Invited Commentary

Promises and Pitfalls of Retinal Biomarkers in Systemic Health and Disease

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In this issue of *JAMA Ophthalmology*, Dong et al[1] provide valuable optical coherence tomography (OCT)– and OCT angiography (OCTA)–based measures of retinal thickness and vascular structure from a large community-based study of older individuals in the US. This study provides several insights for the clinical and scientific community as we attempt to leverage ever-improving methods of in vivo retinal imaging to identify, understand, and eventually intervene in the insidious progression of many chronic diseases such as diabetes, hypertension, cognitive impairment, and dementia. Several lines of evidence including OCT- and OCTA-based measurements suggest that there are cumulative subclinical changes in retinal thickness and capillary structure that are pathophysiologically linked to these underlying systemic diseases.[2,3] As we discuss below, the valuable population-level data from Dong et al[1] can be very helpful in distinguishing subclinical retinal pathology from normal age-related changes and informing future studies aiming to identify such changes.

Related article page 809

Dong et al[1] report differences in foveal avascular zone and ganglion cell complex (GCC) thickness between Black and White participants as well as an age dependence of retinal nerve fiber layer (RNFL) thickness and retinal capillary density. In combination with data from other community-based studies reporting on axial length, signal strength, gender, and blood pressure,[4] the data from Dong et al[1] provide a useful tool for refining multivariable associations in future studies reporting on OCT- and OCTA-based metrics as biomarkers of chronic systemic disease. The study also highlights the possibility of detecting subclinical changes that likely precede clinical disease. For example, the authors report a weak association of contrast sensitivity with GCC and RNFL thickness (change of 10 µm in GCC and RNFL thickness is associated with 0.016 log units contrast sensitivity or half-letter change in Mars chart). Interestingly, this latter association was mostly driven by individuals with the lowest 10% of GCC/RNFL measurements. Only a prospective, longitudinal, community-based study can demonstrate whether this 10% of individuals represent those with progression of some underlying chronic disease or perhaps the tail of the normative distribution. In either case, defining this subpopulation of individuals will be essential in differentiating normal variation from disease pathology.

Lastly, the results from Dong et al[1] also spotlight the challenge of using commonly available retinal structural measures in asymptomatic individuals to capture information about potentially impaired retinal function. While OCT and OCTA are clearly useful for assessing disease-specific changes in symptomatic individuals (eg, manifest diabetic retinopathy or glaucoma), the data from this and other studies suggest that it may be challenging to use the same exact methods for reliably detecting subclinical changes in asymptomatic individuals. Nevertheless, the retina presents an irresistible opportunity to directly visualize subclinical changes in neurosensory and vascular tissue that are very likely to occur in many prevalent chronic diseases and new methods for detecting these changes are in development. For example, studies of asymptomatic, older individuals (many of which are nested within larger population-based studies) have also demonstrated that changes in retinal capillary perfusion are significantly associated with a variety of important determinants of health (eg, hematocrit level,[4,5] blood pressure level,[4,5] and *APOE4* status[6]) as well as chronic disease such as vascular cognitive impairment,[7] diabetes,[8] and radiation exposure.[9] The normative data from Dong et al[1] represent an important step and a very useful tool in differentiating the spectrum of normal retinal anatomy from subclinical pathology associated with chronic disease.

ARTICLE INFORMATION

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