Chapter

Optic Coherence Tomography Angiography in Diabetic Retinopathy

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Abstract

Diabetic retinopathy (DR) is a progressive microvascular disease considerer as the most important cause of acquired vision loss in the world. OCT angiography (OCT-A) has drastically improved the diagnosis and follow-up of DR showing alterations before changes in the fundus will be visible. With OCT-A, it is possible to quantify several parameters such as the macular vascular density (MVD) and foveal avascular zone (FAZ). This new technique will be important for early detection, follow- up, and monitoring treatment response. OCTA is a very promising image technique that is continually improving and offers numerous advantages over FA in DR management; nevertheless, there are technical limitations that must be improved.

Keywords: diabetic retinopathy, retina, optic coherence tomography

1. Introduction

Diabetic retinopathy (DR) is a progressive microvascular disease considered as the most important cause of acquired vision loss in the world [1]. World Health Organization (WHO) estimated that in 2030 about 366 millions of adults will be affected with diabetes mellitus (DM) and 191 million with DR [2].

DR is characterized by functional and structural alterations on retinal microcirculation. Ischemia is one of the most important factors for progression of DR. Retinal ischemia is responsible of oxygen defect in retinal tissues because retinal neurons need high levels of oxygen, and this supposes an increased production of pro-angiogenic factor such as vascular endothelial growth factor (VEGF) [3, 4].

Histopathological findings show the existence of structural changes in vascular wall that preceded the visible changes on fundus [5, 6].

On the last decade, optical coherence tomography (OCT) and its recent evolution to the OCT angiography (OCT-A) have drastically improved the diagnosis and follow-up of DR [7].

OCT-A is a technic that allows analysis i*n vivo*, is painless, and separates the different retinal vascular plexus, something impossible with the traditional techniques. Currently, it has recognized four vascular plexus: superficial capillary plexus (SCP),

intermediate capillary plexus(ICP), deep capillary plexus (DCP), and peripapillary radial plexus (PRP) (localized in the peripapilar retinal nervous fiber layer) [8].

The OCT-A shows alterations in these plexus before changes in the fundus will be visible. The earlier stage of DR is defined for the presence of microaneurysm (MA) on the fundus but before that already exist histopathological changes on retinal capillaries. Thus, OCT-A would allow to identify patients affected with DR without fundus changes.

2. Retinal lesions and OCT-A

OCT-A identifies a large number of MA that cannot be detectable on fundus exploration, but less than fluorescein angiography (FA) due to slow hematic flow in the aneurismatic dilatations [9]. Also it is possible to analyze each plexus separately. For that, it has been possible to observe that the majority of MA is located in the DCP [9, 10]. The MA could be classify following its internal reflectivity (hyper or hypo). The hyperreflective ones are associated with high flow and damage in the hemato-retinal barrier and edema. The hyporreflectives has low flow and are more difficult to detect by the OCT-A [11].

Furthermore, OCT-A is capable of detecting other vascular anomalies such as intraretinal vascular anomalies (IRMA) and define its structural characteristics and extension. It is possible to identify the changes in these vascular anomalies after the treatment with anti-VEGF drugs or laser photocoagulation.

Shimouchi et al. studied the characteristics of IRMAs before and after panretinal photocoagulation and identified five types of IRMA: (1) without changes after laser; (2) tuft type; (3) with reperfusion; (4) mix of 2 and 3; (5) worse after the laser. Types 2 and 5 were more related with proliferative diabetic retinopathy (PDR) [12].

IRMAs were identified as dilated and tortuous vessels near ischemia areas [13–15]. Compared with IRMAs, retinal neovascularization (RNV) alters the internal limiting membrane (ILM) [13] and could be identified by observing the flow signal above ILM [13, 16].

With OCT-A it is possible to identify early points of retinal neovascularization, impossible to differentiate from an MA in FA. Furthermore, OCT-A is better than FA in the accuracy identification of lesion limits as the leakage of the FA could blur the RNV border [13].

3. Measure parameters in OCT-A

With OCT-A it is possible to quantify the macular vascular density (MVD), defined as the proportion of vessels related to the total area studied over the base of a binarized image [9]. It is necessary to interpret the images with caution as the values vary according to sex and age, and they are related with image quality. In general, MVD values are progressively minor from healthy people to diabetic patients without DR and PDR [9, 17].

It is especially clear that the visualization of the foveal avascular zone (FAZ) has improved with the introduction of OCT-A. In healthy eyes, FAZ has very well-defined edges without interruptions [8]. FAZ enlargement can result from capillary occlusion with perifoveal arteriole loss easily identified by OCT-A [17]. In addition, there is a clear association between FAZ enlargement and vision loss in patients with DR [18]. OCTA is better than FA for FAZ detection because there is no interference caused by colorant leakage, it is noninvasive and fast, allowing a better imaging comparison over

the time. Several studies show that FAZ enlargement already occurs in patients with DM1 and DM2 before any sign of DR can be detected [19–22]. These findings could be useful to identify patients without DR but with higher risk to develop the disease. However, there is a great variability in FAZ size in healthy people (0.071–0.527 mm^2), with higher values in eyes with short axial length [9]. For this reason, FAZ circularity more than size may be useful to identify pathological changes. Some of the quantitative parameters about the ZAF include: ZAF area, acircularity index (AI), axis ratio (AR), and perimeter. AI is the ratio between the ZAF perimeter and the perimeter of a circle with equal area. The AR is the ratio between major and minor axis [13]. AI and AR are greater in patients with DR and greater in patients with PDR versus NPDR [23].

3.1 New parameters

Some of the new parameters that are being studied include: vascular diameter index (VDI), fractal dimension (FD), vascular tortuosity (VT), perfusion density (PD), and skeletonized vascular density (SVD) [9, 13]. VDI is an index of the mean vessel caliper [9]. Increased values are related to rapid increases in blood glucose [9]. FD measures the complexity of the vessels pattern. FD values are lower in diabetic eyes in the SCP and DCP, but it is not related to DR severity [24]. VT is higher in diabetic patients and could be useful for early detection of DR [9]. PD is an index of vessel perfusion in a determinate area, and lower values are related with DR severity and BCVA [25]. SVD vessels longitude eliminating potential confusing factors being more sensible in identifying non-perfusion. SVD in SCP and DCP is inversely related with DR severity [26].

OCTA is also useful to identify and quantify macular ischemia (MI) in the different retinal plexus.

Diabetic macular edema (DME) is the leading cause of vision loss in patients with DR and can be visualized in the OCTA en face as non-flow areas with smooth edges that do not follow surrounding vessels [27].

3.2 The role of OCTA in DR early detection

MVD is reduced in DM1 and DM2 patients in the SCP and DCP in the foveal and perifoveal area without detectable DR [28–31].

FAZ is also affected, being greater in patients without DR [22, 32].

Sun et al. have found an association between FAZ, MVD and FD values in the DCP with the risk of develop DR [33]. Greater FAZ area was related with a risk ratio (RR) of 1.829 for increase of standard deviation (SD), low MVD with a RR of 1.908 for decrease of SD and low FD with a RR of 4.464 for decrease of SD [33]. Furthermore, low values of MDV in the SCP are related with the development of DME [33].

3.3 DR severity

Increased FAZ, reduced FAZ circularity, low MVD, increased VDI, reduced FD, and increased VT are associated with DR severity [25, 34–38]. Basing on these findings, it has been investigated the possibility to automatically detect and grade the severity of DR with the aid of the artificial intelligence and using the MVD, vascular caliper, and FAZ in the SCP and DCP with an accuracy of 94.3% (area under the curve (AUC) = 0.92) and reaching an accuracy of 96% (AUC = 0.96) when OCTA is combined with OCT [39].

3.4 DR progression

Actually, we have very limited knowledge about the predictive value of OCTA in DR progression (most of published studies are transversal). Nevertheless, some recent prospective studies have found a relation between DCP parameters and DR progression with statistical significance [33]. On contrary, SCP parameters do not seem to be associated with DR progression, probably because the DCP is more susceptible to ischemia (higher metabolic requirements of external retina) [40].

3.5 OCTA and DME

DME is still a problem for a correct interpretation of OCTA images. In fact, cystic macular edema affects the automatic segmentation of the software and affects image quality. This is especially evident in the DCP, because signal intensity is lower [41]. Cysts may compress the vessel wall, lowering the flow. OCTA can consider these areas as avascular [42].

According to Coscas et al., three patterns of DME can be identified by OCTA [43]:

- Hypointense intraretinal spaces: rounded structures located near non-perfusion areas in the DCP
- Grayish intraretinal spaces: big grayish cysts, can be confused with intervascular spaces
- Focal hyperintense points: hard exudates

3.6 OCTA and choroid

The choroid is the main source of oxygen and nutrients for external retina to understand DR pathogeny. Increased choriocapillaris (CC) non-perfusion has been described already in patients without signs of DR [37]. OCTA surely represents a significant advance compared with FA for studying the CC, but the deep localization of this complex vascular structure makes it difficult to get high-quality images. The perfusion defect (PD) is the area where it is not possible to identify flow between the OCTA limits of detection [44, 45]. PD could be an interesting parameter to study CC involvement in DR and is significantly higher in DM patients compared with normal eyes [45]. New prospective studies are needed to clarify the importance of the CC in DR.

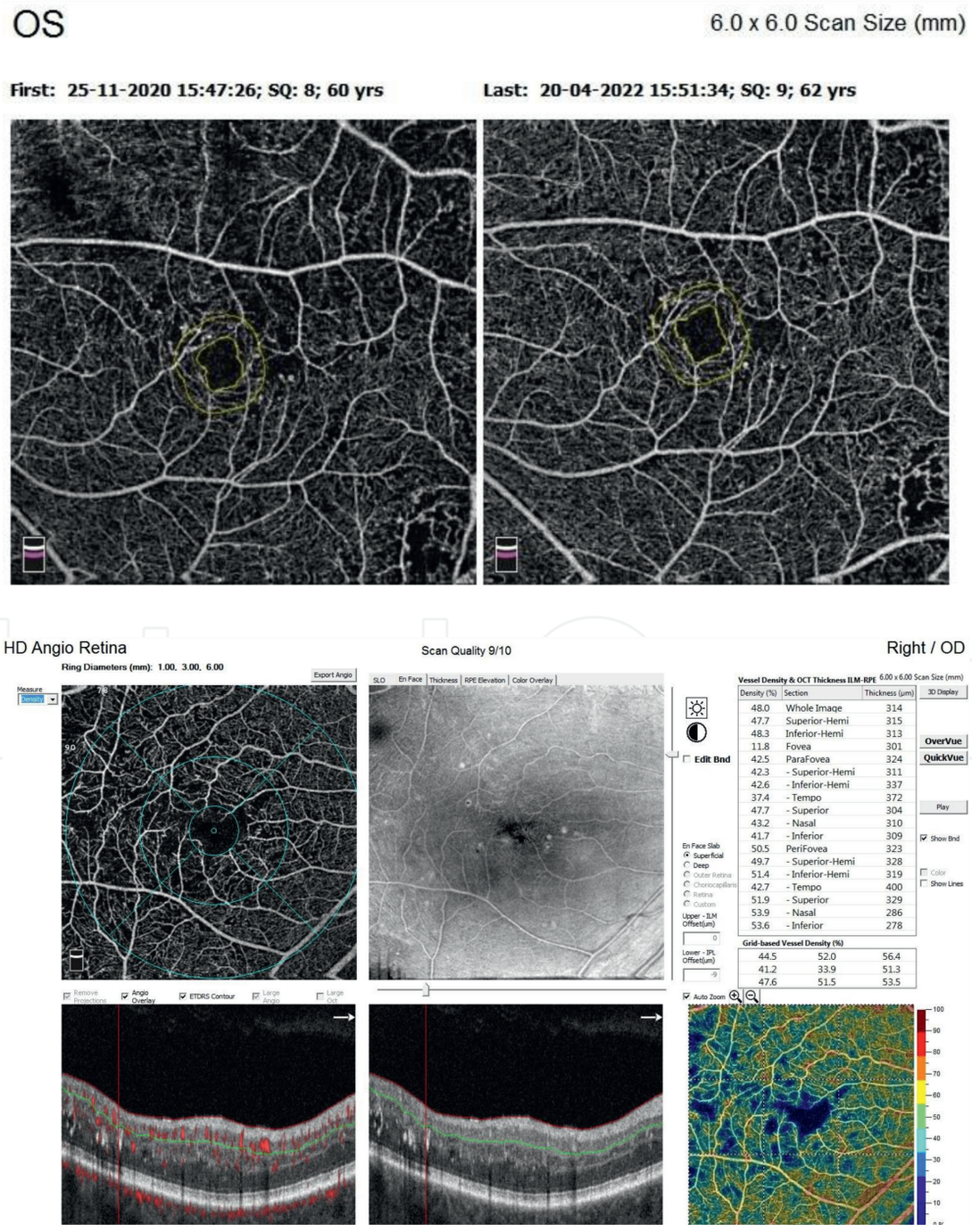
3.7 OCTA limitations

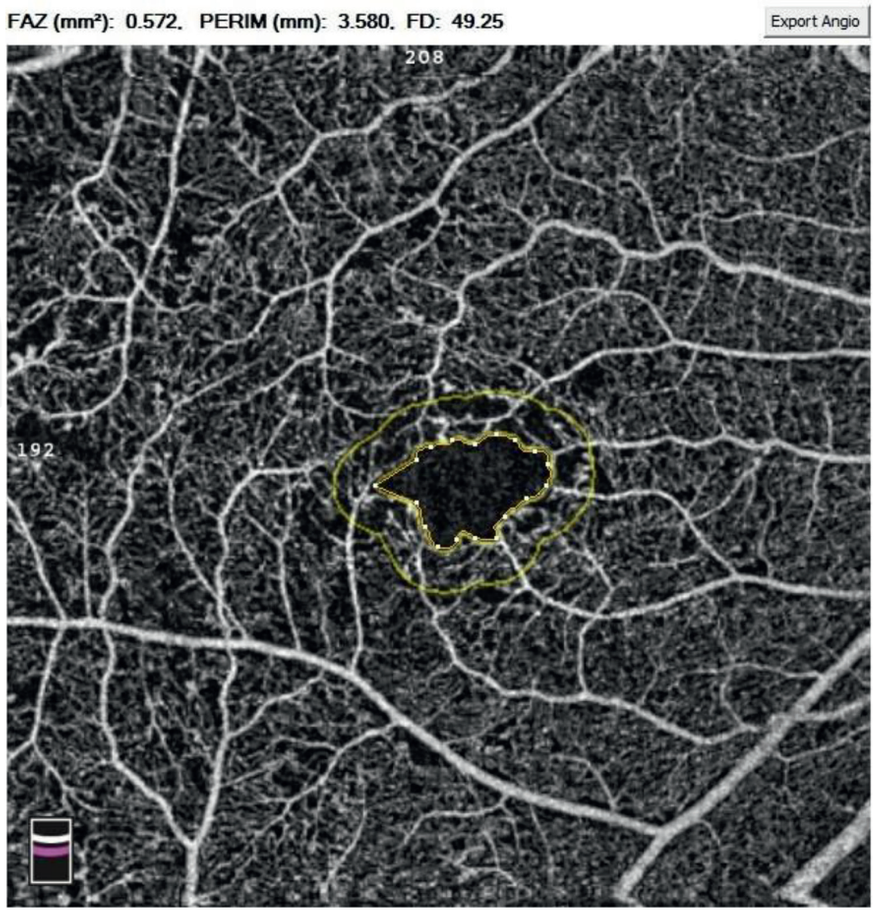
One of the most important limitations of OCTA is the great variability in the algorithms used by different manufacturers. The immediate consequence is the difficulty of comparing images obtained with different devices [13, 46]. Projection and movement artifacts can be especially frequent in patients with macular lesions and DME, severely affecting image quality (up to 30% of images have to be discarded) [38, 46]. Simple vitreous opacities can affect image quality and interpretation [46]. Furthermore, most of the quantitative and qualitative parameters used in the literature are obtained with an external software after exporting the images, through a slow process and, on many occasions, with manual segmentation. This is absolutely unfeasible in clinical practice, where fast processing systems

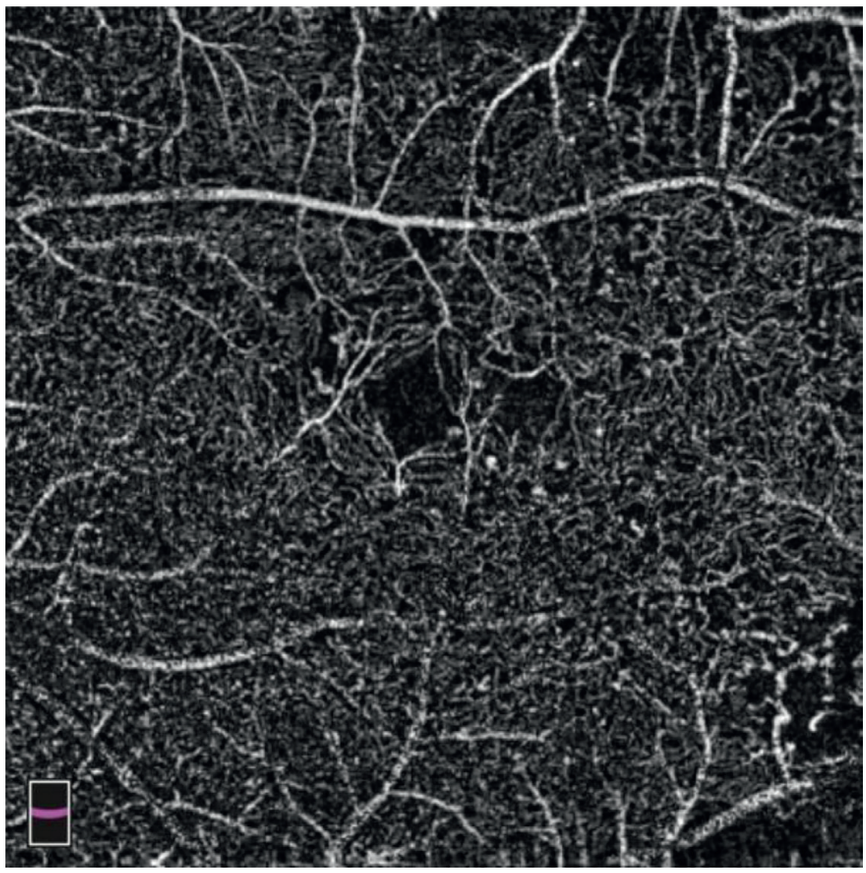
directly associated with the devices are needed [46]. Without these premises, these OCTA parameters will not be useful in clinical practice.

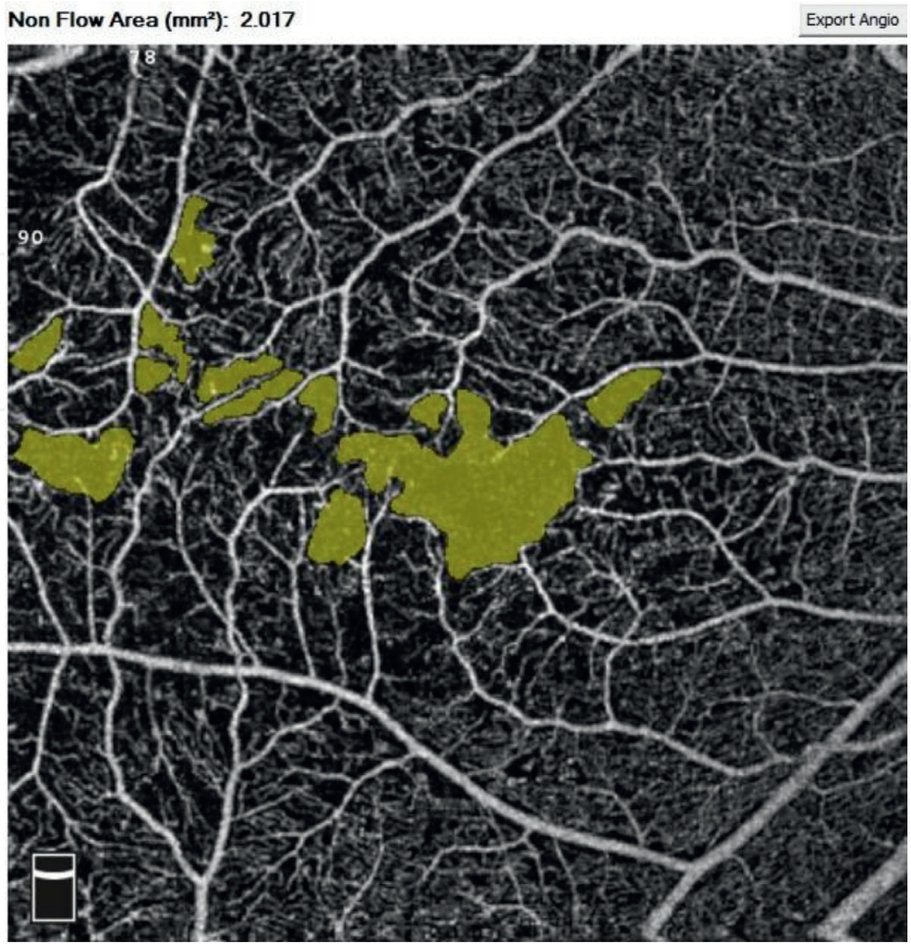
4. Conclusions

OCTA is a very promising image technique that is continually improving and offers numerous advantages over FA in DR management. Many clinical studies indicate their usefulness in early diagnosis, follow-up, identification of prognostic factors, and treatment of DR and related complications. Nevertheless, OCTA is a relatively new technique and the usefulness of most of the quantitative data it allows to obtain needs to be investigated. Finally, it would be important to have greater interchangeability between data offered by different software and improve image quality by reducing artifacts.




FAZ (mm²): 0.572. PERIM (mm): 3.580. FD: 49.25
Export Angio
208
192





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