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REVIEW ARTICLE

Vitreous and intraretinal macular changes in diabetic macular edema with and without tractional components

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Abstract

Diabetic macular edema (DME) is still one of the main causes of visual impairment. Repeated intravitreal injections of ranibizumab are considered the gold standard treatment, but the efficacy in patients with prominent cystic characteristics remains uncertain. In diabetic retinas, the identification of both antero-posterior and, particularly, tangential tractions is crucial to prevent misdiagnosis of tractional and refractory DME, and therefore to prevent poor treatment outcomes. The treatment of tractional DME with anti-VEGF injections could be poorly effective due to the influence of a tractional force. Pars plana vitrectomy (PPV) is a surgical procedure that has been widely used in the treatment of diffuse and refractory DME. Anatomical improvement, although stable and immediate, did not result in visual improvement. PPV with internal limiting membrane (ILM) peeling for the treatment of non-tractional DME in patients with prominent cysts (> 390 μm) causes subfoveal atrophy, defined as "floor effect". Epiretinal tangential forces and intraretinal change evaluation by SD-OCT of non-tractional DME are essential for determining appropriate management.

Keywords Diabetic macular edema · Non-tractional macular edema · Diabetic retinopathy

Introduction

Diabetic macular edema (DME) is the main cause of visual impairment in working-age populations in developed countries [1]. Since the published data by the Early Treatment Diabetic Retinopathy Study Research Group (ETDRS) in 1985, the focal/grid laser photocoagulation was considered the gold standard treatment for DME [2]. However, later studies have shown that, although this approach prevented further visual loss, it did not confer a significant improvement in visual acuity to the majority of cases treated [3].

The pioneering research by Ferrara et al. led to the introduction of ranibizumab, first anti-vascular endothelial growth factor (anti-VEGF) drug licensed for intravitreal use, for the treatment of neovascular diseases [4]. Prospective clinical trials with different dosing regimens and treatment algorithms of intravitreal ranibizumab (IVR) established the rapid and sustained improvements in vision and retinal anatomy in patients with DME, with minimal systemic absorption, thus reducing the risk of side effects associated with biological therapies [5–8].

The RESTORE Study compared the use of IVR, alone or in combined use with laser therapy, against laser monotherapy. The results showed that IVR, alone or in combined use, was more effective than laser alone in improving and maintaining best-corrected visual acuity (BCVA), as well as the central retinal thickness (CRT) [5]. The safety and efficacy profile was also proven with long-term follow-up and established in clinical practice by the progressively declining number of injections needed over 3 years of individualized dosing [9].

The RISE and RIDE studies compared the effect of early use of ranibizumab versus placebo. The study confirmed an increase in BCVA in the ranibizumab treatment group up to 36 months. However, when patients in the control arm were given ranibizumab at 24 months, the improvements in BCVA were limited. The hypothesis suggested for this result is that chronic retinal edema might lead to a degree of retinal atrophy, therefore expedient treatment is crucial to prevent such changes and achieve the best outcomes [10].

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The recent LUCIDATE study compared the functional and structural effects of ranibizumab versus standard laser therapy [11]. The group receiving ranibizumab injections showed an improvement in visual acuity, retinal sensitivity in the central 4 and 12 degrees on microperimetry, and increased color contrast sensitivity in protan and tritan axis compared with the laser treatment group. Electophysiological testing (ERG, pattern ERG, and multifocal ERG) demonstrated an improvement in the visual function in the same group [11].

Browning and Massin investigated the morphological characteristics of refractory DME. They showed that eyes with refractory DME exhibit short-term fluctuation in macular thickness larger than OCT measurement variability. In this group of patients with prominent cystic characteristics, the efficacy of IVR injections was uncertain. Information about short-term fluctuation might, therefore, be clinically important in deciding whether subsequent treatment with anti-VEGF is indicated [12, 13].

The vitreo-retinal interface and the anomalous posterior vitreous detachment

The vitreous gel and the retina join anatomically at the vitreo-retinal interface. In such complex structure, the vitreous cortex adheres to the internal limiting membrane (ILM) of the retina through an extracellular glue-like matrix composed of fibronectin, laminin, opticin, and other extracellular matrix constituents [14]. These attachments are particularly stronger at the anterior vitreous base and the optic nerve and less firm at the macula surface.

Normal aging causes progressive changes in vitreous macromolecules, with liquefaction (synchisis), weakening of vitreo-retinal adhesion and eventually total collapse of collagen fibrils (synaeresis). The initial separation of the vitreous from the ILM, with residual attachment at either the optic disk or macula, is defined as "incomplete" posterior vitreous detachment (PVD); the total separation of the fibrils from ILM is defined as "complete" PVD [15].

High glucose levels, commonly found in diabetes mellitus, alter the structure and function of the vitreo-retinal interface by accumulation of advanced glycosilation end-products (AGEs). AGEs generate a non-enzymatic glycation, abnormal cross linking of collage fibrils that lead to stronger adhesions between the posterior vitreous cortex to the ILM [16, 17]. Such changes can also lead to an "anomalous" PVD, even at younger age [18].

Gella et al. have considered the anomalous PVD the major risk factor in sight-threatening diabetic retinopathy [19]. Anomalous PVD generates antero-posterior and tangential traction forces at the vitreo-retinal interface that act upon the inner and outer retinal layers. In physiological complete PVD, the separation between the posterior vitreous cortex and the retina is total, with no residual adhesions at the macular surface. In anomalous PVD, strong bonds are created at the macular interface, whereas the peripheral vitreous can be completely separated. The anomalous PVD is defined as vitreo-macular adhesions (VMA) if there are no changes of foveal profile. With the progressive increment in antero-posterior vector of tractions, the macular structure changes, leading to the changes of foveal profile, formation of intraretinal cysts with initial onset of visual symptoms. This condition, which can be easily detected by optical coherence tomography (OCT) scans, is defined as vitreo-macular traction (VMT) [20].

The anomalous PVD can also result in vitreoschisis, characterized by a splitting of the posterior vitreous cortex in two layers. The outermost part remains attached to the retina, whereas the remaining vitreous collapses forward [21].

Following the splitting, the hyalocytes left on the retinal surface stimulate migration and proliferation of reticulo-endothelial cells, whose contractile properties generate tangential forces on the retina [22]. Supporting data was added by Sebag et al., with the detection of vitreoschisis by combined OCT/SLO imaging in patients with macular hole and also in those with epiretinal membrane (ERM), suggesting a common pathophysiological basis for the two different conditions.

According to Sebag's work, if the split of the posterior vitreous cortex occurs posterior to the level of hyalocytes, a thin hypocellular membrane (layer of vitreous) remains attached to the macula. This finding, in turn, may induce outward (centrifugal) tangential contraction causing a macular hole. If the split is instead anterior to the level of hyalocytes, a relatively thick, hypercellular, and contractile membrane (layer of vitreous) may induce inward (centripetal) tangential traction upon the underlying retina leading to ERM [23].

Another common consequence of anomalous PVD is the persistence of adhesions at the borders of the optic disk defined as vitreo-papillary adhesions (VPA). In presence of vistreoschisis, VPA may influence the vectors of forces exerted on the macular interface, inducing tangential epiretinal traction and intraretinal changes such as cysts [24]. The identification of both antero-posterior and particularly tangential tractions is crucial to prevent misdiagnosis of tractional and refractory DME, and therefore to prevent poor treatment outcomes. The tractions are, however, very difficult to detect both clinically and with OCT. In order to investigate the optimal indication for the treatment of DME, Abe et al. suggested the use of *en face* SD-OCT imaging pre- and postoperatively [25].

We believe that the tangential traction in DME is currently under-estimated, leading to treat tractional DME as non-tractional DME, thus with anti-VEGF treatments. Looking mainly to the antero-posterior traction, we lose the major component of the anomalous PVD: the tangential traction.

The ectopic inner foveal layer and the ganglion cell complex thickness

ERM formation is a common retinal condition characterized by fibrocellular proliferation at the vitreo-retinal interface, above the ILM, mostly associated with an anomalous PVD. After PVD, glial cells migrate through microscopic defects of ILM and then proliferate on the surface of the retina, forming an ERM [26, 27]. It is important to underline the different intraretinal anatomical changes between idiopatic (i) and diabetic (d) ERM; in fact, these aspects could modify visual prognosis after surgery.

Tractional stress that ERM leads on inner retinal layers of the macula could significantly alter the inner foveal micro-anatomy. In fact, the chronic antero-posterior and centripetal traction of ERM may cause the displacement and reorganization of the inner retinal layers leading a continuous floor of inner retinal tissue across the central fovea and referred to as ectopic inner foveal layers.

The presence of continuous ectopic inner foveal layers in ERMs is a newly described OCT finding associated with significant vision loss [28] (Fig. 1).

The development of ectopic inner foveal layers may result from the combination of both physical displacement of the inner retinal layers and Müller cell activation.

EMR exerts a stress on Müller cells, which in this condition overexpress glial fibrillary acid protein (GFAP). GFAP is involved in cell adhesion mechanisms, interacting with the cytoskeleton, surface receptors, and extracellular matrix [29–32]. In addition, the formation of epiretinal traction involves intraretinal glial proliferation, which has been considered predominantly epiretinal [33]. Glial proliferation could be responsible for the appearance in OCT of ectopic inner foveal layers in the evolved iEMR, and it may result in poor post-surgical visual recovery.

Retinal modifications of iEMRs may not be present in dEMRs, due to the early damage of Müller cells. Diabetic retinopathy (DR) is characterized by inner neuroretinal degeneration; this is observed structurally, as neural apoptosis, ganglion cell (GC) loss, reactive gliosis, and thinning of the inner retina [34] (Fig. 2).

A recent study showed that neuroretinal degeneration precedes micro-vasculopathy in people with diabetes mellitus (DM), and these findings were confirmed in two different mouse models of DM using both OCT image analysis and immunohistochemistry. The retinal neurodegeneration is not mediated by retinal microvascular disease in the form of microscopic capillary loss or the earliest manifestation of DR [35].

Tien et al. have described that high glucose (HG) induces mitochondrial dysfunction and promotes apoptosis in retinal rat retinal Müller cells. In DR, injury to or loss of retinal Müller cells may lead to disruption in the exchange of essential metabolic nutrients necessary to protect retinal neurons. When Müller cells become activated and undergo reactive gliosis, this protective mechanism may be compromised [36]. This could explain the lack of presence in OCT of ectopic inner foveal layers in evolved dEMR.

Treatment based on neuroprotection could be new approach for preventing or arresting DR development. In fact, neurodegeneration is the initial damage in diabetic patient which progressively leads to neuron loss, breakdown of the BRB, vasoregression, and the impairment of neurovascular coupling.

Anti-VEGF therapy and fibrosis

Multiple studies have suggested that anti-VEGF injections in presence of tractions can induce metaplasia of the epiretinal cells causing an increase of fibrosis and tractional complications [37, 38].

A biochemical and ultrastructural study by Walsh et al. has highlighted the presence of atypical chronically contractile myofibroblastic cells in preretinal membranes of patients affected by proliferative retinal diseases. These cells have a strong smooth muscle differentiation supported by the presence of α-smooth muscle actin (SMA) and desmin and are thought to be responsible for tractional phenomena in the tissues [39].

We believe that the multiple anti-VEGF injections in case of proliferative diabetic retinopathy (PDR), in presence of anomalous PVD or ERMs, could increase the tangential contraction, mainly acting through the SMA.

In support of anti-VEGF, induced fibrosis hypothesis has described a case of a patient with DME, in which the formation of a lamellar macular hole occurred following treatment with intravitreal bevacizumab (IVB). In this case, the lamellar

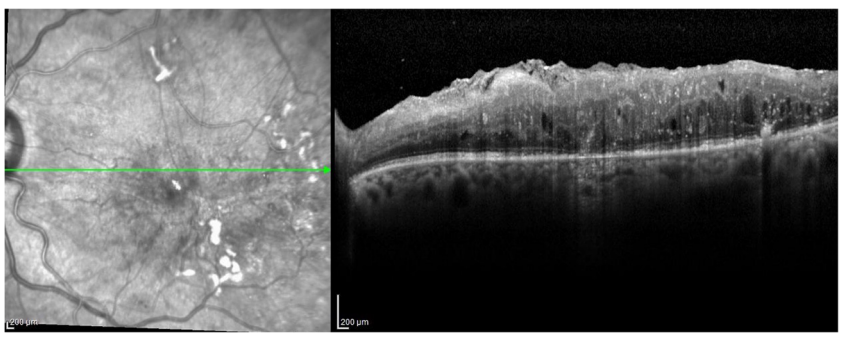

Fig. 1 Optical coherence tomography intraretinal changes under idiopathic epiretinal membranes. The epiretinal traction is responsible Muller cell activation with increase of GFAP and intraretinal gliosis visible as ectopic hypereflective inner foveal layers between INL and IPL

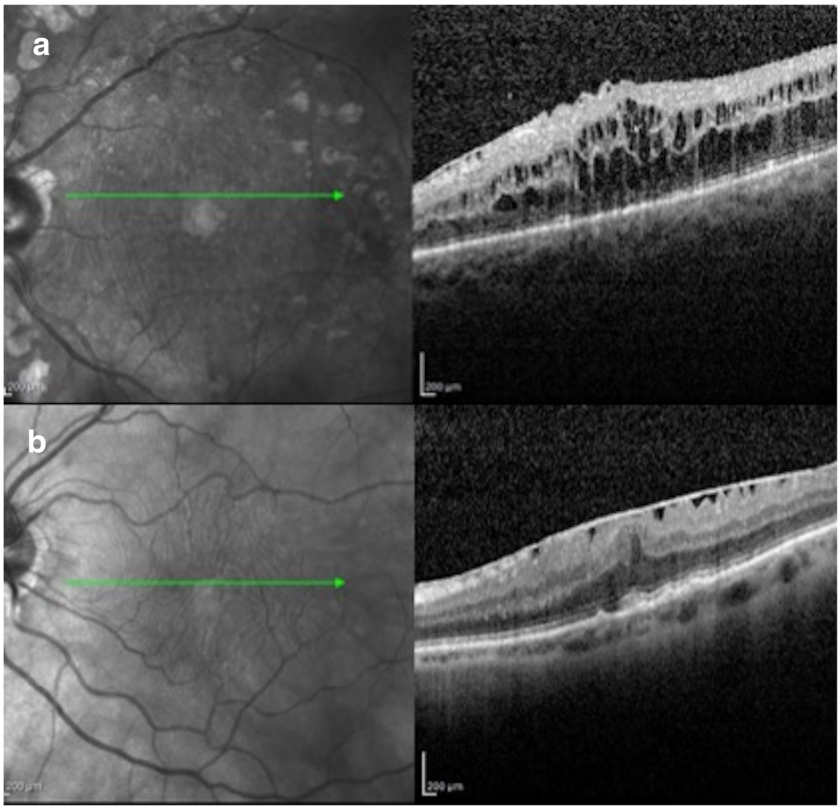

Fig. 2 Optical coherence tomography intraretinal changes in diabetic vs idiopathic epiretinal membrane. The epiretinal traction is not able to induce the increase of GFAP and intraretinal gliosis in diabetic epiretinal traction (**a**), whereas is able to induce the intraretinal gliosis with the ectopic inner foveal layer in idiopathic membranes (**b**)

macular hole occurred despite the absence of ERM in previous OCT scans [40].

Furthermore, in patients with PDR, high vitreal levels of connective tissue growth factor (CTGF) combined with low levels of VEGF after intravitreal therapy lead to an angiofibrotic switch that results in vitreo-retinal traction and fibrosis. This observation may suggest the existence of a critical balance between the VEGF and the CTGF [41].

In conclusion, the treatment of tractional DME with anti-VEGF, under the influence of a tractional force, tangential contraction, and angiofibrotic switch, could be could be poorly effective.

Surgical approach and role of ILM peeling

Pars plana vitrectomy (PPV) is a surgical procedure that has been widely used in the treatment of diffuse and refractory DME unresponsive to other therapies.

The mechanisms that underpin the surgical approach in DME can be essentially summarized as follows: (1) removal of inflammatory mediators present in the pathological vitreous, which cause persistent edema, (2) elimination of clinical and subclinical tractions that are often not visible by conventional means, and (3) increased oxygenation of the inner retinal layers.

The use of PPV in tractional DME has already been evaluated by the Diabetic Retinopathy Clinical Research Network (DRCR.Net) Group. Their study has shown only a slight improvement of visual function after surgical intervention at 6-month follow-up, despite significant reduction of retinal subfield thickness [42]. Similar results have also emerged from the work of Navarrete-Sanchis et al. They evaluated the efficacy of PPV in non-tractional DME at 1-year follow-up. Anatomical improvement, although immediate and stable, did not result in visual improvement. The lack of correlation between macular thickness and vision after surgery suggests that other factors must affect functional status [43].

Romano et al. have compared three different treatments on the anatomy and functional results of patients with non-tractional DME (IVB vs laser photocoagulation vs vitrectomy with ILM peeling). In all three groups the central macular thickness was significantly reduced, while a visual improvement occurred only in the group treated with IVB.

Of interest, subgroup analysis revealed those with large intraretinal cysts (IC) and treated with vitrectomy and ILM peeling had the worst functional outcomes. The authors have identified a negative correlation between postoperative BCVA with a baseline IC size higher than 390 μm. At this threshold size, they speculated that ILM peeling in this subgroup of patients may lead to macular hypotrophy and damage to the outer retinal layers [44].

It is well known that the peeling of the ILM is a traumatic procedure that can cause retinal damage, especially in pathologically impaired retinas [45, 46].

Even in non-diabetic retinas, early and late anatomical changes after ILM peeling were described [47, 48]. The earliest changes in the macula were reported by Clark et al. as the presence of postoperative swelling of the arcuate retinal nerve fiber layer (SANFL), as visualized by autofluorescence (AF), infrared (IR), and SD-OCT imaging [49]. These alterations did not cause any reduction of BCVA and disappeared 3 months after surgery. To explain these changes, the authors proposed two hypotheses. The first a direct surgical damage to the inner retina caused by forceps when the ILM is grasped prior to being peeled. The second, a subclinical acute trauma to the inner layers due to damaged Müller cell endplates attached to the ILM [49].

Three months after surgery, with the disappearance of the SANFL, late changes become evident. Numerous slightly dark arcuate striae within the posterior pole, in the same direction as the optic nerve fibers, have been visualized by blue filter photography. These have been named dissociated optic nerve fiber layer (DONFL) [50]. These defects correspond to "dimples" in the inner retinal layers detected by SD-OCT imaging. They consist of small depressions in the contour of the retina limited to the retinal nerve fiber layer [51].

The same late changes have also been studied by *en face* SD-OCT that showed a different pattern of multiple dark dots along the course of the optic nerve fiber layer in the area of ILM peeling. These have been defined as "concentric macular dark spots" (CMDS) [52].

In addition, a diabetic retina presents some alterations that predispose to further damage after ILM peeling. The diabetic ILM appears thicker than non-diabetic ILM due to the proliferation of cell populations including neutrophilis, macrophages, lymphocytes, and fibroblast-like cells [53].

Moreover the Muller cells and astrocytes of ILM in presence of epiretinal retinal gliosis are associated with an increased expression of the intermediate filament GFAP. This GFAP increases the interactions between the cytoskeleton, surface receptor, and glial extracellular matrix, thereby acting as a bridge between Müller cells and ILM [54].

These stronger adhesions may be responsible for further injury to the cells of Müller after ILM peeling leading to structural collapse of the retina with damage of the outer retinal layers.

This subfoveal atrophy was defined by Romano as "floor effect" [44]. They proposed that this subfoveal atrophy was responsible for the significant reduction in CMT after vitrectomy with ILM peeling in patients with IC greater than 390 μm. The BCVA worsened despite the reduction of the IC size. Vitrectomy with ILM peeling in these patients is not recommended, while the most appropriate treatment is with anti-VEGF injections [44].

A recent study has compared 23 eyes with idiopatic epiretinal membranes iERMs and 19 with diabetic epiretinal membrane dERMs, undergoing ERM-ILM peeling, evaluated with SD-OCT preoperatively, 1 and 6 months postoperatively. The following parameters were examined: CMT, intraretinal cysts (IC), ectopic fovea layers, and GFAP expression in peeled ILMs. The ectopic fovea is associated with functional worsening and it is more present in the eyes with iERM, while the IC and GFAP in those with dERM [55, 56].

In conclusion, tomographic retinal evaluation by SD-OCT of non-tractional DME is essential for determining appropriate management.

Surgical indications consist of (i) refractory DME, unresponsive to anti-VEGF treatment, (ii) presence of subclinical tangential traction associated with VPA or vitreoschisis, (iii) DME with intraretinal cysts smaller than 390 μm in early unresponsive stage.

Microvascular changes in deep and superficial vascular plexus after macular peeling

DR alterations of the blood retinal barrier (BRB) are the consequence of factors such as ischemia, changes in blood flow, increased VEGF, oxygen-free radicals, endothelial and pericyte dysfunction, and inflammation [57].

Central visual loss is caused by DME, may not only be due to the macular edema itself, but also may be due to alterations in the foveal avascular zone (FAZ).

Different imaging modalities may be utilized to diagnosis and follow up of DME, the most important are fluorescein angiography (FA) and OCT. FA requires intravenous dye injection to image perfusion of the retina vessels and dye leakage from increased vascular permeability. OCT is a non-invasive method that allows to evaluate the presence of edema, the effectiveness of intravitreal therapies, and the thickness of the different retinal layers [58].

Optical coherence tomography angiography (OCTA) is a newly available retinal vascular imaging technique, which is able to separately visualize superficial and deep macular capillary plexus. Several studies have shown OCTA as a better imaging modality to examine the capillary perfusion. Spaide et al. demonstrated that OCTA is superior in delineating the retinal capillary networks compared with FA [59].

Emerging evidence suggests that neurodegeneration participates in early microvascular changes that occur in DR such as the breakdown of the BRB, vasoregression, and the impairment of neurovascular coupling [60–62]. Vasoregression is the primary response of retinal microvessels to chronic hyperglycemia and is characterized by the loss of perycites followed by the formation of acellular, non-perfused capillaries [63].

The foveal capillary plexus forms a ring at the margin of the fovea, producing a capillary-free region called FAZ. Previous studies have suggested that the mechanism behind the FAZ enlargement in diabetic retinopathy is associated with capillary closure [59, 64].

In a recent study, Takase et al. demonstrated that diabetic eyes show retinal microcirculation impairment in the macula even before retinopathy develops. Evaluation of the FAZ area OCTA showed that diabetic eyes presented significant FAZ enlargement regardless of the presence of DR. Then, diabetic eyes exhibit impairment of the retinal microcirculation in the macula even before the retinopathy actually develops and that en face OCTA is a useful noninvasive screening tool that can be used for the detection of early microcirculatory disturbance in patients with diabetes [65].

Romano et al. described changes in deep and superficial perifoveal capillary plexus after macular peeling in iERM and dERM. OCTA images were obtained to quantify the deep and superficial layers of FAZ. The deep FAZ area only significantly increased in dERM at the end of the follow-up period (6 months). No statistically significant differences were found between preoperative and postoperative superficial vascular plexus in iERM or dERM. This may be because the impaired diabetic perifoveal capillary plexus is more sensitive to the iatrogenic damage induced on the Müller cells by ILM peeling. This could be a result of early damage to the retinal microvasculature, caused by hyperglycemia. The preoperative size of deep FAZ may be considered as a prognostic factor, influencing the surgical plan of ILM peeling [66].

Combined surgical therapies

Combined treatment was suggested to improve the beneficial effects of PPV. Liu et al. conducted a meta-analysis of randomized controlled trials (RCTs) [67]. They evaluated BCVA and CMT after intravitreal triamcinolone acetonide (IVTA) injection as adjunctive treatment to panretinal photocoagulation (PRP) and macular photocoagulation (MPC) in patients with PDR and DME. At 12-month follow-up, they reported a significant improvement of both BVCA and CMT, without significant ocular complications [67].

In a retrospective study, Kim et al. evaluated combined therapy in 35 patients with non-tractional DME unresponsive to prior treatments [68]. The combination of PPV with ILM peeling, IVTA, PRP laser, and grid/focal laser photocoagulation resulted in functional and anatomical recovery that persisted for 3 years after treatment. An improvement of BVCA from the baseline was achieved in 65% of cases by two lines on a Snellen Chart. A gradual reduction in CMT and improvements of DME (of CMT less than 250 μm) was achieved in 87.5% of the subjects [68].

Similar results were reported by Boyer et al. in a prospective study of 55 eye patients with non-tractional DME [69]. They evaluated the safety and efficacy of the combined therapy with Ozurdex (dexamethasone intravitreal implant) 0.7 mg in association with PPV and focal laser. The peak of improvement in BCVA and CMT was reached 8 weeks after treatment and persisted at 1-year follow-up. An increased IOP occurred in 12% of patients successfully controlled with medical therapy [69].

In conclusion, the intraretinal changes caused by hyperglycemia may lead to poor efficacy of the treatments. High glucose levels, commonly found in diabetes mellitus, can lead to an "anomalous" PVD, that can cause antero-posterior vector of tractions, with changes of foveal profile, formation of intraretinal cysts with initial onset of visual symptoms.

It is important to underline that in the presence of tractions, anti-VEGF injections could induce metaplasia of the epiretinal cells causing an increase of fibrosis and tractional phenomena.

SD-OCT is decisive for appropriate surgical management. Indications are in case of refractory DME, presence of subclinical tangential traction associated with VPA or vitreoschisis, and DME with small intraretinal cysts in early unresponsive stage.

In the future, it would be interesting to identify OCT parameters can allow us to decide the correct surgical timing for a better prognosis.

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Authors' contribution MRR, DA, MF, CDG, SS contributed to conception and design; MRR, DA, IB, GC to acquisition of data, all authors contributed to interpretation of data; all authors drafted the article and approved its final version.

Compliance with ethical standards

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

Conflict of interest The authors declare that they have conflict of interest.

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