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MINIREVIEWS

Malfunction of outer retinal barrier and choroid in the occurrence and progression of diabetic macular edema

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Abstract

Diabetic macular edema (DME) is the most common cause of vision loss in diabetic retinopathy, affecting 1 in 15 patients with diabetes mellitus (DM). The disruption of the inner blood-retina barrier (BRB) has been largely investigated and attributed the primary role in the pathogenesis and progression in DME, but there is increasing evidence regarding the role of outer BRB, separating the RPE from the underlying choriocapillaris, in the occurrence and evolution of DME. The development of novel imaging technologies has led to major improvement in the field of *in vivo* structural analysis of the macula allowing us to delve deeper into the pathogenesis of DME and expanding our vision regarding this condition. In this review we gathered the results of studies that investigated specific outer BRB optical coherence tomography parameters in patients with DM with the aim to outline the current status of its role in the pathogenesis and progression of DME and identify new research pathways contributing to the advancement of knowledge in the understanding of this condition.

Key Words: Diabetic macular edema; External limiting membrane; Hyperreflective foci; Inner segment/outer segment line; Optical coherence tomography; Outer retinal barrier

Core Tip: Progress in optical coherence tomography technology allowed the identification of new pathogenic pathways in diabetic macular edema (DME) involving the outer retina and underlying choroid. The presence of fluid in the subretinal space is suggestive for the alteration of the outer blood retinal barrier and responds better to

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intravitreal triamcinolone as compared to anti- vascular endothelial growth factor. The disruption of external limiting membrane (ELM) is associated with visual impairment being a predictor of poor outcomes following the treatment with triamcinolone. The integrity of ELM and of the inner segment/outer segment line was found to correlate positively with best corrected visual acuity in DME.

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INTRODUCTION

Diabetic macular edema (DME) is the most common cause of vision loss in diabetic retinopathy (DR)[1], affecting 1 in 15 patients with diabetes mellitus (DM)[2]. DME is the first cause of visual impairment within the group of working-age population in the developed countries[3]. The retina is one of the most metabolically active tissues in the organism, having high energetic demands. The complexity of the retinal activity requires a homeostatic microenvironment which is achieved by the functioning of two distinct blood-retina barriers, inner and outer. The disruption of the inner blood-retina barrier (BRB) has been largely investigated and attributed the primary role in the pathogenesis and progression in DME, but there is increasing evidence regarding the role of outer BRB, separating the retinal pigmented epithelium (RPE) from the underlying choriocapillaris, in the occurrence and evolution of DME[4]. The normal functioning of the RPE is crucial for the retina, as it removes the waste resulting from the phagocytosis of the photoreceptors' outer segments, it provides nutrients for the photoreceptors and it substitutes the lymphatics by pumping the fluid from the inner retina to the choriocapillaris[5]. In the diabetic retina, the highly hypoxic microenvironment leads to the over-expression of vascular endothelial growth factor (VEGF) with subsequent depletion of occludin and damage of the tight junctions between the RPE cells[6]. The RPE alteration in DME was demonstrated both morphologically and functionally. Thus, electron microscopy studies performed on the retinas with DME induced in animal models found shrank nuclei, reduced endoplasmic reticulum, infolding cell membrane, altered melanosome and loss of RPE cells[5]. Electroretinography on a mouse model showed the early decrease of c wave before the occurrence of any photoreceptor dysfunction[7]. The impact of VEGF on the RPE function was demonstrated on cell cultures: increase of VEGF led to the increase of transepithelial resistance (TER) which is a marker of RPE barrier's function. Following VEGF neutralization with an antibody, the RPE barrier's function recovered partially[8]. Following the analysis of the RPE cells' proteome, 62% of the proteins involved in the retinoic metabolism were found to be altered in diabetic eyes without retinopathy. Interestingly, these proteins were modified also in nonretinal tissue, proving that the alteration of RPE is part of the systemic effect of diabetes[9].

The development of novel imaging technologies has led to major improvement in the field of *in vivo* structural analysis of the macula allowing us to delve deeper into the pathogenesis of DME and expanding our vision regarding this condition[10]. Within the last decades through the implementation of specialized computer software systems and modern mathematical tools (fractal/multifractal and lacunarity analysis)[11,12] non-invasive predictive complementary tools were developed for an early diagnosis of patients with DME[13].

In this review we gathered the results of studies that investigated specific outer BRB optical coherence tomography (OCT) parameters in patients with DM with the aim to outline the current status of its role in the pathogenesis and progression of DME and identify new research pathways contributing to the advancement of knowledge in the understanding of this condition.

OUTER RETINAL BARRIER AND THE CHOROID IN THE PATHOGENESIS OF DME

The normal functioning of the retina is ensured by the blood-retinal barrier (BRB) which regulates the entry and exit of fluid and molecules, maintaining the retina transparent and dehydrated[14]. BRB is affected early in diabetic retinopathy (DR) which translates into increased vascular permeability and retinal edema[15]. BRB has two components, inner and outer.

Inner BRB is constituted by the tight junctions (zonula occludens) between the endothelial cells within the retinal vessel walls which allow interactions with pericytes and smooth muscle cells[16]. Pericytes have a critical role in maintaining of BRB, by liberating a lipid mediator which modulates it[17]. Retinal Müller cells and astrocytes stabilize the tight junctions between the endothelial cells[18], whereas microglia produces soluble factors which are important for vesicular communication[15].

Outer BRB is formed by the intercellular junction complex of the RPE. More specifically, the basolateral membrane of the RPE faces the Bruch's membrane, separating the RPE from the fenestrated endothelium of the choriocapillaris[19] (Figure 1).

These tight, adherens and gap junctions control the transport of fluids and solutes between the choroidal capillaries and the photoreceptor layers, thus maintaining the integrity of the retina[18]. It was proved that the RPE cells express major histocompatibility complex molecules, adhesion molecules and cytokines, thus playing an important role in immune processes[20]. Healthy RPE also regulates the retinal oxidative stress, therefore its malfunctioning reduces the level of antioxidants[19].

Even if the TER is much lower than the resistance of the inter-endothelial junctions at the inner retinal barrier, it efficiently prevents proteins and water from the choroid to enter the subretinal space and it allows water to exit towards the choroid following an osmotic gradient[14]. RPE dysfunction leads to the disruption of fluid transportation from the subretinal space towards the choriocapillaris which is translated into DME.

Hyperglycemia leads to the alteration of the junctional complexes at the level of the outer blood-retinal barrier subsequently to the activation of metalloproteinases by oxidative and nitrosative stress[14]. Since RPE is a highly polarized epithelium, any cytoskeletal alteration damages not only the junctions, but also the adequate distribution of membrane transporters leading to subretinal fluid accumulation[14].

Serous detachment of the macula which is very suggestive for the breakdown of the RPE barrier is observed in approximately one third of the DME cases[20,21].

Decanini *et al*[9] analyzed the RPE proteome in preretinopathic diabetic human donor eyes and identified significant biochemical changes preceding the clinically evident diabetic retinopathy. Some of the RPE altered proteins overlap with findings from other tissues affected by DM, but others were identified as novel biomarkers, such as proteins involved in retinoid metabolism, membrane dynamics and protein transport, proving that DM affects multiple cellular processes. Given the importance of RPE for the retinal functioning, these alterations may play a major role in the early pathogenesis of DR[9].

The external limiting membrane (ELM) is formed by tight-like and adherens junctions located at the interface between the retinal Müller glial cells and photoreceptor inner segments (Figure 2). Even if its role in the coordination of fluid movement around the macula is not fully understood, earlier studies showed that ELM serves as an important barrier to free protein diffusion across the retina[14]. Hyperglycemia alters the ELM by disrupting the tight junctions by the activation of PKCζ[22]. In DR the disruption of the junction protein complexes from the OLM translates clinically by lower visual acuity[23] and poor response to anti-VEGF therapy in DME[24,25].

Despite the information presented above, experimental studies proved that the RPE junction barrier is highly resistant to acute hypoxia/ischemia[26]. Besides, it is not known in which extent the RPE barrier is affected by retinal ischemia and the *in vivo* mechanisms involved in RPE dysfunction are not fully understood. For these reasons, the alterations of the outer retinal barrier drew less attention to the pathogenesis of DME compared to the ones of the inner retinal barrier[14].

The choroid is a highly vascularized and pigmented structure whose main role is to provide oxygen and nutrients to the intensely metabolic active outer retinal layers, namely the central avascular fovea and the prelaminary portion of the optic nerve[27]. Although the pathogenesis of DR is mainly attributed to the dysregulation of the retinal vasculature, there is evidence pointing to diabetic choroidopathy[28]. Histological studies of the choroid revealed atrophy of the choriocapillary

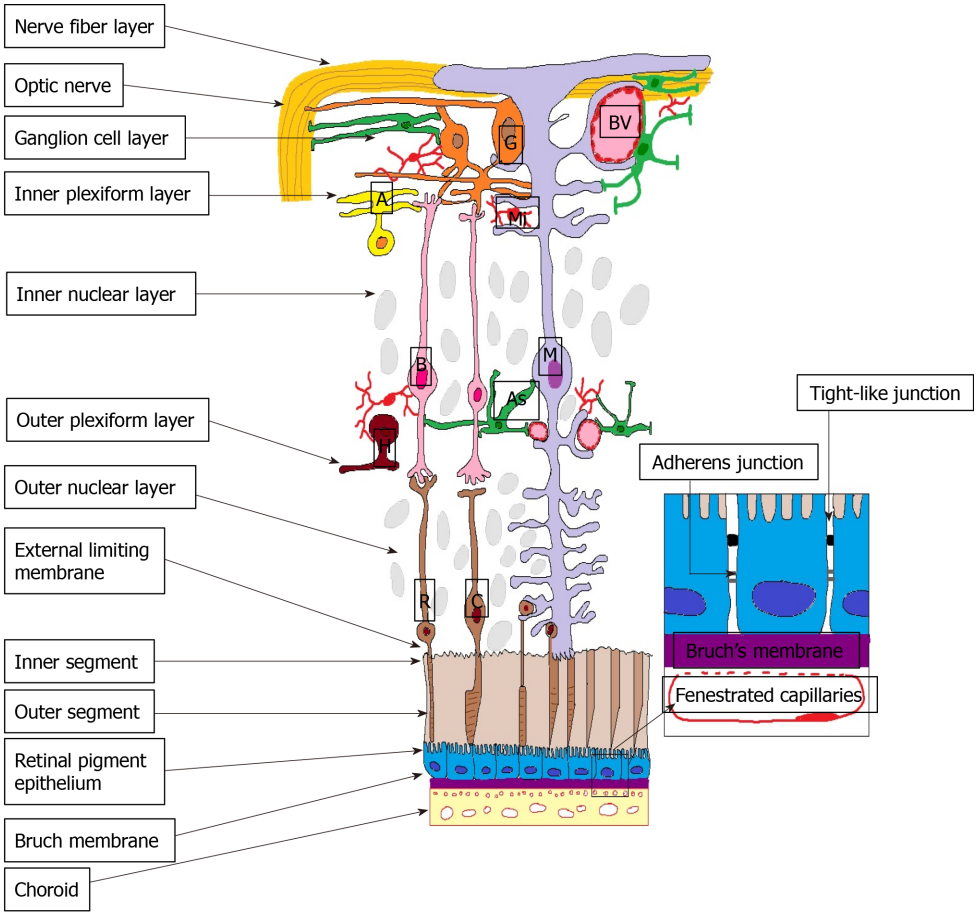

Figure 1 Outer blood-retina barrier. M: Müller cells; A: Amacrine cells; G: Ganglion cells; BV: Blood vessels; As: Astrocyte; B: Bipolar cells; R: Rods; C: Cones; H: Horizontal cells; Mi: Microglia; ON: Optic nerve; NFL: Nerve fibre layer; GCL: Ganglion cell layer; IPL: Inner plexiform layer; INL: Inner nuclear layer; OPL: Outer plexiform layer; ONL: Outer nuclear layer; ELM: External limiting membrane; IS: Inner segment photoreceptors; OS: Outer segment photoreceptors; RPE: Retinal pigment epithelium; BM: Bruch's Membrane; Ch: Choroid.

endothelium, laminar deposits and narrowing of the luminal area in diabetic patients without DR[29,30], as well as basement membrane thickening, capillary dropout and choroidal neovascularization[28].

OPTICAL COHERENCE TOMOGRAPHY BIOMARKERS OF THE OUTER RETINA IN DME

Currently, precision retinology is in-conceivable without the use of OCT which allows early diagnosis, monitoring and individualization of treatment in patients with DM. The normal OCT aspect of the retinal layers is illustrated in Figure 3.

Serous retinal detachment

Based on the OCT appearance, three major types of DME were individualized: diffuse sponge-like thickening type, cystoid type (thickening of the fovea with intraretinal cysts) and serous retinal detachment (SRD) type (thickening of the fovea with subretinal fluid)[18,31,32].

Each of these lesions occurs in individual retinal layers, as follows: cystoid spaces are located mainly in the inner nuclear layer (INL) and outer plexiform layer (OPL); in SRD the extracellular fluid pools between the photoreceptors outer segments (PROS) and RPE; sponge-like retinal swelling at the fovea is identified in the OPL[33]. Whereas the sponge-like retinal swelling is frequently accompanied by abnormalities of the vitreo-macular interface causing the thickening of the retinal parenchyma at the level of the OPL[33], the presence of fluid in the subretinal space suggests the alteration of the outer BRB being caused by the migration of fluid from the retina through a weakened and permeable ELM or from the hyperpermeable vessels in the choriocapillaris through a dysfunctional RPE[18,32]. In the early stage of the disease the subretinal fluid

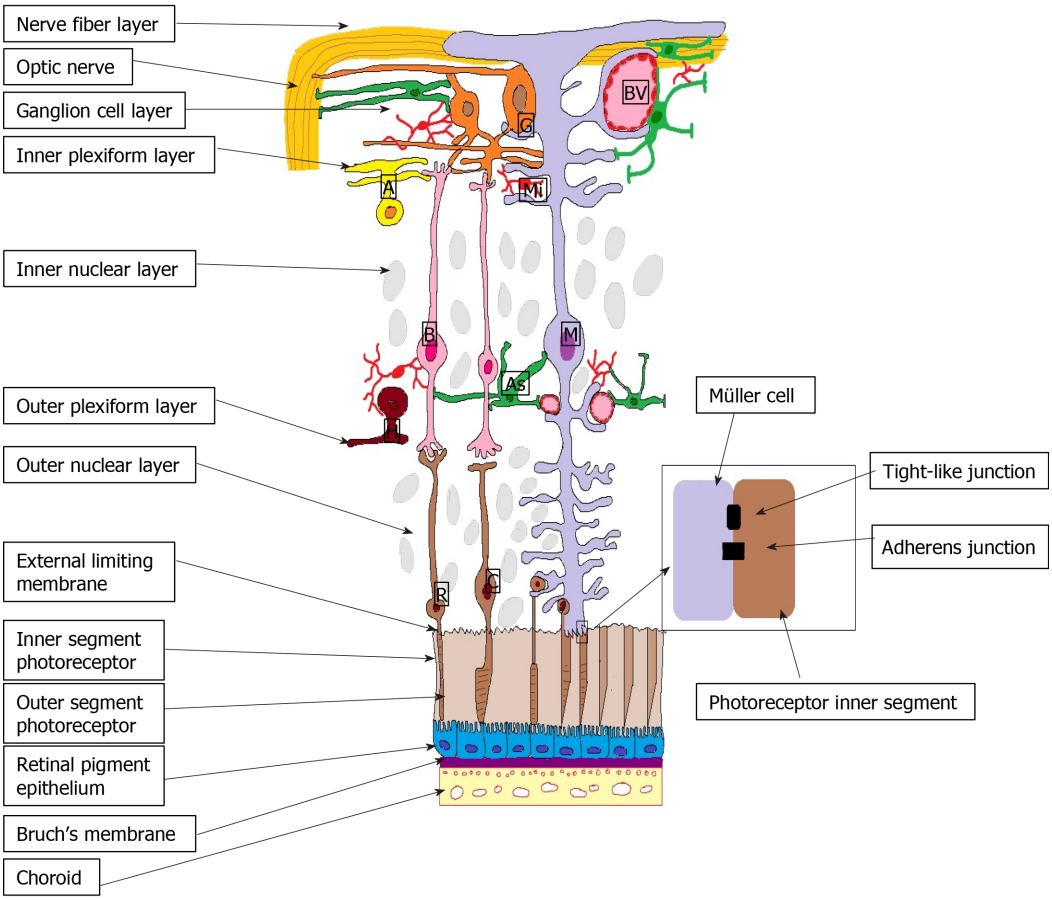

Figure 2 External limiting membrane. M: Müller cells; A: Amacrine cells; G: Ganglion cells; BV: Blood vessels; As: Astrocyte; B: Bipolar cells; R: Rods; C: Cones; H: Horizontal cells; Mi: Microglia; ON: Optic nerve; NFL: Nerve fibre layer; GCL: Ganglion cell layer; IPL: Inner plexiform layer; INL: Inner nuclear layer; OPL: Outer plexiform layer; ONL: Outer nuclear layer; ELM: External limiting membrane; IS: Inner segment photoreceptors; OS: Outer segment photoreceptors; RPE: Retinal pigment epithelium; BM: Bruch's Membrane; Ch: Choroid.

originates in the hyperpermeable choriocapillaris through a dysfunctional RPE and as the disease progresses in the breakdown of the outer BRB through a permeable ELM[34,35]. The clinical significance of SRD derives from the observation that its presence is associated with poor visual prognosis, probably due to the disruption of ELM[36].

Several studies compared the effectiveness of anti-VEGF treatment according to the OCT appearance of DME and found that the SRD type which associated ELM and RPE impairment did not respond well[37,38].

Intravitreal triamcinolone was more effective than anti-VEGF therapy in reducing macular thickness and improving vision in eyes with the SRD type of DME (Figure 4) in a prospective case series[39]. However, the relatively short follow-up period (24 mo) requires careful interpretation of these results, especially since long term steroid related complications (cataract, glaucoma) are well known[40,41]. Recently, good results with a dexamethasone implant in SRD were reported and OCT factors associated with better outcomes were identified as the absence of HF and a continuous ellipsoid zone (EZ) at the fovea[42]. The better outcome of SRD following intravitreal steroids as compared to intravitreal anti-VEGF is explained by the role of inflammation in its pathogenesis. In the SRD type of DME increased concentrations of inflammatory cytokines and higher levels of IL-6 were found in the aqueous humor and the vitreous[36]. It is believed that the source of IL-6 is represented by the scavenger cells attracted by the ELM damage[20].

Outer retinal layers

OCT studies offered insights into the outer retina, proving that the disruption of the EZ occurs subsequently to the disruption of ELM[43]. The base of this observation is that ELM has tight junctions between the Müller cells and photoreceptor cells which are similar to those between the RPE cells. As such, ELM is functioning like a third retinal barrier against macromolecules[44] whose malfunctioning leads to the accumulation of

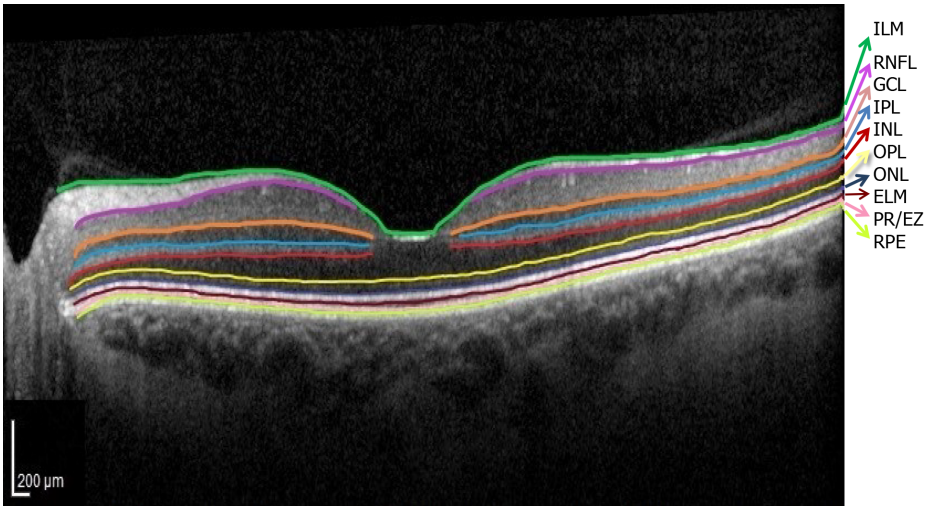

Figure 3 Normal optical coherence tomography aspect of the retinal layers. Segmentation software automatically marked the 10 retinal layers. (ILM: Internal limiting membrane; RNFL: Retinal nerve fiber layer; GCL: Ganglion cell layer; IPL: Inner plexiform layer; INL: Inner nuclear layer; OPL: Outer plexiform layer; ONL: Outer nuclear layer; ELM: External limiting membrane; PR/EZ: Photoreceptor layer/ellipsoid zone (inner and outer photoreceptor segment junction; RPE: Retinal pigment epithelium).

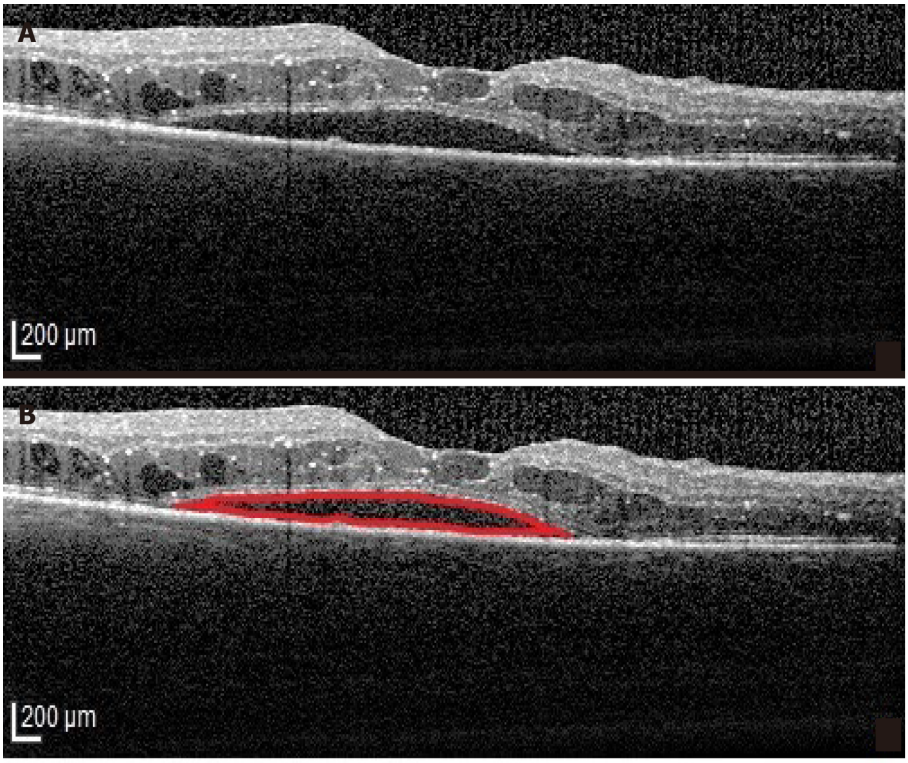

Figure 4 Serous retinal detachment type of diabetic macular edema. A: Optical coherence tomography (OCT)-Retinal neurosensory detachment; B: Highlighted OCT image showing the neurosensory detachment (red).

fluid in DME. As a result, surrogate biomarkers of the outer retina were proposed to determine the progression of DR[45]. A grading of the ultrastructural changes in correlation with the severity of the disease was elaborated, grade 0 meaning no disruption of ELM and EZ, grade 1 meaning ELM disruption with intact EZ and grade 2 meaning disruption of ELM and EZ[46]. The disruption of ELM allows blood components to reach and potentially damage the photoreceptor layer. The damage of ELM in DME could be explained by the extension of the cystoid spaces from the INL to the OPL[47], or by the occurrence of a tear in the outer retinal layers in eyes with SRD[34]. Several studies have shown that ELM disruption is associated with visual impairment in DME[47-49] being a predictor of poor outcomes following the treatment

with triamcinolone[50]. The integrity of ELM and inner segment/outer segment (IS/OS) line was found to be positively correlated with best corrected visual acuity (BCVA) in multiple studies[50-54]. ELM and IS/OS are useful hallmarks for the evaluation of photoreceptor layer whose integrity is closely related to the final BCVA[25].

Murakami *et al*[55] proved that whereas the thickness of the inner retinal layers is positively correlated with the visual impairment, the outer retinal thickness is correlated negatively with poor visual prognosis following vitrectomy for DME. Thus, thinning of the outer retina and photoreceptor degeneration contributes at least partly[33] to the apparently paradoxical changes of visual acuity that were reported by the Diabetic Retinopathy Clinical Research Network[56].

Many studies proved the importance of the inner IS/OS line in DME[47,48,50,51,53,57-60]. It was showed that the transverse length of the disrupted IS/OS line is correlated with the visual acuity[50] and that the length of PROS is associated with the visual function in DME[49]. PROS correlated better with visual acuity than macular thickness, suggesting it as a reliable biomarker of visual acuity in patients with DME[49].

One issue is to point out without a doubt that the IS/OS line that we see on the OCT images corresponds to the actual histological junction between the outer and inner photoreceptors segments. Correlating the microstructures seen on the OCT images with the histological findings, it was speculated that this hyperreflective band was located at the EZ in the inner segments[61]. One important observation is that reflectivity around this band increased after the exposure to light, suggesting that the line is a marker of the photoreceptor function per se[62,63].

Decreased thickness of the PR layer was reported in patients with proliferative diabetic retinopathy-diabetic macular oedema (PDR-DMO) and nonproliferative diabetic retinopathy (NPDR)-DMO[2] and attributed to the reduced values of PROS length in a relatively hypoxic environment at the level of the outer retina[64].

When correlating the OCT parameters of the outer retina with the visual function, Damian *et al*[2] found a low positive correlation between the outer retina and BCVA in the PDR-DME group and a low negative correlation between the RPE thickness and BCVA in the NPDR-DME group. The authors argue that the results are limited by the analyzing of cell thickness not morphology and therefore thickness within normal range is compatible with altered cellular anatomy.

RPE-PR complex

RPE layer is crucial for the survival of PR cells, the two layers being considered as a functional unit due to their interdependence.

In a recent study it was proved that the RPE thickness was decreased in all quadrants in patients with PDR-DME and in some quadrants in the ones with NPDR-DME[2]. This finding may be subsequent to the disruption of the RPE-PR complex possibly due to ischemia[65,66]. Kaarniranta *et al*[67] proved that constant oxidative stress which is a feature of DR leads to the impairment of autophagy and heterophagy in the RPE cells. However, the same authors found occasionally increased RPE thickness in patients with PDR-DME and NPDR-DME[2] which are explained either by the growing of new cells over the RPE cells in order to compensate the fluid leakage within the retina[5] or by the accumulation of shed PROS that are not timely engulfed by the RPE cells due to the alteration of their phagocytosis capacity[68]. The findings of a thickened RPE in diabetic patients may also be a consequence of impaired glycogen metabolism ant its accumulation inside the RPE. It has been shown that glycogen content is increased in the RPE from diabetic donors, as well as in RPE cells grown in hyperglycemic conditions, as consequence of an increase in glycogen synthase activity, whereas the glycogen phosphorylase was normal[69].

Tavares Ferreira *et al*[70] found a thicker RPE layer and thinner PR layer in patients with DM without DR as compared to nondiabetic controls. Xia *et al*[68] reported an increased thickness of the RPE-PR complex measured as a whole, but no changes in the thickness of retinal nerve fiber layer (RNFL) and ganglion cell layer (GCL) in type 2 diabetic patients without retinopathy and concluded that the modifications of the RPE-PR complex preceded the loss of ganglion cells in the diabetic retina without microvascular abnormalities. This finding is consistent with evidence from electrophysiology[71] and color vision which are impaired in patients without clinical DR[72-75].

"Parallelism" of the retinal layers

SD-OCT made it possible to define a new parameter, "parallelism", referring to the integrity of the retinal layers and serving as a potential biomarker to prognosticate visual outcome in DME. The orientation of the photoreceptor status layer at the fovea was categorized including the continuity of ELM, inner segment EZ and presence of

HF in the outer retinal layers. Parallelism was found to be significantly lower in eyes with DME as compared to normal eyes and positively correlated with visual acuity. The absence of HF in the outer retinal layers was associated significantly with higher parallelism and better visual acuity[76].

HF

HF were described as dot like lesions on the OCT images[77] (Figure 5). When identified in the external retinal layers, HF were associated with poor visual outcomes in patients with DME and foveal SRD[34], but also in the ones with DME without SRD[51]. Bolz *et al*[77] postulated that HF in eyes with DME are lipid-laden macrophages and represent the precursors of hard exudates. The observation that the disruption of the ELM and IS/OS line is associated with HF stands for the theory that these lesions reciprocally promote the degeneration of photoreceptor (PR) cells in DME[33].

Correlations between the inner and outer retina

When correlating the inner and outer retinal barriers, Das *et al*[78] found that there is a strong association of disorganization of the inner retinal layers (DRIL) (Figure 6) with the disruption of ELM and EZ in DME, advancing the hypothesis that DRIL could be responsible for the disorganization of the outer retinal architecture. Another study found a highly positive correlation between the thickness of the inner retina and of the central RPE in the NPDR-DME group and a low negative one in the PDR-DME group, stressing the importance of the retinopathy grade on the DME and pointing out that whereas in NPDR the edema involves the entire retina and is mostly vasogenic, in PDR it is driven mainly by ischemia[2].

OPTIAL COHERENCE TOMOGRAPHY (ANGIOGRAPHY) BIOMARKERS OF THE CHOROID IN DME

Enhanced depth imaging OCT and swept source OCT (SS-OCT) allowed to examine the choroid. Vascular changes and thickness alterations of the choroid were reported, outlining the diabetic choroidopathy[79,80].

Choroidal thickness in patients with DM

Several studies have found that DM is associated with decreased choroidal thickness (CT)[80-83]. Since the choroid is the main source of oxygen and nutrients for the outer retina and RPE, this may lead to increased retinal vulnerability to diabetes related hypoxia and ischemia. Moreover, a trend towards choroidal thinning paralleling the increasing severity of DR has been proved[84].

Even in the absence of any clinical retinopathy, some authors reported the significant decrease of CT in patients with DM, suggesting that the decreased choroidal blood flow might be the primary event[80,81] . Choroidal thinning was particularly obvious in the subfoveal and inferior regions in a study conducted by Esmaeelpour *et al*[81]. The same study group noted the perimacular retinal thinning probably caused by the optic nerve fiber layer atrophy[81].

Other studies have shown opposite results, in the sense that thicker choroid was identified in patients with DR[32,80,85]. Tavares Ferreira *et al*[86] measured CT in diabetic patients without DR and found significantly increased CT superiorly to the fovea, proposing it as a possible early preclinical change in diabetes. Using SS-OCT, the same authors identified vascular choroidal remodeling in diabetic patients without retinopathy and choroidal small vessel loss in the areas of previous laser photocoagulation in patients with proliferative diabetic retinopathy[87]. Choroidal thickening increased with the severity of DR, significantly[27] or not significantly[88].

At present there is no consensus on the temporal relationship between the choroidal changes and retinopathy. Some authors claim that the onset of choroidopathy precedes retinopathy, while others argue that the two events are independent[32,80,85,87,89]. Several studies offered evidence of choroidopathy occurring only in the most severe stages of DR[82,83,90] or worsening with the increasing severity of DR[32,89].

CT and DME

Patients with DME have clinically significant thinner subfoveal choroid compared to healthy controls, but when compared to other grades of DR, NPDR and PDR, their choroid is thicker[84]. Kim *et al*[32] reported significantly thicker choroids in DME patients as compared to non-DME patients. When the type of DME was further

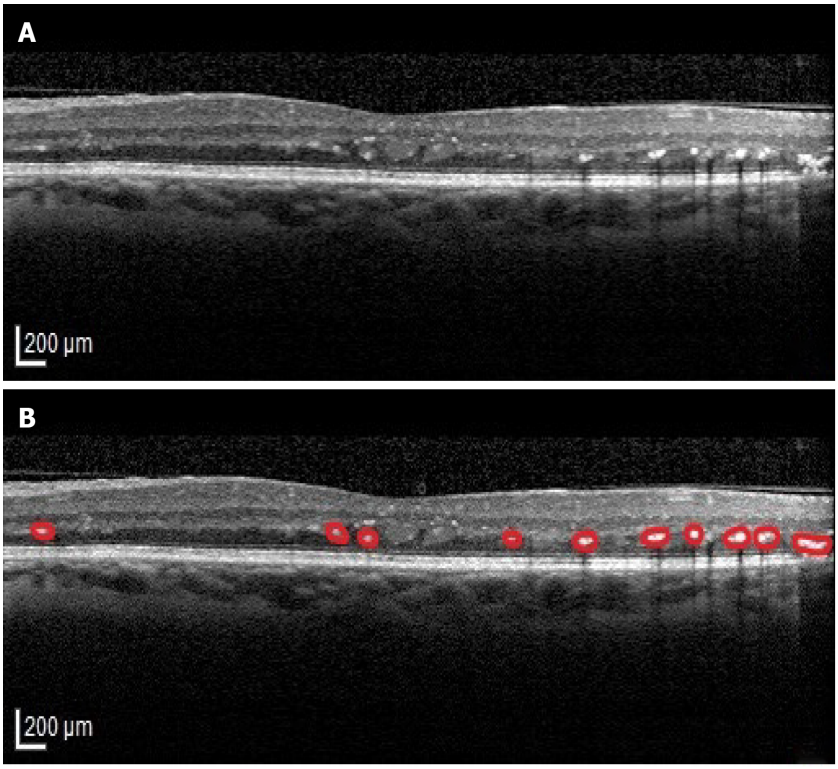

Figure 5 Hyperreflective foci. A: Original optical coherence tomography (OCT) image; B: Highlighted OCT image revealing hyperreflective foci (red).

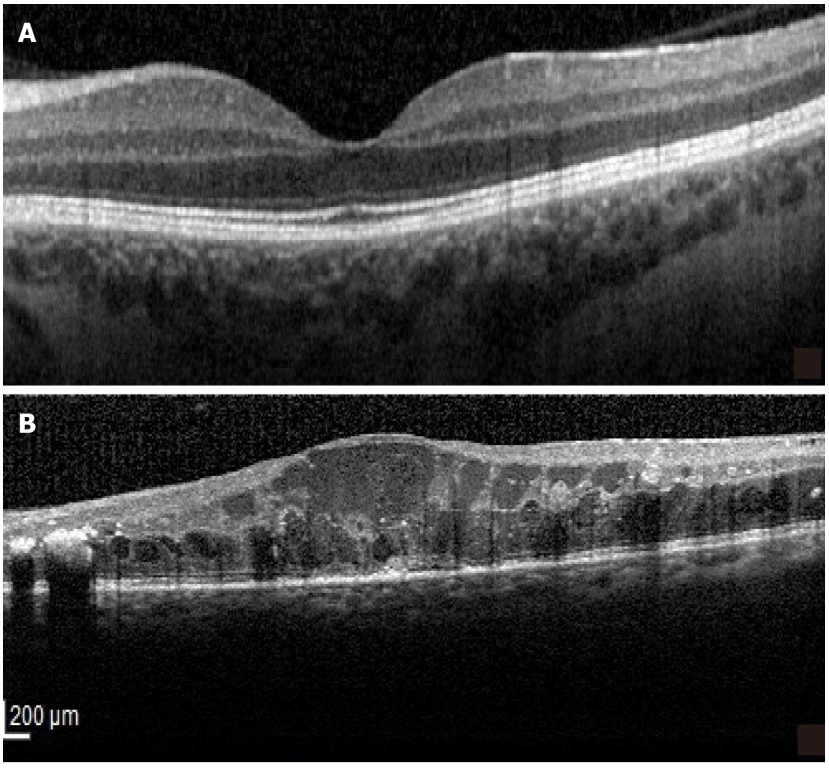

Figure 6 Disorganization of the inner retinal layers. A: Normal optical coherence tomography aspect of the macula; B: Disorganization of the inner retinal layers.

evaluated, CT was significantly greater in the SRD group than in the cystoid type DME[32]. However, other authors reported thinner choroid in case of clinically significant macular edema, explaining this finding as an artifact due to the attenuation of signal transmission and reflection by the edema itself[79,91]. Despite this, Gerendas

et al[91] reported that in the fellow non-affected eye the choroid was also thinner, suggesting that systemic factors are involved in the pathogenesis of this finding. Esmaeelpour *et al*[81] reported no choroidal thinning below the lesions in patients with DME.

CT after treatment for DR

It was shown that panretinal photocoagulation (PRP) is followed initially by choroidal swelling within one week, which is explained by the shifting of vessels from the peripheral retina to the foveal area[92,93], followed by the thinning of the choroid, possibly by downregulation of VEGF[27]. Cho *et al*[93] found at 1 and 3 mo after PRP an increased subfoveal CT concomitant with a significant CT decrease in the photocoagulated area.

Regarding anti-VEGF treatment, several studies reported choroidal thinning over the first 6 mo[94,95]. Rayess *et al*[96] showed that subfoveal choroidal thickness (SFCT) is a predictor of response to anti-VEGF therapy in the sense that a greater SFCT at baseline is associated with better outcomes. One explanation is that greater choroidal thickness stands for intact choriocapillaris, less ischemic outer retina and better preservation of photoreceptors[96].

Systemic factors, like blood hemoglobin, arterial blood pressure and hypercholesterolemia, influence CT[84].

Future developments of CT as biomarker in DME

CT in patients with DR is a highly unreliable parameter and multiple studies show different results because there is a poor control of variables, a wide range of collecting data and different devices are used. There is evidence that the choroid thins with progressing DME as well as following PRP and anti-VEGF injections. It was reported that longer standing DME is associated with worse anatomical and functional outcomes following anti-VEGF treatments. Therefore, a thicker choroid prior to treatment would probably indicate a shorter duration DME and be associated with better outcomes after treatment. Thus, CT may be also attributed the role of prognostic biomarker able to predict the response to treatment in DME. However, in order to get reliable data on CT, future studies should accomplish certain requirements: to define clearly the scleral-choroidal junction, to include local (refractive status), and general (age, diabetes duration, HbA1C) factors in the analysis, to make a longitudinal approach and use longer follow up intervals[28].

Choroidal vascular index in patients with DM

Choroidal vascular index (CVI) is a term that means the ratio of choroidal luminal area to total choroidal area which was recently introduced as a novel biomarker to monitor the progression of DR[97]. CVI may be attributed the role of an early biomarker, because studies proved that while CT is unaltered in DR, CVI correlates with progressing DR[83]. CVI alteration before the onset of DR, supports the theory of choroidal primary damage in DR[98].

Decreased choroidal blood flow creates a hypoxic environment for the RPE and photoreceptor cells, disrupting the phagocytosis and rendering the RPE cells fragile[99,100]. The condition is aggravated by the subsequent production of superoxide and soluble inflammatory factors[68].

Whereas most of the studies focused on the CT showing its thinning in patients with DM, proportional with the severity of DR, a multicenter cross-sectional study used SS-OCT images to analyze choroidal vascularity in different stages of DR and introduced new quantitative parameters, such as choroidal vascular density (CVD) and choroidal vascular volume (CVV)[28]. According to this study, the eyes with DME and PDR had a reduced CVD and eyes with PDR had also a reduced CVV compared to controls, reflecting the notion that vascular abnormalities increase with the severity of DR. In eyes with NPDR without DME, the overall CVD was significantly reduced, but not at macula, suggesting that although diffuse choroidopathy may be present in early stages of DR, submacular choroidopathy only becomes present in later stages of DR. The same authors proved that in diabetic patients without DR, the choroidal vascular indices did not show significant differences compared to controls. Thus, it is suggested that the occurrence of diabetic choroidopathy does not precede that of retinopathy, although further studies are required to elucidate this important issue for understanding the diabetic eye disease[28].

A recent study analyzed CVI after intravitreal injection of ranibizumab in eyes with DME and found the significant reduction of CVI and choroidal blood flow only in the no-PRP group, but not in the PRP-treated group. Moreover, a significant correlation

between the central retinal thickness and choroidal blood flow was found in the no-PRP group[101].

OCTA choroidal biomarkers in DME

In diabetic patients without DR, an OCTA study showed that the choroidal foveal flow area was significantly decreased compared to controls suggesting that the compromise of the circulation starts in the foveal choroidal layer in DR, preceding the occurrence of mycroaneurysms. When DR develops, both the retinal and choroidal capillaries are significantly reduced[102].

INDOCYANINE GREEN ANGIOGRAPHY

Years before the recent studies with OCT, a paper using indocyanine green angiography (ICGA) in patients with NPDR disclosed microvascular findings in addition to those described with fluorescein angiography: lobular spotty hyperfluorescent and hypofluorescent areas in the very late phase, diffuse late-phase hyperfluorescence corresponding to retinal capillary non-perfusion areas on fluorescein angiography and retinal edema[103]. However, due to its invasiveness and lack of quantification, ICGA is limited in detecting ischemia in early DR[102].

CONCLUSION

Advances in OCT technology allow a more detailed investigation of the outer retina and choroid providing biomarkers that mediate the decoding of pathogenesis, monitoring and selection of the best treatment option for DME. By identifying new OCT biomarkers at the level of outer retina and choroid, paths for early diagnosis and identification of novel therapeutic targets in DME are opened.

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