Imaging Biomarkers in Diabetic Retinopathy

Rakesh Porwal, MS; **Hemlata Udenia,** MS
Department of Ophthalmology, Jawahar Lal Nehru Medical College, Ajmer, Rajasthan, India
E-mail Address : drrakeshporwal@gmail.com

Abstract :

Diabetic retinopathy (DR) is one of the leading causes of vision loss globally.[1] Among patients with DR, diabetic macular edema (DME) is the leading cause of moderate visual loss.[2] In the current era, imaging modalities[Optical coherence tomography (OCT), fundus autofluorescence (FAF), OCT angiography(OCT-A) and fluorescein angiography(FFA)] play an important role in deciding the treatment protocol as well as prognosticating outcome.This article will provide comprehensive summary of clinical applicability of OCTA derived quantitative metrics that appear to be clinically relevant to the diagnosis, classification, and management of patients with diabetes or DR.

Introduction :

Retinopathy is one of the most severe diabetes-related complications, and macular edema is the major cause of central vision loss in patients with diabetes mellitus. The initial and follow-up evaluation of patients with diabetes has been based on dilated ophthalmoscopy, fundus color photography, fluorescein angiography and optical coherence tomography (OCT). Newer imaging technologies, such as OCT angiography (OCTA), may further improve the diagnosis and management of the disease and aid us with a better understanding of DR. OCTA is a non-invasive imaging method which is able to provide a vascular map of retinal and choroidal tissues. This review is aimed at discussing the applications and advantages of OCTA in assessing DR.

Fluorescein Angiography :

Fluorescein angiography (FA) uses sodium fluorescein, to assess vascular integrity, and leakage. It can show microaneurysms (seen as punctate areas of hyperfluorescence), areas of nonperfusion (seen as sparse areas of hypofluorescence surrounded by large retinal vessels), and abnormal blood vessels, such as intraretinal microvascular abnormalities or retinal neovascularization (Figure 1). It can also indicate the presence of diabetic macular edema. While FA represents the gold standard to evaluate eyes with DR, this imaging technique is invasive and time-consuming. In addition, the fluorescein dye may unusually provoke nausea and allergic reactions.[3,4]

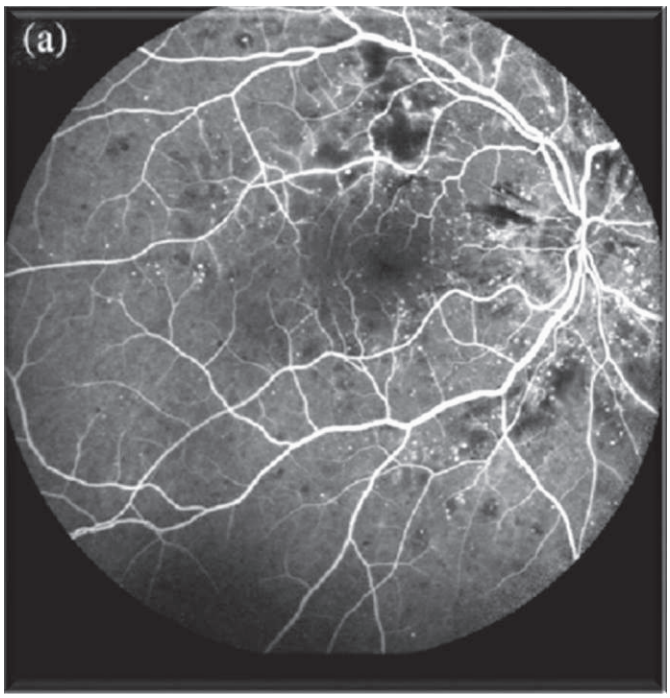

Figure 1 :
Fluorescein angiography revealing blocked fluorescence(retinal hemorrhages), pinpoint areas of hyperfluorescence (microaneurysms), and vascular staining with mild leakage in the mid-periphery with areas of capillary non-perfusion.

Optical coherence tomography (oct) oct :

works by illuminating the retina and then measuring the flying time it takes for light to be reflected back from the tissue of interest. It can provide high-resolution, 3-dimensional topographic maps of the retina non-invasively. Given its excellent reproducibility, OCT measurements of retinal

thickness are used to quantitatively and qualitatively monitor macular edema to guide the therapeutic intervention of DR .

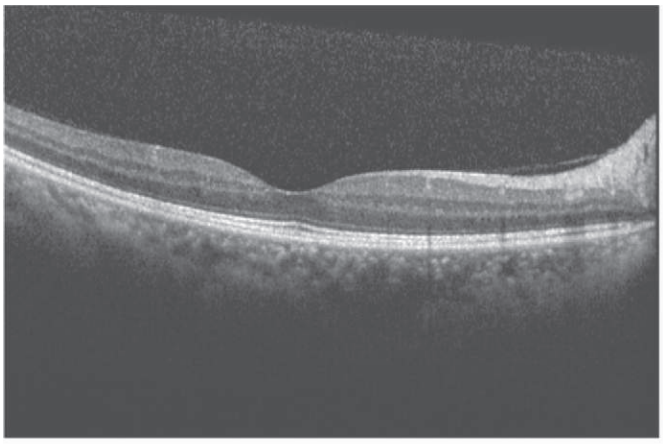

Figure 2 (a):
Widefield optical coherence tomography (OCT) revealing a normal retina.

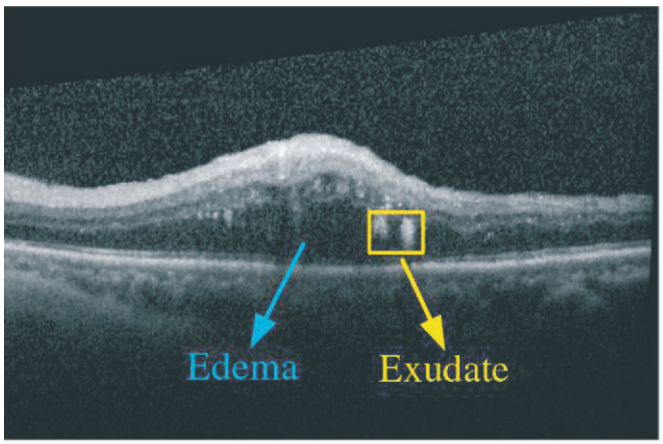

Figure 2 (b):
Wide field OCT revealing marked edema and exudates

Furthermore, OCT can detect subclinical macular edema, that may otherwise be missed on traditional methods, such as slit lamp biomicroscopy, indirect ophthalmoscopy and fundus photography. OCT captures structural information within the retina, and it does not provide angiographic information. In the diagnosis and management of diabetic macular edema, OCT is unable to diagnose macular ischemia.

Optical coherence tomography angiography (octa) :

OCTA is capable of providing depth-resolved images of the microvasculature in the retina and choroid at a depth and clarity, coming close to that of histology.[5] OCTA can display the capillary beds at distinct depths, separating the superficial and deep capillary plexuses as well as the choriocapillaris layer, which has increased our understanding of the microvascular changes in DR.

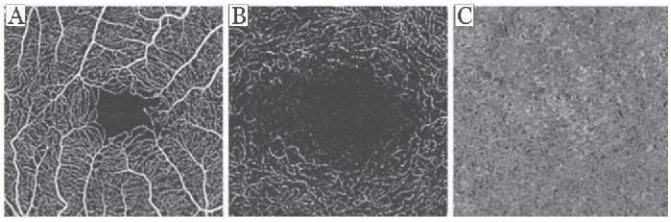

Figure 2 : Optical coherence tomography angiography images (A–C). (A) OCT angiogram of a superficial vascular plexus centered on the macula. The image of the superficial plexus was segmented from the internal limiting membrane (ILM) to the inner plexiform layer (IPL) (B) The OCT angiogram of a deep capillary plexus centered on the macula. The image of the deep plexus was segmented from the IPL to the outer plexiform layer (OPL) (C) An OCT angiogram of a choriocapillaris vascular layer centered on the macular. The image of the choriocapillaris layer was segmented below the retinal pigmented epithelium. The foveal avascular zone (FAZ) is visibly larger in the deep plexus (B) than superficial plexus (A).

(A) Comparison of Optical Coherence Tomography Angiography and Fluorescein Angiography :

Fluorescein Angiography	Optical Coherence Tomography
1. It requires intravenous dye injection and can lead to adverse reactions 2. Since 2-D, is not able to provide - Details of the distinct layers of blood vessels - Depth resolution 3. It can evaluate the breakdown of the blood retinal barrier.	1. It is based on flow motion detection and there is no need for any contrast dye injections 2. Capable of visualizing the distinct retinal vascular layers with high axial resolution. 3. Unable to evaluate the breakdown of the blood-retinal barrier

Lesions that have slow flow (microaneurysms subtypes and fibrotic neovascularization) would not be detected by OCTA. Since OCTA relies on contrast between consecutive B-scans, it will detect flow only above a minimum threshold, which is affected by the time between the two sequential OCT B-scans.[6,8]

(B) Optical Coherence Tomography Angiography Visualization of Diabetic Retinopathy Features :

Many of the common vascular features of DR, as seen on fluorescein angiography, including microaneurysms, neovascularization, and retinal nonperfusion regions, have been comprehensively studied and described using OCTA.[9]

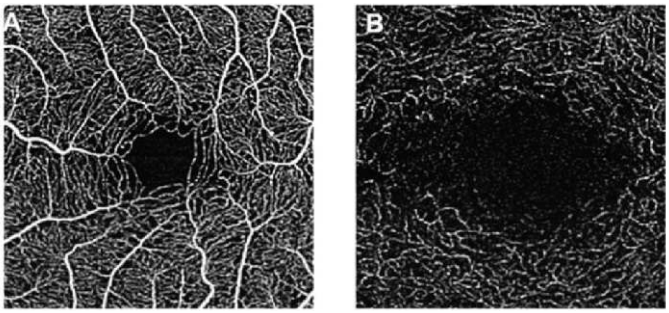

Figure 4 : Optical coherence tomography angiography (A: superficial capillary plexus, B: Deep capillary plexus)- showing network of capillaries of the superficial vascular plexus and a foveal avascular zone is surrounded by the foveal capillary network.

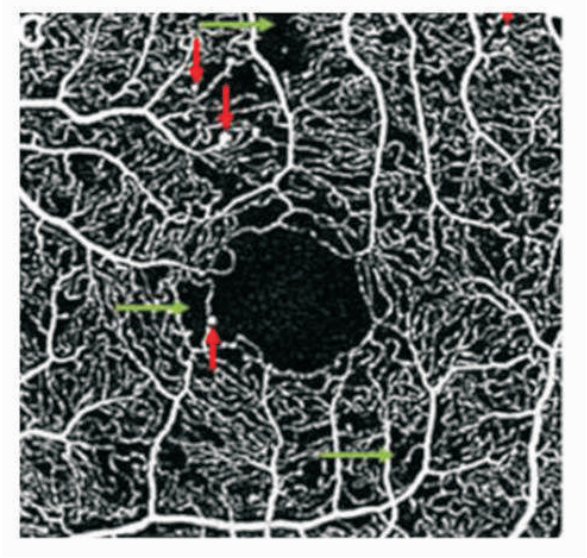

Figure 5 : OCTA (C) showing vascular abnormalities in superficial plexus layers- microaneurysms (red arrows), capillary nonperfusion (green arrows).

Microaneurysms :

Microaneurysms are seen as homogeneous hyperfluorescent punctate spots in fluorescein angiography. In OCTA, microaneurysms can appear as focally dilated saccular or fusiform capillaries, and are found in the superficial and deep vascular plexuses. The detection rate of microaneurysms may be lower in OCTA, due to the relative insensitivity of OCTA to the slow blood flow within certain subtypes of microaneurysms.

Neovascularization :

On fluorescein angiography, retinal neovascularization is identified as characteristic vessels with excessive leakage in the later phase. However, excessive dye leakage can obscure the vascular details of these abnormal vessels. In OCTA, the contrast depends on erythrocyte movement and the images are acquired over a short time, hence, dye leakages have no impact on the quality of images. As such, the vascular characteristic of neovascularization is displayed with greater clarity in OCTA compared to fluorescein angiography.

Since OCTA can provide information on the various retinal layers, it can help to distinguish between retinal neovascularization, which develops anterior to the retinal vessels and above the inner limiting membrane, and intraretinal microvascular abnormalities, which occur in the same plane as the retinal blood vessels. Therefore, OCTA may help to detect subtle neovascularization, which is difficult to differentiate from intraretinal microvascular abnormalities on clinical examination.[10-12]

While OCTA is unable to provide information on vascular leakage, morphologic evaluation of neovascularization using OCTA may be able to estimate the activity status of the neovascularization. Ishibazawa and co-workers reported that exuberant vascular proliferation (irregular proliferation of fine new vessels) in OCTA should be considered as a sign of active neovascularization. Hence, quantitative investigation of the extent of retinal neovascularization with OCTA can be used to guide effective therapeutic strategies.[13]

Peripheral Retinal Nonperfusion :

With fluorescein angiography, nonperfusion regions are seen as dark areas, with loss of capillaries surrounded by larger retinal vessels. OCTA can visualize these corresponding areas of nonperfusion within the superficial vascular plexus and the deep vascular plexus . Previous qualitative studies in DR have shown that OCTA is capable of delineating retinal capillary nonperfusion with better resolution than fluorescein angiography, providing an improved visualization of capillary dropout and changes in the foveal avascular zone (FAZ) . However, the nonperfusion areas, as seen on OCTA, may either represent capillary occlusion, capillary dropout (complete loss of capillaries) or perfusion deficits (presence of extremely slow flow or absence of flow within the existing retinal capillary) and cannot be differentiated.[81] Changes in vessels visualized on OCTA images do not necessarily indicate structural changes to the blood vessel angioarchitecture and capillary dropout, because the OCTA angiograms depict perfused vessels only. When the blood flow is very slow in diseased eyes, the decorrelation values may be below background noise floor, and therefore remain undetected .

Widefield fluorescein angiography revealed that peripheral retinal nonperfusion is a common finding in eyes with DR . These peripheral nonperfusion lesions have been associated with higher risks of DR progression and support the hypothesis that peripheral nonperfusion may be a useful surrogate for and potential predictor of proliferative DR . Therefore, numerous researchers have explored the use of widefield OCTA to identify peripheral capillary nonperfusion. They reported that widefield OCTA shows comparable diagnostic performance to that of widefield fluorescein angiography for retinal nonperfusion areas. Tan and co-workers further improved the diagnostic performance of widefield OCTA in detecting nonperfusion areas, by removing the influence of larger retinal vessels from capillaries in OCTA scans.[15] Furthermore, widefield OCTA

resulted in the higher detection of retinal neovascularization than on clinical examination, which suggests that widefield OCTA could be considered for the purpose of early detection of neovascularization.[16-17] Of note, the widefield fluorescein angiography remains a vital clinical tool in its ability to detect both peripheral retinal nonperfusion and eventual peripheral active neovascularization, which remains difficult to visualize clinically and is less accurately identified with widefield OCTA.

(C) Quantification of microvascular alterations from OCTA images :

Several methods to quantify OCTA vascular density outcomes have included perfusion density (or vessel area; calculated as the percentage of the area occupied by vessels), vessel density (or vessel length; calculated as the total length of skeletonized vessels in an area; in mm / mm2). These two parameters are widely used in DR studies. Other vascular parameters have also been described, including vessel diameter index (the average vessel caliber), fractal dimension (an index of the branching complexity of the capillary network), intercapillary area, vessel length fraction (total length of vessels), vascular architecture (such as branching angles, tortuosity and fractal dimension), and nonperfusion index.[18-21] Apart from static vascular biomarkers, another promising OCTA biomarker is vascular reactivity (the dynamic response of the vessels) .[22]

Foveal avascular zone (FAZ) measurements :

The human foveola, a rod-free region of the central retina, is responsible for central vision, as it has the maximum cone photoreceptor packing density. The absence of vasculature and the overlaying inner retinal tissue are believed to maximize the optical quality by reducing light scattering. This central avascular region is known as the foveal avascular zone (FAZ). In DR, enlargement of FAZ occurs due to the loss of capillaries in the adjacent vessels.[23] Therefore, the most common approach is to measure the area of the FAZ. FAZ area is believed to be a measurement that can indicate diabetic microvascular changes. In addition, other metrics have also been adopted to measure the FAZ, such as the FAZ perimetry, FAZ radius and FAZ circularity. The FAZ becomes irregular in shape once the obstruction of the innermost capillaries surrounding the fovea occurs. Hence, FAZ circularity on OCTA also serves as an indicator of capillary dropout and macular ischaemia.

Vessel density (VD) :

It is defined as the proportion of blood vessel area over the total measured area.

Vascular length density (VLD)/skeleton density (SD):

Vessel length density (VLD) or skeleton density (SD) is proposed to serve as a counterpart of VD which quantifies the vessel density by only considering whether the vessel exists per unit area, regardless of the vessel diameters. Consequently, compared with VD, VLD is thought to more sensitive to the perfusion changes at the capillary level.[24]

Vessel diameter index (VDI) :

It is calculated as the area occupied by blood vessel from the binarized image over the total length of blood vessel from the skeletonized image, representing the average vessel calibre of blood vessels.[25]

Fractal dimension (FD)

Fractal dimension (FD) measures the complexity of a vasculature branching pattern. FD is calculated from a skeletonized line tracing using the box-counting method, which divides each image into a series of squares for various side lengths and the number of boxes is counted.

Vessel tortuosity :

Retinal vessel tortuosity is defined as the integral of the curvature square along the path of the vessel, normalized by the total path length. The vessel tortuosity may be an early indicator of vascular damage to the retina since patients with DM were found to have increased vessel tortuosity as compared to healthy controls.[26]

(D) Quantitative OCTA metrics in diabetic retinopathy

➢ Quantitative metrics are correlated with severity of DR

Several studies demonstrated quantitative OCTA metrics on SCP and DCP are correlated with severity of DR.

Enlarged FAZ, Decreased FAZ circularity, Lower VD, Increased VDI, Decreased FD, Increase vessel tortuosity, Decreased SD	Worsen DR[27,28]
FAZ- Foveal avascular zone, VD- Vessel density, VDI- Vessel diameter index, FD- Fractal dimension, SD- Skeleton density.	

➢ Quantitative metrics are associated with DR progression

Only metrics at the DCP (FAZ, VD, and FD) showed significant associations with the risk of DR progression. The DCP may be more susceptible to ischaemic damage because it may reside in a watershed zone, where the deep layer of the retinal circulation next to high oxygen requirements of the outer plexiform layer. Taken together, quantitative OCTA analysis, indicative of diabetic macular ischaemia likely, may identify DM individuals at risk of developing DR progression independently.[29]

(E) OCTA of the choroidal vascular changes in diabetic eyes :

The choroid is mainly composed of vessels and stroma. Most choroidal space is occupied by vessels differentiated in three vascular layers- the choriocapillaris (CC), the Sattler's layer and Haller's layer. Measuring the choroidal blood flow remains challenging by using traditional dye-based angiography. The advent of OCTA makes it possible to visualize and quantify the choroidal vasculature, particularly the CC. There has been concerns about the insufficient resolution of commercial OCTA systems to measure CC because the CC is extremely dense in the posterior pole with small intercapillary distances (5–20 μm) that are smaller than the OCT system's lateral resolution (15–20 μm).[30] Therefore, researchers have proposed to use the flow deficit to analyse CC perfusion.[31] The flow deficit

represents the area where there is a lack of CC flow or CC flow below the OCT system's detectable threshold.[32] Dai and associates have reported increase CC flow deficits in diabetic eyes without retinopathy compared to age-matched controls .

Limitations of Optical Coherence Tomography Angiography :

1.The field of view with OCTA is smaller as compared with available FFA platforms. Although this issue has been overcome with montage OCTA using 12 mm × 12 mm scan, issues such as increased acquisition time and misalignment of images are still a problem.

2.It is unable to assess the dynamic characteristics of flow velocity.

3.Motion and projection artifacts are commonly encountered while analyzing the images.

Summary and conclusion :

Recent advancements in imaging techniques have allowed a multimodal approach in diagnosis and management of various retinal diseases. OCTA being a non-invasive, dyeless procedure clearly delineates the abnormal retinal vasculature and non-perfusion areas. Introduction of wider scans helps detecting vascular abnormalities involving the peripheral retina. These imaging techniques may help in the detection of subclinical disease and retinal vascular changes, even before clinically detectable changes, or development of visual symptoms.

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Association of Public Health Measures During the COVID-19 Pandemic With the Incidence of Infectious Conjunctivitis

Juan M. LavistaFerres, MSC[1]; Thomas Meirick, MD[2]; Whitney Lomazow, MD[2]; et al Cecilia S. Lee, MD, MS[2]; Aaron Y. Lee, MD, MSCI[2]; Michele D. Lee, MD[2]

Author Affiliations Article Information

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COVID-19 Resource Center

Key Points

Question What were the associations of COVID-19–associated public health measures with the epidemiology of infectious conjunctivitis?

Findings A model involving publicly available smartphone mobility data was able to show the difference in actual behavior compared with expected trends based on data from previous years and included analysis of noninfectious eye conditions for comparison. The adoption of COVID-19–associated public health measures was associated with a 34% decrease in conjunctivitis-associated search activity and a 37% decrease in emergency department encounters for infectious conjunctivitis.

Meaning These findings show that search metrics in conjunction with mobility data may provide quantifiable metrics of the associations of public health interventions with transmissible diseases.