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REVIEW

The promising retinal optical coherence tomography biomarkers in common macular diseases: A brief summary of the literature

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Abstract

The recent developments in imaging technologies such as optical coherence tomography (OCT) helped produce high-quality and high-resolution retinal images. This progress revealed some parameters called biomarkers, which are helpful clinical decision-making indicators. This review aims to highlight valuable OCT biomarkers related to common macular diseases. Besides the most frequent disorders such as diabetic retinopathy and age-related macular degeneration, also retinal vein occlusion and epiretinal membrane were evaluated in the current article. The mentioned markers can help determine prognosis, assess treatment response, and even predict surgical success; however, there is a need for wider and prospective studies. It is essential to evaluate biomarkers together with multimodal imaging and the clinical characteristics of the patients.

Keywords: Age-related macular degeneration; biomarker; diabetic retinopathy; epiretinal membrane; macular diseases; optical coherence tomography; retinal vein occlusion.

Optical coherence tomography (OCT) has been an essential tool for the routine clinical examination of macular diseases since it was first developed.[1] While the technology behind expanded furiously, appliances became faster and provided detailed images with better resolution. OCT may offer information about diagnosis, activation, staging, course, and treatment response of diseases. The technological revolution in retinal imaging and high-quality images of retinal layers have revealed several new parameters in common macular disorders. By interpreting such information gained from high-quality OCT images, visual and anatomical prognosis of macular disorders became more viable. Such parameters are called biomarkers and are particularly helpful in clinical decision-making.[2,3]

The purpose of this review is to look over some valuable retinal OCT biomarkers on most frequently studied macular diseases such as Diabetic Retinopathy (DR), Age-related Macular Degeneration (AMD), Retinal Vein Occlusion (RVO), and Epiretinal Membrane (ERM).

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The Definition of a Biomarker

Biomarkers are measured indicators of specified biological conditions. Biomarkers are widely used in clinical practice: They may help estimate the prognosis of a disease, evaluate the response of an intervention or understand the stage of diseases.[4] Although biomarkers have a variety of classifications, Frank and Hargreaves suggested three types of it: Type 0 helps to predict the longitudinal outcomes of a disease such as high-risk criteria in non-proliferative diabetic retinopathy (NPDR), type 1 biomarkers deal with the direct treatment results, for example, the vitreous levels of vascular endothelial growth factor (VEGF) after intravitreal anti-VEGF injection, type 2 biomarkers are the most helpful ones which provide clinical endpoints of parameters such as macular thickness on DR.[5]

DR, Diabetic Macular Edema (DME), and Retinal Biomarkers

DR is one of the leading causes of acquired vision loss and is a result of diabetes mellitus, which is expected to affect more than 366 million individuals by 2030, almost like a pandemic.[6] DR may be divided into two stages, NPDR with its characteristic fundus findings and proliferative diabetic retinopathy (PDR) with neovascularization (NV). DME is a sight-threatening complication that may occur in any stage of DR. OCT is an indispensable appliance in the clinical management of retinopathy (Fig. 1a, b).[7]

Disorganization of the Inner Retinal Layers (DRIL)

In DR, when predicting the prognosis or the severity of the disease, the first thing that comes to mind as a biomarker is DRIL (Fig. 1b) In DME, DRIL defines the homogeneity of ganglion layer, inner plexiform layer, and outer nuclear layer and the absence of their boundaries in the central macula.[8] DRIL is associated with baseline visual acuity (VA). Also, an increase in DRIL of more than 300 µm at 4 months linked to a 1-line decrease in VA.[8] Even with no DME but the presence of DRIL in OCT imaging is correlated with the severity of maculopathy.[9] DRIL also has a relationship with other severity markers primarily related to outer retinal layers.[10] Foveal hypo-perfusion may also be predicted with the presence of DRIL; the foveal avascular zone is greater in patients with DRIL recommended by Nicholson et al.[11]

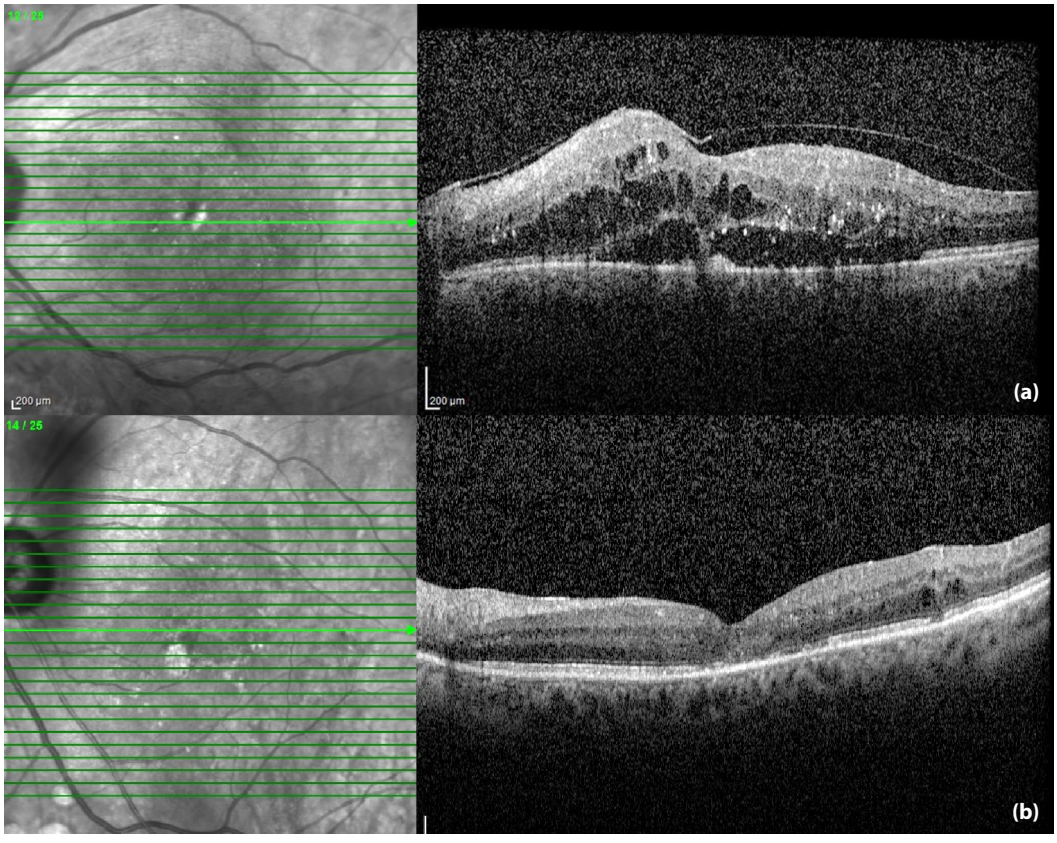

Fig. 1. Diabetic retinopathy, **(a)** a severe patient suffers diabetic macular edema with an increase in retinal thickness, multiple hyperreflective retinal foci, intraretinal cystoid spaces and outer retinal layers disruption, **(b)** disorganization of inner retinal layers, and disruption of outer retinal layers may be seen on a patient with poor visual expectations.

Hyperreflective Retinal Foci (HRF)

HRF may be defined as hyperreflective small dots, which are as reflective as the neural fiber layer with no back-shadow on OCT imaging (Fig. 1a and 2a). HRFs are thought to result from leakage of protein exudates, and some studies declared that they might include microglial cells inactive form.[12,13] HRFs reflect the inflammation in DME and DR and may guide the treatment options. The number of HRFs tends to decrease after injections. In addition, in patients with multiple HRFs, dexamethasone implants seem to have better results compared to anti-VEGF injections. There is research indicating that patients with a high number of HRFs tend to develop DME recurrence more.[14,15]

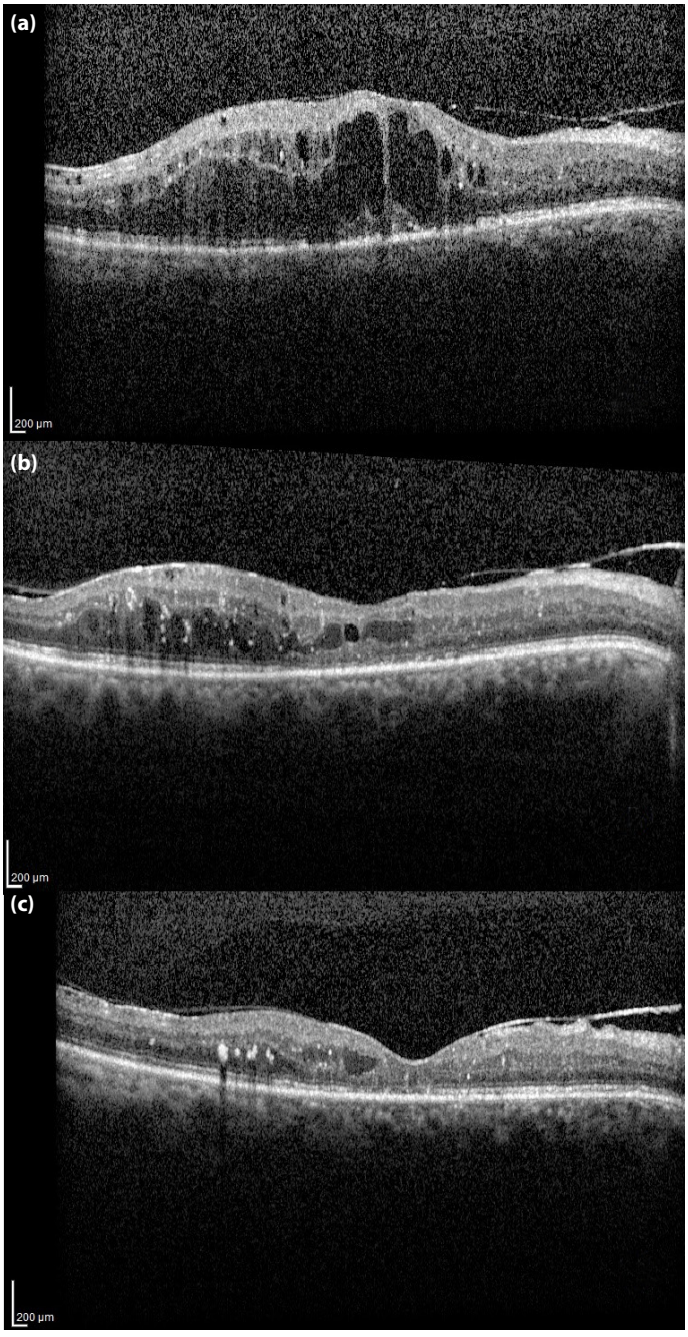

Fig. 2. Follow-up of a diabetic retinopathy patient. **(a)** Initial imaging with severe cystoid macular edema, multiple hyperreflective retinal foci, intraretinal cystoid spaces, and outer retinal layers disruption, initial visual acuity was 1.00 logMAR. **(b)** Imaging of the patient after three doses of anti-vascular endothelial growth factor treatment. **(c)** Final imaging, although an intensive treatment regimen final visual acuity was 0.90 logMAR due to the presence of disorganization of the inner retinal layers and the disruption of the outer retinal layers.

Intraretinal Cystoid Spaces

DR triggers microvascular damage and affects the blood-retinal barrier, which may cause cystoid changes in the retina. These cystoid spaces are a reason for photoreceptor damage[16] (Fig. 1a). Especially cysts larger than 200 µm are signs of late disease and related with worse VA than more minor ones.[17] Treatment may help to decrease the number or size of the cysts with an association in the VA. The more damage in the blood-retinal barrier, the more hyperreflective signals in the cysts observed, and response to anti-VEGF treatment may be insufficient.[18,19]

Subfoveal Retinal Thickness (SRT)

The increase in retinal thickness is a result of retinal edema. It may be measured easily with OCT imaging. Although SRT is one of the first measurements that come to mind historically, no clear correlation with final VA has been found. SRT may reflect the treatment response, but the edema may resolve with atrophic changes after the treatment. Rather than the thickness, volume and cross-sectional analysis are new focuses.[20]

Photoreceptor Outer Segment (PROS) Length

The measurement from RPE to photoreceptor outer-inner segment junction is the definition of the PROS length. Studies report that it is reduced in DME patients than healthy volunteers and a better biomarker than the macular thickness. However, it is much earlier for a final decision, and further studies are needed.[21,22]

Subfoveal Neurosensory Detachment

About 15–30% of the DME patients show subfoveal serous retinal detachment (SRD). There are controversial studies about SRD. Some authorities reported that the presence of SRD is associated with better anatomical results, and some said with poor outcomes. After the RESTORE[23] and RISE/RIDE[24] studies, SRD is considered a protective factor in DME. Patients with SRD gained better visual results and showed a better response to ranibizumab treatment.[23,24]

The aflibercept studies VIVID, and VISTA showed SRD at baseline is related to better treatment response.[25] More studies proved eyes with SRD have increased levels of interleukin-6, which may be considered as an inflammatory response, and dexamethasone implants are more helpful for eyes with SRD.[26,27]

External Limiting Membrane (ELM) and Ellipsoid Zone (EZ) Integrity

Without interruption, the continuity of the outer retinal layers has a direct relationship with the retina pigment epithelial and photoreceptor health. The treatment response is limited in DME patients with ELM/EZ interruption (Fig. 1b and Fig. 2a-c). The discontinuity can be graded, and it may be related to the severity of the retinopathy.[27,28]

AMD and Retinal Biomarkers

AMD is one of the leading causes of legal blindness and affects the macular region with the neovascular organization or degenerative changes. While the population is aging, more AMD cases in the future are expected with various severity. As in the other macular diseases, OCT is quite helpful for the ophthalmologic evaluation of a patient. Besides the classical findings such as drusen, some OCT discoveries may reflect the prognosis or visual expectations from a patient.[29,30]

Pigment Epithelial Detachment (PED)

PED was not used to be considered as an activation sign for AMD. Especially for exudative AMD patients, PED is a quite frequent finding (54–80%), and after monthly treatment, it is expected for them to regress.[31,32] The sub-type of the PED is also essential when comparing the treatment response; serous dominant PEDs generally heal entirely[33] (Fig. 3b).

PEDs are typically associated with minor changes in the VA, such as metamorphopsia. According to the literature, the presence of PED at the presentation is related to better visual outcomes. However, it is reported that eyes with PED gain less treatment response over time.[32,34] For pigment epithelial tears, large PEDs are an important risk factor, especially PEDs higher than 600 µm and encircled with a hyperfluorescent ring carry higher risk.[35] Failure to accept PEDs as an activation in the most conventional pro-re nata treatment regimen may cause choroidal NV activation. These flexible on-demand treatment options pause the treatment when SRF regresses completely, and monitoring by OCT continues. Slow reactivation of neovascular lesions

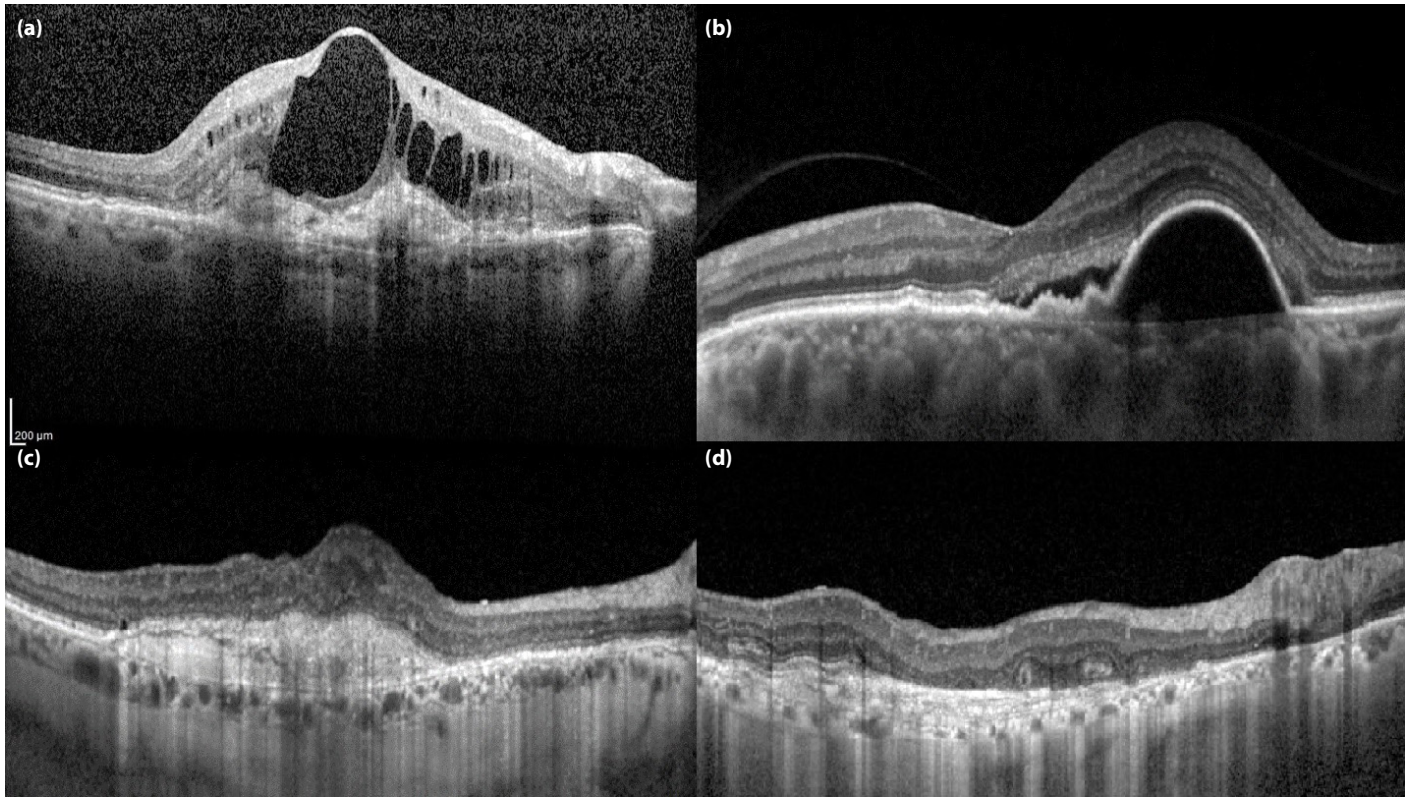

Fig. 3. Some of the retinal biomarkers for age-related macular degeneration; **(a)** intraretinal cystoid fluid, **(b)** subretinal fluid with serous pigment epithelial detachment, **(c)** subretinal hyperreflective material, **(d)** outer retinal tubulation.

during the treatment pause may result in further retinal damage and VA loss.[34,36,37]

Subretinal Hyperreflective Material (SHM)

With the anti-VEGF treatment, primarily classic choroidal NV becomes inactive and may be visualized between retina and pigment epithelium as a hyperreflective mass (Fig. 3c). This organization is referred to as SHM, and after the regression of vascular component may result in scarring.[38,39] The increase in SHM thickness is related to reduced VA.[40] Studies reported reduced contrast sensitivity and less treatment response in patients with SHM.[38,41] The scar development is a cause of severe vision loss.[42]

Drusen and Subretinal Drusenoid Deposits (SDD)

Drusen is an almost pathognomonic finding in AMD and located between Bruch's membrane and pigment epithelium in the OCT. Generally, internal reflection is homogenous and may be classified by inner homogeneity or size.[43] Medium inner reflectivity with hyper-reflectivity beneath the pigment epithelium may indicate NV. With middle (≥63 µm) and large (≥125 µm) size drusen, the late-stage AMD development risk is expected to be higher.[44] Loss of internal homogeneity or rapid regression on the drusen volume has a relationship with geographic atrophy.[45]

Pseudodrusen or SDD are seen on the apical side of the pigment epithelium as a hyper-reflective deposition. Many studies confirmed that in eyes with SDD, late-stage AMD is more common.[46,47] Especially for the type 3 NV, there is a superior relation with SDD.[48] Also, eyes with SDD tend to develop late-stage AMD, and geographic atrophy during follow-up seems to appear more often.[49,50] The functional parameters such as dark adaptation and contrast sensitivity are also insufficient in patients with SDD.[51]

Hyperreflective Foci (HF)

In exudative AMD, hyperreflective dots may appear in the neurosensory retina.[52] The lesions generally seem close to the SRF, and there is a disagreement about their pathophysiology. HFs are suggested as activated macrophages-microglias or as exudative materials.[53,54] Apart from their origin, mainly in the early stage of AMD, HFs are considered a risk factor for developing the late-stage disease. In those with adjacent pigment epithelial pathologies, this risk may rise.[55] The treatment response in patients with HF seems insufficient, and the resolution may be considered a prognostic sign.[56,57]

Intraretinal Cystoid Fluid (ICF)

The expansion of the neovascular lesion result in leakage to the retina, and this condition may be diagnosed in OCT as an increase in the retinal thickness and/or cystoid areas (Fig. 3a). ICF is generally associated with retinal angiomatous proliferation or classical NV lesions or a late result of occult NV and has a 52–76% prevalence at the treatment naïve exudative AMD patients.[31,32,58] ICF presence at the treatment naïve stage is related to poor VA and diminished microperimetry sensitivity.[31,59] Also, the disruption of the retinal functions is a cause for degenerative cystoid changes and should be differentiated from an NV activation. The neovascular ICF responds to the anti-VEGF treatment, and VA gains should be expected.[60] Degenerative ones are generally accompanied with atrophic pigment epithelial areas, and they are imaged as hypo-reflective, sharp lesions. Further, they are not responsive to the treatment.[34,61]

Central Retinal Thickness

Almost in all macular diseases, the first OCT measurement evaluated is the central thickness.[62] Although there is an effort to measure the thickness automatically, there is a failure in standardization. By the recent studies, only the amount of thickness cannot reflect the retinal structural changes, and the limitations of the measurement may explain the weak correlation with visual outcomes.[63–65] Although it is not very effective in follow-up, a negative correlation was found between retinal thickness and VA at the first admission.[31]

Subretinal Fluid (SRF)

SRF is related to better visual outcomes, although it seems to be a pathologic finding.[32] 70 to 85% of the patients have SRF at the first examination, and the presence of SRF is associated with higher final VA. Furthermore, SRF presence is related to a better response to the anti-VEGF treatment, and after monthly treatment, patients with SRF develop less pigment epithelial atrophy.[31,66,67]

SRF is an activation criterion for AMD, and with its absence, on-demand treatment may result in poor visual outcomes compared with aggressive regimens.[66] Further studies focus on the structural features of the fluid. The amount of SRF may positively correlate with VA, but increased inner reflectivity may result in poor visual outcomes.[58,68]

Outer Retinal Tubulation

Outer retinal tubulation reflects a hypo-reflective tubular organization in the outer nuclear layer, encircled with a hyperreflective ring[69] (Fig. 3d). This finding may cause unnecessary treatment interventions due to the misdiagnosing as fluid. The outer border is composed of an inner photorecep-

tor segment and an ELM, and this structure is recommended as a response to retinal damage.[69,70] The final VA of the patients with tubulation is poorer.[71] The presence of the outer retinal tubulation is associated with a lower gain of VA during treatment.[72] The prevalence of the tubulation escalates while the duration of the disease increase.[72]

Outer Retinal Layers and Pigment Epithelial Atrophy

Photoreceptors are sensitive to the NV damage, and outer nuclear layers on OCT may be the indicator of it.[73] The association is significant between the integrity of the EZ and the ELM with VA, but the adequate evaluation is quite tricky due to the uncertain contours.[52,56]

Pigment epithelial atrophy may be diagnosed easily with OCT imaging, and in some cases, this is the main reason for the poor visual outcomes despite all the treatment. Type 2 and 3 NV are mainly associated with atrophy.[74] Although there are studies in which anti-VEGF therapy and the number of injections are associated with atrophy, the results are still controversial.[75,76]

Bacillary Layer Detachment (BD)

BD, as an extremely novel parameter, is defined by the thickening of the photoreceptor inner segment due to the fluid accumulation. It was first described in posterior inflammatory disorders associated with pachychoroid or toxoplasmosis.[77] A recent report by Jung and associates revealed Type 2 macular NV is related to BD and after anti-VEGF treatment, BD tends to resolve. BD is also significantly associated with subretinal hemorrhage.[78] However, prospective studies in different retinal diseases are still needed.

Subretinal Lipid Globules (SLG)

SLG are identified as round-shaped, hyporeflective structures settle between RPE/Bruch membrane complex and EZ.[79] Recent studies disclosed a relationship among SLG and the course of the NV. SLG has a positive correlation with the number of anti-VEGF treatment. This marker, which is thought to be of choroidal origin, is especially associated with type 1 NV and is typically detected at the border of the lesion. Articles on SLG are mostly associated with multiple diseases and investigate the link with macular NV, but the patient groups in the studies seem to be predominantly AMD. Further studies are needed to strengthen the relationship.[80]

RVO and Retinal Biomarkers

RVO is a retinal vascular entity that may affect the central vein or a branch of it. Ischemia and macular edema are the leading cause of visual loss and may be resulted in NV. Treatment options such as laser, intravitreal anti-VEGF, or steroid injections are helpful, but the response of the patients and VA gains are limited.[81]

The usual concept for anti-VEGF treatment starts with monthly injections followed by on-demand care. Considering that the treatment includes many complications and unnecessary visits, various clinical and imaging features have

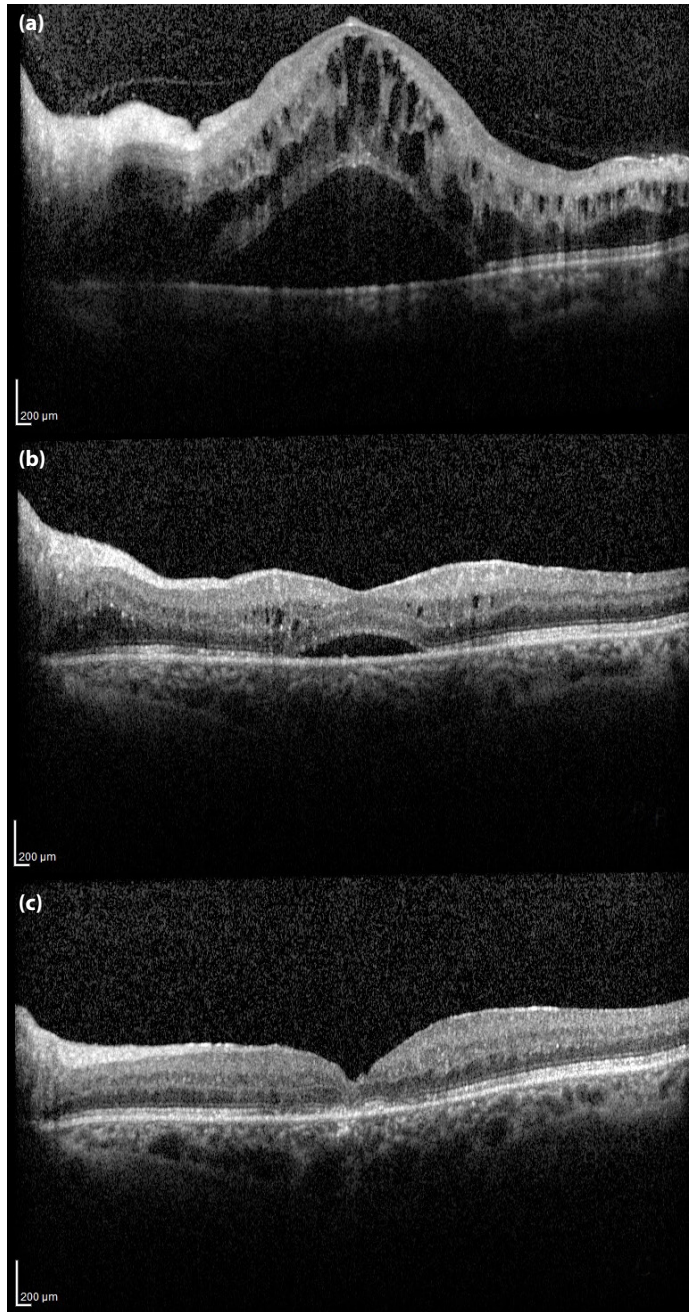

Fig. 4. **(a)** Initial imaging of a patient with central retinal vein occlusion, cystoid macular edema, subretinal fluid, and outer retinal layers disruption may be seen. **(b)** The regression of the edema after three doses of anti-vascular endothelial growth factor treatment. **(c)** Final imaging of the patient with the presence of inner and outer retinal layers disorganization resulted in poor visual acuity gain.

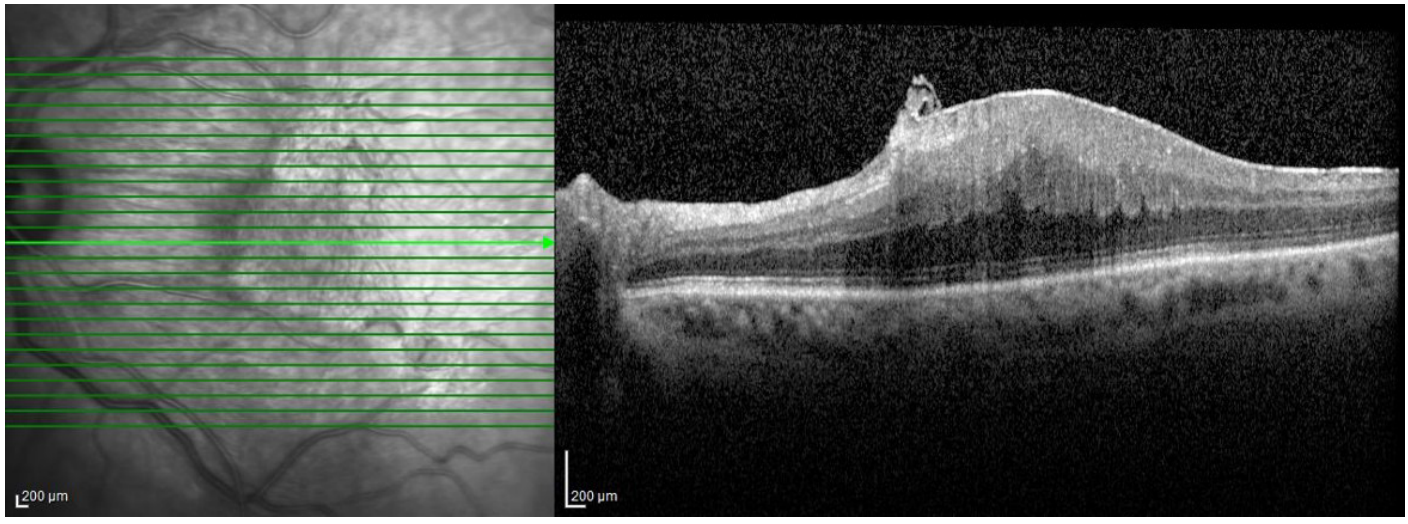

Fig. 5. The disorganization of inner retinal layers and increase in retinal thickness may be seen on a patient with epiretinal membrane.

been investigated in patients who do not respond and need more injections. The evaluation parameters are close to the DME patients; however, the outcomes are still limited.[82,83]

The health of outer nuclear layers is essential for the visual pathway. ELM and EZ discontinuity in branch-RVO is significantly associated with poorer visual outcomes[82] (Fig. 4a-c). The differentiated reflectivity of the inner retinal layers in OCT is also crucial to predict the prognosis. The absence of this differentiation is named DRIL and should expect better VA gains with its lack. The increase or the persistence of the DRIL is also related to more flawed VA improvement.[84]

Another new suggested outer retinal/photoreceptor-related prognostic parameter is PROS length. The PROS length has a significant correlation with final VA and number of injections at 1 year.[82]

As in the DR, some inflammatory markers are similarly evaluated nowadays in RVO. While SRF seems to be a beneficial finding, having more than 30 HF seems to be a reason for VA loss.[83]

Idiopathic ERM and Retinal Biomarkers

The most common type of the ERM is the idiopathic one, which occurs without any accompanying ocular disease, and is more frequent in elder patients. Especially for patients with disturbing symptoms such as metamorphopsia and visual impairment, surgery is the primary treatment option.[85] However, even surgeries without any complications may result in poor visual gain. The interpretation of the preoperative retinal anatomy on OCT may help to predict the visual prognosis or the potential benefits of the operation.[86,87]

Outer retinal layers and photoreceptor integrity, especially at the foveal region, were deeply investigated to predict ERM surgery outcomes. The outer retinal biomarkers such as EZ integrity and PROS length seem to be the most valuable and reliable ones.[88,89] After surgery, outer layers tend to restore, and the persistence of an outer retinal defect after surgery is strongly associated with poor visual outcomes.

Lately, the inner retinal layers and related markers have been of interest to clinicians. An OCT-based DRIL grading system for ERM surgery has been suggested for predicting postoperative results. The severity of the DRIL is strongly correlated with preoperative VA, and patients with mild or no DRIL end up with better anatomical and functional improvement[90] (Fig. 5). Another recommended marker is the inner retinal irregularity which reflects the deformation of inner retinal layers, has an association with visual progress.[89]

Conclusion

OCT is a rapid, high-resolution imaging system and provides information likewise a tissue biopsy of the retina and further. It is crucial to consider OCT biomarkers for the accurate management of common macular diseases. Thorough evaluation of OCT images may help to create treatment algorithms and may avoid further complications. Another significant contribution may be the prevention of unnecessary treatments and predict the visual prognosis.

Most reports mentioned in the current study are based on retrospective analyses, and prospective, large case-control studies are needed. Multimodal evaluation of each stated marker with the patient's clinical features and other imaging methods will be more helpful.

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