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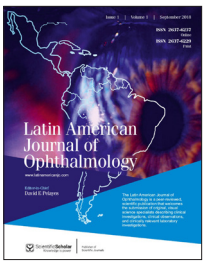

Review Article

Optical coherence tomography angiography findings in diabetic macular edema

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ABSTRACT

Optical coherence tomography angiography (OCT-A) was developed as an extension of OCT imaging. This technology allowed for the visualization of retinal microvasculature *in vivo,* without the need for contrast dye, provides depth-resolved images of blood flow in the retina and choroid with levels of detail far exceeding that obtained with older forms of imaging. OCT-A has been recently used for noninvasive evaluation of macular and peripapillary capillary network alterations in diabetic retinopathy, and the ability to clearly visualize microvascular changes has allowed for a better assessment of the microvascular retinal alterations, retinal ischemia, and neovascularization in diabetic macular edema (DME) patient. The present paper aims to review the most recent information about the findings for diagnostic interpretation in DME using OCT angiography.

Keywords: OCT-angiography, Diabetic macular edema, Optical coherence tomography angiography, Diabetic retinopathy

INTRODUCTION

Optical coherence tomography (OCT) is one of the biggest advances in ophthalmic imaging, described in the literature in 1991.[1,2] OCT angiography (OCT-A) was developed as an extension of OCT imaging and became commercially available in 2014,[1] before its commercial release, OCT-A was available as a research tool.[1] This technology allowed for the visualization of retinal microvasculature *in vivo*, without the need for contrast dye,[1] provides depth-resolved images of blood flow in the retina and choroid with levels of detail far exceeding that obtained with older forms of imaging.[1,3]

CHARACTERISTICS OF OCT-A

Fluorescein angiography (FA) and indocyanine green angiography (ICGA) have been the principal modalities for retinovascular visualization, but these imaging modalities generated a two-dimensional (2D) view on the face of the retinal vasculature and did not allow individual visualization of retinal capillary plexuses,[1] unlike OCT-A.

OCT-A has several advantages over dye angiography in terms of acquisition speed and imaging information.[4] This imaging technique can demonstrate microaneurysms (MAs), precise areas of vascular non-perfusion, vascular loops, microvascular abnormalities, neovascularization (NV), some intraretinal fluid patterns, presence of collaterals or retinal/optic nerve head NV, abnormalities of the foveal avascular zone (FAZ),[5] and cotton wool spots consistent with

fundus FA findings.[6] Additionally, OCT-A provides better volumetric visualization of the deep capillary plexus (DCP) and choroid with higher resolution compared to FA and ICGA.[1,7,8]

As a functional extension of structural OCT uses repeated B-scans to detect motion,[1,9] acquiring information by analyzing decorrelation signals of erythrocyte movement to visualize capillary network, to offer *in vivo* visualization of the retinal and choroidal capillary networks in different layers in a depth-resolved fashion, without the need for time-consuming dye administration.[1,4,7,10]

The fact of not using dye to visualize vessels confers multiple advantages.[1] OCT-A generates high-contrast images that are not blocked by dye leakage from vessels and can clearly delineate the abnormal vasculature and capillary non-perfusion areas (NPAs),[5] leading to more pronounced definition of retinal vasculature,[1] thus allowing a higher detection rate of capillary NPAs.[4] Besides, this dye-free imaging modality does not expose patients to the risks associated with contrast dye, which range from mild allergic reactions to anaphylaxis.[1]

This novel imaging modality allows for detailed visualization of the posterior retina in a cross-sectional fashion[1] and it can separately analyze each of the three retinal capillary plexus which is important for understanding the pathophysiologic changes in diabetic retinopathy (DR),[5] mainly as an essential tool in the detection and monitoring of diabetic macular edema (DME), and diabetic macular ischemia (DMI) with inner retinal thinning.[4] This segmentation of volumetric data leads to the identification of retinal capillary plexuses individually, providing detail, and resolution similar to that of histologic studies.[1]

OCT-A offers a non-invasive, rapid imaging modality which is performed through repeated scans at the same retinal location, and each scan capture is separated by a brief lapse in time. As light is reflected back, a difference in signal will be detected between the two scans. This difference is due to motion between the scans and is termed decorrelation signal. Because the retina is a static tissue, the decorrelation signal is attributed to the movement of blood through the retinal vasculature.[1,4,9] Thus, a decorrelation map is generated that mirrors the flow of blood in the back of the eye, rendering a representation of its vascular networks.[1]

OCT-A technology has the advantage that it enables three-dimensional (3D) visualization of retinal microvasculature at different depths[7] and offers the possibility of also imaging the radial peripapillary capillary network and the intermediate and DCPs. This capability opens a variety of possibilities for disease description and quantification, research into pathogenesis of disease, and development and evaluation of new treatments.[3]

Widefield OCT-A has emerged as a promising tool with the potential to replicate or replace FA in the diagnosis or monitoring of disease progression. Widefield OCT-A has been compared to ultra-widefield FA in DR patients. Recent observational studies have shown that wide-field OCT-A is comparable to ultra-wide-field FA in the detection of NV.[5] Likewise, as an aid in DME in terms of the differentiation of cystoid space and non-perfused area by the location of the empty flow area.[6]

Beyond its many advantages OCT-A has a number of limitations.

OCT-A cannot visualize dye leakage, a common landmark of inflammatory vascular pathology and a sign of blood-retinal barrier breakdown,[1] and it is unable to assess dynamic characteristics of flow velocity, and leakage which is sometimes necessary to assess various retinal pathologies.[4]

OCT-A cannot provide information on transit time or vascular filling either,[1] and it is unable to assess the dynamic characteristics of flow velocity.[5]

Flow detection in OCT-A requires scanning a single location multiple times, as previously mentioned. This increases image acquisition times, especially for larger scan areas;[1] and while newer devices with faster scan speeds have shorter image acquisition times, capturing large amounts of data at high speeds translates into slower processing and savings times.[1]

The ability of OCT-A to detect pathology in the retinal periphery, such as peripheral non-perfusion, remains limited.[1] The largest scanning area that is achievable with commercially available OCT-A devices is 8 mm by 8 mm which grants a field of view of approximately 30° and even with the introduction of wide-field OCT-A that is able to generate images of 12 mm by 12 mm the field of view is still not comparable to standard and ultra-wide field FA/ICGA; thus, OCT-A has poor ability in generating good quality peripheral retinal images.[4,5] To overcome this limitation, it has been created the montaging algorithm with the finality of generating a wider field of view.[4] This approach, however, results in an increase in scan acquisition time and misalignment of the images.[5]

One of the major limitations of the OCT-A technology used is the accuracy of segmentation. The automated segmentation lines are not always precise, especially when there are major changes to the retinal architecture (like in the case of DME).[9]

OCT-A images themselves result from an automated algorithm might cause several artifacts that lead to misinterpretation of images,[6] and problems such as motion and projection artifacts are commonly encountered while analyzing the images.[5] While this can be corrected through projection removal algorithms, the method may potentially

result in loss of flow information within the deeper layer, giving a disjointed image.[4]

OCT-A imaging is vulnerable to artifacts that arise from image acquisition and processing.[1] Although the purpose of this review is not to mention in detail the artifacts that can be generated with this innovative technology, it is very important to recognize them to achieve an adequate correlation with the clinical aspect and to achieve a precise interpretation of the information added and presented with other imaging modalities.

A very brief mention will be made of the artifacts, reported in the literature,[1] to take them into account when interpreting the images, even more so when analyzing cases of DR, especially in cases of DME.

Projection artifacts

These are perhaps the most prominent and principal artifacts seen in OCT-A. As the OCT beam penetrates the retina, it first encounters the superficial capillary plexus (SCP) and some of the light is reflected from this plexus to be interpreted by the device. The light that is not reflected continues to travel through the retina until it reaches the retinal pigment epithelium (RPE). The RPE acts as a natural reflector, reflecting light back toward the OCT-A device. The light that arrives at the RPE is influenced by the flow above it and generates a decorrelation signal that mimics the superficial vascular beds. The result is the erroneous appearance of superficial vessels in the external retina and the RPE, and this misinterpretation of flow is called a projection artifact.[1]

Signal intensity

For example, in the case of cataracts or opacities that reduce the penetration of light through the vitreous, the result is a reduction in the signal-to-noise ratio and the overall quality of the image.[1]

Motion artifact

During the taking of the images and the execution of the study, patients can move their head, neck, and eyes. This type of movement is known as a bulk motion. Any movement can be misinterpreted as a flow rather than the movement of the erythrocytes. Thus, bulk motion creates a type of artifact called a "motion artifact." On an en face image, motion artifacts appear as horizontal lines throughout the scan.[1]

Shadowing artifact

This artifact is generated when the light beam from the OCT is blocked and cannot reach the outer layers of the retina. Drusen, hemorrhage, and vitreous floaters are pathological features that can cause shadows.[1]

Segmentation artifacts

Some retinochoroidal pathologies, drusen in age-related macular degeneration (AMD), myopia and fluid and distortion of the retinal architecture in DME cases can drastically alter the anatomy of the retina and cause the algorithms to mismark the boundaries of the layers. It is necessary to mention that the segmentation algorithms were developed obtaining images of healthy eyes with different retinal layers.[1]

Different OCT-A platforms and segmentation algorithms have been described. These devices vary in their light source, as well as their light detectors.[1]

The AngioVue software of RTVue XR Avanti (Optovue, Fremont, CA) was the first commercially available OCT-A system.[8]

The AngioPlex OCT-A instrument (Carl Zeiss Meditec, Dublin, CA) improved the CIRRUS HD OCT scanning rate to 68,000 A-scans per second and introduced a tracking software known as Fast-Trac retinal-tracking technology.[8]

Spectral domain OCT-A (SD OCT-A) uses a near infrared super luminescent diode with a wavelength of ~840 nm as the light source and a spectrometer as the detector; on the other hand, swept source OCT-A (SS OCT-A) uses a tunable scanning laser with a wavelength of ~1050 nm as a light source and a single photodiode as a detector.[1]

DME

DME, as widely described, is the most common cause of visual impairment in diabetic eyes, especially in patients with non-proliferative DR (NPDR).[11] DME can occur at any stage and is identified by retinal thickening and hard exudates.[12]

DME refers to the accumulation of fluid in the macula due to leaking blood vessels.[4] Pericyte loss and endothelial cell proliferation in patients with DR weaken the vascular walls, resulting in the formation of MAs and increased vascular permeability by upregulation of inflammatory cytokines.[6] Leakage of MA, NV, and abnormal capillary staining are the factors contributing to DME.[10]

The pathophysiology of DR/DME is complex and multifactorial and is currently considered to be a chronic, low-grade inflammatory disorder, involving all cellular elements (vascular, neural, and glial) in the retina.[13] The common pathological changes are blood-retina barrier (BRB) disruption by increased vascular endothelial growth factor (VEGF) and inflammatory cytokines under hyperglycemia conditions.[10]

It has been established that under normal circumstances, and relating it to the retinal plexuses, the production of fluid can originate from the SCP that runs through the interstitial

tissue of the retina to be absorbed by the actions of the Müller cells and the DCP.[9] The rupture of the internal hemorrhagic barrier and the consequent increase in leakage from the SCP could reach a level where the fluid removal capabilities would be exceeded.[9]

In addition, disruption or damage to the DCP may lead to DME development because DCP is the principle venous outflow system for retinal capillary plexus.[5]

According to parameters used in the DR Clinical Research Network, DME has been defined as: Macular edema identified as center-involved macular edema (central subfield thickness ≥ 305 mm in men or ≥ 290 mm in women)[9] and can occur at any stage and is identified by retinal thickening and hard exudates.[12]

OCT-A has been recently used for noninvasive evaluation of macular and peripapillary capillary network alterations in DR,[13] and the ability to clearly visualize microvascular changes has allowed for a better assessment of the microvascular retinal alterations, retinal ischemia, and NV in DME patient.[14,15]

There are limited data in the literature on its use in patients with DME.[13] This is because in DME, OCT-A can be difficult to interpret due to the presence of artifacts (previously described) that can be caused by intraretinal cystoid spaces, which can displace retinal vessels and impact the evaluation of areas of reduced/no perfusion.[13] While OCT can illustrate structural changes prominently and help in the detection of these cystic spaces, OCT-A has low reliability in visualizing the DCP in patients with DME.[5]

Severely altered anatomical features of the macular area (such as severe cystoid macular edema [CME]) cause segmentation errors.[16,17] The accumulated fluid can interfere with the OCT imaging and segmentation capabilities, as accurate identification of anatomical landmarks is required for the complex automated process required for correct segmentation, and incorrect segmentation can affect the OCT-A image[4] and, therefore, influence its correct interpretation.

As mentioned, in cases of retinal edema, the segmentation of the retina can be problematic due to an increase in the thickness of one or more layers and a decrease in others, which causes failure in their automatic recognition.[15,16] In addition, increasing the thickness of the retinal layers could reduce the signal intensity of the underlying choroid, thus causing a distorted vessel density (VD) analysis.[15,16] However, using an internal segmentation of the inner edge of the retina and an external segmentation of the RPE, allow to obtain details of the perfusion of the macula in the presence of DME, although it can be difficult to differentiate between SCP and DCP.[4]

In DME there is an inverse relationship with OCT-A signal intensity because the fluid weakens the reflected signal from deeper layers.[4]

Several morphological changes of DR and DME can be detected by OCT-A: MAs, intraretinal micro-vascular abnormalities (IRMAs), vascular loops, NPAs, NV, even before they are appreciated clinically or on fundus photography,[5] and it is able to offer additional information with respect to the localization of these changes.[4,6] The most relevant characteristics of the OCT-A findings are shown in Table 1.

MAS

The loss of pericytes and the proliferation of endothelial cells in patients with DR weaken the vascular walls, resulting in the formation of MAs;[6] are a hallmark of this disease and the alterations in the BRB are characterized by their loss and endothelial cell-cell junction breakdown.[2]

A MA itself is one imaging biomarker used to detect the progression of DR and assess the pathophysiological treatment response of central-involved macular edema in patients with Type 2 diabetes.[6] These lesions often manifest in early DR. OCT-A is able to localize MAs precisely and is able to pick up MAs, not otherwise shown on a dilated clinical examination.[4,18,19] There are, however, discrepancies, among studies, in regard to the detectability of MAs between FA and OCT-A.[4]

It is not still clear whether OCT-A is comparable to FA in terms of MA detection.[4,5] It has been reported most MAs detected by OCT-A has a corresponding finding in FA.[4] Schwartz *et al.* and Ishibazawa *et al.* demonstrated that OCT-A can detect MA that would not otherwise be detectable in FA.[19,20]

Ishibazawa *et al.* concluded that OCT-A techniques could be used to study the origin of MAs, describing them as demarcated saccular or fusiform shapes of focally dilated capillary vessels in the inner retina.[2,19]

Salz *et al.* reported that the sensitivity and specificity of detection of MAs by SS OCT-A versus fundus FA were 85% and 75%, respectively, and the retinal depth of 100% of MAs could be located by SS OCT-A.[6,21] Detection of MAs using OCT-A, however, may be influenced by blood flow turbulence within the MAs and hence the discrepancy found among the studies.[4]

Parravano *et al.* have identified a correlation between the reflectivity of MAs and its detectability in OCT-A: They are hyper-reflective lesions that can be easily visualized and more likely to be detected, but this can also be affected by turbulent blood flow in them.[22,23]

Hasegawa *et al.* examined the association between the distribution of MAs detected by OCT-A and DME, encountered there was a significant increase in the density

inside the edema in the DCP. These results demonstrated that the density of the MAs in the DCP was significantly associated with the macular volume. Moreover, their results also indicated that the MAs in the DCP contributed to the pathogenesis of DME, especially for the CME type of DME.[24] MAs detected by OCT-A in DME suggest that MAs in the DCP might contribute to the pathogenesis of DME.[24] Compared with non-DME eyes, DME eyes have more MAs in DCP.[10]

The result is consistent with the theory that MA leakage is one of the main reasons leading to DME. Furtherly, OCT-A combined with B-scans can provide precise location of MA, which is helpful to guide focal laser photocoagulation treatment for DME.[10] The presence of MA is a biomarker that predicts the response to anti-VEGF therapy, the severity of DME, and progression of DR.[6]

IRMAs

IRMAs are shunt vessels due to abnormal branching or dilation of existing capillaries within the retina that help to supply areas of non-perfusion in DR[4] and on en face images appear as dilated or looping vessels with greater caliber near these areas.[5,10]

The difference between IRMAs and NV is that IRMAs appear as dilated retinal vessels without an internal limiting membrane (ILM) or posterior hyaloid rupture, unlike NV that it expands to the vitreous with ILM rupture.[10]

These are irregular branching flow lesions consisting solely of flow internal to the ILM on cross-sectional B-scan, definition that is constant with the previous structural OCT and histopathologic studies.[25]

The visualization as dilated or looping vessels near the areas of capillary loss been made possible with a higher detection rate on OCT-A than color fundus photography.[4,5] Moreover, with this technology has emerged as an effective tool to differentiate between IRMAs and NVs.[5]

Other features that allow the identification of IRMAs include the presence of intraretinal hyper-reflective dots and outpouching of the ILM. IRMAs appear as focal areas of increased intraretinal blood flow within the superficial capillary slab on OCT-A.[4,5]

IRMAs appear on widefield OCT-A as tortuous intraretinal vascular segments not exceeding the inner limiting membrane boundaries and are better morphologic characterized due to the absence of late dye leakage compared to FA.[26]

Greig *et al*. in their study to assess the association between quantitative OCT-A metrics and DR disease progression macular analysis showed that the presence of IRMA at baseline was significantly associated with increased odds of disease progression at 12 months.[25]

Lui *et al*. found in their research that IRMA was more found in severe NPDR indicating the severity of DR eyes and the risk of PDR.[10]

IRMA shows heterogeneous behavior after panretinal photocoagulation (PRP) treatment: Some remain unchanged, some show regression, and some others may be worse. IRMA that regresses may be adjacent to areas of restored vascular perfusion after PRP.[26]

RETINAL NV

NV appears as disorganized vessels originating from retina into vitreous on OCT angiograms, which can be found on disk or somewhere adjacent to NPAs.[10]

Retinal NVs are detectable on OCT-A through observation of flow signal above the ILM and often appear next to retinal NPAs.[4]

Hyperfluorescent lesions on FA that appeared indistinguishable from an MA were identified as NVs using OCT-A. This information may help us to understand why some patients with PDR and vitreous hemorrhage do not have a definitive NV on FA, as long as this method does not always identify all NV.[2]

OCT-A can detect early retinal NVs and identify the origins and morphological patterns of NVs in PDR, hence allowing classification of the lesion, offering a better understanding of the pathophysiology, and helps to guide the management strategies.[4]

OCT-A can also detect NVs intraretinal, which is difficult to differentiate from the MA in FA,[4] and also allows to clearly visualize new vessels in the disc (NVD) that persist as a spiral, loop, and irregular structures sometimes described after anti-VEGF therapy.[2]

With widefield OCT- A may be particularly advantageous in the case of small neovascular lesions, which could be missed by FA or misdiagnosed as IRMA or MA. With these field of view, both NV elsewhere and neovascularization of the disc (NVD), appear as irregular, convoluted masses of large and small caliber vessels, better visualized in the vitreoretinal interface slab, which covers the most posterior portion of the vitreous body (the hyaloid) and the most anterior part of the retinal surface.[26,27]

RETINAL VASCULAR DENSITY

VD is defined as the ratio of blood vessel area to the total measured area.[5] Is one of the most studied parameters of OCT-A, which is implicated in the presence and progression of DR.[28]

Compared with non-DME eyes, DME eyes showed lower vascular density,[10] and it has been demonstrated that VD decreases in both SCP and DCP in patients with DR.[5]

VD has also been shown to decrease in diabetic patients without DR. This is attributed to the fact that parafoveal capillary non-perfusion in DCP may be an early sign of DR.[5]

The relationship between VD and DME is unclear: Some studies have found that DME's VD declines while others are found to have no difference.[28]

The VD of both superficial and DCPs of the DME patients have been described lower than in the healthy controls with DCP density being much more affected than SCP density.[10,15]

Xie *et al*. investigated the association of macular VD in participants with DME, founded a significantly lower average parafoveal VD and temporal parafoveal VD than those without DME when adjusted for confounding factors.[28] They also demonstrated that parafoveal VD was decreased in patients with DR. Age, HbA1c, and DME were also negatively correlated with parafoveal VD.[28]

Kim *et al*. detected a progressively decreasing capillary density, branching complexity, and progressively increasing average vascular caliber in eyes with different stages of DR.[29] In the study by Agemy *et al*., a significantly reduced density in the SCP in mild NPDR in comparison to control subjects was also observed.[30,31]

Various measures of VD have been investigated in several preliminary studies using different OCT-A devices and processing algorithms. Matsunaga *et al*. have measured VD parameters in healthy subjects using SS OCT- and optical microangiography algorithm.[32] Jia *et al*. have used SS OCT-A and split-spectrum amplitude-decorrelation algorithm (SSADA) to localize and quantify the area of choroidal NV in subjects with AMD.[33] Hwang *et al*. have measured vessel densities within a para- and perifoveal ring in 12 diabetic subjects using SS OCT-A and SSADA.[34] Finally, Agemy *et al*. have investigated retinal capillary perfusion density in DR with skeletonized SD OCT-A images processed with SSADA.[29,31]

INTERCAPILLARY SPACING

The OCT-A cannot show the capillary leakage but is able to delineate clearly areas of capillary changes.[35] Wall staining and arteriolar narrowing have been illustrated as intense attenuation of microcirculation caliber on OCT-A.[2]

Studies have shown intercapillary spacing is a more sensitive parameter than VD and FAZ to detect early capillary dropouts or areas of non-perfusion.[5]

CYSTOID SPACES

In 2016, a pioneering study from De Carlo *et al*. described the cystoid spaces of DME patients as black areas, devoid of signal, with an oblong shape on OCT-A, in contrast with the grey areas representing NPAs.[11,36]

Another important critical point was highlighted in 2017 by Kashani *et al*. that recognized a new OCT-A feature in retinal vascular diseases, including CDME, called suspended scattering particles in motion (SSPiM). SSPiM represents an extravascular OCT-A signal related to varying degrees of hyper-reflective material on structural OCT, likely due to Brownian motion of particles within the intraretinal fluid that appears as a flow-on OCT-A B-scans.[36,37]

The features of DME on OCT-A images and the characteristics of the internal reflectivity of cysts are not yet fully understood and there is still no consensus on their interpretation.[36] However, Cosca *et al*. propose the following description:

The intraretinal cystoid spaces appear as hypo-intense intraretinal spaces, which are roundish structures, are mainly located in proximity of non-perfused areas, may vary in dimension and the location depending on the depth of the C-scan section.[38]

Hypointense intraretinal spaces are the most common pattern of DME on OCT-A, associated with intra retinal fluid accumulation.[38]

Hypointense intraretinal spaces in terms of distribution may be noticed between the superficial and the DCP and the aspect is highly variable depends on the degree of involvement of these vascular layers.[38]

The larger ones are more frequently located in sub foveal and para-foveal area, while smaller ones are more peripheral in macular and extramacular area.[38]

Large intraretinal cystoid spaces may sometime appear with a greyish aspect, and this peculiar aspect might be due to the presence of active motion inside these spaces, as mentioned before.[38]

The cystoid spaces in DME appear devoid of flow and are easily differentiated from areas of capillary drop-out, despite the fact that cystoid spaces are located within the capillary dropout areas.[35]

In clinical, anti-VEGF, the principal method to treat DME, has shown that foveal macular thickness and cystoid spaces tended to decrease and the cystoid spaces can be replaced by retinal tissues after the treatment.[10]

NPAS

DME presents oval black areas surrounded with an abrupt stop of capillaries on OCT angiograms, which has similar features with NPA. However, the capillaries surrounded NPAs show different morphologies.[10]

NPAs appear as grey regions with some internal signal noise and bordered by capillaries.[36]

Non-perfused vessels are normally not detectable with OCT-A, since no decorrelation signal is comes from flowing blood: The difference in terms of signal intensity between these vessels and greyish cystoid spaces around makes them clearly distinguishable.[38] The presence of non-perfused vessels in the inter-cystoid tissue appear as well-defined tubular structures, without any decorrelation signal inside.[38]

Compared with DME, NPAs have different responses to anti-VEGF treatment, that the areas can remain unchanged or re-perfused on OCT angiograms.[10]

FRACTAL DIMENSION (DF)

Fractal analysis evaluates the microvascular alterations and the geometric alterations of the retinal vasculature. Fractal dimension in both the SCP and DCP has shown a significant decrease in diabetic eyes compared with normal control subjects.[5]

Ting *et al*. documented structural changes in the retinal microvasculature associated with severity of DR and systemic metabolic and vascular risk factors in patients with diabetes using df, confirming a positive correlation between the retinal capillary df with an increasing DR severity level.[39]

As an interesting fact, Sun *et al*. reported that df of DCP predicts DR progression, whereas VD of SCP predicts DME development.[9]

FINDINGS IN THE CAPILLARY PLEXUS (SCP AND DCP)

Lee *et al*. after properly and carefully adjusting the boundaries between SCP and DCP in eyes with severe DME demonstrated that DME patients have significant damage to the integrity of the DCP but not the SCP. Also showing that OCT-A could help to quantify macular perfusion in patients with DME.[4,40]

Vujosevic *et al*. evaluated modifications on OCT-A, after subthreshold micropulse yellow laser (SMPL) treatment in DME, documenting more pronounced changes in the DCP than in the SCP (decrease in FAZ area, number of MA, and area of the cysts). A significant decrease in the number of MA in the DCP occurred as early as 3 months after SMPL.[23]

HYPERREFLECTIVE RETINAL SPOTS (HRS)

DME with subfoveal neuro-retinal detachment (SND) is a distinct pattern of DME, present in 15–30% of DME cases, and easily detected on OCT.[13] These condition has been associated with major local (ocular) inflammatory condition including higher levels of IL-6 in the vitreous and increased number of HRS, considered as signs of activated microglial cells in the retina.

In DR, the retinal microglial cells undergo a change in phenotype from resting to activated one and can be visualized as HRS on OCT.[13] These HRS have specific characteristics such as small size (<30 micron), reflectivity similar to nerve fiber layer and no back-shadowing.[13] In fact, SND and HRS have been recently proposed as noninvasive OCT-imaging bio-markers of retinal inflammation in DME/DR, findings also identifiable in OCT-A.

Increased number of HRS has been documented in DME as well as in early stages of DR,[10] and a greater number of HRS was found if SND was present compared to DME without SND.[13]

DME with SND has been associated with decreased retinal sensitivity, increased choroidal thickness, and disrupted external limiting membrane (ELM).[13]

It has also been described that intraretinal hyper-reflective material due to hard exudates appears hyperintense on OCT-A, because completely reflects the refracted signal coming from the perfused (decorrelated) vessels above, with typical dark back shadowing, which could differentiate them from MAs.[38]

3D OCT-A ANALYSIS

Borrelli *et al*. have recently described *in vivo* rotational 3D analysis of MAs using OCT-A.[41]

Both OCT and OCT-A provide structural cross-sectional and en face imaging of the retina, respectively. This 2D visualization cannot provide information about the origin, orientation, and location of MAs within the retina. This shortcoming can be overcome using 3D analysis of MAs on OCT-A.[41]

Using 3D visualization, it has been shown that MAs are associated with two vessels and not at the vascular junctions besides the different morphological varieties of MAs.[41]

The authors also quantified DME using 3D vascular volume and perfusion densities in patients with DR.[5,24]

CHORIOCAPILLARIS CHANGES (CC)

The earliest description of CC abnormalities in diabetic eyes was from the observation of postmortem or enucleated eyes with advanced PDR, in which significantly narrowed CC lumina, widened inter-capillary spaces, and extensive CC dropouts were observed throughout the choroid.[42]

OCT-A is a relatively new imaging technique that enables non-invasive volumetric visualization choriocapillaris vasculatures.[7]

Studies have shown diabetes to be associated with choriocapillaris (CC) degeneration and basal laminar deposit formation; the term diabetic choroidopathy has been used to refer to CC alterations associated with diabetes.[7]

Dai *et al*. studied the possibility of visualizing and quantifying CC using SS OCT-A, finding that CC perfusion in DR can be objectively and quantitatively assessed with flow deficits (FD)% and FD size. In the macular region, both CC FD% and CC FD size were increased in eyes with DR.[42]

There is a need for careful interpretation of CC OCT-A images, underscored by the variation seen among normal subjects. This variation leads to consider a diabetic patient's CC as abnormal only if the CC exhibit pronounced flow impairment relative to normal subjects, or if it shows pronounced inhomogeneity in the microvascular density over the OCT-A field of view.[7]

CHOROIDAL THICKNESS

DME with SND has been associated with decreased retinal sensitivity, increased choroidal thickness, and disrupted ELM.[13]

FAZ AREA

There is a condition called, DMI, in which, the structure of the foveal capillary network is damaged. Such damage includes enlargement and irregularity of the FAZ and the appearance of macular non-perfusion, which leads to alterations in macular function.[16] It has been postulated that the selective loss of pericytes and thickening of the basement membrane in retinal capillaries occur due to the effects of chronic hyperglycemia, leading to capillary occlusion, and one of the characteristics findings of DMI.[2]

DMI is characterized by the occlusion and loss of the macular capillary network or capillary dropout.[2,4] Clinically was defined as enlargement or disruption of the FAZ and capillary dropout in parafoveal area and was first established using FA decades ago.[9]

In healthy people, the diameter of normal FAZ commonly varies from 500 μm to 600 μm (less than the area within 300 μm radius circle equaling to 0.282 mm^2).[16]

According to ETDRS Report No. 11, the macular ischemia is defined as a FAZ area enlarging more than 1000 μm in greatest diameter (supposing the FAZ is round or oval), equaling to the size of FAZ more than the area within 500 μm radius circle, and/or broken perifoveal capillary rings at the borders of FAZ with areas of macular capillary nonperfusion within the a 1 disk diameter of the foveal center according to FA.[16]

DMI is associated with functional retinal damage, and its diagnosis predicts DR progression.[2] It also has been shown that a larger FAZ and a poorer VD were associated with poorer visual acuity in patients with DR.[8]

Because of the advent of OCT-A, DMI can be assessed noninvasively and, more importantly, in distinct retinal capillary plexuses.[9] The analysis of the FAZ is also more accurate with OCT-A than with FA.[35]

The enlarged FAZ area in the DCP in DME could occur because (a) vascular changes secondary to DME occur more prominently in the DCP or (b) fluid accumulation in DME may cause a reflection effect on OCT-A and loss of the OCT signal in the deeper layers. This may cause the FAZ to appear larger in the DCP, but the apparent enlargement in the FAZ might also be due to artifact.[6]

When a macular region is affected by ischemia, it presents in varying degrees, including the disappearance of a part of the macular arch ring capillary network, expansion of the FAZ area, damage in perifoveal capillaries, and appearance of MNP area in the macular region.[16]

The most prominent changes in the FAZ area overtime occurred in the DCP, which is consistent with the pathogenesis of DME.[6]

Vascular quantitative measures of OCT-A have also shown to be able to help screen and monitor DMI in patients with no clinical evidence of DR.[4]

Jia *et al*. imaged neo-vascularization and quantified areas of macular ischemia in DR. The quantification of macular ischemia involved measuring the diameter of the FAZ and the total area of vessel non-perfusion.[38,43]

With further advancement in the technology, OCT-A may serve as an alternative non-invasive method to FA to detect DMI and help predict visual prognosis.[4]

OCT-A BIOMARKERS AND PREDICTIVE FACTORS IN DME

Recently, there has been an interest in determining the prognostic value of changes on OCT such as foveal intraretinal cysts and edema, including size and location, presence of subretinal fluid, and integrity of retinal layers in DME.[5] More interestingly, a correlation has been found between capillary changes observed with OCT-A and macular photoreceptor disruption and DR severity.[35]

Unlike the DR progression, DME development is associated with VD of the SCP, but not with DCP metrics. In theory, an imbalance in fluid entry versus fluid exit would lead to formation of DME, as commented before.[9]

It has been proposed that the efficacy of anti-VEGF treatment can be estimated according to MA and intraretinal capillary abnormalities and vascular networks by OCT-A.[10]

Compared with anti-VEGF responders, poor responders showed more MAs, lower vascular density, and larger FAZ area in DCP, but without significant difference in SCP.[10] Various reasons for poor response can be: The poor responder eyes accumulate more protein within the intraretinal cysts, preventing the agent to diffuse into the DCPs. Another explanation is that the poor responder eyes show severe deep retina ischemia, leading to a decreased ability to remove the fluid.[10]

In contrast to DME eyes that respond well to anti-VEGF drugs, poor responder DME eyes showed significantly lower flow density, larger number of MAs, and larger area of the FAZ in the DCP.[40]

Lee *et al*. reported that a SD OCT finding associated with the response to anti-VEGF treatment was the optical density of the intraretinal cysts. Chronic inflammation with highly exudative DME might cause protein-rich intraretinal cysts that appear as hyper-reflective signals on SD OCT, as in other retinal diseases.[40]

It is important to remember that a structural correlation and other multimodal images must be performed, taking into account that the resolution of the EMD does not always correspond with an improvement in visual acuity. Photoreceptor damage with ellipsoid zone disruption and macular ischemia are two possible reasons for poor visual improvement after the remission of macular edema.[8]

In some patients with DME, central visual loss may not only be due to the macular edema itself but also to changes in the FAZ and retinal capillary alterations in the macula.[6]

Hsieh *et al*. investigated the correlation of quantitative OCT-A parameters and the best corrected visual acuity (BCVA), finding that poorer VD in both the SCP and DCP at the parafoveal area was correlated with both poorer BCVA and thicker central retinal thickness. However, the reason of this is still controversial since, in DME, this finding may suggest that poorer parafoveal vascular perfusion itself could result in poorer vision, or it could be caused by macular edema, which is the real reason for poorer vision.[8]

As a relevant finding, it was also found that the density of parafoveal vessel in the superficial retinal layer at baseline was an independent predictor for visual improvement after the load ranibizumab treatment in eyes with DME and that the OCT-A offers measurement for VD in the macula and could be used to predict the visual prognosis of anti-VEGF treatment in DME.[8]

The previous studies have shown that increased FAZ area or FAZ contour irregularity (FAZ-CI), increased NPA, decreased VD, and decreased fractal dimension of the central macula were associated with the worsening of DR.[8]

Sun *et al*. conducted a prospective study, the objective was to demonstrate the predictive value of OCT-A metrics, indicative of DMI, for progression of DR and DME, in which several OCT-A biomarkers were identified. Eyes with larger

Table 1: OCT-A findings in diabetic retinopathy.

Microaneurysm	Hyper-reflective lesions Demarcated saccular or fusiform shapes of focally dilated capillary vessels in the inner retina
Intraretinal microvascular abnormalities	Dilated or looping vessels with greater caliber near NPAs These are irregular branching flow lesions consisting solely of flow internal to the ILM on cross-sectional B-scan Appear as focal areas of increased intraretinal blood flow within the superficial capillary slab
Retinal neovascularization	Appear as disorganized vessels originating from the retina into vitreous Can be detectable by the observation of flow signal above the ILM and often appear next to retinal NPAs
Retinal VD	DME eyes showed lower vascular density VD decreases in both SCP and DCP
Intercapillary spacing	Wall staining and arteriolar narrowing have been illustrated as intense attenuation of microcirculation caliber on OCT-A
Cystoid spaces	Hypo-intense intraretinal spaces are the most common pattern of DME Black areas, devoid of signal, with an oblong shape Intraretinal cystoid spaces appear as hypo-intense intraretinal spaces, which are roundish structures, are mainly located in proximity of non-perfused areas, and may vary in dimension and the location depending on the depth of the c-scan section
NPAs	NPAs appear as grey regions with some internal signal noise and bordered by capillaries
Hyper-reflective retinal spots	Considered as signs of activated microglial cells in the retina • Small size (<30 micron) • Reflectivity similar to nerve fiber layer • No back-shadowing Intraretinal hyper-reflective material due to hard exudates appears hyper-intense on OCT-A • Back-shadowing
FAZ area	Enlargement and irregularity of the FAZ and the appearance of macular non-perfusion

DCP: Deep capillary plexus, DME: Diabetic macular edema, ILM: Internal limiting membrane, NPAs: Non-perfusion areas, FAZ: Foveal avascular zone, OCT-A: Optical coherence tomography angiography, SCP: Superficial capillary plexus, VD: Vascular density

FAZ area, lower VD, and lower fractal dimension on DCP are associated with a higher risk of DR progression, whereas eyes with lower VD on SCP are more likely to develop DME,[9] and similarly, eyes with DME had decreased perfusion of DCP as well as larger FAZ area and decreased VD.[9]

Some previous studies have reported retinal capillary network and choriocapillaris abnormalities in patients with DR, such as a decrease of VD, with a significant decrease of capillary perfusion density values as retinopathy progresses.[15] The reduction of VD is more consistent in the DCP and choriocapillaris compared to the superficial plexus.[15]

Apart from choriocapillaris, DCP can still provide 15% of the nutrients to outer retinal layers. Oxygen from choriocapillaris to photoreceptors is gradient decrease, so the impairment of DCP might affect structural integrity of photoreceptor layers and other outer retinal layers. As expected, the DCP loss was corresponded well with the disruption of outer plexiform layer in DME eyes, which was also related to vision recovery closely.[10] Thus, it has been speculated that integrity of the DCP could be a possible predictor of the effectiveness of the treatment, probably related to its role in excess fluid removal from the retina, thus preserving it from macular edema.[15]

As an additional finding, a significant correlation was found between the status of the DCP and the treatment response. The DCP of poor responders showed greater damage, such as a lower vascular flow density, a higher mean number of MAs, and a larger FAZ in comparison with the good responders.[15]

Vujosevic *et al*. showed that DME with SND may represent a specific "more inflammatory" pattern of DME, with high number of HRS, and a better response to intravitreal steroids rather than to anti-VEGF treatment.[13]

CONCLUSION

OCT-A technology keeps great promise for the identification of early retinal vascular disease, including DR with the potential for determining risk for future DME and DR progression.[44]

Quantitative information evaluated by OCT-A offers a promising new path of study and will likely be useful in the future as an objective marker for progression of retinal disease,[29] estimating the microvascular status and therapeutic effect of treatments for DME.

Choriocapillaris flow impairment at different stages of DR merits further investigation, as well as, further research is needed to identify new biomarkers that are involved in disease progression, providing more accurate pathophysiological picture of DR and macular edema. The next step might be the automatic detection and quantification of diabetic macular changes.[35]

The approach of OCT-A images has to be enriched with the structural OCT scan to correlate the structures and avoid mistakes of interpretation.

Declaration of patient consent

Patient's consent not required as there are no patients in this study.

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Conflicts of interest

There are no conflicts of interest.

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