Review Article

Optical coherence tomography angiography in the management of diabetic retinopathy

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The introduction of optical coherence tomography angiography (OCTA) has granted a significant improvement in the assessment of patients with diabetes. In this review, we will provide a description of the prominent OCTA findings in diabetes. In detail, this imaging technology proved that both the retinal and choroidal circulation is affected in diabetic subjects. The recent employment of widefield technology and a three-dimensional (3D) visualization in OCTA imaging are also discussed.

Key words: Choriocapillaris, choroid, image analysis, microaneurysms, optical coherence tomography angiography, retinal vessels, three-dimensional

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Diabetic retinopathy (DR) is a vascular disorder localized at the level of the retina that is featured by an impairment of the retinal vessels secondary to the chronic effects of diabetes. Although diabetes may also cause other damages to the retina with a loss of neurons and supporting cells,[1,2] the retinal vascular modifications represent the main clinical manifestation. DR may be classified into nonproliferative (NPDR) and proliferative (PDR) stages.

The introduction of optical coherence tomography angiography (OCTA) has offered a quick and noninvasive imaging tool to obtain angiographic images of the retinal and choroidal vasculature.[3-6] This review is aimed at describing recent applications of OCTA in diabetes.

OCTA and Retinal Perfusion in Diabetes

OCTA has significantly improved the evaluation and quantification of retinal perfusion. The retinal vascularization is known to be characterized by a peculiar organization as it may be divided into four plexuses according to the topographical localization: the radial peripapillary capillary plexus (RPCP), the superficial capillary plexus (SCP), the middle (or intermediate) capillary plexus (MCP), and the deep capillary plexus (DCP).[7-10] Several studies have grouped the MCP and DCP together into the deep vascular complex (DVC) as these two plexuses are closely arranged. The foveal avascular zone (FAZ) is a vessel-free round-shaped or oval-shaped region that is delimited by the three latter plexuses (SCP, MCP, and DCP).

The FAZ size proved to be significantly larger in patients with diabetes. Of note, the FAZ area was demonstrated to be increased also in subjects with type 1 diabetes and without evidence of clinically detectable DR, the latter finding suggesting that this alteration is early in diabetes.[11] Uniformly, a larger FAZ was also displayed in type 2 diabetic patients without DR.[12] Recent evidence using OCTA suggests that there is a correlation between FAZ size and peripheral ischemia in DR eyes.[13]

OCTA metrics have been employed to quantitatively demonstrate reduced retinal perfusion in diabetic patients.[14,15] OCTA analysis showed that diabetic patients without evidence of clinically detectable DR are characterized by reduced retinal perfusion as compared with healthy controls.[16,17] In patients with type 2 diabetes and DR, OCTA metrics (perfusion and vessel length densities) were demonstrated to be strictly dependent on the DR stage and to be correlated with visual acuity.[18]

Sequential OCTA scans may be employed to assess and compare the vascular impairment throughout follow-up visits. Repeated OCTA scans were employed to assess the association between treatment with intravitreal aflibercept and changes in macular retinal perfusion in PDR patients without macular edema.[19] The latter report demonstrated that macular perfusion is stable over 12 months of follow-up

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during intravitreal treatment. Assuming that nonperfusion is assumed to advance over time in eyes with DR, these results may suggest a beneficial effect of antivascular endothelial growth factor (VEGF) therapy on retinal perfusion, as also suggested using fluorescein angiography (FA).[20]

Furthermore, OCTA analysis may be employed to predict DR disease progression. In a prospective study on 73 diabetic patients, the authors showed a disease progression in 15 out of 73 subjects over a 12-month follow-up period.[21] More importantly, the latter study demonstrated that a larger FAZ size, detection of intraretinal abnormalities (IRMA), and a reduction in radial peripapillary capillary plexus perfusion at baseline were significantly associated with increased odds of progression.

OCTA was also used to assess the radial peripapillary capillary plexus in eyes with DR.[22-24] These studies displayed a significant injury of this vascular plexus in diabetic eyes. The authors in these reports did not clarify whether this damage may be directly secondary to diabetes-associated vascular damage or it is a consequence of retinal nerve fiber layer thinning and the associated decrease in metabolic demand.

Artificial intelligence has also been applied to OCTA in DR patients.[25] Sandhu and colleagues[25] displayed that artificial intelligence on OCTA data has high values of diagnosis accuracy (94.3% area under the curve of 92.4%).

Widefield OCTA in diabetes

OCTA imaging has recently granted the acquisition of wider images of the retinal and choroidal vasculature (widefield OCTA – Fig. 1). Given that widefield (and ultra-widefield) FA imaging is considered as the gold standard in the identification of DR-associated retinal neovascularization, previous reports have compared widefield OCTA and FA images to validate the former imaging modality in patients with DR.[26-28] Overall, these reports showed that widefield OCTA may detect minute neovascularization not individuated on clinical examination or color photographs and can therefore improve the clinical assessment of DR. Of note, the rate of identification of neovascularization with either widefield OCTA or FA was equivalent.[27] The main issue in widefield OCTA imaging is the occurrence of artifacts,[29,30] and the incapacity of OCTA in detecting neovascular leakage. Furthermore, widefield OCTA is still characterized by a limited extension in the visualization of the retina as compared with ultra-widefield FA systems,[31] and this may result in an underestimation of the retinal ischemia. A previous study performed a comparison between widefield OCTA and ultra-widefield color fundus photography in the identification of other DR-associated vascular lesions (i.e., microaneurysms, IRMA, and regions of nonperfusion).[27] This study showed that widefield OCTA is characterized by high-detection rates for these alterations.

Retinal perfusion using 3D OCTA in diabetes

OCTA data are mainly visualized employing *en face* two-dimensional (2D) images. However, previous reports have demonstrated that a three-dimensional (3D) visualization may grant a reliable assessment and quantification of the retinal perfusion [Fig. 2].[32-36] Two-dimensional images are obtained by flattening flow data within any given predefined space (e.g., SCP).[3-5] However, this visualization may be affected by an undervaluation of flow in the presence of overlapping vessels that may erroneously be merged when segmented in the same space. A further limit of 2D assessment is that retinal vessels crossing succeeding slabs may also be erroneously displayed twice on two different *en face* OCTA images.[34] Nonetheless, segmentation artifacts may significantly affect *en face* 2D images, more frequently in pathological conditions.[37] The latter limitation was demonstrated to significantly influence the repeatability of 2D OCTA metrics in eyes with DR.[38,39]

Conversely, a 3D visualization does not need flattening of flow data and it is independent of data segmentation.[34,35] Our group has recently used and validated an algorithm aimed at visualizing the macular retinal vasculature in 3D.[36] Moreover, we obtained two novel 3D OCTA metrics: (i) 3D vascular volume; and (ii) 3D perfusion density.[36] In the latter study, we retrospectively analyzed 15 diabetic patients and 15 healthy controls who had OCTA imaging obtained, and OCTA data were processed to generate 2D and 3D OCTA metrics. The latter study demonstrated a significant association between 2D and 3D variables. More importantly, 3D OCTA metrics significantly differ between diabetic patients and controls, and 3D OCTA metrics were characterized by elevated interobserver agreement levels. A successive study did evaluate 3D OCTA metrics in diabetic eyes with diabetic macular edema.[40] The latter report demonstrated that intrasession repeatability between repeated scans for 3D OCTA metrics was higher as compared with 2D OCTA metrics. Assuming that eyes with diabetic macular edema may be characterized by significant segmentation artifacts, our study seemed to suggest that a 3D OCTA assessment may represent a promising tool to quantify diabetic macular ischemia in DR.

Qualitative OCTA in DR

OCTA imaging has also been used to provide a qualitative description of DR-associated vascular abnormalities, which include venous loops, IRMA, and retinal neovascularization. Venous loops are visualized as lesions containing flow and localized in proximity to hypoperfused areas, the latter feature in agreement with the ischemic pathogenesis of these alterations.[41] Furthermore, OCTA may be able to detect IRMAs as tiny retinal vascular networks within the SCP and near ischemic regions.[42,43] In contrast to retinal neovascularization that protrudes into the vitreous, IRMAs are completely located within the retina as assessable using OCTA B-scans.[44] Shimouchi and colleagues[45] were also able to identify five subtypes of IRMAs (unchanged, tuft regression, reperfusion, mixed [combined tuft regression/reperfusion], and worsening with the new appearance of tuft) according to the IRMAs' changes following pan-retinal photocoagulation (PRP). Of note, the latter study displayed that some IRMAs were not characterized by morphological changes before and after PRP, these results suggesting that IRMAs may represent vascular remodeling of existing capillaries without neovascularization.[45] Using OCTA, retinal and optic disc neovascularization are visualized as well-defined microvascular structures composed of fine vessels protruding into the vitreous, as asserted above.[46] Assuming that OCTA is limited in the detection of neovascular leakage, the presence of an exuberant vascular proliferation was suggested as an indirect OCTA biomarker of leakage.

Microaneurysms are retinal capillaries' dilations that usually emerge as gross outpouchings of the vessel wall. On

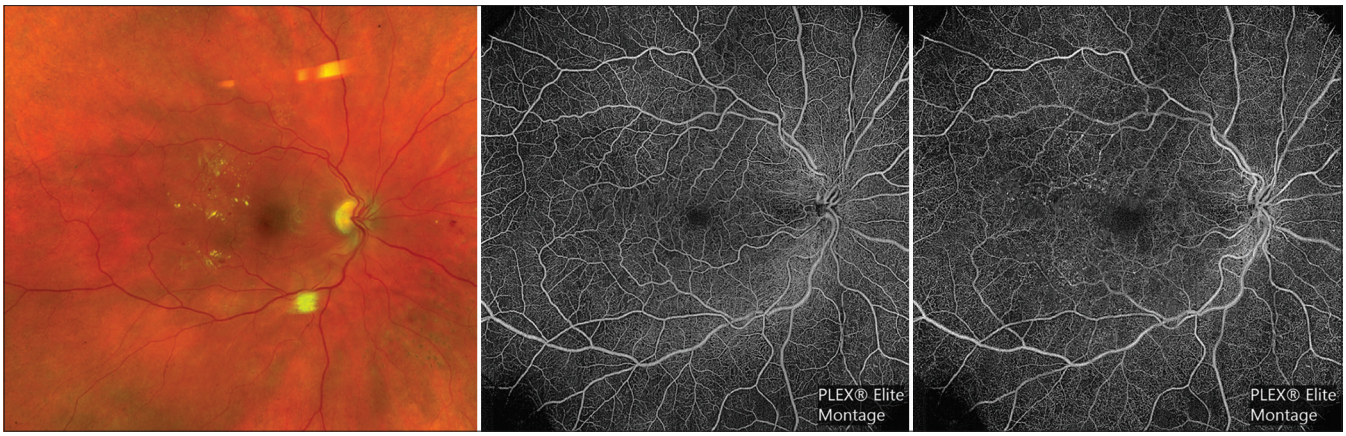

Figure 1: OCTA in diabetic retinopathy. The right eye of a diabetic patient with proliferative diabetic retinopathy. The pseudocolor image (left image) shows retinal hemorrhages, microaneurysms, cotton wool spots, and hard exudates. The widefield *en face* OCTA images segmented at the level of the superficial capillary plexus (SCP – middle image) and deep vascular complex (DVC – right image) demonstrate regions of retinal ischemia

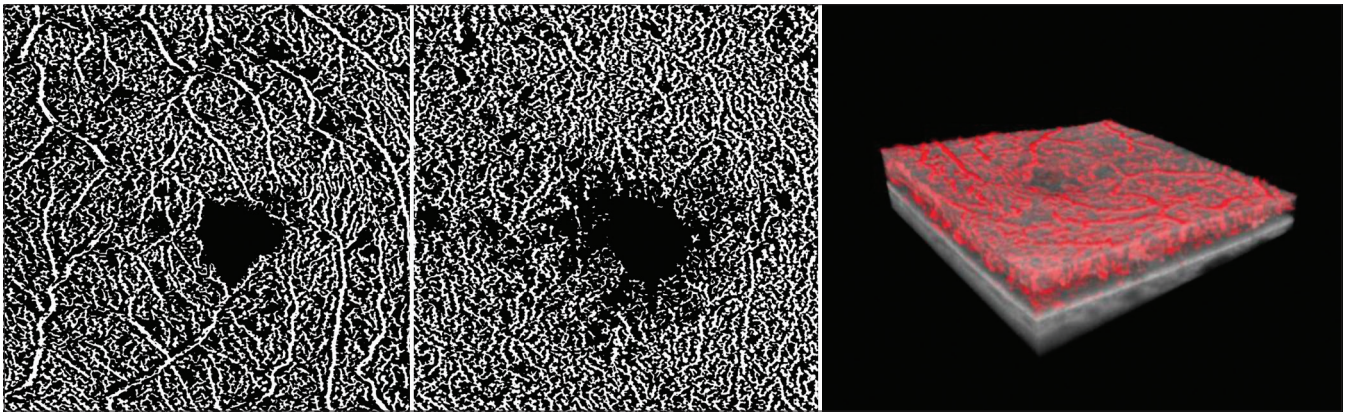

Figure 2: Representation of two-dimensional and three-dimensional OCTA visualizations. To obtain OCTA metrics, OCTA volume scans may be imported in ImageJ and elaborated. The images of the superficial capillary plexus (SCP – left image) and deep vascular complex (DVC – middle image) are binarized to measure the SCP and DCP 2D densities. To obtain 3D OCTA metrics (right image), a thresholding algorithm may be also applied to 3D OCTA data to exclude all those voxels falling below this threshold—remaining voxels are displayed in red in this figure—within the neuroretina

2D OCTA *en face* and B-scan images, microaneurysms usually appear as saccular or fusiform capillary dilations [Fig. 3].[47-49]

Using structural OCT and OCTA, our group has extensively characterized microaneurysms in diabetic patients.[48,49] Using structural OCT, microaneurysms may be characterized by a variable internal reflectivity[48] that may modify throughout the follow-up.[48] Importantly, these OCT features were showed to significantly affect the OCTA ability to detect microaneurysms, as hyporeflective microaneurysms were less prone to be detectable on OCTA images.[48] Hyporeflective microaneurysms are probably characterized by a slower flow inside, that is undetectable using OCTA.[48] On contrary, hyperreflective microaneurysms are more frequently visualized using OCTA, this probably reflecting a higher blood flow rate within these microaneurysms.[48] Given that a faster blood flow may result in damage of the blood-retinal barrier, our group also proved that the presence at baseline of hyperreflective microaneurysms was associated with a higher likeliness of accumulation of extracellular fluid at the 1-year follow-up visit.[49]

A rotational 3D OCTA assessment was employed by our group to assess diabetic microaneurysms *in vivo* [Fig. 3].[34] In the latter study, we analyzed data from 20 patients (20 eyes) with DR who had OCTA imaging obtained with the PLEX Elite 9000 device (Carl Zeiss Meditec Inc., Dublin, CA, USA). OCTA volume data were first manipulated with a novel volume projection removal algorithm and subsequently imported in ImageJ software[50] to gain a 3D representation of microaneurysms. In the latter study, we analyzed 52 microaneurysms and we showed that a 3D visualization may be helpful for an accurate assessment of these vascular abnormalities. In the 3D analysis, microaneurysms were demonstrated to invade at least two retinal layers with the inner nuclear layer as the most frequently occupied by microaneurysms.[34] Importantly, these 3D OCTA findings were in agreement with previous histopathological microaneurysms' characterizations[51] and with reports employing structural OCT.[52,53] Moreover, given that a single microaneurysm may be contained in different retinal layers, microaneurysms may be erroneously visualized on two distinct 2D *en face* OCTA images (e.g., SCP and DVC) and thus counted twice with a 2D OCTA visualization.[47] A volume-rendered 3D visualization on microaneurysms also demonstrated that most of the analyzed microaneurysms

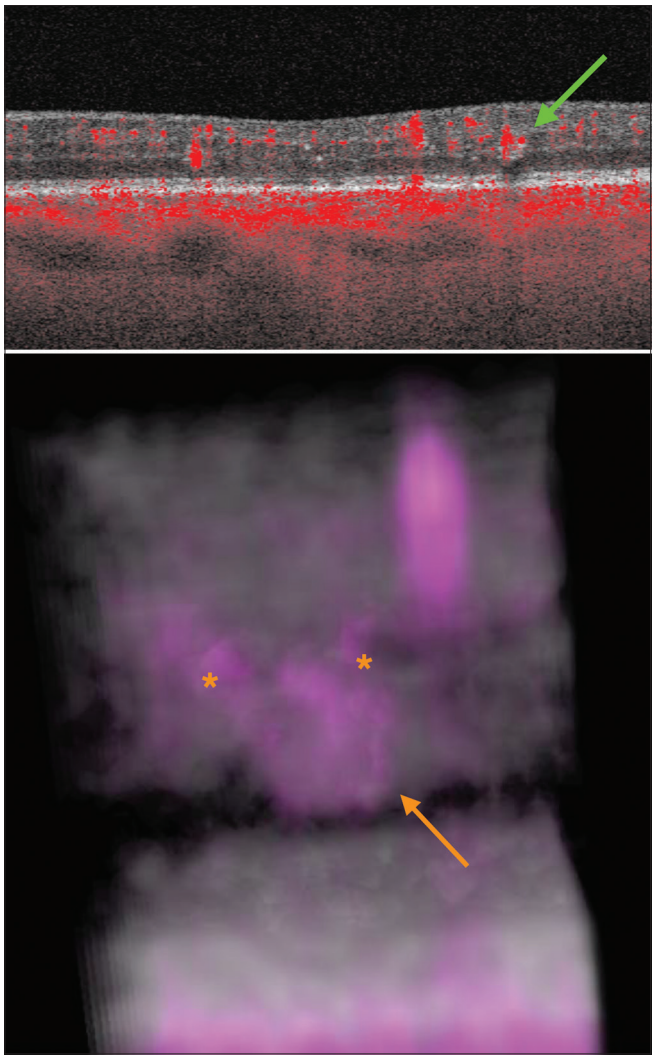

Figure 3: Two-dimensional and three-dimensional visualization of a microaneurysm. The 2D OCTA B-scan (upper image) image grants the visualization of a microaneurysm (highlighted with a green arrow). The 3D visualization (lower image) grants a better characterization of the microaneurysm and an assessment of its shape, localization, and orientation. In the 3D visualization, the microaneurysm is highlighted with an orange arrow and the two retinal vessels that seem to be connected with the microaneurysm are highlighted with orange asterisks

may be connected with two retinal vessels,[34] the latter feature suggesting microaneurysms have no tendency to grow at vascular junctions, as previously suggested with histology.[51] Of note, a small number of microaneurysms was graded to be connected with both SCP and DVC retinal vessels, this feature likely indicating the eventuality of microaneurysms to occur at the level of vessels connecting the SCP and DVC vascular beds.[34] Using 3D OCTA, our analysis was also able to assess the spatial orientation of microaneurysms with respect to the retinal layers.[34] Our results showed that microaneurysms are characterized by peculiar orientations on the three dimensions and most of them have an oblique orientation this probably reflecting the presence of Müller cells driving microaneurysms' arrangement, as these cells are known to be characterized by an oblique orientation.[34]

OCTA has also been employed to image iris perfusion.[54] OCTA was demonstrated to be a useful tool to early detect iris neovascularization in patients with DR.[55]

OCTA and Choroid in Diabetes

The choriocapillaris (CC) may be significantly affected in diabetic patients and this impairment has been suggested to be partially implicated in the raised vascular endothelial growth factors (VEGF) levels in these eyes.[4,56-58] In detail, the CC perfusion was demonstrated to be reduced in both NPDR and PDR eyes.[57] A similar impairment in CC perfusion was also shown in a subgroup of diabetic patients without clinically detectable DR.[57] Furthermore, the lower CC perfusion was proved to be significantly associated with the DR stage, with advanced stages featured by greater CC hypoperfusion.[57] Finally, two different studies employing OCTA and structural OCT demonstrated that the CC hypoperfusion in diabetic patients is significantly associated with photoreceptor damage in NPDR patients, the latter finding further increasing the relevance of CC impairment in macular damage in these eyes.[58,59]

Conclusion

In diabetes, OCTA is a key technology allowing a better characterization of vascular modifications. A number of reports have shown that diabetic eyes are featured by retinal and choroidal hypoperfusion. Moreover, OCTA-based quantitative analysis of macular perfusion may represent a useful biomarker of disease. Although widefield OCTA systems are still limited in the assessment of the periphery in contrast to ultra-widefield FA technologies, an improvement in imaging extension with the upcoming devices may significantly spread the use of this technology in eyes with DR. Finally, a 3D analysis has already granted incredible *in vivo* rendering of microaneurysms that, for the first time, resemble the histopathological visualization. In summary, OCTA is a powerful imaging tool in the clinical practice of patients with diabetes and DR.

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Conflicts of interest

There are no conflicts of interest.

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