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# Optical Coherence Tomography Angiography in Diabetes

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**Abstract:** The introduction of optical coherence tomography angiography (OCTA) has significantly improved our knowledge on the ocular vascular alterations occurring in diabetes. In this article, we will provide a review of the prominent OCTA findings in diabetes. In details, OCTA demonstrated that both the retinal vessels and the choriocapillaris are affected in diabetic subjects. The recent employment of widefield technology and a 3-dimensional (3D) visualization in OCTA imaging are also discussed.

**Key Words:** choriocapillaris, choroid, image analysis, microaneurysms, optical coherence tomography angiography

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## INTRODUCTION

Diabetic retinopathy (DR) is a retinal disorder characterized by a damage of the retinal vessels resulting from the chronic effects of diabetes. Although diabetes is known to have other effects on the retinal tissue, including a damage on the neurons and support cells of the retina,[1,2] the retinal vascular modifications constitute the main clinical manifestation. DR may be classified into nonproliferative (NPDR) and proliferative (PDR) stages.

Optical coherence tomography angiography (OCTA) is a quick and noninvasive imaging technique that may capture angiographic images of the ocular vasculature.[3–6] This review is aimed at describing recent applications of OCTA to diabetes.

## OCTA AND RETINAL PERFUSION IN DIABETES

OCTA has profoundly ameliorated the assessment and quantification of the retinal perfusion. The retinal vascularization has a peculiar organization that may be divided into 4 plexuses: 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] The MCP and DCP may be grouped together into the deep vascular complex (DVC). The 3 latter plexuses (SCP, MCP, and DCP) delimitate the foveal avascular zone (FAZ) that is round- or oval-shaped in healthy eyes.

In patients with diabetes mellitus, the FAZ area was demonstrated to be bigger in comparison with healthy subjects. Importantly, the FAZ size was proved to be larger also in subjects with type 1 diabetes mellitus and without signs of DR, suggesting that this alteration is early in patients with diabetes mellitus.[11] Similarly, De Carlo et al[12] also demonstrated that subjects with type 2 diabetes mellitus and without signs of DR are characterized by a larger FAZ. Moreover, the FAZ size was proved to be correlated with the region of peripheral ischemia in eyes with DR.[13]

Several studies have employed OCTA metrics to show a reduced retinal perfusion in eyes of patients with diabetes mellitus. Importantly, OCTA analysis demonstrated that patients with diabetes mellitus with no signs of DR have a reduced retinal perfusion in comparison with controls.[14,15] In subjects affected by type 2 diabetes mellitus and DR, OCTA metrics (perfusion and vessel length densities) were demonstrated to be strictly dependent on DR stage and associated with visual acuity.[16]

Furthermore, OCTA may be used to observe and compare the vascular impairment between following visits by performing sequential scans. Alagorie et al[17] employed repeated OCTA scans to estimate the association between treatment with intravitreal aflibercept and modifications in macular perfusion in patients with PDR without diabetic macular edema. This study proved that macular perfusion is stable over 12 months of follow-up during therapy with intravitreal aflibercept. Considering that nonperfusion is expected to progress in eyes with DR, these findings were speculated to represent a beneficial effect of antivascular endothelial growth factor therapy on retinal perfusion, as also suggested using fluorescein angiography (FA).[18]

Moreover, OCTA has been recently proved to be helpful to predict DR disease progression. In a prospective study on 73 subjects, the authors detected a disease progression in 15 of 73 patients over a follow-up period of 12 months.[19] Importantly, the latter study showed that a larger FAZ area, presence of intraretinal microvascular abnormalities (IRMA), and reduced peripapillary perfusion at baseline were significantly associated with increased odds of progression.

OCTA was also employed to investigate the radial peripapillary capillary plexus in eyes with DR.[20–22] These studies demonstrated a significant impairment of this vascular complex in eyes with diabetes. It is unclear whether this impairment is directly secondary to a diabetes-associated vascular damage or it is a consequence of retinal nerve fiber layer thinning and the associated decrease in metabolic demand.

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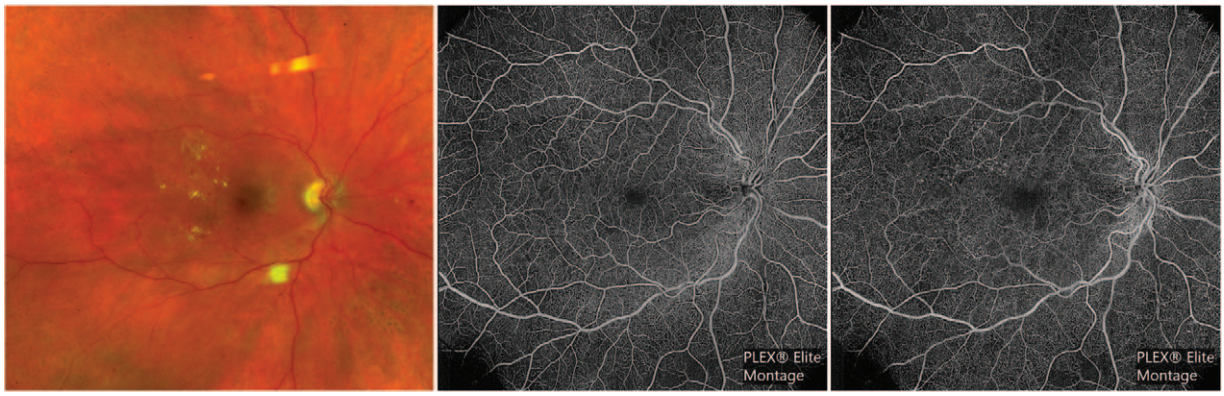


**FIGURE 1.** OCTA in diabetic retinopathy. Right eye of a diabetic patient with proliferative diabetic retinopathy. The pseudocolor image (left image) shows retinal hemorrhages, microaneurysms, cotton wool spots, and hard exudates. The widefield en face OCTA images segmented at the level of the superficial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

The variable interscan time analysis algorithm is an extension of OCTA which may assess blood flow speeds. Arya et al[23] employed this technology to demonstrate an inverse association between disease severity and blood flow speed.

Finally, a previous study has applied artificial intelligence on OCTA.[24] In details, Sandhu et al[24] demonstrated that artificial intelligence applied to OCTA has high values of diagnosis accuracy (94.3%—area under the curve of 92.4%).

## Widefield OCTA in Diabetes

Many OCTA instruments have been implemented with the capability to acquire wider images of the retinal and choroidal vasculature (Fig. 1). Assuming that widefield (and ultra-widefield) FA imaging modality has been historically considered as the criterion standard in the detection of DR-associated retinal neovascularizations, several authors have made comparisons between widefield OCTA and widefield FA images to validate the former modality in patients with DR.[25–27] Overall, these studies were able to demonstrate that widefield OCTA can individuate small neovascularizations not seen on clinical examination or color photographs and can thus ameliorate the clinical evaluation of patients with DR. Importantly, rates of detection of neovascularizations using either widefield OCTA or FA were comparable.[26] A major problem in the widefield OCTA assessment is the presence of artifacts,[28,29] and the inability of OCTA in assessing neovascular leakage. Moreover, widefield OCTA is still limited in covering the whole retina, in contrast with widefield FA (ie, especially in comparison with ultra-widefield FA systems)[30] and this may result in an underestimation of the retinal ischemia (Fig. 2). Widefield OCTA was also compared with ultra-widefield color fundus photography and widefield FA for detecting other DR-associated vascular lesions (ie, microaneurysms, intraretinal microvascular abnormalities, and nonperfusion areas).[26] The latter study's data demonstrated that detection rates of these findings were elevated using widefield OCTA.

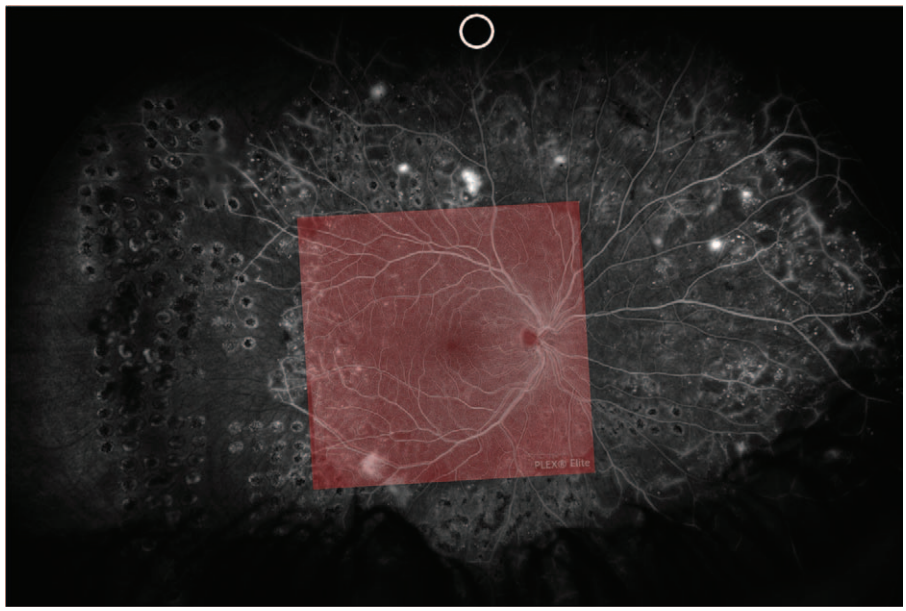

**FIGURE 2.** Widefield OCTA and ultra-widefield FA from a patient with proliferative diabetic retinopathy. The widefield OCTA image (highlighted in red) is overlapped on the ultra-widefield FA image. This assessment is aimed at demonstrating that the widefield OCTA technology is still limited in the evaluation of the retinal periphery. OCTA indicates optical coherence tomography angiography; FA, fluorescein angiography.

### Retinal Perfusion Using 3D OCTA in Diabetes

Although OCTA data are mostly displayed with en face 2-dimensional (2D) images, a 3-dimensional (3D) analysis grants a reliable visualization and quantification of the retinal perfusion.[31–35] Importantly, 2D images are obtained by flattening of data in any given specific space (eg, SCP).[3–5] However, this process may result in an undervaluation of flow as overlapping vessels segmented in the same space may erroneously be merged. An additional limitation of 2D images is that retinal vessels crossing different slabs may also be erroneously visualized twice on 2 different OCTA images (eg, SCP and DVC).[33] Finally, the en face 2D visualization may be significantly affected by segmentation artifacts, especially in pathological conditions.[36] The latter limitation was demonstrated to significantly influence the repeatability of 2D OCTA metrics in eyes with DR.[37,38]

Differently, a 3D visualization does not need flattening of flow information and it is independent of data segmentation.[33,34] Our group has recently adopted a methodology to visualize the macular retinal vasculature in 3D and successively we obtained 2 novel 3D OCTA metrics: 3D vascular volume and 3D perfusion density.[35] In the latter study, 15 patients with diabetes mellitus and 15 healthy subjects were retrospectively enrolled and their OCTA data were processed for generating 2D and 3D OCTA metrics. Results from the latter study illustrated that 2D and 3D parameters are significantly associated and 3D quantitative metrics differ between patients and controls. Importantly, 3D OCTA metrics were characterized by elevated interobserver agreement levels. Based on these findings and assuming that 2D en face OCTA images are limited by underestimation/overestimation of flow and segmentation errors, we concluded that the possibility to quantify diabetic macular ischemia using 3D analysis is promising.

## QUALITATIVE OCTA IN DR

Although OCTA may provide a quantification of retinal perfusion, this imaging modality has also been employed to describe and characterize DR-associated vascular abnormalities, including venous loops, intraretinal microvascular abnormalities, and retinal neovascularizations. In details, venous loops are detected as lesions with flow in proximity to regions of hypoperfusion, in agreement with the ischemic pathogenesis of these lesions.[39] Moreover, OCTA is able to visualize IRMAs as tiny retinal vascular networks with focal areas of increased blood flow within the SCP and in proximity to ischemic regions.[40,41] OCTA is also useful in distinguishing retinal neovascularizations from IRMAs by examining OCTA B-scans, as IRMAs are located within the retina, whereas retinal neovascularizations protrude into the vitreous.[42] Using OCTA, Shimouchi et al[43] identified 5 subtypes of IRMAs [unchanged, tuft regression, reperfusion, mixed (combined tuft regression/reperfusion), and worsening with new appearance of tuft] on the basis of IRMAs' modifications after panretinal photocoagulation. Noteworthy, the authors demonstrated that some IRMAs did not exhibit morphological changes before and after panretinal photocoagulation, suggesting that IRMAs might represent vascular remodeling of existing capillaries without neovascularizations.[43] OCTA imaging also grants the visualization of retinal and optic disc neovascularization that are displayed as well-delineated microvascular structures of new vessels.[44] Importantly, in OCTA images, most new vessels were visualized as irregular proliferation of fine vessels, which were defined as exuberant vascular proliferation. Presence of exuberant vascular proliferation was suggested as an OCTA sign of neovascular leakage.

Microaneurysms represent capillaries' dilations, which usually emerge as gross outpouchings of the vessel wall. On 2D OCTA images, microaneurysms may appear as saccular or fusiform capillary dilations (Fig. 3).[45–47]

Using structural OCT and OCTA, previous studies from our group have fully characterized diabetic microaneurysms.[46,47] On structural OCT, these vascular lesions may have variable internal reflectivity as they may be characterized by a hyperreflective, intermediate reflective, or hyporeflective content.[46] The internal reflectivity may modify throughout the follow-up.[46] Noteworthy, the structural OCT characteristics were demonstrated to influence the OCTA capability to detect microaneurysms, as lesions with a hyporeflective content are less prone to be detected on OCTA images.[46] The latter feature is probably dependent on the slow flow rate within these hyporeflective microaneurysms, which is lower than that detectable using OCTA.[46] Conversely, hyperreflective microaneurysms are more frequently visualized using OCTA, probably reflecting a higher blood flow rate within these microaneurysms.[46] Assuming that a faster blood flow may cause a damage of the blood-retinal barrier with consequent fluid accumulation, our group also demonstrated that the presence at baseline of hyperreflective microaneurysms, which are more frequently seen on OCTA, is associated with a higher probability of extracellular fluid accumulation at 1 year of follow-up.[47]

Our group first applied a rotational 3D OCTA visualization to describe diabetic microaneurysms in vivo (Fig. 3).[33] To do so, we collected data from 20 patients (20 eyes) with DR who had

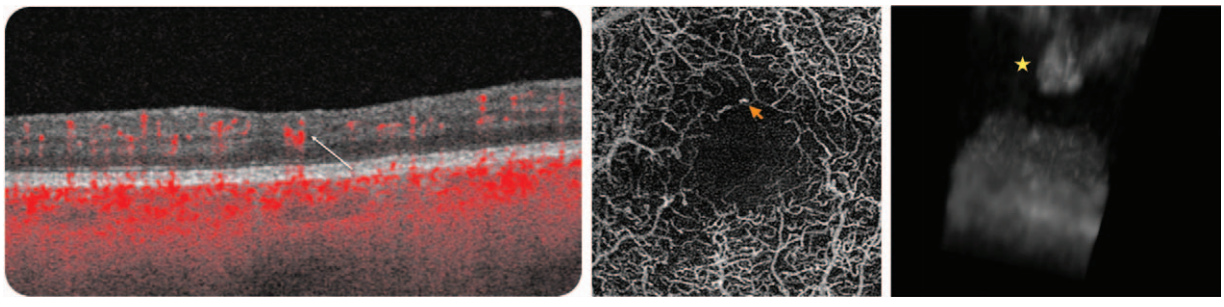

**FIGURE 3.** Two-dimensional and 3D visualization of a microaneurysm. The 2D OCTA B-scan (left) and en face DVC (middle) images grant the visualization of a microaneurysm (highlighted with white and orange arrows, respectively). The 3D visualization grants a better characterization of the microaneurysm and an assessment of its shape, localization and orientation. DVC indicates deep vascular complex; OCTA, optical coherence tomography angiography.

OCTA imaging obtained with the PLEX Elite 9000 device (Carl Zeiss Meditec Inc., Dublin, CA). OCTA volume data were first processed with a novel volume projection removal algorithm and therefore imported in imageJ software (National Institutes of Health, Bethesda, MD; available at http://rsb.info.nih.gov/ij/index.html)[48] to obtain a 3D visualization of the analyzed microaneurysms. Our study included 53 microaneurysms and, overall, our approach was proved to be helpful for an accurate evaluation of these vascular malformations. Our 3D analysis showed that most microaneurysms occupied at least 2 retinal layers and the inner nuclear layer was demonstrated to be the retinal layer most frequently occupied by microaneurysms.[33] Therefore, these 3D OCTA findings confirmed previous histopathological descriptions.[49] Notably, these findings were also in agreement with studies using structural OCT.[50,51] Furthermore, given that a single microaneurysm may be included in different retinal layers, a 2D OCTA visualization may be prone to visualize the same microaneurysm on 2 distinct 2D en face OCTA images using different slabs (eg, SCP and DVC). Therefore, the same microaneurysm may be counted twice using a 2D OCTA visualization.[45] Our study with 3D OCTA on microaneurysms also proved that most of the analyzed microaneurysms were connected with 2 vessels,[33] suggesting no tendency of microaneurysms to develop at vascular junctions, in agreement with histology.[49] Of note, a small number of microaneurysms was rated to be connected with both SCP and DVC vessels; this aspect likely reflects the eventuality of microaneurysms to develop at the level of vessels connecting the SCP and DVC vascular beds.[33] Finally, the 3D analysis provided a way to investigate the spatial orientation of microaneurysms with respect to the retinal layers.[33] In details, each microaneurysm was characterized by a peculiar orientation on the 3 dimensions and most microaneurysms had an oblique orientation as they had angles $>0$ degree with the 3 axes of the 3D Cartesian coordinate system.[33] Considering that microaneurysms traverse different retinal layers, we speculated that this oblique orientation was secondary to the presence of Müller cells, whose processes are known to be featured by an oblique orientation.[33] Of note, the 3D visualization of microaneurysms demonstrated that those microaneurysms with a horizontal orientation were mainly included in the ganglion cell complex or outer plexiform layer, probably reflecting the presence of horizonal cells within these 2 layers.[33]

Finally, anterior segment OCTA has been recently employed to investigate iris perfusion.[52] The application of OCTA to early detect iris neovascularizations may be useful in eyes with DR for timely medical intervention before complications.[53]

## OCTA AND CHOROID IN DIABETES MELLITUS

The choriocapillaris (CC) may be significantly impaired in patients with diabetes mellitus and this impairment has been speculated to be partially involved in the increased vascular endothelial growth factors levels in these eyes.[4,54–56] In details, the CC perfusion was proved to be lower in both NPDR and PDR eyes.[55] Of note, similar changes were also demonstrated in a subgroup of subjects with diabetes and no signs of DR.[55] Moreover, the reduced CC perfusion was demonstrated to be significantly dependent on the DR stage, with advanced stages characterized by a more significant CC hypoperfusion.[55] Finally, 2 different studies employing OCTA and structural OCT showed that the CC hypoperfusion in patients with diabetes mellitus is significantly correlated with photoreceptor damage in patients with NPDR; this finding further highlights the importance of CC impairment in macular dysfunction in these eyes.[56,57]

## CONCLUSIONS

OCTA represents a key technology to better characterize vascular alterations in diabetes. Several reports have demonstrated that diabetic eyes are characterized by a retinal and choroidal hypoperfusion. Furthermore, quantitative analysis of the macular ischemia with OCTA may represent a useful biomarker of disease. The employment of OCTA to detect regions of retinal hypoperfusion cannot be underrated, even though widefield OCTA systems are still restricted in the assessment of the periphery in comparison with ultra-widefield FA technologies. Finally, a 3D analysis has already furnished incredible *in vivo* visualizations of microaneurysms that, for the first time, resemble the histopathological representations.

In summary, OCTA is a powerful tool to describe and assess in the clinical practice patients with diabetes mellitus and DR.

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