Quantitative Parameters Relevant for DME Evaluation by OCTA

Subjects: Ophthalmology

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Diabetic macular edema (DME) is one of the main ocular complications of diabetes mellitus (DM) that can lead to important vision loss in diabetic patients. In clinical practice, there are cases of DME with unsatisfying treatment responses, despite adequate therapeutic management. Diabetic macular ischemia (DMI) is one of the causes suggested to be associated with the persistence of fluid accumulation. The optical coherence tomography angiography (OCTA) devices currently available can provide various OCTA metrics that quantitatively assess the retinal microvasculature. OCTA metrics are useful instruments that can contribute to the evaluation of patients with DME.

diabetic macular edema | optical coherence tomography angiography | vessel density | perfusion density | fractal dimension | FAZ

1. Introduction

Diabetic macular edema (DME) is known to be the main cause of vision loss in the working-age category of diabetic patients [1]. Current data estimate that the worldwide prevalence of this condition will rise by 51.9% until the year 2045 [2]. Macular edema is an ocular complication of diabetes mellitus (DM), which results from an imbalance between the accumulation and elimination of fluid in and out of the retina, being the consequence of a multifactorial process that implies oxidative stress, inflammation and blood-retinal barrier dysfunction [3]. Macular edema can develop at any stage of diabetic retinopathy (DR), independently of the DR severity [4]. One of the triggers suggested to be responsible for fluid accumulation at the macular level is ischemia, another frequent and debilitating complication of DR [5]. Fluid accumulation in the setting of ischemia is thought to result from endothelial cell injury, the disruption of tight junctions that form the blood-retinal barrier, and consequent vascular hyper-permeability [5], which is also intensified by the concurrent inflammatory processes associated [5].

In clinical practice, an unsatisfying treatment response was noticed in some cases of patients with DME, suggesting that the association between DME and diabetic macular ischemia (DMI) may decrease the response to the treatment modalities for macular edema, with the persistence of long-standing fluid accumulation [6].

Moreover, one of the most important consequences of DMI, in the presence or absence of other ocular complications of diabetes mellitus, is the decrease in visual acuity which may be progressive and irreversible [7].

When associated with other ocular complications of diabetes, such as macular edema, the vision loss can still persist, even if the macular fluid was successfully resolved [8].

Even though fluorescein angiography (FA) has been the mainstay in imaging the retinal vasculature, its usage is limited to a two-dimensional visualization of the superficial vascular plexus (SVP) in the retina [9].

Optical coherence tomography angiography (OCTA) is a noninvasive modality of investigating the retinal and choroidal circulation, without the necessity of intravenous dye injection [10]. It can provide qualitative and quantitative information, increasingly becoming a very useful tool in clinical practice in terms of diagnosis, follow-up and therapeutic decisions in patients with vascular ocular conditions [10]. Compared to FA, it can provide a three-dimensional image of the fundus, allowing us to individually evaluate each of the retinal plexuses, as well as the choriocapillaris and the choroid [10].

2. Quantitative OCTA Assessment in Diabetic Macular Edema

2.1. Vessel Density

Vessel density (VD) is a parameter defined by the total length of perfused blood vessels per unit area in the region of measurement [11][12]. This metric is obtained after skeletonization [13]. For its calculation, each vessel, regardless of its caliber, is reduced to only one pixel-line, so to remove the effect of the vessel diameter from the analysis of the microcirculation [13]. It was reported that vessel density metrics were significantly lower in eyes with type 2 diabetes and DME when compared to patients with no diabetes [12]. The results of the same study showed lower central VD in patients with DME compared to healthy subjects [12] and also significantly lower inner VD and full VD in patients with DME compared to diabetic patients without diabetic retinopathy and patients with no diabetes [12]. Moreover, in patients with diabetic retinopathy, a lower VD of SCP, as well as a higher flow deficit of choriocapillaris was associated with an increased risk of DME development, independent of known risk factors [11].

Vessel skeletonized density (VSD) reduces the impact of large vessels on measurement and is considered to be more sensitive to retinal microvascular changes [13][14].

When comparing quantitative parameters between eyes with the same DR severity, in eyes with mild NPDR and DME, there was significantly lower skeleton density (SD) in the superficial retinal layer (SRL) and the deep retinal layer (DRL) compared to those without DME [13].

The measurement of OCTA metrics with a wider field swept-source OCTA device revealed that in mild NPDR associated with DME, there was a decrease in VSD in the DCP on 6 × 6 mm angiograms, whereas on 12 × 12 mm angiograms there was reduced VSD in the SCP and the full-thickness retina [14]. In the case of moderate-severe NPDR patients with DME, there was a significant reduction in VSD in the SCP and also of VSD in the full-thickness retina on 6 × 6 mm angiograms [14].

Regarding the influence of various treatment modalities on the quantitative parameters assessed by OCTA, in patients with DME treated with intravitreal anti-vascular endothelial growth factor (anti-VEGF), the first-line treatment for DME at the moment, one study concluded that the vessel length density (VLD)—based thresholding was more accurate for quantifying the retinal vascular changes after a single injection [15]. However, several studies showed no significant changes in this parameter after the anti-VEGF treatment [15].

Another study found that, at the second month of follow-up after an intravitreal dexamethasone implant (IDI), the vascular density in the perifoveal ring in the SCP on a 6 × 6 mm scan was significantly decreased [16]. Furthermore, in patients with previously treatment-naïve DME, after subthreshold micropulse yellow laser (SMYL) treatment, it resulted that there were no significant differences regarding the VD in the SCP, DCP and choriocapillary plexus (CCP) after the procedure [17].

Related to the correlations between visual acuity and quantitative OCTA microvascular parameters, in DME, it was noticed that low skeleton density in the DCP was correlated with poorer best-corrected visual acuity (BCVA), suggesting that macular ischemia plays an important role in the visual acuity drop associated with DME [18].

2.2. Perfusion Density

Perfusion density, defined as the total area of perfused blood vessels per unit area in the region of measurement, is another metric used to quantitatively assess DME by OCTA. Compared to vessel density as defined above, this parameter takes into consideration both the length and the diameter of the vessel for the analysis, therefore being better in estimating the real vascular density [19]. However, in situations when perfusion reduction coexists with vascular dilations, it can induce false results regarding the microvascular quantification [19].

In diabetic chronic cystoid macular edema, compared to non-diabetic subjects, the mean value of this parameter was reduced in both SCP and DCP [20]. However, there was a greater reduction in perfusion density in the SCP, compared to DCP [20]. The authors of the study suggested two possible explanations for these results: either a software overestimation in the DCP due to the projection artifacts or a false interpretation of the walls between the cystic cavities and the lipid deposits in the cystoid spaces, inducing a correlation signal [20]. The same study concluded that in the cases of spontaneous or therapeutic remission of macular edema, the mean values of this parameter did not show significant changes [20].

Another study concluded that the global capillary density index (CDI), an equivalent metric used for quantifying the area occupied by vessels, was lower in patients with DME compared to patients without DME, independent of the capillary plexus affected [21].

In patients with diabetic retinopathy, a lower PD of SCP was associated with an increased risk of DME development, independent of known risk factors [11]. When comparing quantitative parameters between eyes with the same DR severity, in eyes with mild NPDR and DME, there were significantly lower values of this metric in the superficial retinal layer (SRL) and the deep retinal layer (DRL) in the eyes with DME compared to those without DME [13]. The impact of DME on deep vessel densities (DVD) was also confirmed by another study which showed

that patients with NPDR with DME presented with reduced DVD, compared with patients without DR and also compared with patients with NPDR but without DME [22]. The same study also showed that the level of ANGPTL4, a cytokine correlated with the presence of DME, was an influencing factor for DVD [22]. Moreover, it was reported that density perfusion metrics were significantly lower in eyes with DME compared to patients with no diabetes and that, in the DME group of patients, PD was significantly lower in the DCP compared to the non-DME group of patients [12]. Furthermore, the peripapillary vessel density, as well as the retinal superficial and deep vascular density, and also the choriocapillaris density in the foveal and parafoveal areas, were significantly reduced in a study that compared patients with moderate NPDR with DME, with healthy subjects [23].

DME development was also associated with lower values of this metric in the SCP, independent of established risk factors including age, duration of diabetes, HbA_{1c}, mean arterial blood pressure and severity of DR at baseline [24]. However, the eyes with DME had also impaired perfusion at the level of DCP, even though the alterations of SCP were the ones linked to the DME formation [24].

The OCTA assessment with a wider field swept-source OCTA device revealed that, on 6 × 6 mm angiograms, in mild NPDR associated with DME, at the DCP level, there was a decrease in the total area of perfused vessels per unit area in the region of measurement [14]. In the case of moderate–severe NPDR patients with DME, on 6 × 6 mm angiograms, there was a significant reduction in this metric in the SCP and in the full-thickness retina [14].

Differences were also noted regarding the OCTA quantitative parameters in patients with DME of different grades of severity [25]. It was concluded that patients with severe DME presented lower perfusion in the DVP, compared to early and advanced DME [25].

It was also shown that treatment naïve diabetic eyes with moderate or severe NPDR and DME had significantly lower superficial and deep perfusion values compared to healthy eyes [26]. Moreover, the diabetic eyes with DME presented lower values at the level of the deep retinal plexus, with the macular perfusion being more impaired compared to the superficial one in patients with DME compared to eyes without DME [26]. Furthermore, in patients with DME, a lower visual acuity was associated with a lower vessel area density at the level of the superficial retinal plexus [26].

Related to the influence of various therapeutic approaches on the perfusion density measurements in patients with DME, when comparing responders to anti-VEGF treatment with non-responders, it was noticed that in both groups of patients, there were lower values in the DCP than in the SCP [27], but poor responder DME eyes exhibited lower vascular flow density in the DCP and a lower flow density in the total capillary plexus (TCP) [27]. However, there were no significant differences between the two groups in the SCP [27]. It was suggested that the integrity of the perifoveal DCP is associated with anti-VEGF treatment response and the study found that there was an outer plexiform layer disruption in SD-OCT corresponding with the non-flow area of the DCP in OCTA [27]. The poor response to anti-VEGF in patients with impaired vascular flow in the DCP was explained by several theories. The first one stressed the inability of anti-VEGF agents to diffuse through the protein-rich intraretinal cysts and reach the capillaries in the DCP [27]. On the other hand, given the ischemic alterations in the deep retina, there may be an

abundance of VEGF expression at that level, which may limit the efficacy of anti-VEGF agents [27]. Moreover, due to the selective tightening effect of anti-VEGF agents on the endothelial junctions, inhibition of VEGF cannot restore absent or broken vessels [27]. Last, given the implication of DCP in removing the excess fluid from the retina, its reduced vascular density limits the fluid evacuation, despite the action of the anti-VEGF agents [27].

A study on patients treated with fluocinolone acetonide intravitreal implant showed an increase in the parafoveal and perifoveal SCP perfusion density at the 4-month follow-up [28]. The improvement was considered to be the consequence of the beneficial effect of corticosteroids on leukostasis, a process that facilitates retinal non-perfusion and vascular leakage in patients with diabetic retinopathy [28].

Regarding the intravitreal dexamethasone implant (IDI) for the treatment of DME, it has been shown that the SCP density and the DCP density in the foveal and parafoveal area did not modify significantly during the follow-up at 7 days, 30 days, 60 days, 90 days and 120 days after the IDI implantation, despite the significant reduction in the macular thickness [23]. This was considered to be mainly induced by the irreversible ischemic alterations that occur in the retina [23]. In the same study, the choriocapillary density tended to increase after treatment, but the explanation was that, in the setting of edema, the OCT signal could have been attenuated, this being the reason why the choriocapillaris could have seemed reduced before the dexamethasone implant [23]. On the other hand, another study found that, at the second month of follow-up after IDI, vascular perfusion in the perifoveal ring in the SCP on a 6x6 mm scan was significantly decreased, and also reported a reduction in the vascular perfusion in the perifoveal ring in the DCP at months 2 and 3, and parafoveal ring at month 2, suggesting the importance of permanent capillary occlusion in DME [16].

After subthreshold micropulse yellow laser (SMYL) treatment in patients with previously treatment-naïve DME, no significant differences were found regarding the PD in the SCP, DCP and choriocapillary plexus (CCP) [17]. In another study, that evaluated the effect of SMYL on OCTA quantitative parameters in cases with persistent DME after pars plana vitrectomy for tractional DME, it resulted that, at 3-month and 6-month follow-up, the parafoveal density in the SCP and DCP was significantly higher in the SMYL group compared to the patients with DME that were only observed and not treated [29]. Similarly, it was found that during the first month after subthreshold yellow pattern laser therapy for DME, there was an increase in the mean values of this metric in the DCP [30].

2.3. Vessel Diameter Index (VDI)

Vessel diameter index (VDI) is defined by the proportion of area occupied by vessels divided by the skeletonized density [18] and it refers to the average vascular caliber on OCTA images [13]. When comparing quantitative parameters between eyes with the same DR severity, in eyes with mild NPDR and DME, there was a significantly higher VDI in the DRL compared to those without DME [13]. In cases of severe NPDR, the eyes with DME showed a significantly higher VDI in the DRL compared with the eyes without DME [13].

2.4. Foveal Avascular Zone (FAZ) Parameters

When studying angiopoietin-like levels in the aqueous humor of patients with DME, it resulted that the levels of ANGPTL4 and ANGPTL6 were significantly higher in patients with DME, and ANGPTL4 correlated positively with the FAZ perimeter [12].

The measurement of the OCTA metrics with a wider field swept-source OCTA device showed that in mild NPDR associated with DME, there was a decrease in FAZ circularity on 6 × 6 mm angiograms [14]. Furthermore, in the case of moderate-severe NPDR patients with DME, on 6 × 6 mm angiograms, there was a decrease in the FAZ area [14].

It was also concluded that patients with severe DME presented a significant increase in the acircularity index, compared to early and advanced DME [25].

Moreover, the treatment naïve diabetic eyes with moderate or severe NPDR and DME had a significantly larger FAZ area at the level of the SCP than the diabetic eyes without edema and also than healthy subjects [26]. Furthermore, in patients with DME, a lower visual acuity was associated with a larger FAZ at both the superficial and the deep retinal plexuses [26].

When comparing responders to anti-VEGF treatment with non-responders, it was noticed that the DME eyes had a larger FAZ in the DCP than in the SCP, in both groups of patients [27]. Poor responder DME eyes, however, exhibited a larger FAZ area in the DCP, whereas there were no significant differences between the two groups in the SCP [27].

After SMYL laser treatment in patients with previously treatment-naïve DME, it resulted that the FAZ did not change significantly in the SCP, but there was a significant reduction in it in the DCP at 6 months compared to the initial evaluation [17]. In another study that evaluated the effect of SMYL, in cases with persistent DME after pars plana vitrectomy for tractional DME, on OCTA quantitative parameters analysis, it resulted that the FAZ area was significantly smaller in the SMYL group at 6-month follow-up [29]. In another study, though, it was found that during the first month after subthreshold yellow pattern laser therapy for DME, the FAZ area did not change significantly after the laser treatment [30].

2.5. Fractal Dimension

The fractal dimension characterizes the architecture of the vascular network and provides an index of the branching complexity of the capillary network [13]. When comparing quantitative parameters between eyes with the same DR severity, in eyes with mild NPDR and DME, there was a significantly lower fractal dimension (FD) in the superficial retinal layer (SRL) and the deep retinal layer (DRL) compared to those without DME [13].

Regarding the correlations between the visual acuity and the quantitative OCTA microvascular parameters, in DME, a low FD in the DCP was correlated with a poorer BCVA, suggesting that macular ischemia plays an important role in the visual acuity drop associated with DME [18].

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