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REVIEW

Optical coherence tomography angiography findings in diabetic retinopathy

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ABSTRACT

Introduction: Diabetic retinopathy (DR) is a common complication of diabetes and a leading cause of blindness in working age population. Fluorescein angiography is still the gold standard in the evaluation of retinal vascular perfusion and diagnosis of macular ischemia. However, it is a costly, time-consuming procedure and it requires intravenous injection of contrast agent, exposing patients to potential side effects. Optical coherence tomography angiography (OCTA) is a novel, non-invasive imaging technique that provides dyeless visualization of blood flow in different retinal layers.

Areas covered: An extensive review of the literature was performed to detail technical principles of OCTA and to discuss the current concepts on its application in diabetic patients.

Expert commentary: In patients with DR, OCTA shows early features in unprecedented detail: enlargement of the FAZ, areas of capillary non-perfusion, and some microvascular abnormalities can be seen with much better clarity than with fluorescein angiography. OCTA is also able to detect several features that are currently accepted as prognostic indicators in patients with DME. The most relevant are the presence of diabetic macular ischemia and pronounced microvascular abnormalities. It has been shown that these alterations may influence the response to anti-VEGF therapy.

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OCT; optical coherence tomography; OCTA; optical coherence tomography angiography; DME; diabetic macular edema; superficial capillary plexus; deep capillary plexus; macular ischemia; prognostic indicator

1. Optical coherence tomography angiography

Optical coherence tomography angiography (OCTA) is a recent, noninvasive angiography technique that provides detailed assessment of the retinal vasculature using motion contrast instead of intravenous dye. It is based on generating three-dimensional (3D) volumetric data on retinal and choroidal tissue with fast high-definition scanning.

1.1. Background

High-definition Fourier domain OCT images provide *in-vivo* detailed structural reconstruction generated from variance in light reflection (backscatter) from retinal tissues that mimic histological appearance [1]. The computational algorithms provided with commercial OCT systems have auto-segmentation capabilities which facilitate en-face viewing of the compiled b-scan images.

OCTA is based on detecting moving blood cells within retinal vessels to construct images of the retinal microvasculature (motion contrast). It exploits the specific image acquisition techniques of OCT devices and, by employing special image processing technology, extracts details of the retinal microcirculation. In general, OCTA is based on decorrelation of sequential b-scan signals (amplitude or phase or both) from the same specific location in the retinal tissue to construct an angiographic image. Therefore, it requires multiple OCT acquisitions at a very fast rate and additional motion correction to compensate for artifact induced by saccadic eye movements.

1.2. Technology

The basic platform for OCTA is a fast OCT that provides rapid successive scanning of the retina at a given point of interest, usually the posterior pole. Current commercially available systems offer small scan areas ranging from 3 × 3 to 12 × 12 mm. The resultant high-definition b-scan images are analyzed for relative change in tissue reflectivity induced by moving blood cells in retinal and choroidal vessels.

The interpretation of this large amount of data is subjected to different computing methods.

Phase Doppler approach (DOCTA) is based on calculating Doppler shift, and various terms are used to describe this process including phase contrast, phase variance, and phase subtraction [1]. Moving blood cells in vessels lead to a phase shift. This information is obtained on routine OCT scans but is not conventionally used.

Magnitude (amplitude)-based approaches are described by various terms and techniques including correlation mapping OCT, speckle variance OCT, and split spectrum amplitude decorrelation angiography (SSADA). These different techniques are used to generate angiographic imaging deployed in

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various commercially available systems [2–7]. An intensity ratio analysis called OCTARA (OCT angiography ratio analysis) is an innovative algorithm in which the full spectrum is kept intact allowing a better axial resolution [8].

Combination of both phase-based and magnitude-based calculations is exploited in optical micro-angiography (OMAG). OMAG algorithm combines phase-based and magnitude-based signals for analysis of the blood flow within the static tissue [2,9]. Recently, a comparison among OMAG, speckle variance, phase variance, SSADA, and correlation mapping was conducted. Zhang et al. reported that OMAG was able to provide the best visual results of the retinal microvasculature in terms of image contrast and vessel connectivity [6].

1.3. Commercially available systems

Currently, several commercially available OCTA devices utilize the abovementioned algorithms:

- CIRRUS OCT (Carl Zeiss Meditec, Dublin, CA) with AngioPlex uses the OMAG algorithm;
- AVANTI RTVue XR (Optovue, Inc., Fremont, CA) with Angiovue uses the SSADA algorithm;
- Swept Source OCT DRI OCT Triton (Topcon, Tokyo, Japan) with SS OCT Angio™ utilizes OCTARA;
- Spectralis platform with OCTA Module (Heidelberg Engineering, Dossenheim, Germany) uses a probabilistic amplitude decorrelation algorithm;
- RS3000 Advance OCT (Nidek Co, Ltd, Gamagori, Japan) with AngioScan OCT employs a complex algorithm with both phase and amplitude information similar to OMAG algorithm (motion detection and decorrelation analysis).

Potential efficacy of OCTA in clinical practice is described in a number of published reports based on cases and case series. There are many potential applications in the retinal field, especially for age-related macular degeneration, diabetic maculopathy, retinal vascular occlusion, macular telangiectasia type 2, and optic nerve vascular diseases [10–18]. Additionally, interesting OCTA features of disorders such as polypoidal choroidal vasculopathy, paracentral acute middle maculopathy, central serous chorioretinopathy, and sickle cell retinopathy have been reported [19–22].

However, OCTA is still an emerging technology and has its own limitations. It is based on an 'inference' of retinal circulation at a fixed time point generated by a computer software and it does not provide real information as fluorescein angiography. Additionally, OCTA cannot provide information about vascular leakage or source of leakage. Moreover, it is dependent on automatic segmentation and it is prone to artifacts and resultant errors in interpretation.

Common artifacts are vessel duplication, residual motion lines, and blood vessel discontinuity. Those are caused by motion error and improper software correction [23].

For this reason, an advanced eye-tracking system and sophisticated artifact-suppression algorithms are crucial to obtain high-quality images.

In summary, OCTA has several advantages [7,24–31]. It allows the evaluation of the retinal and choroidal vascular networks, providing structural and blood flow information at the same time. In addition, it proves a fast and 3D clear visualization of vascular structures; it is noninvasive, using motion contrast instead of the injection of a contrast dye; and therefore, it does not produce adverse reactions. On the other hand, OCTA is characterized by some disadvantages [7,24–30]. It has an increased potential for artifacts and the signal may be masked by optically dense material (such as thickened retinal pigment epithelium [RPE], hemorrhages, or hard exudates). In addition, OCTA is not able to assess leakage and vascular permeability or to detect blood flow below the lowest detectable movement. It has a limited field of view and produces lower resolution images when the scanning area is increased.

2. Macular retinal vasculature in histologic and OCTA studies

Several histologic studies showed that four retinal vascular networks can be identified in the macular region [32,33]. The superficial vascular plexus (SVP), situated in the ganglion cell layer (GCL), originates from the central retinal artery and it is mainly composed of larger arteries, arterioles, capillaries, venules, and veins vessels. The intermediate vascular plexus (ICP) is located above the inner nuclear layer (INL) and it is supplied by vertical anastomoses from the SVP [32,33]. The deep capillary plexus (DCP) lies below the INL and it is also supplied by vertical anastomoses from the SVP [32,33]. Finally, the radial peripapillary capillary plexus (RPCP) is characterized by capillaries set in parallel with the nerve fiber layer (NFL) axons [34,35].

Fluorescein angiography imaging of the macular region is dominated by the signal originating from the SVP, with poor visualization of the ICP and DCP [36,37]. As opposed to fluorescein angiography, OCTA allows the isolation of vascular plexuses due to its ability to produce depth-resolved images of the macular microvascular structure permitting a direct comparison between histologic findings and *in-vivo* imaging.

OCTA observations have shown that the SVP is characterized by large and small vessels linked to the retinal arteries and veins, supplying all other vascular plexuses. In the macular area, the SVP is organized in a centripetal scheme that converges on the parafoveal capillary ring [38]. In addition, thanks to the OCTA, it is now possible to visualize the vertical precapillary arterial segments through which SVP is linked to the other vascular plexuses [38]. SVP's vessel density decreases with distance from the optic nerve as the adjacent GCL decreases in thickness [38].

The ICP is localized within bipolar cell processes and the DCP is located in the area near the horizontal cells in the outer INL. The capillary vessels of these vascular plexuses are distinguished by a lobular structure [38]. They are uniform in size, apart from the vessels that interconnect the plexuses which are of larger diameter. According to histologic studies, these plexuses are regarded as terminal anastomotic capillary networks linked to the SVP through vertically oriented interconnecting arteries and veins [39]. Due to OCTA, it has been possible to demonstrate that these plexuses have a constant capillary density from the optic nerve to the periphery along

the maculo-papillary axis and fuse roughly at 6–7 mm from the temporal side of the fovea [38].

According to the histologic studies [34,35], the RPCP is situated in the peripapillary region and its course is longer and more linear than other plexuses. Histologic studies prove that its vessels are situated only in the posterior pole where they run near the NFL axons in an asymmetric arrangement around the optic nerve and the vascular arcades [35].

Campbell et al. proposed a new system of nomenclature for retinal vascular anatomy based on OCTA findings, grouping the four retinal vascular plexuses into a superficial and a deep vascular complex (SVC and DVC). The SVP and the RPCP constitute the superficial vascular complex and the ICP and the DCP constitute the deep vascular complex [38].

3. OCTA and the diabetic eye

Diabetes mellitus is a progressive disease affecting 422 million people worldwide [40]. About 35% of people with diabetes will develop some degree of diabetic retinopathy (DR) and 10% of them will manifest visual impairment as a result of the disease [41–43]. DR can be divided into two main stages: 'non-proliferative' and 'proliferative.' Early visible signs of non-proliferative DR (NPDR) are microaneurysms, retinal hemorrhages, and hard exudates. Proliferative DR is the most advanced condition, characterized by the proliferation of new abnormal blood vessels in response to the worsening of retinal ischemia [44].

Visual impairment in diabetes usually occurs as a result of diabetic macular ischemia (DMI), diabetic macular edema (DME), and complications of retinal neovascularization (vitreous hemorrhage, neovascular glaucoma, fibrosis, and tractional retinal detachment) [44–46].

Ophthalmoscopy, standard fundus photography, OCT, and fluorescein angiography are the principal exam techniques used for the diagnosis, staging, and management of DR [47]. Fluorescein angiography, using intravenous fluorescein dye injection, allows the detection of areas of nonperfusion, microaneurysms, intraretinal vascular abnormalities, and leakage of the dye from retinal neovascularization in proliferative DR [47]. Fluorescein angiography can visualize the superficial capillary plexus and it is the gold standard to assess foveal avascular zone (FAZ) because it allows the visualization of the perifoveal anastomotic capillary arcade defining FAZ limits. Despite the diagnostic value of fluorescein angiography, it is invasive and time consuming [48]. It also has a large number of potential side effects such as transient eye and skin discoloration, skin rashes, nausea, vomiting, and severe anaphylactic reactions [47]. Furthermore, fluorescein angiography is not recommended, unless absolutely necessary, during pregnancy and in patients with severe renal disease [47].

OCTA allows a 3D view of the retinal vasculature at different depths [7,49]. In diabetic eyes, viewing the superficial, intermediate, and deep plexus individually improves the detection of microvascular abnormalities and the understanding of pathophysiologic mechanisms [50]. Furthermore, segmentation of the retina in individual layers enables en-face visualization of vascular supply for each single layer [46]. On the one hand, OCTA images lack of information regarding vascular leakage and cystoid pooling, but on the other hand, the absence of such confounding signals allows a clearer visualization of retinal microvascular structures [47] providing detailed insights regarding DR pathophysiology.

3.1. OCTA findings in the absence of ophthalmoscopically visible DR changes

Early vascular changes in diabetic eyes consist of pericyte loss and endothelial cell proliferation leading to the development of microaneurysms and impairment of the blood–retinal barrier. The gold standard to screen for DR is dilated biomicroscopic fundus examination, where microaneurysms in the posterior pole are typically the first sign on ophthalmoscopy. However, diabetic patients often manifest early microvascular retinal changes in the absence of clinically evident retinopathy, such as capillary dropout, dilated capillary loops, tortuous capillary branches, patches of reduced capillary perfusion, irregular FAZ contours, and/or FAZ enlargement, focal, or diffuse choriocapillaris flow impairment [48,49]. OCTA is able to generate high-resolution microvascular detail allowing an easy detection of early vascular changes and delineation of the FAZ (Figure 1).

Using OCTA, De Carlo et al. defined FAZ remodeling as capillary nonperfusion adjacent to the FAZ, asymmetry of the FAZ, or loss of the normal spider web-like architecture of perifoveal capillaries [48].

Dimitrova et al. showed that superficial and deep retinal vessel density in the parafovea of diabetic patients without DR is decreased as compared to healthy subjects [51]. These microvascular findings in the foveal microcirculation of diabetic eyes are supposed to precede microaneurysms formation.

As a result, OCTA is able to detect microvascular changes in diabetic eyes before they become identifiable by clinical examination and thus it may have important implications as a powerful screening tool [48]. Moreover, vessel density measured by OCTA provides a quantitative metric of capillary closure that correlates with severity of DR and may allow staging, diagnosis, and monitoring that do not require subjective evaluation of fundus images [52].

3.2. OCTA in NPDR

NPDR is characterized by several changes in retinal microvascularization such as loss of pericytes, basement membrane thickening, and smooth muscle cell loss that leads to the development of microaneurysms, which are often the first visible sign of NPDR [47,49]. Microaneurysms are described as focally dilated capillaries with round, saccular, or fusiform shape. OCTA allows the visualization of microaneurysms in either superficial or DCPs [13]. Ishibazawa et al. reported that the detection rate of microaneurysms by OCTA is significant lower than by fluorescein angiography (FA) [13]. It is likely that some microaneurysms cannot be detected by OCTA because their blood flow is too slow. Indeed, SSADA algorithm does not allow the detection of a retinal capillary flow slower than 0.3 mm/s. Moreover, some microaneurysms are nonperfused and they contain only polymorphonuclear cells and no moving erythrocytes. Also, blood flow inside microaneurysms is often turbulent and inconstant, so OCTA is not always able to distinguish dilations from capillary ends or vertically

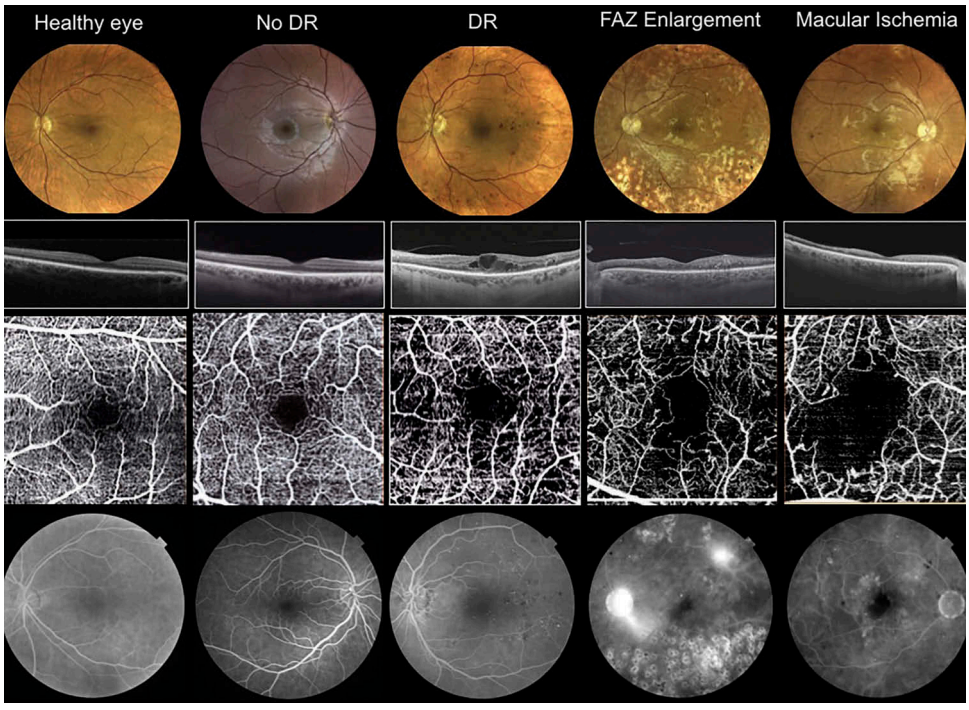

Figure 1. A comparison of FAZ changes in a healthy patient and in different DR stages.

oriented capillaries [53]. Despite these limitations, OCTA may have an important role in the study of microaneurysms and their turnover. Previous histologic studies reported that microaneurysms are mainly located in the DCP, within the INL and at its edges [53]. Since fluorescein angiography explores with more resolution the SCP, but it is not able to resolve details from the DCP, OCTA remains the only available *in-vivo* imaging technique that allows the detection of microaneurysms located in the DCP. This may be of particular interest during the early phases of DR [13].

OCTA is able to study vessel tortuosity, an indicator of the severity of NPDR. In NPDR, vessel tortuosity increases with the progression the diabetic disease either in superficial retinal layers or in deep retinal layers [54].

OCTA can also detect venous beading as contiguous focal dilations of retinal vessels, which sometimes are not homogeneously perfused, causing a partial visualization of vascular dilations [55].

Cotton–wool spots are lesions that develop as a result of ischemic injury causing accumulation of axoplasmic material inside NFL. On ophthalmoscopic examination, they are visible as whitish lesions. On both fluorescein angiography and OCTA, cotton–wool spots may correspond to areas of decreased perfusion [56].

Previous studies reported that projection-resolved OCTA (PR-OCTA) allows the identification of dilated vessels forming hairpin loops in the deeper plexus of ischemic areas. These lesions are consistent with intraretinal microvascular abnormalities, which are difficult to detect by conventional imaging but can easily be seen with PR-OCTA [50].

Finally, intraretinal hemorrhages may stop or attenuate the signal coming from decorrelated structures resulting in blocking of signal from perfused vessels [54].

3.3. OCTA in proliferative DR

On fluorescein angiography, retinal neovascularization is characterized by fluorescein leakage. However, leakage doesn't allow a clear visualization of vascular details of these pathologic vessels [47]. Conversely, OCTA allows an explicit view of vascular details [49]. Previous studies reported that, compared with healthy eyes, OCT angiograms of patients affected by PDR showed lower retinal capillary density, higher capillary tortuosity, dilated capillary segments, capillary dropouts, capillary loops, and enlarged FAZ with asymmetric contours [49]. Preretinal new vessels can be detected by focusing anteriorly to the internal limiting membrane. In PDR, en-face OCTA image enables to measure pathologic neovascularization [47] quantifying flow index and vessel area (Figure 2) [57].

Interestingly, Hwang et al. reported that areas of leakage on FA, attributed to large microaneurysms, were identified on OCTA as small tufts of vertical neovascularization protruding into the vitreous cavity [58].

Two different morphologic features of new vessels are identifiable with OCTA: exuberant vascular proliferation (EVP), which consists of fine vessels with irregular proliferation, and pruned vascular loops. EVP is present in treatment-naïve eyes with PDR and it is associated with high degree of leakage on fluorescein angiography, representing active proliferation. It has been shown that EVP may convert to pruned new vessels after PRP [59].

OCTA has also been used to study papillary vascular changes in DR. Yanoga et al. used a prototype analysis software to generate pixel density maps and color-coded retinal perfusion density maps inside the optic nerve head and in the 0.75-mm-width ring in the peripapillary region. They found that diabetic eyes had a lower perfusion inside the nerve head and in the peripapillary region compared to normal

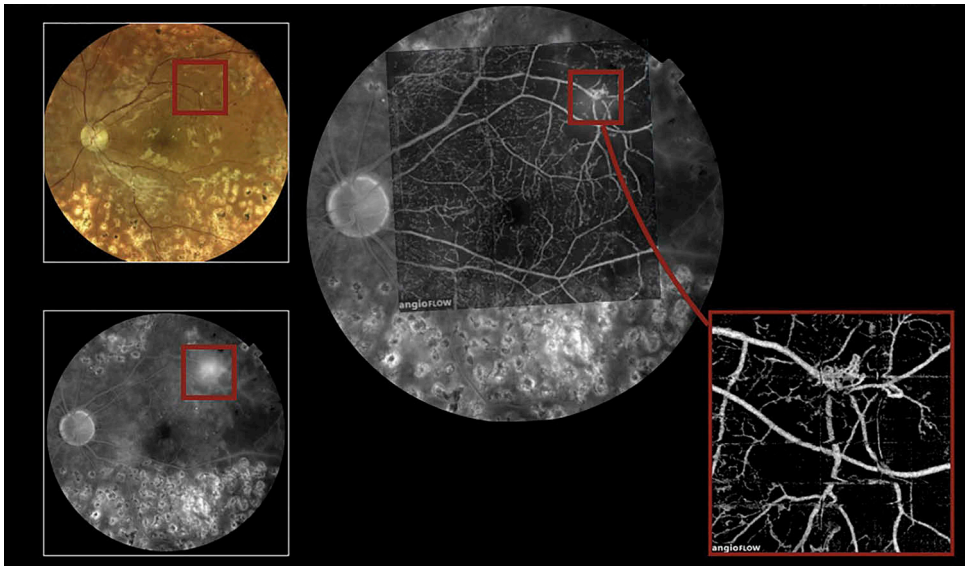

Figure 2. A 52-year-old male affected by PDR laser treated. OCTA (6x6 and 3 × 3 mm) allows a better delineation of epiretinal new vessels than fluorescein angiography.

controls. The decrease of optic nerve head perfusion correlated with the increasing stage of DR, leading to the development of disk neovascularization [60]. Clinical research showed that OCTA readily recognize disk neovascularization with a 'sea fan' configuration [61].

3.4. OCTA in DME

DME is the most common cause of visual impairment in diabetic patients. DME is associated with different capillary changes: microaneurysms, capillary closure, and leakage from perfused capillaries. Cystoid DME is due to a breakdown of the blood–retinal barrier with accumulation of fluid in a typical petaloid pattern, located in the outer plexiform and INLs. Diabetic edema mainly develops in the macular region because of the higher susceptibility of this tissue to oxidative and ischemic stress and because of its histological features: loose intercellular adhesion and absence of Müller cells in the fovea [55]. The current gold standard for the diagnosis of DME is conventional OCT. Fluorescein angiography is not strictly necessary for the diagnosis of DME, but it allows to identify the origin of leakage from impaired macular capillaries or microaneurysms [55,62].

Current prognostic indicators in DME are mainly represented by morphological and angiographic features: focal versus diffuse DME, cystoid versus non-cystoid DME, degree of macular ischemia, central retinal thickness, tractional versus non-tractional DME, and photoreceptor integrity. Other prognostic indicators are best-corrected visual acuity, cytokine profile, and polymorphisms [63–66]. OCTA has the advantage of being able to compare structural retinal changes and capillary perfusion changes in a single acquisition [55].

In eyes with DME, both the SCP and DCP show a decrease in capillary density. Cystoid spaces are localized within non-perfused areas, especially in the DCP. For these reasons, it has been suggested that fluid preferentially accumulates in areas of deep capillary dropout [62].

Spaide et al. found that in eyes with DME, flow voids are present in the region of cystoid spaces within the DCP. Flow voids colocalize with the cystoid spaces in topographic location but do not necessarily have the same size. In some eyes, flow voids are larger than cystoid spaces. This difference in size indicates that flow abnormalities cannot be explained only by the extent of the cystoid spaces. It is likely that hydrostatic pressure compresses vessels of the deep vascular plexus determining a decrease of flow below the detection limits of OCTA. It is also plausible that the expansion of cystoid spaces causes loss of viable retinal tissue, thus determining a decrease in the need of blood supply.

Typically, anti-vascular endothelial growth factor (VEGF) treatment is able to largely reduce DME. However, persistent abnormalities of the blood flow within the DCP can still be present. These abnormalities usually colocalize with areas of disorganization of the retinal inner layers, detected by conventional OCT, and may be due to poor retinal perfusion [67].

Lee et al. investigated OCTA structural integrity of the SCP and DCP in eyes with DME and its association with response to anti-VEGF agents. Microvascular abnormalities such as microaneurysms, enlargement of FAZ, and reduced flow density are more evident in the DCP than in the SCP among eyes with DME. These abnormalities are significantly more evident in DME eyes than in non-DME eyes, suggesting that integrity of the DCP is involved in the pathogenesis of DME. Moreover, only the integrity of the DCP seems to be associated with response to anti-VEGF treatment. In fact, poor responders show more vascular abnormalities in the DCP and a lower flow density in the total capillary plexus, but there are no significant differences for these abnormalities in the SCP. Furthermore, the authors found outer plexiform layer (OPL) line disruption on SD OCT as a negative predictive factor for visual acuity in eyes with DME. Interestingly, OPL disruption on spectral domain OCT topographically corresponds to areas of lower flow density in the DCP [68]. However, caution should be exercised when interpreting these results. One of the main

limitations of OCTA is its dependency on flow speed. Too slow or too fast flows are missed due to the image-processing algorithms. Moreover, in some eyes, OCTA signal from deeper layers may be reduced in thickened retinas. FAZ and flow density calculation can be biased by these issues.

3.4.1. DMI

Areas of retinal nonperfusion can be detected on fluorescein angiography as dark regions with loss of capillaries. The same nonperfusion areas can be identified with OCTA either in the SCP or in the DCP (Figure 3) [47]. Approximately 7% of eyes with DR develops DMI. This condition is one of the most important prognostic factors predicting response to anti-VEGF therapy in DME patients. It is characterized by an enlargement of the FAZ along with capillary loss in the perifoveal area [69]. Several studies showed a significant increase in the dimension of FAZ in diabetic eyes compared to normal subjects [70–72]. Gozlan et al. recently performed an accurate evaluation of DMI in eyes with NPDR through a detailed quantitative analysis of FAZ and perifoveal microcirculation using OCTA. The authors developed a nonperfusion index (NPI) of the total area of SCP by calculating the ratio between the total area of pixels with a brightness beneath a predetermined value and the total area of the image. The study reported a significant progression of FAZ grade, surface, perimeter, and NPI among NPDR stages [45]. Couturier et al. showed that areas of capillary nonperfusion are predominant in the SCP than in the DPC [53]. Similarly, Ishibazawa et al. found that capillary nonperfusion areas are larger in the SCP than in the DCP around the macula [13]. Conversely, Sambhav et al. noted a significant decrease in perfusion index of both the superficial and deep plexus but more pronounced in the deep plexus [46]. Zhang et al. found that avascular area was larger in superficial and deep plexuses compared with the intermediate plexus, which is probably affected later in the progression of DR [73]. Bradley et al. compared OCTA and traditional fluorescein angiography in the grading of DMI. The level of DMI of OCTA images of the SCP and conventional angiography was graded according to standard ETDRS protocols. Because traditional fluorescein angiography images have not allowed separate visualization of the superficial and deeper layers of the retinal vasculature, a novel grading system was developed by the authors to assess the degree of macular ischemia in the DCP and the choriocapillaris. This study demonstrated that, when ETDRS standard protocols are used, a moderate agreement in DMI grading of SCP is achieved between traditional fluorescein angiography and OCTA. Moreover, the results revealed that images of the retinal vasculature obtained with OCTA can be graded for DMI with substantial intergrader agreement. The authors suggested that this high level of intergrader agreement in evaluating macular ischemia could mean that OCTA could potentially be a valuable clinical and research tool by providing consistent and reproducible ischemia grades [74].

3.5. OCTA of the choroid in healthy and diabetic subjects

In addition to retinal blood flow, OCTA can also provide information about choroidal blood flow. In both spectral-domain and swept-source systems, the wavelength of the light source plays an important role in the visualization of choroidal structures, particularly at deeper locations beneath the RPE. Compared to conventional spectral domain platforms, swept-source OCT utilizes longer wavelength infrared light that improves penetration of light signal beyond the RPE layer. The longer wavelength of light allows swept source OCT to improve penetration into deep layers such as the choriocapillaris and the choroid. For these reasons, swept-source-based OCTA devices are to be favorite when imaging the choroid.

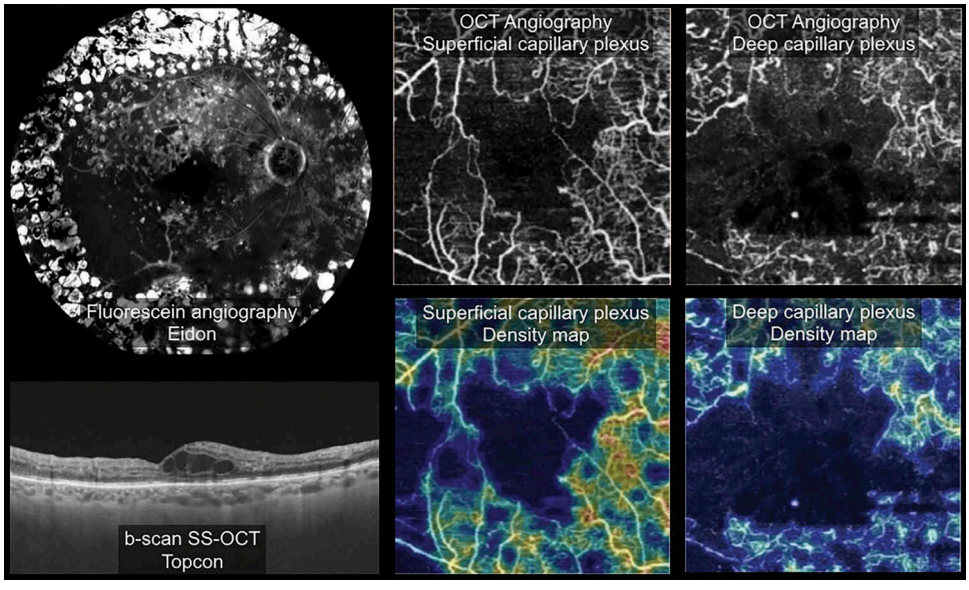

Figure 3. A 66-year-old male affected by PDR laser treated. At the baseline BCVA LE was 20/50. Late frame of fluorescein angiography (Eidon, Centervue Spa, Padova, Italy) showed microaneurysms and capillary nonperfusion throughout the posterior pole, indicating marked ischemia. Cystoid macular edema was clearly visible at swept-source OCT. Compared to fluorescein angiography, OCTA (3x3 mm) provides a better delineation of nonperfusion areas in the macular region either in superficial vascular plexus and deep vascular plexus.

Choriocapillaris c-scans are usually derived by the analysis software with a 20-μm thick slab starting 10 μm below the RPE–Bruch's membrane (BM) complex [55]. The choriocapillaris layer in healthy subjects shows a diffuse hyper-intense signal with no appreciable fine capillary network. En-face scans, shaped on the BM profile, demonstrate a relatively homogenous gray image composed by a large number of either hyper or hypo-intense pixels [55]. This pattern could correspond to the very richly anastomosed vascular network of the choriocapillaris.

Below the choriocapillaris, OCT angiograms allow the visualization of the choroid, composed by the Sattler's and Haller's layers. Sattler's layer is usually exposed at a thickness of 70 μm from the BM and, on angio b-scan, it appears as a quite continuous hyper-intense signal mixed with some hypo-intense structures [55]. A 20-μm thickness c-scan reveals the presence of several hypo-intense, black lines within a relatively continuous hyper-intense grayish background [55]. The black structures resemble to the medium vessels network, while the diffuse hyper-intense signal is due to the choriocapillaris that does not allow a clear visualization of medium choroidal vessels [55].

Below Sattler's layer, Haller's layer consists of larger diameter blood vessels. At this level, b-scan sections reveal areas of hypo- (black, tubular) and hyper-intense (grayish, diffuse) signals that correspond to the large choroidal vasculature. As it is for Sattler's layer, OCT angiogram does not allow a clear visualization of Haller's layer because of the presence of the overlying choriocapillaris and Sattler's layer that may mask the OCT signal [55].

In diabetic eyes, the choriocapillaris and the choroid are involved in the pathogenetic process, although DR is mainly considered a disease affecting retinal circulation. Different imaging modalities, such as fluorescein angiography, indocyanine green angiography, along with electron microscopy and histology, show that diabetes is associated with choriocapillaris degeneration and basal laminar deposit formation. These alterations are known as diabetic choroidopathy [75,76].

In spite of OCTA providing limited data from medium and large choroidal vessels, few studies have reported a detailed description of the choriocapillaris layer in eyes affected by DR.

Choi et al. found that in a cohort of 29 eyes with NPDR, 15 eyes showed some degree of flow impairment at the level of choriocapillaris. In detail, en-face OCTA identified choriocapillaris flow impairment that in some cases was predominantly evident in localized areas while in other cases had a diffuse appearance [49].

In severe NPDR, a careful evaluation of OCTA c-scans can show focal flow voids related to an impairment of the perfusion due to diabetic micro-angiopathy [55].

However, it must be noted that even in the most severe diabetic conditions, OCTA might not show clear signs of choriocapillaris involvement because of device limitations and due to the nature of diabetic physiopathological process [55].

4. Conclusions

OCTA technology is a significant advance over previous retinal angiography methods because it provides substantially improved identification of blood vessels in the macular region in a non invasive fashion. OCTA rapidly generates simultaneous structural OCT images and depth-encoded angiography. It works by taking sequential b-scans at the same retinal location and then calculating the logarithmic intensity difference between successive b-scans. This is referred to as the decorrelation signal, which detects both amplitude changes and phase changes. The result is high-resolution 3D OCT-based angiograms offering visualization of blood flow in the retinal and choroidal microvasculature. The three-dimensionality allows localization of flow within each specific tissue layer, a feature not available with traditional fluorescein angiography. Moreover, OCTA does not require contrast dyes, such as those used to obtain images during fluorescein angiography or indocyanine green angiography. Also, OCTA images are not compromised by dye leakage, pooling, and staining – characteristics of conventional angiography methods.

In patients with DR, OCTA shows certain early features in unprecedented detail. Enlargement of the FAZ, areas of capillary non-perfusion, and some microvascular abnormalities can be seen with much better clarity than with fluorescein angiography. On the other hand, certain microaneurysms are not visible on OCTA, probably due to slow blood flow below the detection sensitivity of the technique. OCTA is also very efficient at diagnosing areas of retinal and optic disk neovascularization within its field of view. The retina community is following with enthusiasm the novel developments in OCTA and several studies are investigating the prognostic value of OCT angiographic features in both DME and other macular conditions.

Three are the major limitations of OCTA in diabetic patients. First, the acquisition time required to produce detailed images is still relatively long and this may be an issue in patients with poor fixation. Second, due to the large amount of data processing involved, image artifacts are not unusual and may interfere with accurate interpretation of images. Lastly, OCTA provides a limited field of view, producing low resolution images when the scanning area is increased. Presently, several montage techniques provide a larger field of view, but they do not yet allow an adequate assessment of the retinal periphery in the diabetic eyes.

In conclusion, macular OCTA is a relatively fast, sensitive, and noninvasive technique. It is able to detect microvascular changes in diabetic eyes before they become identifiable by clinical examination. It also may be useful for quick, noninvasive screening for diabetes in individuals who have not yet received a systemic diagnosis. Moreover, it provides prognostic information on treatment response to anti-VEGF in DME eyes.

5. Expert commentary

OCTA is a relatively recent angiographic technique that has potential advantages in clinical practice. Currently, OCTA is the only technique that allows 3D evaluation of the retinal vasculature in different layers. Particularly, OCTA enables the identification of four vascular plexuses that cannot be portrayed by fluorescein angiography. The visualization of individual plexuses is very important in diabetic eyes because it enables the identification of vascular supply for every single layer and improves the detection of microvascular abnormalities and the

understanding of the underlying pathophysiologic mechanisms.

In the present review, we analyzed several prognostic factors obtained through OCTA. Diabetic eyes with lower flow density and higher degree of central retinal ischemia and remodeling show a poorer response to treatment with intravitreal anti-VEGFs. An important prognostic factor is FAZ enlargement. In fact, previous studies reported a significant correlation of FAZ grade, surface, perimeter, and NPI with the progression of NPDR [45]. Using OCTA, it is possible to study vessel tortuosity in both the superficial retinal layer and the deep retinal layer. This has been suggested to be a marker of hemodynamic changes and progression of NPDR [54]. Agemy et al. recently developed a system of color-coded perfusion maps and capillary perfusion density values for every single microvascular layer that can be used for DR staging with a good reproducibility and reliability [12].

The detection and evaluation of microvascular abnormalities within the retina is a critical component of managing patients with diabetes. Thus, we believe that OCTA has the potential to revolutionize the diagnosis, monitoring, and classification of diabetes-related retinal conditions.

Even though the traditional gold standard for the diagnosis of DME has been fluorescein angiography and color fundus photography, fourth-generation conventional OCT together with OCTA allows one to detect several morphological and angiographic features that are currently accepted as strong prognostic indicators in DME: cystoid versus non-cystoid DME, degree of macular ischemia, FAZ appearance, central retinal thickness, tractional versus non-tractional DME, and photoreceptor integrity.

It must be noted that the clinical research on DME-associated microvascular alterations on OCTA and their role as prognostic indicators is still at an early stage. Further studies are needed to improve reproducibility of the exam and the reliability of the technique for assessing prognostic factors associated with the response to anti-VEGF agents.

After proper validation with large and well-designed studies, OCTA may become a useful, fast, and noninvasive technique that can be applied in everyday clinical practice for the diagnosis, staging, and management of DR.

6. Five-year view

Future advancements in OCTA technology should provide faster acquisition times and expanded fields of view. In addition, new algorithms will likely be developed in order to avoid significant motion and flow projection artifacts. OCT analytics, or software tools for enhancing flow detection and reducing motion-related noise, are among the many features of this new technology that are expected to develop considerably in the next few years. Although fluorescein angiography still represents the gold standard for a precise evaluation of the retinal periphery in diabetic eyes, in the coming years, OCTA may become an alternative angiography technique that can be safely and routinely applied for the management of DR.

Key issues

- OCTA is a revolutionary imaging technique that allows non-invasive, three-dimensional visualization of the retinal and choroidal vasculature via motion contrast imaging.
- OCTA is able to detect microvascular changes in diabetic eyes before they become identifiable by clinical examination.
- In patients with DR, OCTA shows enlargement of the FAZ, areas of capillary non-perfusion, and microvascular abnormalities with a better detail than fluorescein angiography.
- OCTA provides an accurate evaluation of diabetic macular ischemia and areas of capillary non-perfusion.
- Diabetic macular ischemia and pronounced microvascular abnormalities imagined by OCTA are currently accepted as strong prognostic indicators in DME.
- Current limitations of OCTA:
- presence of artifacts
- acquisition speed
- field of view
- Advances in OCTA technologies and algorithm implementation are expected in coming years

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