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Review Article

OCT Angiography for the Evaluation of Diabetic Retinopathy

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Abstract

Purpose: To highlight the role of optical coherence tomography angiography (OCTA), a relatively new investigative modality, in the evaluation of diabetic retinopathy.

Methods: To evaluate the above-mentioned item based on recently published data.

Results: OCTA proves to be a safer investigative tool as compared to the traditional fluorescein angiography (FFA) and of superior benefit in better delineation of the pathological changes in both the superficial and deep retinal vascular plexuses.

Conclusion: OCT angiography may be clinically useful to evaluate the microvascular status and therapeutic effect of treatments for DR.

Keywords: *OCTA; Diabetic Retinopathy; FFA*

Introduction

The present body of knowledge on retinal vascularization morphology is derived from the works of many investigators, dating from 1930 to 1960.

These studies show that there are two (superficial and deep) retinal networks located in the inner retina [1].

Since the pioneer studies by Novotny and Alvis more than 50 years ago, fluorescein angiography of the retina has been considered to be the best imaging modality to assess and study the retinal vascular network [2,3].

Although fluorescein angiography is able to detect significant microvascular details, the intravenous dye injection can cause some side effects [4].

Furthermore, in a diseased eye, the fluorescein leaks radially through the damaged fenestrations of the vessels, not allowing an evaluation of anatomical details of the vascular morphology. The main problem with fluorescein angiography is that it cannot dissociate the two (superficial and deep) retinal networks [5].

Innovative and promising OCT angiography is able to assess retinal vessels without intravenous dye injection [6].

Fingler., *et al*. [7] and Kim., *et al*. [8] described the retinal microvasculature for the first time using phase variance OCT. In this new approach, the identification of the vessels is based on areas of motion between consecutive B-scans that are compared with static areas.

In the retina, the regions showing motion correspond to the vasculature because the vessels are distinct from other retinal tissues that are static.

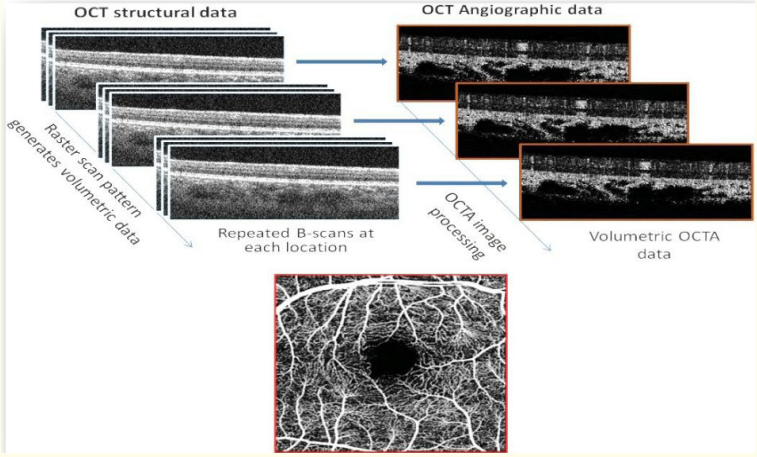

Figure 1: *At each location in a volume scan multiple B-scans are obtained and compared. Regional variation in images is inferred to represent motion [9].*

How is Motion Detected? Speckle or Intensity Decorrelation

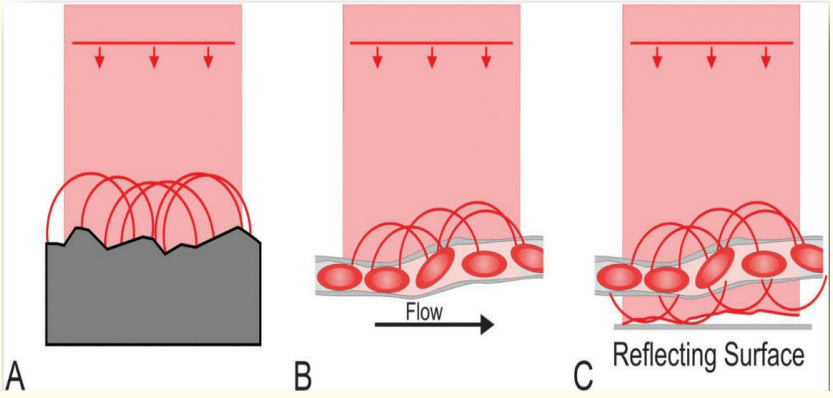

Figure 2: *A. The wave front of incoming light is shown by the straight line, and when reflected by the surface, numerous secondary waves radiate outward in a spherical fashion. These waves may cause varying amounts of constructive and destructive interference with each other setting up the condition for speckle formation. Because the reflecting surface is stable, so are the speckles.*

B. In the case of moving blood cells, the reflecting pattern changes through time as the cells change position. Thus, the speckle pattern will change.

C. Light striking the blood vessel will do more than just be reflected back to the instrument, the light will pass through the vessel, be refracted, absorbed, and scattered to varying degrees. The light passing through the vessel is free to strike deeper reflecting surfaces. The light reaching these surfaces varies over time because of the effects of the blood flow in the vessel. Therefore, any reflecting surface will seem to change over time and will be rendered as having flow [9].

A newer analytical algorithm, split-spectrum amplitude-decorrelation angiography with optical coherence tomography, was described by Jia., *et al*. [10] and is able to improve the signal-to-noise ratio of flow detection using the spectral bands separately and then averaged, showing the microvascular network and allowing the automated removal of motion errors.

Retinal vasculature

All classical histology publications highlight that there are two parallel vascular networks at the inner retinal level [11]. The superficial network consists of about 75 mm caliber vessels in a network, lying in the nerve fiber layer. The deep network is represented by a dense and complex system of smaller vessels (about 20 mm), lying in the outer plexiform layer. The superficial network is interconnected to the deep network through small vessels in vertical course [12-15].

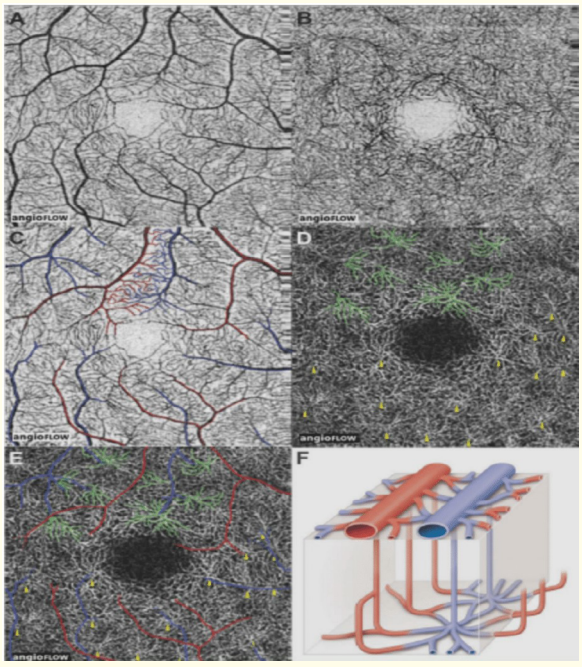

Figure 3: *Superficial capillary plexus and DCP shown by OCTA in a 3-mm · 3-mm field in a 39-year old man (right eye).*
A. Autosegmented SCP, negative image.
B. Customized DCP segmented between 70 mm and 50 mm beneath the inner plexiform layer, negative image.
C. Image A with drawing of arterioles (red) and venules (blue). The SCP is organized into transverse capillaries forming an interconnected plexus connecting arterioles and venules.
D. Image B with superimposition of vortex (green) drawing in the upper area. Other vortexes are showed using yellow arrows.
E. Superimposition of Image D and the image of arterioles and venules (from Image C).
F. Model of microvessel arrangement based on Image E: the deep capillaries are organized into polygonal lobules and converge toward a vortex, which drains into a superficial venule.

This was a simplification of the actual retinal capillary anatomy because the SCPs and DCPs were probably bilaminar, and the z-axis was exaggeratedly elongated to better display the assumed organization of each capillary bed [16].

Diabetic retinopathy

1) Non-proliferative diabetic retinopathy: Comparison of the capillary density and organization on OCTA in a healthy control and in a case of non-proliferative DR.

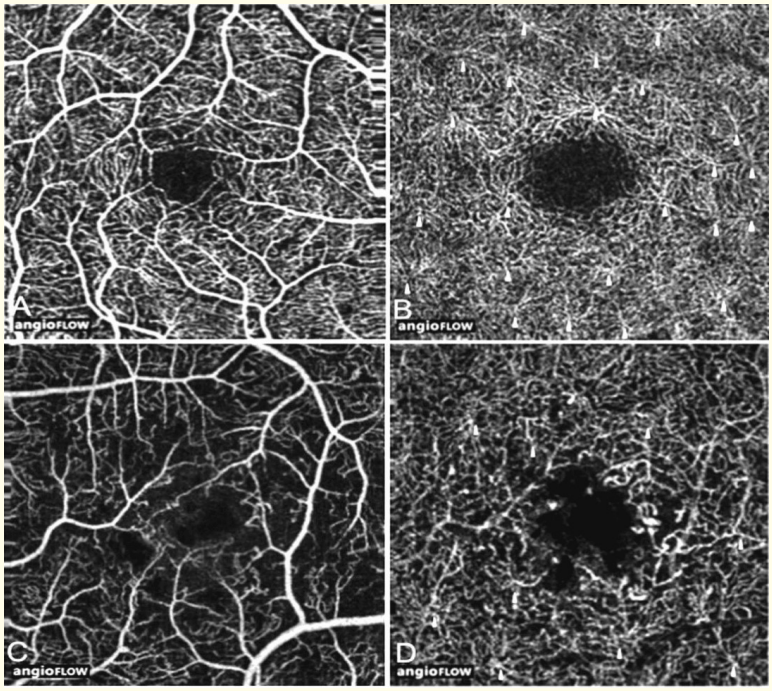

Figure 4: *A and B. Optical coherence tomography angiography of a healthy control (39-year-old man)*
A. Superficial capillary plexus with a normal capillary density.
B. Deep capillary plexus showing the regular pattern of the capillary vortex (arrowheads). C and D. Optical coherence tomography angiography of a 38-year-old man with a moderate non-proliferative DR.
C. Superficial capillary plexus showing capillary rarefaction compared with the capillary density in the healthy control. Capillary nonperfusion areas are detected outside the FAZ.
D. Optical coherence tomography angiogram of the deep vascular plexus showing less capillary nonperfusion areas than in the superficial plexus. In the deep capillary plexus, the pattern of capillary vortexes is severely impaired. Only a small number of capillary vortexes (arrowheads) could be identified compared with the regular vortex pattern in the healthy control [17].

Fluorescein angiography and OCTA comparing the detection of microaneurysms

Circles indicate the microaneurysms detected by OCTA. More microaneurysms are seen in the deep than in the superficial vascular plexus. Overall, less microaneurysms are detected by OCTA than by FA [17].

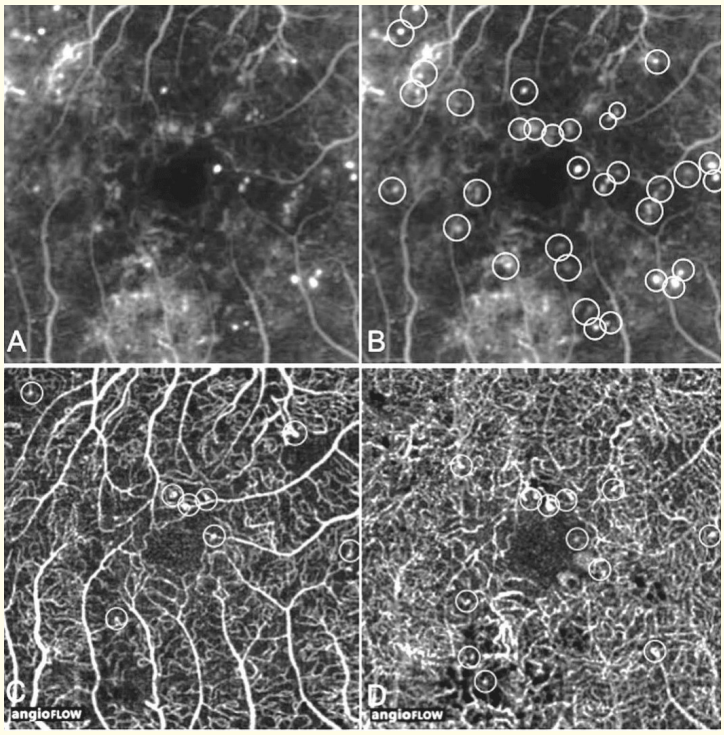

Figure 5: *In a 38-year-old woman with type 2 diabetes and severe nonproliferative retinopathy.*
A and B. Magnified view of a 3x3 mm square of early phase FA.
White circles indicate multiple aneurysms.
C and D. Optical coherence tomography angiogram of the superficial and deep vascular plexus, respectively.

Why microaneurysms are seen less on OCTA as compared to FFA?

Optical coherence tomography angiography allowed visualizing microaneurysms in both superficial and deep capillary plexus, as reported by Ishibazawa., *et al*. [18]. Microaneurysms were identified as focally dilated round, saccular or fusiform capillaries [18]. In one study, [17] microaneurysms were significantly more numerous in the deep than in the superficial capillary plexus.

However, the detection of microaneurysms by OCTA was significantly lower than by FA [17], Both large and small microaneurysms were detected by OCTA, so that the size did not appear as a predictor for identifying microaneurysms on OCTA [17].

It can be assumed that some microaneurysms were not detected by OCTA because their blood flow was too slow. It has indeed been suggested that the split-spectrum amplitude-decorrelation angiography algorithm does not allow detecting retinal capillary flow less than 0.3 mm per second [19].

Ishibazawa., *et al*. [18] have also hypothesized that the blood flow inside microaneurysms is turbulent and may not be shown using OCTA.

Another explanation could be that only some plasma is present in microaneurysms and no erythrocytes so that OCTA cannot detect the flow in microaneurysms. Histologic studies have also shown that some microaneurysms are nonperfused and their lumens contain only polymorphonuclear cells [20].

Importance of microaneurysm detection

Retinal microaneurysms are an early and important sign of the progression of retinal vascular diseases, and they are used as a main component of classification of DR severity [21-23].

Microaneurysms are believed to be an indirect sign of retinal ischemia, and OCTA findings confirmed that they mainly developed at the edge of capillary nonperfusion areas [17].

FFA vs OCTA in the detection of capillary drop outs

Optical coherence tomography (OCT) angiography showing retinal nonperfusion near the optic disc in a case of severe non-proliferative diabetic retinopathy.

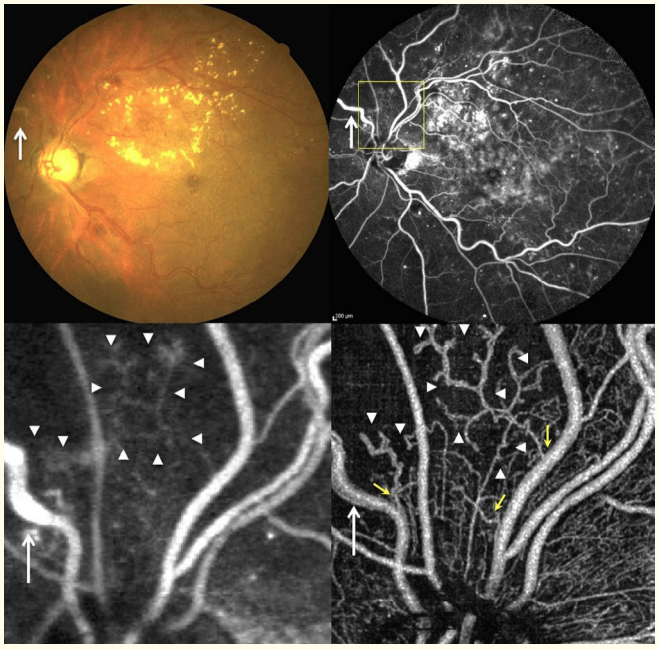

Figure 6: *(Top left) Color fundus photograph. The white arrow indicates venous beading in the superior nasal venule.*
(Top right) Early-phase fluorescein angiography (FA) shows extensive areas of retinal nonperfusion in the nasal retina. The white arrow indicates venous beading with hyperfluorescence of the venous wall.
(Bottom left) Magnified view of early-phase FA within the yellow square. White arrowheads indicate intraretinal irregular capillaries in the edge of the nonperfused area between the superior large vessels near the optic disc.
(Bottom right) An OCT angiogram of the superficial vascular layer near the optic disc. The nonperfused area is seen as a capillary-nonvisible area. White arrowheads indicate irregular capillaries [18].

The extent of capillary nonperfusion areas is quite well assessed on OCTA, and their visualization in the macular region on OCTA could be a useful parameter for grading DR severity. Indeed, edges of capillary nonperfusion areas are better delimited on OCTA than on FA, and some capillary nonperfusion areas detected on OCTA were visualized as perfused on FA. This could be explained by the superposition of the two-capillary plexus and some early leakage on FA [17].

The assessment of capillary nonperfusion areas on OCTA could be a clinically relevant parameter for DR progression monitoring [25].

The FAZ was also well visualized on OCTA and could be better delimited than on FA. The FAZ enlargement based on FA was investigated to grade DR severity [26], but OCTA may provide a more precise delineation of this area.

Intraretinal microvascular abnormalities

Unlike microaneurysms, intraretinal microvascular abnormalities were very well detected on OCTA in all cases. This could be explained by the nature of these vascular lesions as they could correspond to intraretinal neovascularization or more likely to abnormal shunts or anastomosis that developed at the edge of capillary nonperfusion areas. These intraretinal shunts could have a more rapid blood flow than do microaneurysms, which could enhance their detection by OCTA [17].

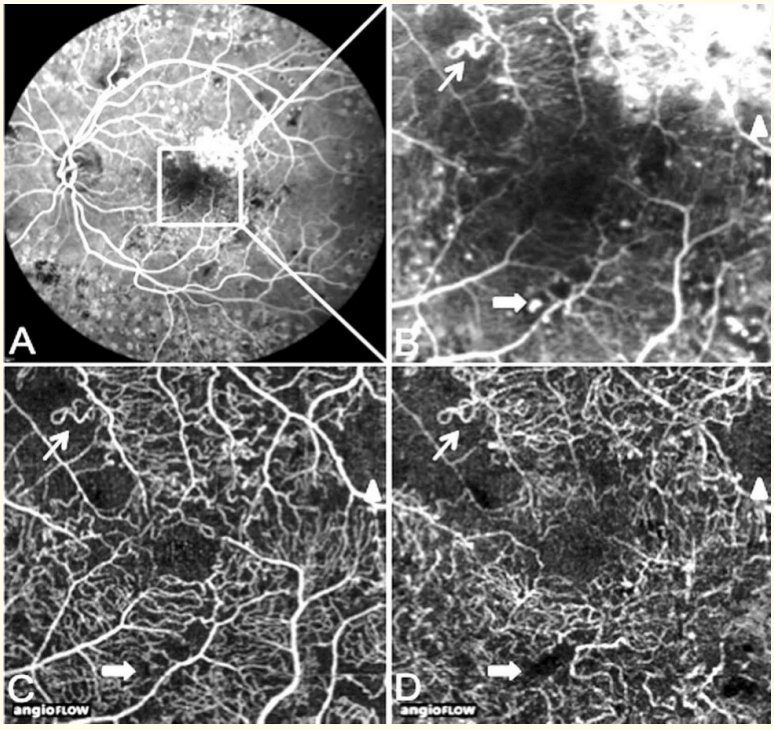

Figure 7: *Thin arrow shows an intraretinal microvascular abnormality well detected both by FA and OCTA [17].*

Diabetic macular edema

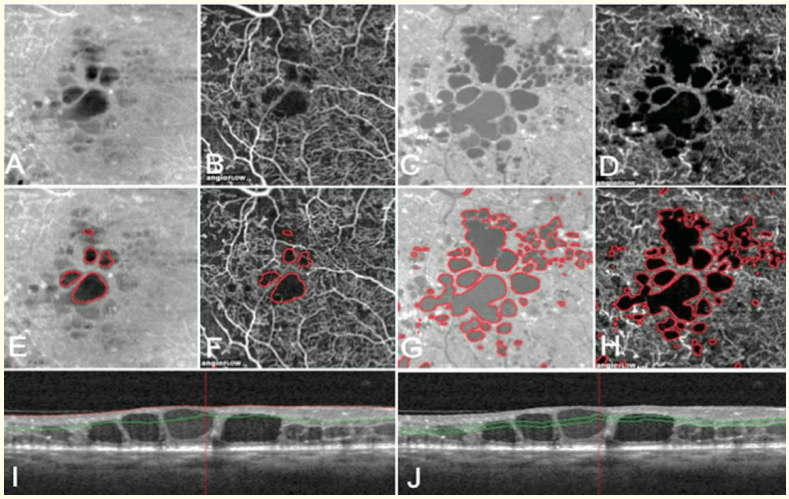

Figure 8: *Optical coherence tomography angiography of a 47-year-old man with moderate nonproliferative DR and central diabetic macular edema (DME)*

A–D. En face image and OCT angiogram of the superficial (A and B) and deep (C and D) capillary plexus.

E–H. The DME was manually delineated on the en face image, and the OCT angiogram showed the same hyporeflective areas. No capillaries are detected in the cysts nor in the superficial (F) or deep (H) capillary plexus. This could be due either to a capillary closure or the displacement of capillaries at the periphery of the cyst.

I and J. Horizontal OCT B-scans (at a larger scale than OCTA) showing the DME and the superficial and deep segmentation [17].

Proliferative diabetic retinopathy

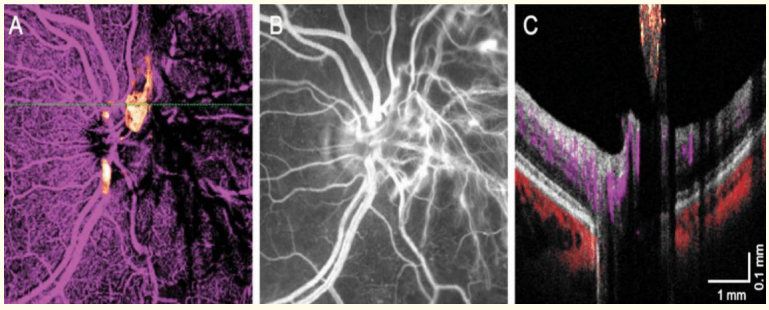

Figure 9: *A right eye with neovascularization of the disk (NVD).*

A. En face OCT angiogram discloses flow in the abnormal vessels above the disk. The NVD was cropped outside the OCT scan volume nasal to the disk and is seen as shadows rather than flow.

B. Neovascularization of the disk is clearly seen on FA. Clinically, the NVD appeared elevated above the retinal surface.

C. A cross-sectional OCT angiogram through the area of the NVD shows flow signal (orange) in the neovascular tissue that is close to the retinal surface. Further nasally, similar shadowing seen in (A) is displayed in crosssection [24].

Changes of NVD after anti–vascular endothelial growth factor (VEGF) therapy could be quantitatively observed

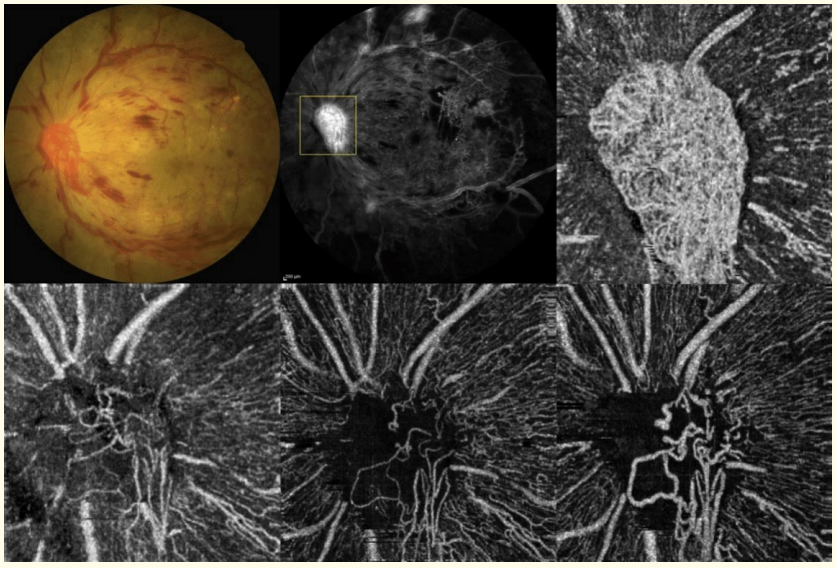

Figure 10: *(Top left) Color fundus photograph showing a fibrovascular membrane including NVD.*
(Top center) Early-phase fluorescein angiography showing excessive leakage from NVD. The detailed vascular structures of NVD could not be visualized. The yellow square outlines the area shown in the angiograms below.
(Top right) An OCT angiogram of the optic disc. Massive structures of neovascularization in the fibrovascular membrane above the optic disc are clearly seen.
(Bottom left) An OCT angiogram taken 2 weeks after intravitreous injection of ranibizumab. Neovascular vessels are remarkably reduced.
(Bottom center) An OCT angiogram taken 4 weeks after ranibizumab injection. The NVD area has further decreased. Spiral, looped, and irregular microvasculature remains on the optic disc.
(Bottom right) An OCT angiogram taken 8 weeks after the ranibizumab injection. The diameter of the abnormal vessels composing NVD has enlarged, and an increase in irregular vasculature can be observed [18].

Conclusion

OCTA proves to be a safer investigative tool as compared to the traditional fluorescein angiography (FFA) and of superior benefit in better delineation of the pathological changes in both the superficial and deep retinal vascular plexuses.

OCT angiography may be clinically useful to evaluate the microvascular status and therapeutic effect of treatments for DR.

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