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Agreement between OCT Leakage and Fluorescein Angiography to Identify Sites of Alteration of the Blood–Retinal Barrier in Diabetes

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Purpose: To compare the location of the sites of lower reflectivity, as determined by OCT leakage using spectral domain (SD)-OCT, with sites of fluorescein leakage identified by fluorescein angiography (FA) in eyes with diabetic retinopathy.

Design: Prospective consecutive case series.

Participants: Fifty-two eyes from 28 patients with type 2 diabetes and presence of nonproliferative diabetic retinopathy.

Methods: All patients were imaged with FA and SD-OCT (Angioplex, Carl Zeiss Meditec, Inc). All FA images were analyzed by 2 experienced graders, and the area surrounding well-defined sites of leakage was outlined by the graders. The SD-OCT scans were processed using OCT leakage proprietary software and semiautomated segmentation. Both procedures were performed without access to the clinical data.

Main Outcome Measures: Agreement of OCT leakage with FA findings.

Results: In eyes that were classified as having well-defined sites of leakage on FA, OCT leakage showed a sensitivity of 95.9% and a specificity of 75.4% regarding agreement between these sites of alteration of the blood–retinal barrier. The areas of abnormal extracellular fluid increase were larger than the areas of fluorescein leakage and included the well-defined leakage sites identified by FA. On OCT leakage, localized increases in extracellular space were identified, mainly in the inner nuclear, outer plexiform, or outer nuclear layers, even in eyes without leakage on FA.

Conclusions: Using SD-OCT, OCT leakage was found to better identify abnormal retinal fluid than did FA and showed good sensitivity and specificity in comparison with FA for identification of sites of alterations of the blood–retinal barrier. *Ophthalmology Retina 2017;■:1–9 © 2017 by the American Academy of Ophthalmology. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).*

According to the International Diabetes Federation,[1] the number of people with diabetes will rise from 387 million (in 2014) to 592 million (in 2035), worldwide, representing a prevalence of 8.3% and 11.3%, respectively. Diabetes mellitus is one of the most commonly encountered diseases in clinical practice, and both the prevalence and incidence of this multifactorial disease have shown an increase in recent years. Diabetic retinopathy (DR) is also a frequent complication of diabetes mellitus and is the main cause of vision loss in the active working population in Western countries. It is responsible for 10% of new cases of blindness each year.[2]

In DR, the blood–retinal barrier (BRB) has been shown to be altered as early as the initial stages of DR.[2,3] In the healthy retina, the BRB, structurally based on the tight junctions of the endothelial cells of the capillary network and the tight junctions of the retinal pigment epithelium (RPE), prevents fluid diffusion into the retina and vitreous.[4] Fluorescein angiography (FA) is the imaging technique most frequently used to document the changes occurring in the BRB in DR. It uses sodium fluorescein as a dye, and images are acquired after intravenous administration. Minor adverse reactions occur in 5% of cases. Severe complications, although more rare, may also occur, and this is the reason why that imaging technique requires the presence of a medical doctor. Death may occur in the first 24 to 48 hours for 1 in 220 000 cases.[5]

The current study compared the identification of fluorescein leakage, or lack thereof, with abnormal fluid accumulation detected by spectral domain (SD)-OCT, using OCT leakage software, to further explore the possibility of using SD-OCT to detect and locate fluorescein leakage noninvasively.[6]

Recently, OCT microangiography has been introduced for noninvasive vascular imaging in the eye.[7] It may replace FA by identifying neovascularization and is capable of quantifying capillary dropout in the retinal circulation,[8] but it does not identify sites of leakage, namely, alteration of the BRB. Thus far, there has been no noninvasive method proposed to image leakage or breakdown of the BRB.[9]

In this work, we demonstrate the possibility of using a noninvasive imaging technique, OCT leakage, to identify

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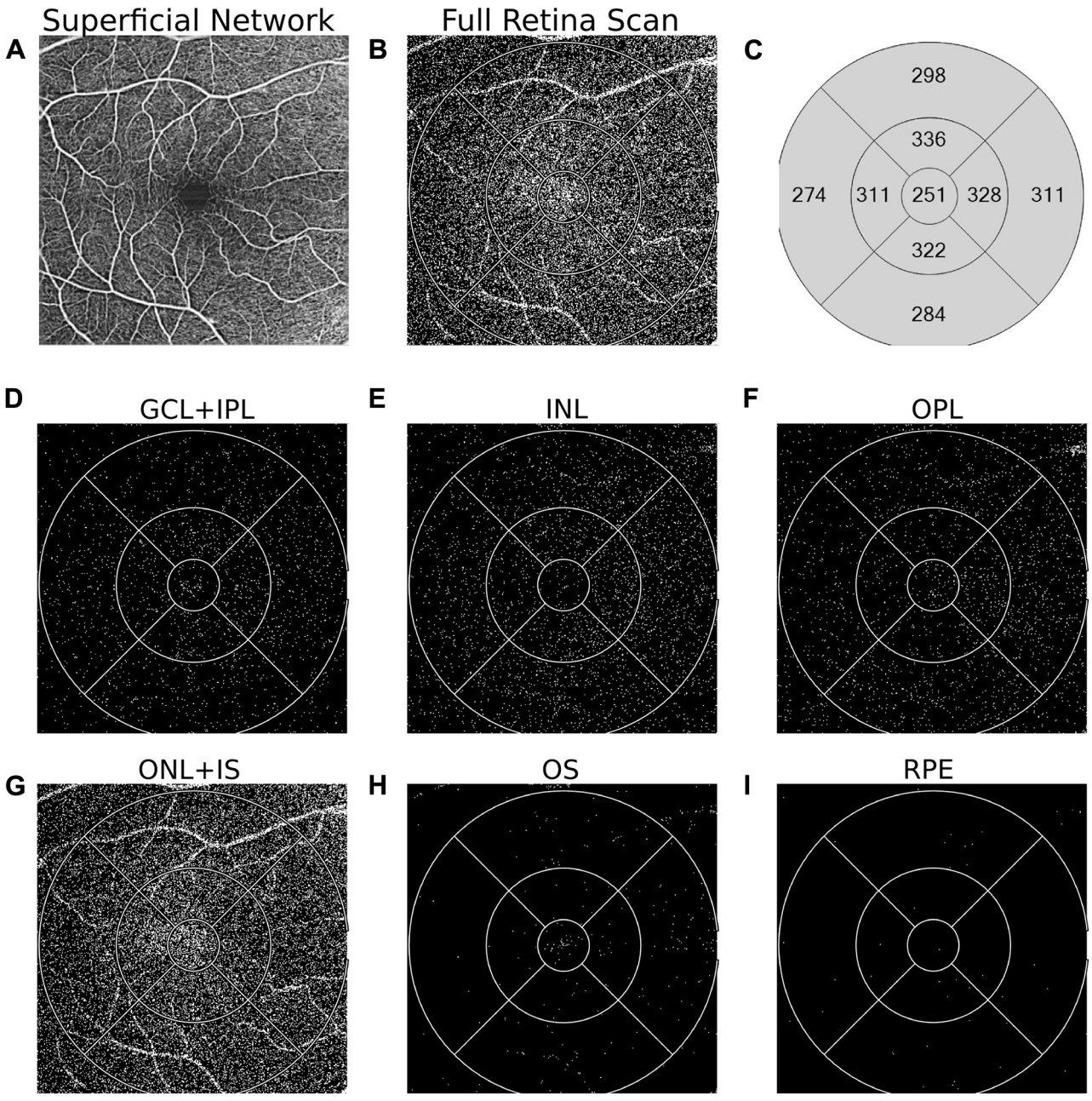

Figure 1. AngioPlex optical coherence tomography angiography low optical reflectivity (LOR) maps for the right eye of a healthy subject for the full retina scan and for each of the segmented retinal layers. **A**, Superficial vascular network acquired by the AngioPlex system. **B**, Full retina scan LOR map. **C**, Early Treatment Diabetic Retinopathy Study (ETDRS) grid of the retinal thickness obtained by the Cirrus 5000. **D–I**, The LOR maps layer by layer for the ganglion cell layer (GCL) + inner plexiform layer (IPL), inner nuclear layer (INL), outer plexiform layer (OPL), outer nuclear layer (ONL) + inner segment (IS), outer segment (OS), and retinal pigment epithelium (RPE), respectively. Locations of LOR are identified in white. The ETDRS grid is centered at the fovea.

the location and measure extracellular space increases, which are surrogate indicators of alteration of the BRB, that is, to complement the conventional OCT-microangiography.

Methods

This prospective imaging study used a prototype Cirrus 5000 AngioPlex (Carl Zeiss Meditec, Dublin, CA) modified to perform OCT-angiography (ClinicalTrials.gov no. NCT02391558). The tenets of the Declaration of Helsinki were followed. Approval was obtained from the ethics committee of the clinical site and informed consent to participate in the study was obtained from all subjects after all procedures were explained. Fifty-two eyes with non-proliferative DR (NPDR) from 28 patients with type 2 diabetes, aged between 50 and 76 years (mean ± standard deviation, 64.9±7.7) were imaged with OCT angiography using both our OCT leakage software and standard FA. Hemoglobin A_{1C} and duration of diabetes were also recorded. We classified NPDR using the Early Treatment Diabetic Retinopathy Study (ETDRS) grading.