes, Yang et al[1] showed that baseline subclinical diabetic macular ischemia was associated with increased odds of DR progression (2.7- to 3.7-fold), development of diabetic macular edema (4.6-fold), and deterioration of vision (1.8- to 2.1-fold) over 4 years. It is critical to note that since most participants in the study had moderate DR or less severe disease, the characterization of diabetic macular ischemia with OCTA (irregular foveal avascular zone with or without other parafoveal capillary loss) could not be documented by clinical examination or dye-based angiography. Moreover, the associations persisted even after adjusting for common contributing factors, such as age, duration of diabetes, hemoglobin A_{1c}, baseline DR severity, and ganglion cell inner plexiform thickness. The latter finding demonstrates that OCTA-derived metrics can provide unique information above and beyond structural OCT measures. One of the main obstacles to more widespread use of OCTA is the laborious process of identifying good images and quantifying relevant changes, both of which can be subjective and time consuming. Thankfully, AI tools appear to be well poised to address this task.

Yang et al[1] used a DenseNet-161 model to automatically identify high-quality 2-dimensional OCTA images and 4 categories of diabetic macular ischemia, and then analyzed the diabetic macular ischemia information using classical machine learning (regression analysis) in conjunction with other relevant clinical variables. This appears to be a good first choice for 2-dimensional classification and resulted in area under the receiver operating characteristic curve, sensitivities, and specificities for detection of their end points above 90%. Given the considerable advances in AI, future studies could consider training a deep learning–based model using baseline 2-dimensional superficial capillary plexus en face images, 2-dimensional deep capillary plexus en face images, or 3-dimensional volumetric images (combining structural and vascular information) as inputs and then concatenate the deep learning–based model with tabular clinical variables. Furthermore, the authors curated a highly valuable data set, which, if analyzed with more advanced computer vision approaches such as vision transformers, could yield yet more insights. The ideal solution would ultimately be a fully automated algorithm that is robust across multiple data sets, multiple sites, and multiple OCTA devices.

In conclusion, the study by Yang et al[1] is important in at least 3 ways. First, it provides a foundation for revisiting the classification of early DR stages to incorporate measures of subclinical impairment in capillary perfusion. Second, it makes a compelling case to adopt OCTA as a standard care platform for assessment of early ischemic retinal disease, at least in patients with diabetes. Third, it is a case example that demonstrates the powerful combination of relatively basic AI methods and highly sensitive noninvasive imaging markers that can provide significant clinically impactful prognostic information about DR. Changes to our clinical practice based on these lessons will set the stage for clinical trials aimed at treatment of capillary nonperfusion rather than secondary complications of DR, such as macular edema and neovascularization. Much like the observation that OCT and antivascular endothelial growth factor therapies have made focal laser photocoagulation essentially obsolete, we are standing at the edge of a new era in diagnosis and treatment of retinal vascular disease enabled by the combination of OCTA and AI.

ARTICLE INFORMATION

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