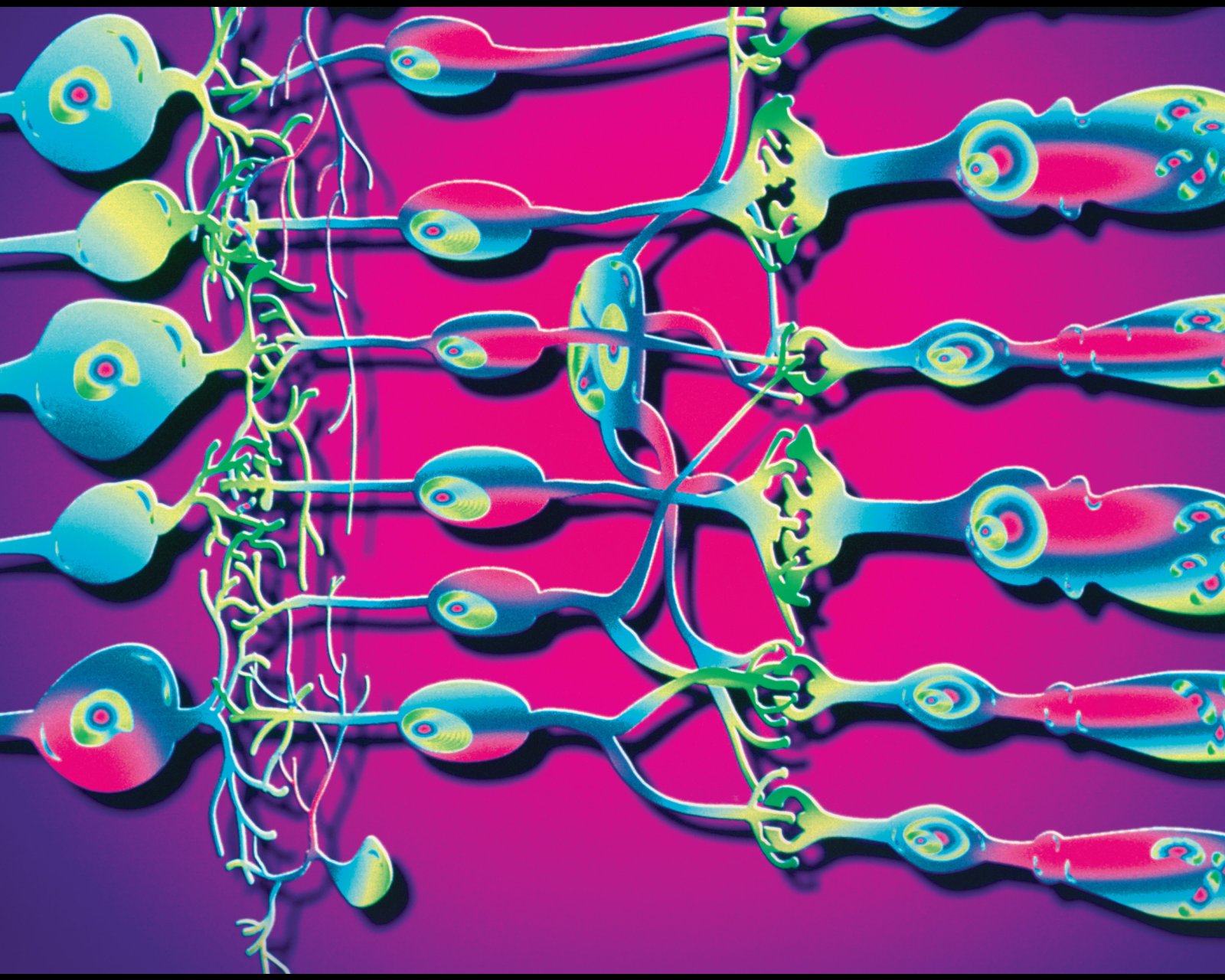
Journal of Ophthalmology

Vitreomacular Interface: From Anterior to Tangential Traction

Guest Editors: Mario R. Romano, Xavier Valldeperas, and John Byron Christoforidis



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Editorial Board

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Editorial

Vitreomacular Interface: From Anterior to Tangential Traction

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Anomalous posterior vitreous detachment (PVD) plays a major role in the formation of anterior-posterior and tangential epiretinal traction. Advances in the tomographic analysis of vitreous traction vectors have highlighted the selected cases that can benefit from "*parasurgical*" approaches, providing a different perspective for therapeutic strategies. The symptomatic anterior-posterior traction recently gained crescent interest for the application of enzymatic vitreolysis (ocriplasmin, IVO), mainly in small traction associated with full thickness macular hole.

On the other hand, the outer layer of posterior vitreous cortex leads to tangential traction responsible for the formation of macular pucker. As reported by M. R. Romano et al., the presence of vitreoschisis associated with a strong vitreopapillary adhesion of posterior cortex enhances the force of the tangential vector, inducing potential damage to the inner nuclear and outer plexiform layers. They also reported the epiretinal presence of glial fibrillary acidic protein (GFAP), indicating the ability of these cells to proliferate and migrate on the retinal surface. The transdifferentiated epiretinal cells are characterized by a downregulation of GFAP and cytokeratins, while proteins involved in motility and proliferation, such as α-smooth muscle actin, are upregulated. Therefore, the GFAP content in epiretinal tissues has been shown to correlate directly with tractional forces and inversely with the clinical contractility.

D. Compera et al. reported interesting histology findings on the presence of GFAP positive cells in lamellar-hole (LMH) associated epiretinal proliferation. The authors hypothesize that the vitreous derived cells, rather than cells of glial origin, may play a relevant role in the pathogenesis of tangential traction. In LMH, differently from macular pucker, the traction is not increased by the contraction of α-smooth muscle actin (α-SMA), as α-SMA-positive myofibroblasts were an infrequent finding in epiretinal proliferation associated with LMH, in their report.

D. Agarwal et al. highlighted the presence of a tangential traction due to the thickened premacular vitreous cortex in diabetic patients. The authors also described a significant relationship between PVD and lack of macular edema, suggesting the importance of the vitreous cortex, embedded with fibroblasts and astrocytes, in the development and progression of diabetic retinopathy. The different adhesion at the interfaces seems to be sustained by factors such as VEGF, CCL2, IL-6, IL-8, and IL-18, also encouraging neovascularization and therefore worsening visual outcome.

Surgical treatment is still the main approach in the management of the tangential tractional membranes. F. Semeraro et al. showed that the pathological vitreoretinal adhesion on the inner limiting membrane (ILM) offers different surfaces on which transdifferentiated glial cells migrate and thereby configures different aspects of traction maculopathies. The removal of ILM has become a routine practice in the surgery of the epiretinal membranes (ERM). However, many recent studies have shown that ILM peeling may cause immediate iatrogenic damage and progressive modification on the underlying inner retinal layers. R. Gelman et al. reported retinal damage induced by ILM peeling including dye-induced toxicity, Müller cell dysfunction, dissociated optic nerve fiber layer, paracentral hole formation, and phototoxic damage.

Interestingly, W. J. Mayer et al. reported, in prospective study on 42 eyes, the evidence of mechanical trauma of ERM and ILM peeling due to the use of intraocular forceps that may affect the outer retinal structure. In fact, they observed a significant correlation between the integrity of the ellipsoid zone and retinal sensitivity, overall and in the peeled areas.

M. Asencio-Duran et al. reported that the earliest change in the macula is postoperative swelling of the arcuate retinal nerve fiber layers that appears as hypoautofluorescent arcuate striae on infrared and autofluorescence imaging. Such findings induced by the swelling may disappear in 3 months; however they may potentially cause permanent functional damage in patients already affected by glaucoma.

Finally, vitreomacular adhesion (VMA) can also affect the progression of the age-related macular degeneration (AMD), as reported by E. C. Kang and H. J. Koh. In neovascular AMD, VMA may induce inflammation, decrease in oxygenation, and sequestering of VEGF and other cytokines. Moreover, VMA may also interfere with the therapeutical effects of anti-VEGF treatment.

Considering movement towards future, a more updated classification of the tangential traction is needed, whereas the anterior-posterior traction has been better classified thanks to the recent interest in the enzymatic vitreolysis.

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Review Article

The Vitreomacular Interface in Diabetic Retinopathy

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Diabetic retinopathy (DR) is a leading health concern and a major cause of blindness. DR can be complicated by scar tissue formation, macular edema, and tractional retinal detachment. Optical coherence tomography has found that patients with DR often have diffuse retinal thickening, cystoid macular edema, posterior hyaloid traction, and tractional retinal detachment. Newer imaging techniques can even detect fine tangential folds and serous macular detachment. The interplay of the vitreous and the retina in the progression of DR involves multiple chemokine and other regulatory factors including VEGF. Understanding the cells infiltrating pathologic membranes at the vitreomacular interface has opened up the possibility of new targets for pharmacotherapy. Vitrectomies for DR remain a vital tool to help relieve tension on the macula by removing membranes, improving edema absorption, and eliminating the scaffold for new membrane formation. Newer treatments such as triamcinolone acetonide and VEGF inhibitors have become essential as a rapid way to control DR at the vitreomacular interface, improve macular edema, and reduce retinal neovascularization. These treatments alone, and in conjunction with PRP, help to prevent worsening of the VMI in patients with DR.

1. Introduction

Diabetic retinopathy (DR) is a leading health concern and a major cause of blindness. Worldwide, there are approximately 93 million people with DR, 17 million with proliferative diabetic retinopathy (PDR), 21 million with diabetic macular edema (DME), and 28 million with vision threatening DR [1]. In the United States alone, 4.1 million have DR, with 1 out of 12 suffering from vision threatening DR [2]. DR on exam is characterized by microaneurysms, intraretinal hemorrhages, venous beading, cotton-wool spots, macular edema, neovascularization, retinal ischemia, vitreous hemorrhages, and preretinal scar tissue formation that may lead to tractional retinal detachment [2, 3]. Treatments for macular edema and the complications of neovascularization include focal/grid photocoagulation of retinal tissue, intravitreal therapy with steroid compounds, and agents that block vascular endothelial growth factor (VEGF) as well as surgical intervention for vitreous hemorrhages and repair of tractional formation of retinal detachment.

The role of the vitreomacular interface (VMI) is key in many processes including DR. From macular holes to even influencing age related macular degeneration [4], the VMI plays an outsized role in the emergence and development of several retinal diseases. In DR patients, the VMI can significantly influence the emergence, progression, and response to treatment of DR. Further understanding the vitreomacular interfaces of diabetic retinopathy is warranted in order to better design imaging techniques and treatments to arrest and possibly even reverse progression of DR.

2. OCT Imaging of the Vitreomacular Interface

Optical coherence tomography (OCT) has become an increasingly important tool to help better understand the VMI in DR. OCT classification for DME consists of retinal thickness, volume, morphology, diffusion, and epiretinal traction [5]. OCT has found that patients with DME often have diffuse retinal thickening, cystoid macular edema, posterior hyaloid traction, serous retinal detachment, and tractional retinal detachment. Increased retinal thickness, macular edema, and posterior hyaloid traction are associated with worse vision [6]. One study on 9 patients with DME

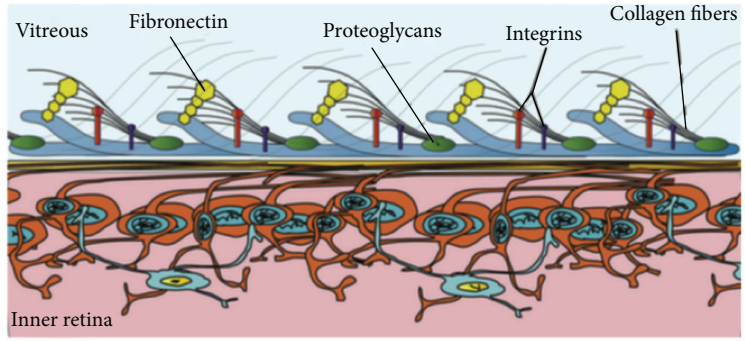

Figure 1: Vitreoretinal attachments at the vitreoretinal interface. Source: [11].

and posterior hyaloid traction found that all patients had retinal thickening, but interestingly 8/9 also had a subclinical shallow macular tractional detachment as well, possibly explaining improved visual acuity after vitrectomy [7].

One study used OCT to examine 48 eyes of patients with persistent DME after at least one session of focal laser treatment. The authors found that 25/48 eyes demonstrated definite VMI abnormalities including vitreoretinal adhesions and epiretinal membrane (ERM). They found that OCT was 1.94 times more sensitive in detecting vitreomacular abnormalities than with standard techniques (slit lamp exam, fluorescein angiography, and fundus photography) [8]. Other studies have found higher detection levels of serous macular detachment with OCT. One study looked at 78 eyes of 58 patients with diabetic cystoid macular edema. Patients were examined with slit lamp exam, fluorescein angiography, and OCT. Serous macular detachment was detected at higher levels than previously known, with OCT allowing for *in vivo* subtle detection of serous macular detachment [9].

Higher resolution OCT imaging, including 3D visualization, has also helped to better visualize the vitreoretinal interface in patients with DR. One study by Abe et al. examined 26 eyes with DME utilizing 3D OCT pre- and postoperatively. The 26 patients were separated into 3 groups: those that had a smooth retinal interface on OCT and 3D imaging, those that had tractional forces only visible on 3D imaging, and those that had an obvious ERM or taut posterior vitreous cortex visible on OCT and 3D imaging. Of the 26 eyes, 11 demonstrated vitreoretinal traction on time domain OCT due to the presence of ERM or a taut posterior hyaloid. 3D imaging of the remaining 15 eyes found that 11 had tangential fine folds [10].

3. The Role of Posterior Hyaloid and Vitreous on the Vitreomacular Interface

The role of the posterior hyaloid and vitreous in the VMI and the formation of DME has been examined. In normal eyes, the posterior vitreous is attached to the internal limiting membrane (ILM) by collagen at the VMI. Collagen fibers fuse with ILM and help anchor the vitreous cortex to the retina along with laminin, fibronectin, and chondroitin (Figure 1) [11].

Early studies pointed to the vitreous as playing a key role in DME. Nasrallah and colleagues examined the charts of 125 eyes that had undergone a vitreous examination, 105 of which had macular edema. They found a statistically significant relationship between posterior vitreous detachment (PVD) and lack of macular edema, indicating the importance of the vitreous in DME [12]. Another study of 82 diabetic patients with clinically significant macular edema showed that 22 eyes had vitreomacular separation at the onset of the study. Macular edema resolved in 27/82 eyes within 6 months of diagnosis. Interestingly, 12/22 eyes with vitreomacular separation at study onset had spontaneous resolution of their macular edema within 6 months versus 15/60 with vitreomacular adhesion. The authors found that vitreomacular separation led to a statistically significant increase in macular edema resolution [13].

Examining more carefully, one study looked at the vitreoretinal relationship in diabetic patients with and without DME using OCT. Forty-nine eyes of diabetic patients with DME and 49 sex and age matched diabetic control eyes without DME were studied. OCT of the vitreoretinal interface showed that 53% of patients with macular edema had perifoveal PVD, while only 11% of patients without DME had perifoveal PVD. The authors hypothesize that the vitreous may provide traction on the macula during the perifoveal PVD [14]. More recently, swept-source OCT (SS-OCT) was used to examine microstructural tomographic features in proliferative diabetic retinopathy in 4 patients. They were found to have inner and outer layers of vitreoschisis, taut ILM, cortical vitreous separation, and vitreoretinal adhesions [15].

Histologic examination of vitreoretinal tissue was performed in 61 specimens of ILM and epimacular tissue in patients with diffuse DME. Thickened premacular cortical vitreous was found in 47 eyes. Epimacular membrane was found in 23 eyes. Retinal striae and vessel distortion consistent with vitreomacular traction was found in 25 eyes. The authors confirmed a higher incidence of complete PVD in patients with nonproliferative DR versus those with PDR, emphasizing the importance of the vitreous in the development and progression of diabetic retinopathy. Vitreous collagen covered the ILM in 60/61 specimens. PVD in diabetic eyes is likely due to splitting of the vitreous cortex, leaving a layer of collagen on the ILM. Ultrastructure of the VMI in eyes with diffuse DME reveals a layer of vitreous collagen

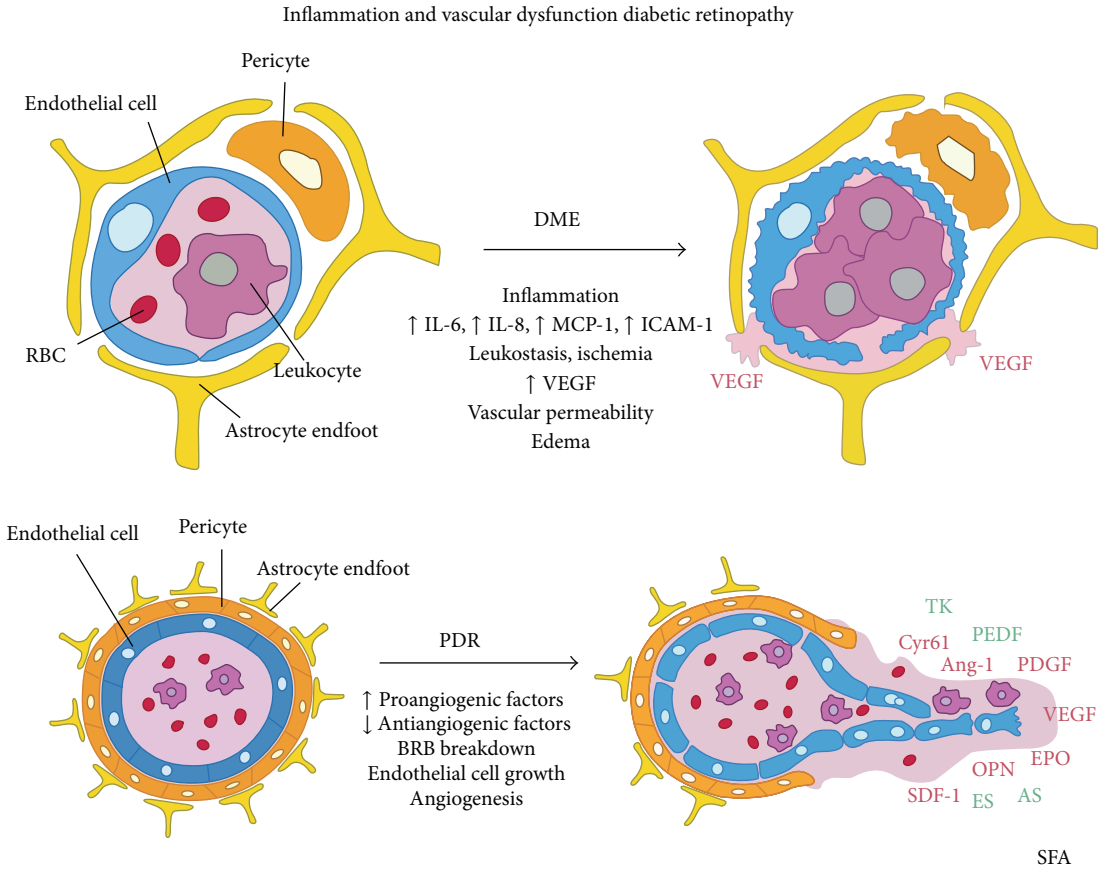

Figure 2: Inflammatory cytokines and their role in PDR. Source: [23].

covering the ILM, fibroblasts, and astrocytes embedded in vitreous collagen in prominent premacular cortical vitreous and single or multilayers cell membranes on a layer of vitreous collagen in eyes with vitreomacular traction [16]. Better understanding of the cellular components of the interface will allow for future medical and pharmacologic treatments that may negate the need for vitrectomy in at least some patients.

4. Immune and Molecular Pathways Mediating the VMI in DR

Examining the immunocytochemical processes that underlie the VMI in DR is critical in the understanding of the pathophysiology of DR. Electron microscopy of the posterior hyaloid in 2 patients with DME revealed evidence of glial and epithelial cell infiltration. These cells have been implicated in causing tractional forces found in DR. The breakdown in the blood-retina barrier caused by DR may cause increased concentrations of chemoattractants in the vitreous cavity that can then stimulate cell migration [17].

A study of 30 vitrectomized eyes for DME found VEGF and IL-6 in 8/8 epimacular membranes tested, showing that these molecules may play a role in the development of macular edema [18]. Chemokines including CCL2 have been implicated in inflammation of the diabetic retina, including the activation of retina microglia and macrophages in mice that could lead to disruption of the blood-retina barrier [19]. Examining the relationship between vitreous and PDR more carefully, one study showed the possible role of vitreous levels of IL-8 in deteriorating visual acuity caused by DR, finding that elevated IL-8 levels were independently associated with worse visual outcome [20]. Funatsu and colleagues showed patients with DME had elevated VEGF, ICAM-1, IL-6, and MCP-1 in vitreous fluid, with VEGF and ICAM-1 having a stronger influence on retinal vascular permeability and DME severity [21]. Further studies of vitreous fluid confirmed increased levels of IL-6 and IL-8, as well as elevated levels of IL-1B, VEGF, CCL2, EDN1, and TNF in PDR patients (Figure 2) [22, 23]. Other studies have shown elevated levels of D-serine and glutamate, products believed to be involved in retinal ganglion cell excitotoxicity, in patients with PDR [24].

Kase and colleagues conducted immunohistochemical studies on 16 patients, 13 with PDR and 3 without DM who underwent pars plana vitrectomy (PPV) and ERM peeling. In PDR patients, a statistically significant association was shown between high levels of lymphocyte infiltration into the ERM and poor visual prognosis after vitrectomy because of reproliferation of the ERM [25].

Recently, Dai et al. studied 58 eyes of patients requiring PPV, of which 32 had PDR, to determine the levels of chemokines and growth factors in the vitreous and their relationship with PDR. In non-PDR eyes, levels of 11 chemokines and growth factors tested were similar in patients with macular hole versus those with ERM. However, patients with PDR

showed significantly higher levels of 11 chemokines, including CCL17, CCL19, and TGFβ3. Moderate to strong correlations were also found between VEGF and other mediators. The authors postulate that these chemokines and growth factors could be targeted along with anti-VEGF therapy for PDR treatment [26]. Other chemokines such as IL-18 and serum vascular adhesion protein-1 have been correlated with VEGF levels in patients with DR and could serve as targets for future pharmacotherapy [27, 28].

However, a study of fibrovascular membranes removed from patients with PDR showed more nuanced results. Forty patients with PDR had fibrovascular membranes removed via vitrectomy. T-lymphocytes, B-lymphocytes, and macrophages were found in the fibrovascular membranes, with B-lymphocytes only in active PDR patients. The authors demonstrated a relationship between the density of inflammatory cells and activity of retinopathy. However, they found no association between proinflammatory cells and density of vessels or visual acuity changes postoperatively [29].

5. Vitrectomy for DME

Vitrectomy has been shown in some studies to be an effective treatment for DME but chronic changes might still persist [30]. Lewis and colleagues performed PPV with separation of the posterior hyaloid in 10 eyes with DME and thickened, taut posterior hyaloids. Patients had improvement in vision with resolution of macular traction and edema [31]. Ikeda et al. performed vitrectomies on 5 eyes with DME and detached posterior hyaloid membranes, resulting in resolution of DME in 4 of the patients [32]. One study of 30 vitrectomized eyes of patients with DME resulted in statistically significant improvements in visual acuity and reductions in foveal macular edema [18].

Gandorfer and colleagues operated on 12 eyes with diffuse DME, performing PPV with surgical removal of the posterior hyaloid and peeling of the ILM. Retinal thickening improved or resolved in all cases, with visual acuity improvements in 11/12 eyes. Furthermore, no recurrence of macular edema or ERM occurred 8–31 months postoperatively [33]. Their study indicated that not only does vitrectomy release tractional forces on the retina, but also removing the ILM eliminates the scaffold for proliferating astrocytes on the retinal surface. Improved results with peeling of the ILM were also shown by Stefaniotou et al. when they analyzed the surgical outcomes in 73 eyes of 52 patients with DME. In the study, 18 eyes underwent posterior hyaloid membrane removal while 55 eyes underwent ILM peeling as well. More patients that underwent ILM peeling had complete resolution of macular edema than those that just underwent posterior hyaloid removal [34]. Kumagai and colleagues examined ILM peeling in vitreous surgery for DME patients on 135 eyes. Of the 135 eyes, 74 underwent ILM peeling. The authors found that ILM peeling accelerated the absorption of edema in severe DME but did not further improve visual acuity [35].

Another study looked at sixty eyes of patients with chronic DME that underwent pars plana vitrectomy and ILM removal. Reduced leakage within the macula and a decrease in macular thickening were observed in 93% of patients, yet visual acuity improved significantly (2+ lines) in 43% of patients. This suggests that chronic DME may cause structural changes that are difficult to reverse [36]. One study showed that, even without signs of traction on exam, vitrectomy in DME could help to resolve macular edema and improve vision [37]. Another study of 87 eyes with DME and vitreomacular traction found that vitrectomy resulted in reduction in macular edema in most eyes with a more questionable amount of visual acuity improvement. Researchers estimated that 28–49% of patients gained greater than 10 letters' vision improvement while 13–31% demonstrated greater than 10 letters' deterioration [38].

6. Retinal Oxygenation

The improvement of macular edema after vitrectomy may be secondary to improved oxygenation of the retina. Primate models have shown that improving systemic oxygenation reduced VEGF mRNA expression in induced ischemic retinas [39]. Vitrectomies performed on rabbit eyes showed a statistically significant increase in oxygen tension of the vitreous that persisted 8 weeks after vitrectomy [40]. Stefansson et al. showed how vitrectomy and lensectomy in cat eyes improve oxygen uptake by the retina from aqueous humor migration [41]. In other states of retinal hypoxia such as induced BRVO in cats, eyes vitrectomized prior to the BRVO event showed no significant change on intraocular oxygen tension, unlike in nonvitrectomized eyes [42].

Studies in humans have also demonstrated an increase in intravitreal oxygen levels after vitrectomy. Holekamp et al. demonstrated that vitrectomy in patients caused a statistically significant increase in oxygen tension both near the lens and in the vitreous. Furthermore, they found that, in patients undergoing repeat vitrectomy, the oxygen tension was significantly higher than in eyes undergoing vitrectomy for the first time, indicating a lasting effect of vitrectomy on ocular oxygen levels [43]. One study analyzing oxygen tension in PDR found that oxygen tension in the midvitreous was 46% lower in PDR patients than in controls, with increased oxygen levels in PDR patients near the posterior pole likely from extensive neovascularization. The study also found upregulation of VEGF in diabetic vitreous, indicating its role in neovascularization [44].

7. Retinal Laser Photocoagulation

Retinal laser photocoagulation has been used as a treatment for DME to help reduce visual loss. The Early Treatment Diabetic Retinopathy Study established the efficacy of combination of focal and grid photocoagulation to arrest loss of visual acuity in patients with DR [45]. Yanyali et al. showed that PPV and removal of the ILM were superior to grid laser photocoagulation in the treatment of DME, with greater reductions in foveal thickness and greater improvement in visual acuity [46].

Panretinal photocoagulation (PRP) has been found to be effective especially in combination with other therapies. Yang and colleagues showed that, in high-risk PDR patients,

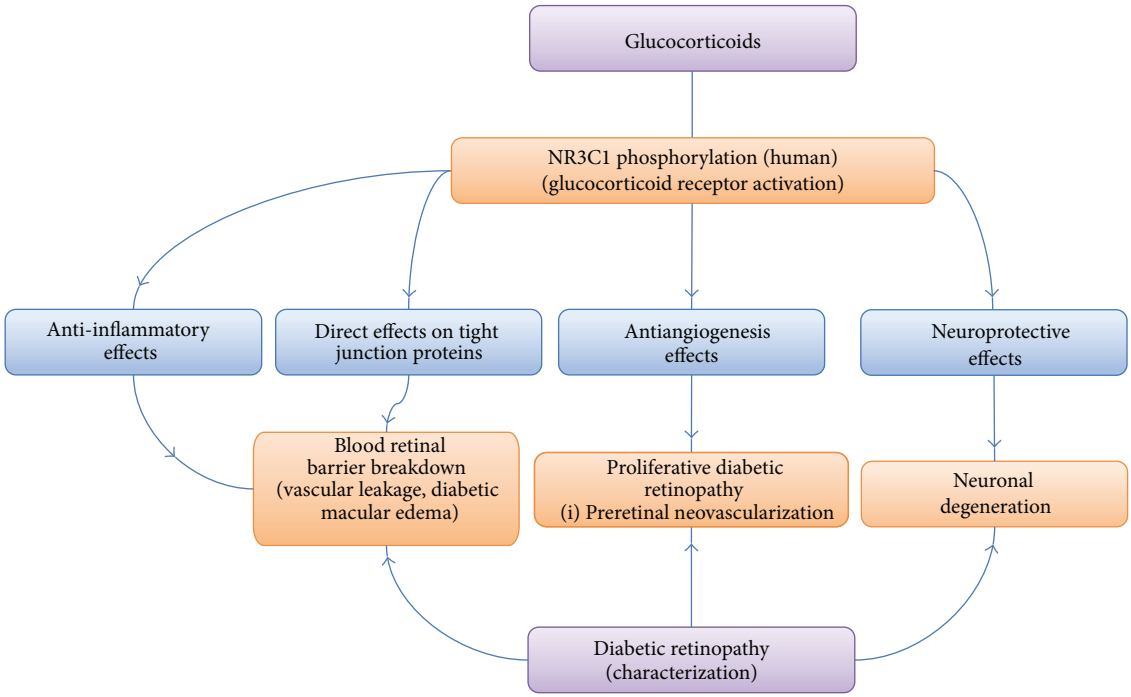

Figure 3: Effects of glucocorticoids on diabetic retinopathy. Glucocorticoids act through several pathways to counteract the negative aspects of DR on the eye. Source: [63].

combining intravitreal bevacizumab with PRP provided better short-term regression of retinal neovascularization, rapid clearance of vitreous hemorrhage, and visual improvement. They note that the use of bevacizumab helped to clear the vitreous to allow for more complete laser treatment. In effect, it allows for the rapid onset of bevacizumab to be combined with the more durable effect of laser PRP to provide better visual outcomes and prevent the need for vitrectomy [47]. Tran et al. performed PPV and fibrovascular membrane delamination in 5 patients with PDR, 4 of which had prior PRP. They demonstrated that PRP induces a decrease in ambient mitogen (promitotic signal) and activates apoptosis in diabetic fibrovascular membranes, suggesting an additional mechanism by which PRP helps treat DME [48].

PRP is not without its complications. McDonald and colleagues were one of the earlier groups to report complications from PRP in patients with PDR, noting the most common cause of decreased visual acuity was chronic macular edema and vision loss developing after laser treatment in 8% of eyes. Their study notes that 31 eyes developed posttreatment macular edema but without visual changes [49, 50]. In comparison of weekly versus biweekly PRP treatments for DR, Shimura et al. reported that either frequency did not affect visual acuity but that biweekly treatments allowed for faster recovery of macular thickening after PRP [51].

In addition, Soman and colleagues looked at the effect of PRP on macular morphology in patients with DME but without CSME. They examined 76 eyes of 68 patients and found that 14 eyes had worsened vision 3 months after laser, which the authors believed was secondary to macular edema. All of these patients were reported to have multiple other medical problems such as hypertension, nephropathy, cardiac disease, and dyslipidemia. PRP induced a statistically significant increase in central foveal thickness that persisted for 3 months. Furthermore, 34% of patients with a normal macula suffered morphologic changes after laser including cystoid macular edema, vitreomacular traction, ERM, and subfoveal serous detachment [52]. These patients may require further treatment such as intravitreal injections, further laser, or vitrectomy with membrane removal to control their macular edema.

8. Intravitreal Corticosteroids and the Vitreomacular Interface

Intravitreal corticosteroids have been a key tool in the armamentarium against DR and can alter the VMI. Multiple studies have demonstrated the effectiveness of intravitreal triamcinolone acetonide (IVTA) in reducing DME and improving vision in patients with DR [53–58]. Glucocorticoids are believed to inhibit macrophages promoting angiogenesis and ICAM-1 mediating leukocyte adhesion [59–62]. In addition, glucocorticoids help to suppress basement membrane degradation and strengthen tight junctions, both helping to reduce macular edema [59–61, 63]. IVTA has been shown to inhibit the degradation of capillary basement membranes and reduced VEGF and TGF-β expression [59, 63, 64].

One study revealed that triamcinolone *in vitro* reduced bovine retinal endothelial cell viability and even induced apoptosis. Triamcinolone *in vivo* caused a reduction in choroidal thickness while downregulating basal expression of COX-2 and VEGF [65]. Increased efficacy of IVTA has been

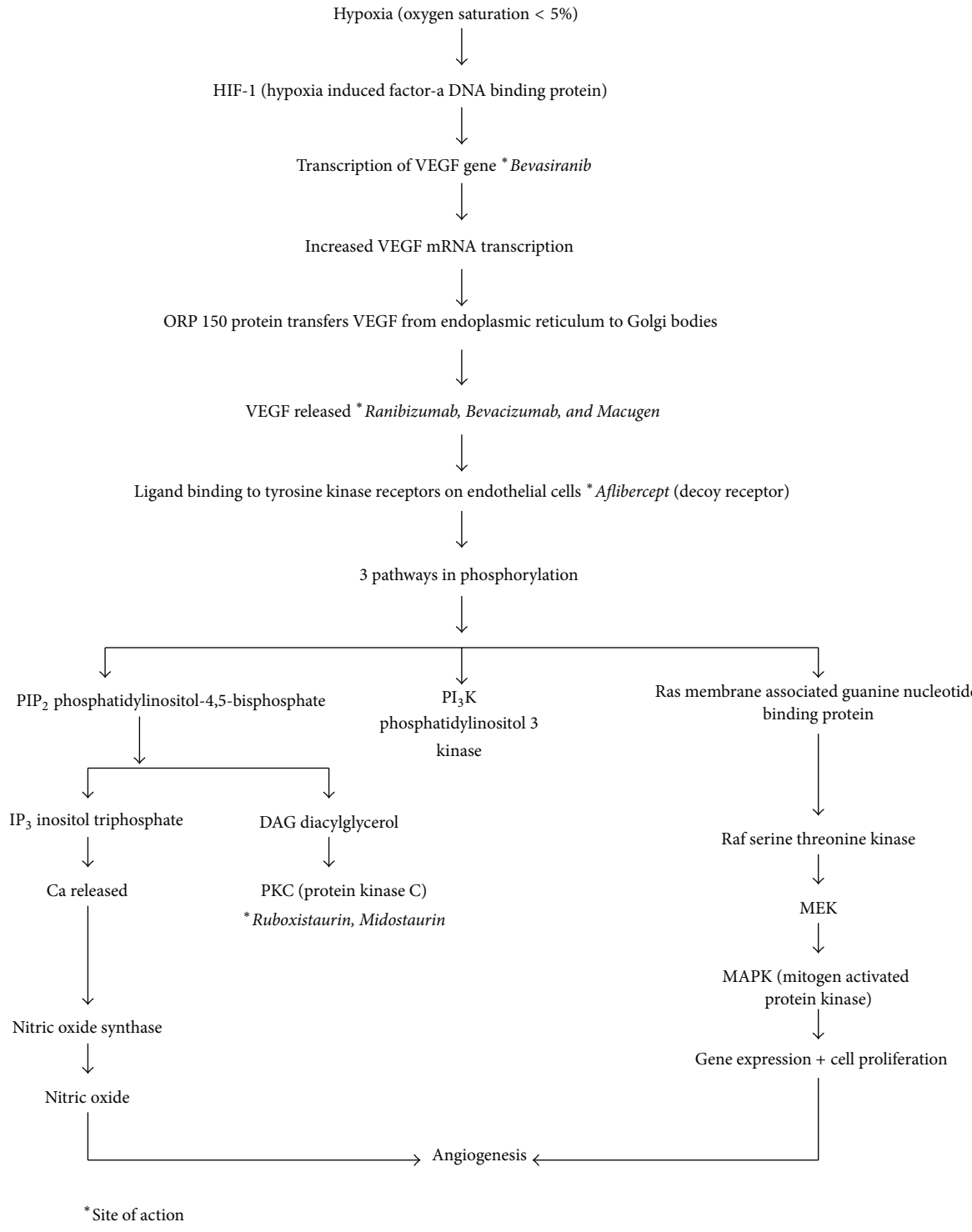

Figure 4: VEGF cascade in retinal hypoxia. Source: [73].

related to elevated baseline levels of IL-8, a proinflammatory cytokine [57]. Uckermann and colleagues discovered that triamcinolone reverses osmotic swelling of Müller glial cells in rat retinas with induced ischemia and inflammation. Triamcinolone stimulates activation of protein kinase A and helps open pathways for K^+ and Cl^- ions to help quickly resolve edema in human patients [66].

Lee et al. demonstrated that IVTA reduced central macular thickness in patients with DME. Furthermore, they discovered a correlation between increased intraretinal fluid turbidity and greater reduction in the central macular thickness after IVTA [67]. Interestingly, Sonoda et al. showed that IVTA in DME patients reduced not only central macular thickness, but also subfoveal choroidal thickness lasting 12 weeks [68].

Horii and colleagues examined patients treated with intravitreal or sub-Tenon's injection of triamcinolone for DME with OCT imaging. They found that reflectivity levels of foveal cystoid spaces increased 1 month after triamcinolone administration ($p = 0.019$) but then decreased to baseline levels at 3 and 6 months. The authors show that lower OCT reflectivity in foveal cystoid spaces may signal rebound macular thickening and visual decline in patients treated with triamcinolone for DME [69]. These studies indicate that triamcinolone works on a molecular level to help inhibit inflammation, strengthen tight junctions, and reduce VEGF production in order to improve DME in DR patients (Figure 3).

9. VEGF and the Vitreomacular Interface

The role of VEGF in influencing the vitreomacular interface has been well investigated. Multiple studies have implicated VEGF in promoting neovascularization of the retina and involvement in PDR (Figure 4) [70–73]. VEGF levels have been shown to decline in response to laser photocoagulation [71]. One study in particular examined preretinal fibrovascular tissue excised during vitrectomy and found that VEGF was expressed in all fourteen patients tested [72]. VEGF levels in vitreous fluid have even been shown to be predictive factors for progression of PDR after vitrectomy in patients with PDR [74]. Chen and colleagues examined ERMs and found that, in PDR patients, 9/11 ERMs stained for VEGF and its receptors. They suggest that an autocrine or paracrine loop may be involved in progression of ERMs [75].

Treatments for retinal neovascularization have included anti-VEGF agents such as bevacizumab. Bevacizumab has been shown to be effective in reducing neovascularization of the retina and resolution of vitreous hemorrhage [76, 77]. Rizzo et al. reported the efficacy of preoperative treatment (5–7 days before surgery) with bevacizumab in patients undergoing pars plana vitrectomy for complications of PDR. They demonstrated that surgical time and intraoperative bleeding were both reduced in patients with preoperative PPV, indicating the rapid regression of neovascularization in the retina [78]. On a molecular level, bevacizumab was shown by Suzuki et al. to reduce not only VEGF, but also other inflammatory cytokines including IL-1RA, IL-5, IL-10, IL-12, IL-13, and interferon-γ [79]. A 2014 study found that, in patients injected multiple times with anti-VEGF treatments, patients with vitreomacular interface abnormalities such as ERMs or vitreomacular adhesions had less change in best-corrected vision than those with only DME after 3 injections. This indicates a possible role of vitreomacular interface abnormalities in reducing the therapeutic effects of anti-VEGF agents [80].

10. Conclusion

In conclusion, there are multiple factors at work in the vitreomacular interface including ERM, taut posterior cortices, vitreoschisis, PVD, and adhesions. Evidence of glial cells, collagen, fibroblasts, astrocytes, and retinal pigment epithelial cells has been found on either the hyaloid, cortical vitreous, or the ILM. Interestingly, complete PVDs seem to improve macular edema in some cases, possibly by reducing traction. Factors such as CCL2, IL-6, IL-8, IL-18, and VEGF may also play roles in altering the vitreomacular interface by increasing edema, encouraging neovascularization, and worsening visual outcome. Multiple treatments that alter the VMI, including ILM/posterior hyaloid peeling, PRP, triamcinolone acetonide, and VEGF inhibitors, have been shown to help in various degrees to arrest the progression of PDR and/or improve vision. Overall, there are multiple elements and significant interplay in the vitreomacular interface of diabetic retinopathy.

Conflict of Interests

The authors declare that there is no conflict of interests related to any topic in this paper.

References

[1] J. W. Y. Yau, S. L. Rogers, R. Kawasaki et al., "Global prevalence and major risk factors of diabetic retinopathy," *Diabetes Care*, vol. 35, no. 3, pp. 556–564, 2012.

[2] J. H. Kempen, B. J. O'Colmain, M. C. Leske et al., "The prevalence of diabetic retinopathy among adults in the United States," *Archives of Ophthalmology*, vol. 122, no. 4, pp. 552–563, 2004.

[3] American Academy of Ophthalmology, *Preferred Practice Pattern: Diabetic Retinopathy*, American Academy of Ophthalmology, 1998.

[4] A. E. Green-Simms and S. J. Bakri, "Vitreomacular traction and age-related macular degeneration," *Seminars in Ophthalmology*, vol. 26, no. 3, pp. 137–138, 2011.

[5] G. Panozzo, B. Parolini, E. Gusson et al., "Diabetic macular edema: an OCT-based classification," *Seminars in Ophthalmology*, vol. 19, no. 1-2, pp. 13–20, 2004.

[6] B. Y. Kim, S. D. Smith, and P. K. Kaiser, "Optical coherence tomographic patterns of diabetic macular edema," *American Journal of Ophthalmology*, vol. 142, no. 3, pp. 405.e1–412.e1, 2006.

[7] P. K. Kaiser, C. D. Riemann, J. E. Sears, and H. Lewis, "Macular traction detachment and diabetic macular edema associated with posterior hyaloidal traction," *American Journal of Ophthalmology*, vol. 131, no. 1, pp. 44–49, 2001.

[8] N. G. Ghazi, J. B. Ciralsky, S. M. Shah, P. A. Campochiaro, and J. A. Haller, "Optical coherence tomography findings in persistent diabetic macular edema: the vitreomacular interface," *The American Journal of Ophthalmology*, vol. 144, no. 5, pp. 747–754, 2007.

[9] H. Ozdemir, M. Karacorlu, and S. Karacorlu, "Serous macular detachment in diabetic cystoid macular oedema," *Acta Ophthalmologica Scandinavica*, vol. 83, no. 1, pp. 63–66, 2005.

[10] S. Abe, T. Yamamoto, Y. Kashiwagi, E. Kirii, S. Goto, and H. Yamashita, "Three-dimensional imaging of the inner limiting membrane folding on the vitreomacular interface in diabetic macular edema," *Japanese Journal of Ophthalmology*, vol. 57, no. 6, pp. 553–562, 2013.

[11] Y. Barak, M. A. Ihnen, and S. Schaal, "Spectral domain optical coherence tomography in the diagnosis and management of Vitreoretinal Interface pathologies," *Journal of Ophthalmology*, vol. 2012, Article ID 876472, 7 pages, 2012.

[12] F. P. Nasrallah, A. E. Jalkh, F. Van Coppenolle et al., "The role of the vitreous in diabetic macular edema," *Ophthalmology*, vol. 95, no. 10, pp. 1335–1339, 1988.

[13] T. Hikichi, N. Fujio, J. Akiba, Y. Azuma, M. Takahashi, and A. Yoshida, "Association between the short-term natural history of diabetic macular edema and the vitreomacular relationship in type II diabetes mellitus," *Ophthalmology*, vol. 104, no. 3, pp. 473–478, 1997.

[14] A. Gandorfer, C. Haritoglou, and A. Kampik, "Optical coherence tomography assessment of the vitreoretinal relationship in diabetic macular edema," *The American Journal of Ophthalmology*, vol. 141, no. 1, pp. 234–235, 2006.

[15] M. M. K. Muqit and P. E. Stanga, "Swept-source optical coherence tomography imaging of the cortical vitreous and the vitreoretinal interface in proliferative diabetic retinopathy: assessment of vitreoschisis, neovascularisation and the internal limiting membrane," *British Journal of Ophthalmology*, vol. 98, no. 7, pp. 994–997, 2014.

[16] A. Gandorfer, M. Rohleder, S. Grosselfinger, C. Haritoglou, M. Ulbig, and A. Kampik, "Epiretinal pathology of diffuse diabetic macular edema associated with vitreomacular traction," *American Journal of Ophthalmology*, vol. 139, no. 4, pp. 638–652, 2005.

[17] J. M. Jumper, S. N. Embabi, C. A. Toth, B. W. McCuen II, and D. L. Hatchell, "Electron immunocytochemical analysis of posterior hyaloid associated with diabetic macular edema," *Retina*, vol. 20, no. 1, pp. 63–68, 2000.

[18] T. Yamamoto, N. Akabane, and S. Takeuchi, "Vitrectomy for diabetic macular edema: the role of posterior vitreous detachment and epimacular membrane," *American Journal of Ophthalmology*, vol. 132, no. 3, pp. 369–377, 2001.

[19] S. Rangasamy, P. G. McGuire, C. F. Nitta, F. Monickaraj, S. R. Oruganti, and A. Das, "Chemokine mediated monocyte trafficking into the retina: role of inflammation in alteration of the blood-retinal barrier in diabetic retinopathy," *PLoS ONE*, vol. 9, no. 10, Article ID e108508, 2014.

[20] M. G. Petrovič, P. Korošec, M. Košnik, and M. Hawlina, "Association of preoperative vitreous IL-8 and VEGF levels with visual acuity after vitrectomy in proliferative diabetic retinopathy," *Acta Ophthalmologica*, vol. 88, no. 8, pp. e311–e316, 2010.

[21] H. Funatsu, H. Noma, T. Mimura, S. Eguchi, and S. Hori, "Association of vitreous inflammatory factors with diabetic macular edema," *Ophthalmology*, vol. 116, no. 1, pp. 73–79, 2009.

[22] J. Zhou, S. Wang, and X. Xia, "Role of intravitreal inflammatory cytokines and angiogenic factors in proliferative diabetic retinopathy," *Current Eye Research*, vol. 37, no. 5, pp. 416–420, 2012.

[23] S. F. Abcouwer, "Angiogenic factors and cytokines in diabetic retinopathy," *Journal of Clinical & Cellular Immunology*, supplement 1(11), pp. 1–12, 2013.

[24] H. Jiang, J. Du, T. He, J. Qu, Z. Song, and S. Wu, "Increased D-serine in the aqueous and vitreous humour in patients with proliferative diabetic retinopathy," *Clinical and Experimental Ophthalmology*, vol. 42, no. 9, pp. 841–845, 2014.

[25] S. Kase, W. Saito, S. Ohno, and S. Ishida, "Proliferative diabetic retinopathy with lymphocyte-rich epiretinal membrane associated with poor visual prognosis," *Investigative Ophthalmology and Visual Science*, vol. 50, no. 12, pp. 5909–5912, 2009.

[26] Y. Dai, Z. Wu, F. Wang, Z. Zhang, and M. Yu, "Identification of chemokines and growth factors in proliferative diabetic retinopathy vitreous," *BioMed Research International*, vol. 2014, Article ID 486386, 9 pages, 2014.

[27] N. Yoshikawa, K. Noda, H. Shinoda et al., "Serum vascular adhesion protein-1 correlates with vascular endothelial growth factor in patients with type II diabetes," *Journal of Diabetes and its Complications*, vol. 27, no. 2, pp. 162–166, 2013.

[28] Z. Song, M. Sun, F. Zhou, F. Huang, J. Qu, and D. Chen, "Increased intravitreous interleukin-18 correlated to vascular endothelial growth factor in patients with active proliferative diabetic retinopathy," *Graefe's Archive for Clinical and Experimental Ophthalmology*, vol. 252, no. 8, pp. 1229–1234, 2014.

[29] M. Urbančič, Š. Štunf, A. M. Živin, D. Petrovič, and M. G. Petrovič, "Epiretinal membrane inflammatory cell density might reflect the activity of proliferative diabetic retinopathy," *Investigative Ophthalmology and Visual Science*, vol. 55, no. 12, pp. 8576–8582, 2014.

[30] J. B. Christoforidis and D. J. D'Amico, "Surgical and other treatments of diabetic macular edema: an update," *International Ophthalmology Clinics*, vol. 44, no. 1, pp. 139–160, 2004.

[31] H. Lewis, G. W. Abrams, M. S. Blumenkranz, and R. V. Campo, "Vitrectomy for diabetic macular traction and edema associated with posterior hyaloidal traction," *Ophthalmology*, vol. 99, no. 5, pp. 753–759, 1992.

[32] T. Ikeda, K. Sato, T. Katano, and Y. Hayashi, "Improved visual acuity following pars plana vitrectomy for diabetic cystoid macular edema and detached posterior hyaloid," *Retina*, vol. 20, no. 2, pp. 220–222, 2000.

[33] A. Gandorfer, E. M. Messmer, M. W. Ulbig, and A. Kampik, "Resolution of diabetic macular edema after surgical removal of the posterior hyaloid and the inner limiting membrane," *Retina*, vol. 20, no. 2, pp. 126–133, 2000.

[34] M. Stefaniotou, M. Aspiotis, C. Kalogeropoulos et al., "Vitrectomy results for diffuse diabetic macular edema with and without inner limiting membrane removal," *European Journal of Ophthalmology*, vol. 14, no. 2, pp. 137–143, 2004.

[35] K. Kumagai, N. Ogino, M. Furukawa et al., "Internal limiting membrane peeling in vitreous surgery for diabetic macular edema," *Nippon Ganka Gakkai Zasshi*, vol. 106, pp. 590–594, 2002.

[36] P. Dillinger and U. Mester, "Vitrectomy with removal of the internal limiting membrane in chronic diabetic macular oedema," *Graefe's Archive for Clinical and Experimental Ophthalmology*, vol. 242, no. 8, pp. 630–637, 2004.

[37] T. Ikeda, K. Sato, T. Katano, and Y. Hayashi, "Vitrectomy for cystoid macular oedema with attached posterior hyaloid membrane in patients with diabetes," *British Journal of Ophthalmology*, vol. 83, no. 1, pp. 12–14, 1999.

[38] Diabetic Retinopathy Clinical Research Network Writing Committee, "Vitrectomy outcomes in eyes with diabetic macular edema and vitreomacular traction," *Ophthalmology*, vol. 117, no. 6, pp. 1087.e3–1093.e3, 2010.

[39] C. J. Pournaras, J. W. Miller, E. S. Gragoudas et al., "Systemic hyperoxia decreases vascular endothelial growth factor gene expression in ischemic primate retina," *Archives of Ophthalmology*, vol. 115, no. 12, pp. 1553–1558, 1997.

[40] I. A. Barbazetto, J. Liang, S. Chang, L. Zheng, A. Spector, and J. P. Dillon, "Oxygen tension in the rabbit lens and vitreous before and after vitrectomy," *Experimental Eye Research*, vol. 78, no. 5, pp. 917–924, 2004.

[41] E. Stefansson, M. B. Landers III, and M. L. Wolbarsht, "Vitrectomy, lensectomy, and ocular oxygenation," *Retina*, vol. 2, no. 3, pp. 159–166, 1982.

[42] E. Stefánsson, R. L. Novack, and D. L. Hatchell, "Vitrectomy prevents retinal hypoxia in branch retinal vein occlusion,"

Investigative Ophthalmology and Visual Science, vol. 31, no. 2, pp. 284–289, 1990.

[43] N. M. Holekamp, Y.-B. Shui, and D. C. Beebe, "Vitrectomy surgery increases oxygen exposure to the lens: a possible mechanism for nuclear cataract formation," *American Journal of Ophthalmology*, vol. 139, no. 2, pp. 302–310, 2005.

[44] C. A. K. Lange, P. Stavrakas, U. F. O. Luhmann et al., "Intraocular oxygen distribution in advanced proliferative diabetic retinopathy," *American Journal of Ophthalmology*, vol. 152, no. 3, pp. 406.e3–412.e3, 2011.

[45] The Early Treatment Diabetic Retinopathy Study Research Group, "Photocoagulation for diabetic macular edema: early treatment diabetic retinopathy study report no. 4," *International Ophthalmology Clinics*, vol. 27, no. 4, pp. 265–272, 1987.

[46] A. Yanyali, A. F. Nohutcu, F. Horozoglu, and E. Celik, "Modified grid laser photocoagulation versus pars plana vitrectomy with internal limiting membrane removal in diabetic macular edema," *The American Journal of Ophthalmology*, vol. 139, no. 5, pp. 795–801, 2005.

[47] C.-S. Yang, K.-C. Hung, Y.-M. Huang, and W.-M. Hsu, "Intravitreal bevacizumab (Avastin) and panretinal photocoagulation in the treatment of high-risk proliferative diabetic retinopathy," *Journal of Ocular Pharmacology and Therapeutics*, vol. 29, no. 6, pp. 550–555, 2013.

[48] A. T. Tran, D. V. Bula, K. D. Kovacs, J. Savageau, and J. G. Arroyo, "Apoptosis in diabetic fibrovascular membranes after panretinal photocoagulation," *Ophthalmic Surgery, Lasers and Imaging Retina*, vol. 41, 2010.

[49] H. R. McDonald and H. Schatz, "Visual loss following panretinal photocoagulation for proliferative diabetic retinopathy," *Ophthalmology*, vol. 92, no. 3, pp. 388–393, 1985.

[50] H. R. McDonald and H. Schatz, "Macular edema following panretinal photocoagulation," *Retina*, vol. 5, no. 1, pp. 5–10, 1985.

[51] M. Shimura, K. Yasuda, T. Nakazawa, T. Kano, S. Ohta, and M. Tamai, "Quantifying alterations of macular thickness before and after panretinal photocoagulation in patients with severe diabetic retinopathy and good vision," *Ophthalmology*, vol. 110, no. 12, pp. 2386–2394, 2003.

[52] M. Soman, S. Ganekal, U. Nair, and K. G. R. Nair, "Effect of panretinal photocoagulation on macular morphology and thickness in eyes with proliferative diabetic retinopathy without clinically significant macular edema," *Clinical Ophthalmology*, vol. 6, no. 1, pp. 2013–2017, 2012.

[53] J. W. Lim, H. K. Lee, and M. C. Shin, "Comparison of intravitreal bevacizumab alone or combined with triamcinolone versus triamcinolone in diabetic macular edema: a randomized clinical trial," *Ophthalmologica*, vol. 227, no. 2, pp. 100–106, 2012.

[54] F. Bandello, C. Preziosa, G. Querques, and R. Lattanzio, "Update of intravitreal steroids for the treatment of diabetic macular edema," *Ophthalmic Research*, vol. 52, no. 2, pp. 89–96, 2014.

[55] Diabetic Retinopathy Clinical Research Network, M. J. Elman, L. P. Aiello et al., "Randomized trial evaluating ranibizumab plus prompt or deferred laser or triamcinolone plus prompt laser for diabetic macular edema," *Ophthalmology*, vol. 117, no. 6, pp. 1064.e35–1077.e35, 2010.

[56] M. J. Elman, N. M. Bressler, H. Qin et al., "Expanded 2-year follow-up of ranibizumab plus prompt or deferred laser or triamcinolone plus prompt laser for diabetic macular edema," *Ophthalmology*, vol. 118, no. 4, pp. 609–614, 2011.

[57] S. Jeon and W. K. Lee, "Effect of intravitreal triamcinolone in diabetic macular edema unresponsive to intravitreal bevacizumab," *Retina*, vol. 34, no. 8, pp. 1606–1611, 2014.

[58] Q. Liu, Y. Hu, H. Yu et al., "Comparison of intravitreal triamcinolone acetonide versus intravitreal bevacizumab as the primary treatment of clinically significant macular edema," *Retina*, vol. 35, no. 2, pp. 272–279, 2015.

[59] T. A. Ciulla, A. Harris, N. McIntyre, and C. Jonescu-Cuypers, "Treatment of diabetic macular edema with sustained-release glucocorticoids: intravitreal triamcinolone acetonide, dexamethasone implant, and fluocinolone acetonide implant," *Expert Opinion on Pharmacotherapy*, vol. 15, no. 7, pp. 953–959, 2014.

[60] Y. Tokida, Y. Aratani, A. Morita, and Y. Kitagawa, "Production of two variant laminin forms by endothelial cells and shift of their relative levels by angiostatic steroids," *Journal of Biological Chemistry*, vol. 265, no. 30, pp. 18123–18129, 1990.

[61] C. L. Stokes, P. B. Weisz, S. K. Williams, and D. A. Lauffenburger, "Inhibition of microvascular endothelial cell migration by β-cyclodextrin tetradecasulfate and hydrocortisone," *Microvascular Research*, vol. 40, no. 2, pp. 279–284, 1990.

[62] D. E. Ingber, J. A. Madri, and J. Folkman, "A possible mechanism for inhibition of angiogenesis by angiostatic steroids: induction of capillary basement membrane dissolution," *Endocrinology*, vol. 119, no. 4, pp. 1768–1775, 1986.

[63] X. Zhang, N. Wang, A. P. Schachat, S. Bao, and M. C. Gillies, "Glucocorticoids: structure, signaling and molecular mechanisms in the treatment of diabetic retinopathy and diabetic macular edema," *Current Molecular Medicine*, vol. 14, no. 3, pp. 376–384, 2014.

[64] R. Crum, S. Szabo, and J. Folkman, "A new class of steroids inhibits angiogenesis in the presence of heparin or a heparin fragment," *Science*, vol. 230, no. 4732, pp. 1375–1378, 1985.

[65] F. Valamanesh, M. Berdugo, F. Sennlaub et al., "Effects of triamcinolone acetonide on vessels of the posterior segment of the eye," *Molecular vision*, vol. 15, pp. 2634–2648, 2009.

[66] O. Uckermann, F. Kutzera, A. Wolf et al., "The glucocorticoid triamcinolone acetonide inhibits osmotic swelling of retinal glial cells via stimulation of endogenous adenosine signaling," *Journal of Pharmacology and Experimental Therapeutics*, vol. 315, no. 3, pp. 1036–1045, 2005.

[67] K. Lee, H. Chung, Y. Park, and J. Sohn, "Efficacy of intravitreal anti-vascular endothelial growth factor or steroid injection in diabetic macular edema according to fluid turbidity in optical coherence tomography," *Korean Journal of Ophthalmology*, vol. 28, pp. 298–305, 2014.

[68] S. Sonoda, T. Sakamoto, T. Yamashita et al., "Effect of intravitreal triamcinolone acetonide or bevacizumab on choroidal thickness in eyes with diabetic macular edema," *Investigative Ophthalmology & Visual Science*, vol. 55, no. 6, pp. 3979–3985, 2014.

[69] T. Horii, T. Murakami, T. Akagi et al., "Optical coherence tomographic reflectivity of cystoid spaces is related to recurrent diabetic macular edema after triamcinolone," *Retina*, vol. 35, no. 2, pp. 264–271, 2015.

[70] A. P. Adamis, J. W. Miller, M.-T. Bernal et al., "Increased vascular endothelial growth factor levels in the vitreous of eyes with proliferative diabetic retinopathy," *The American Journal of Ophthalmology*, vol. 118, no. 4, pp. 445–450, 1994.

[71] L. P. Aiello, R. L. Avery, P. G. Arrigg et al., "Vascular endothelial growth factor in ocular fluid of patients with diabetic retinopathy and other retinal disorders," *The New England Journal of Medicine*, vol. 331, no. 22, pp. 1480–1487, 1994.

[72] F. Malecaze, S. Clamens, V. Simorre-Pinatel et al., "Detection of vascular endothelial growth factor messenger RNA and

vascular endothelial growth factor-like activity in proliferative diabetic retinopathy," *Archives of Ophthalmology*, vol. 112, no. 11, pp. 1476–1482, 1994.

[73] N. Gupta, S. Mansoor, A. Sharma et al., "Diabetic retinopathy and VEGF," *Open Ophthalmology Journal*, vol. 7, pp. 4–10, 2013.

[74] J. Wang, S. Chen, F. Jiang et al., "Vitreous and plasma VEGF levels as predictive factors in the progression of proliferative diabetic retinopathy after vitrectomy," *PLoS ONE*, vol. 9, no. 10, Article ID e110531, 2014.

[75] Y.-S. Chen, S. F. Hackett, C.-L. Schoenfeld, M. A. Vinores, S. A. Vinores, and P. A. Campochiaro, "Localisation of vascular endothelial growth factor and its receptors to cells of vascular and avascular epiretinal membranes," *British Journal of Ophthalmology*, vol. 81, no. 10, pp. 919–926, 1997.

[76] R. F. Spaide and Y. L. Fisher, "Intravitreal bevacizumab (Avastin) treatment of proliferative diabetic retinopathy complicated by vitreous hemorrhage," *Retina*, vol. 26, no. 3, pp. 275–278, 2006.

[77] R. Jorge, R. A. Costa, D. Calucci, L. P. Cintra, and I. U. Scott, "Intravitreal bevacizumab (Avastin) for persistent new vessels in diabetic retinopathy (IBEPE study)," *Retina*, vol. 26, no. 9, pp. 1006–1013, 2006.

[78] S. Rizzo, F. Genovesi-Ebert, E. Bartolo, A. Vento, S. Miniaci, and G. Williams, "Injection of intravitreal bevacizumab (Avastin) as a preoperative adjunct before vitrectomy surgery in the treatment of severe proliferative diabetic retinopathy (PDR)," *Graefe's Archive for Clinical and Experimental Ophthalmology*, vol. 246, no. 6, pp. 837–842, 2008.

[79] Y. Suzuki, K. Suzuki, Y. Yokoi, Y. Miyagawa, T. Metoki, and M. Nakazawa, "Effects of intravitreal injection of bevacizumab on inflammatory cytokines in the vitreous with proliferative diabetic retinopathy," *Retina*, vol. 34, no. 1, pp. 165–171, 2014.

[80] D. Yoon, I. Rusu, and I. Barbazetto, "Reduced effect of anti-vascular endothelial growth factor agents on diabetics with vitreomacular interface abnormalities," *International Ophthalmology*, vol. 34, no. 4, pp. 817–823, 2014.

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Review Article

Effects of Vitreomacular Adhesion on Age-Related Macular Degeneration

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Herein, we review the association between vitreomacular adhesion (VMA) and neovascular age-related macular degeneration (AMD). Meta-analyses have shown that eyes with neovascular AMD are twice as likely to have VMA as normal eyes. VMA in neovascular AMD may induce inflammation, macular traction, decrease in oxygenation, sequestering of vascular endothelial growth factor (VEGF), and other cytokines or may directly stimulate VEGF production. VMA may also interfere with the treatment effects of anti-VEGF therapy, which is the standard treatment for neovascular AMD, and releasing VMA can improve the treatment response to anti-VEGF treatment in neovascular AMD. We also reviewed currently available methods of relieving VMA.

1. Introduction

Age-related macular degeneration (AMD) is one of the leading causes of severe visual loss in developed countries and affects approximately 8.7% of elderly people >55 years old [1, 2]. Visual loss from this disease is mainly due to neovascular AMD or geographic atrophy (GA), and neovascular AMD accounts for 10% to 15% of patients with AMD [3]. Neovascular AMD is characterized by choroidal neovascularization (CNV), which is promoted by vascular endothelial growth factor (VEGF) and VEGF-A in particular [4]. A number of studies have identified risk factors for progression to neovascular AMD, including aging, cigarette smoking, and genetic factors [5]. Several studies have also postulated that vitreomacular adhesion (VMA) is associated with AMD pathogenesis or progression, and herein we review effects of VMA on neovascular AMD.

Krebs et al. first reported an increased incidence of VMA in eyes with neovascular AMD (18/50 [36%]) compared with dry AMD (4/57 [7%]) and controls (6/56 [11%]) [6]. Mojana et al. demonstrated a higher incidence of VMA in eyes with neovascular AMD compared with controls (27.8% versus 16%) [7]. In addition, a paired eye study revealed an increased rate of VMA in eyes with neovascular AMD compared with contralateral eyes which had dry AMD or no sign of AMD [8]. Roller et al. showed that progression of AMD, including geographic atrophy and CNV, was observed more frequently in nonvitrectomized eyes compared with vitrectomized eyes [9]. Together, these studies led us to speculate VMA might be a risk factor for the development of neovascular AMD and, if so, VMA might be a modifiable risk factor for neovascular AMD.

Currently, intravitreal anti-VEGF injections have been established as the standard treatment for neovascular AMD [10]. However, the study of ranibizumab in patients with subfoveal choroidal neovascularization secondary to age-related macular degeneration (SUSTAIN) showed that 26% of AMD patients were nonresponders to ranibizumab and showed no initial gain of vision or gain of vision during the course of treatment [11]. Another study reported that up to 45% of patients with neovascular AMD were nonresponders to bevacizumab [12]. Lee and Koh reported that VMA has an adverse effect on visual outcomes following anti-VEGF treatment, and studies by Üney et al. and Nomura et al. also showed the same results [13–15]. Thus, VMA might be a possible characteristic of nonresponders, and releasing VMA might be a feasible method to improve responses to anti-VEGF treatment in some eyes with VMA and neovascular AMD.

The purpose of this review is to understand the associations between VMA and neovascular AMD and suggest possible treatment options for VMA with neovascular AMD.

2. Definitions

2.1. Posterior Vitreous Detachment. The vitreous consists of water (98%) and structural macromolecules, including collagen and hyaluronan [16, 17]. The posterior vitreous is attached to the internal limiting membrane (ILM) of the retina by the macromolecular attachment complex including fibronectin and laminin. Posterior vitreous detachment (PVD) is defined as the dehiscence between the posterior vitreous and ILM. The vitreous gradually liquefies with age so that more than half of vitreous is liquid by the eighth decade [18]. PVD usually initiates as a focal detachment in the perifoveal macula, with persistent attachment to the fovea and optic nerve head [19]. Complete PVD describes the complete separation of the vitreous from the macula and optic nerve head. Incomplete or partial PVD naturally progresses to complete PVD.

Anomalous PVD may occur when vitreous liquefaction outpaces vitreoretinal dehiscence or abnormal adhesion is present between posterior vitreous and ILM. If anomalous PVD occurs in the macular area, macular hole or macular pucker may develop [16]. Retinal tears or retinal detachment can also occur if the abnormal adhesion exists in the peripheral retina in anomalous PVD.

2.2. Vitreomacular Adhesion. With the development of optical coherence tomography (OCT), the vitreomacular interface (VMI) can be conveniently assessed. The international vitreomacular traction study (IVTS) group proposed the classification of vitreomacular adhesion, traction, and macular hole according to anatomic features detected with OCT [20]. The vitreous and ILM are completely adherent at birth, so the concept of vitreoretinal adhesion is a normal anatomic state. However, the term VMA is clinically defined as the vitreous being attached within a 3-mm radius of the fovea, with surrounding separation of the cortical vitreous above the neurosensory retina [20, 21]. In addition, the retina should have no changes in surface contour or morphologic features on OCT. VMA can be subclassified as focal ($\leq$1500 μm) or broad (>1500 μm) based on the size of the adhesion. Moreover, VMA should be referred to as concurrent when VMA is associated with retinal diseases (such as AMD, diabetic macular edema, or retinal vein occlusion) and isolated without retinal diseases.

2.3. Vitreomacular Traction. IVTS postulated that vitreomacular traction (VMT) is characterized by macular attachment of the vitreous cortex within a 3-mm radius of the fovea with distortion of the foveal surface, intraretinal pseudocyst formation, and elevation of the fovea from the retinal pigment epithelium (RPE). In VMT, the retinal layer should display no full-thickness interruptions [20]. VMT may be subclassified into focal ($\leq$1500 μm) or broad (>1500 μm) like VMA according to the width of macular attachment. Furthermore, VMT can be termed concurrent or isolated, like VMA as previously described. However, it can be challenging to differentiate between VMT and VMA in eyes with neovascular AMD which have irregular retinal surfaces owing to underlying CNV and intraretinal cysts. In this review, we will focus on VMA but not VMT and discuss the effects of VMA in AMD.

3. The Roles of Vitreomacular Adhesion in Neovascular Age-Related Macular Degeneration

3.1. Inflammation and Oxidative Stress. Many immune-related genes that can induce inflammation, including age-related maculopathy susceptibility 2 (ARMS 2), complement factor H (CHF), and interleukin-8, are risk factors for AMD. Therefore, we speculate that inflammation can contribute to AMD pathogenesis [22, 23]. Inflammation can trigger tissue injury, oxidative stress, extracellular matrix remodeling, angiogenesis, and fibrosis in injured tissue [24]. In addition, retinal circulation has high metabolic rates with respect to oxygen consumption and the mitochondrial oxidative pathway, including phototransduction, neurotransmitter utilization, and protein/organelle transport [25, 26]. Dysregulation between oxidative stress and repair processes can lead to damage at the level of RPE cells, which cause AMD [27, 28]. VMA can induce chronic, low-grade inflammation with mechanical forces that can aggravate AMD [6]. However, there is currently no definite evidence whether VMA can cause the development of neovascular AMD or whether VMA is a consequence of the inflammation in neovascular AMD.

3.2. Tractional Macular Detachment, Retinoschisis, and Macular Edema Formation. Intraretinal cysts and retinoschisis can be induced by VMA according to Newton's third law: for every action, there is always an equal and opposite reaction [29]. When anomalous PVD gives rise to tractional force at the retina, there is an equal force in the opposite direction. This causes the retinal tissue of the retina to be pulled apart and leads to tractional macular detachment and retinoschisis formation [30]. In addition, interstitial tissue pressure decreases when the retina is pulled apart, which results in an influx of the fluid from blood vessels according to Starling's law of hydrostatic pressure [21]. This fluid influx contributes to the macular edema that is clearly evident in neovascular AMD.

3.3. Decreased Vitreous Oxygenation. The retina has dual blood supply from both choroidal and retinal circulation. Choroidal circulation primarily supplies the outer retina, which includes the highly metabolic photoreceptors and RPE, while retinal circulation supplies the inner retina [31]. However, some studies have proposed that the retina might be partially oxygenated by the vitreous [32, 33]. The speed of diffusion is inversely related to the viscosity of the vitreous. Therefore, vitrectomized eyes that have a lower viscosity than intact eyes show increased vitreous oxygenation in both humans and animals [34–36]. Complete PVD induced by

ocriplasmin also increases vitreous oxygen levels in the vitreous cavity [37]. Conversely, VMA, which is mostly located over the area of the CNV in neovascular AMD [8, 38], may disturb oxygenation from the vitreous to the retina.

3.4. Increased VEGF and Proangiogenic Cytokines in front of the Macula. Increased VEGF can cause CNV in AMD and the current gold standard treatment for AMD is anti-VEGF treatment with ranibizumab or bevacizumab [10, 39]. In neovascular AMD, the prevalence of retinal vascular abnormalities is increased [40]. VEGF and other proangiogenic cytokines can diffuse into the vitreous cavity from these abnormal retinal vessels [41]. Vitreous collagen fibrils are altered with aging, and VEGF and other cytokines can be retained by binding to altered collagen fibrils between ILM and posterior vitreous cortex in VMA above the CNV area [42]. This can cause an increase in the concentration of VEGF and other proangiogenic cytokines in front of the macula and they can aggravate neovascularization and inflammation.

3.5. Expression of VEGF by Mechanical Stretch. Many studies have shown that mechanical stretching of the retina can induce VEGF expression [43–46]. A previous study supposed that VMA can disrupt choroidal blood supply to the retina and lead to hypoxia and result in increased VEGF levels [43]. Mechanical stress can also be an important regulator of gene expression, protein synthesis, growth, and the differentiation of many cell types [44]. Recent in vitro studies show that mechanical stress on RPE cells can induce elevated levels of succinate, which results in increased VEGF expression [45].

4. VMA and Neovascular AMD

It is generally accepted that there is an association between VMA and neovascular AMD. A recent meta-analysis on the prevalence of VMA in AMD reported that VMA in eyes with neovascular AMD, dry AMD, and normal controls were 22.6%, 9.5%, and 7.7%, respectively. Thus, eyes with neovascular AMD are 2.15 times more likely to have VMA than normal controls [47]. However, there is a controversy regarding prognosis after anti-VEGF treatment in VMA with neovascular AMD.

Some studies have reported that VMA is associated with poor visual outcome after anti-VEGF treatment for neovascular AMD. Lee and Koh reported that visual acuity after intravitreal anti-VEGF treatment decreased from 0.87 logarithm of the Minimum Angle of Resolution (logMAR) to 0.98 logMAR in eyes with VMA (3.87 injections per year) and improved from 0.82 logMAR to 0.72 logMAR in eyes without VMA (3.58 injections per year) between baseline and the 12 months of follow-up [13]. Üney et al. showed that eyes with VMA had a tendency to lose 4.9 early treatment diabetic retinopathy study (ETDRS) letters in eyes with VMA (3.5 injections per year) and gain 9.2 ETDRS letters in eyes without VMA (4.0 injections per year) after 12 months of anti-VEGF treatment [14]. Nomura et at. also described that visual acuity was unchanged from 0.42 logMAR to 0.39 logMAR in eyes with VMA (5.1 injections per year) but increased from 0.41 logMAR at baseline to 0.29 logMAR in eyes without VMA (5.2 injections per year) within the 12-month follow-up period [15].

A randomized, double-masked, active-controlled, multicenter study comparing the efficacy and safety of ranibizumab administered as two dosing regimens in patients with subfoveal choroidal neovascularization secondary to age-related macular degeneration (EXCITE) compared the efficacy of monthly versus quarterly ranibizumab injections after a loading phase for eyes with neovascular AMD and also investigated the influence of VMA on the efficacy of ranibizumab [48]. The EXCITE study group divided patients into three groups: (1) PVD, patients with PVD; (2) RELEASE, patients with VMA at first but not at last follow-up; and (3) VMA, patients with persistent VMA. In a protocol of quarterly injections after a loading phase (six injections per year), mean changes in ETDRS letters were +4.7 for PVD, +3.2 for RELEASE, and −0.2 for VMA within 12 months. These data were similar to results reported by Lee and Koh, Üney et al., and Nomura et al. from the viewpoint that eyes with VMA have poorer responses to anti-VEGF treatment [13–15].

However, in the monthly injection protocol group (12 injections per year) of the EXCITE study, the mean gains in ETDRS letters were +4.9 for PVD, +12.7 for RELEASE, and +7.5 for VMA. With continuous anti-VEGF injections, RELEASE and VMA groups, which include patients with VMA at baseline, showed better visual acuity than the PVD group after 12 months of follow-up [48]. They speculated that visual outcomes of neovascular AMD with VMA differed according to the frequency of intravitreal ranibizumab injections, and eyes with VMA in neovascular AMD can achieve favorable vision outcomes through an aggressive and continuous injection protocol.

Waldstein et al. investigated the influence of VMA on the efficacy of pro re nata (PRN) anti-VEGF injections after a loading phase. They reported that changes in ETDRS letters from baseline to the 12-month follow-up visit were +3.5 for PVD, +4.3 for RELEASE, and +6.3 for VMA, which were not significantly different [49]. In contrast to other studies that showed no significant differences in the number of anti-VEGF injections between eyes with VMA and without VMA, there were more injections in the RELEASE (6.6 injections per year) and VMA groups (5.3 injections per year) compared to the PVD group (4.9 injections per year).

Recently, the comparison of AMD treatments trials (CATT) study for 2 years of follow-up compared the visual acuity and number of injections according to the presence of VMA or VMT assessed by OCT [50]. In 598 eyes treated as needed protocol, there were 90 eyes (15.1%) with VMA at any time, 63 eyes (10.5%) with VMT at any time, and 445 eyes with neither VMA nor VMT at any time. Visual acuity outcomes between groups were not significantly different ($P = 0.70$). However, there were more frequent injections in VMA group and VMT group compared with the neither VMA nor VMT group (13.8 ± 0.73, 15.4 ± 0.87, and 12.9 ± 0.35, resp., $P = 0.02$).

Overall, it is probable that eyes with VMA and neovascular AMD may be less effective to loading plus PRN treatment, which is one of the most common protocols for neovascular AMD. A greater number of anti-VEGF injections in eyes with

VMA and neovascular AMD might be helpful to achieve similar visual outcomes in eyes without VMA, and even favorable visual outcomes can be attained with continuous anti-VEGF injections. A strategy for reducing the number of anti-VEGF injections should also be considered in eyes with VMA and neovascular AMD, as continuous injections can cause an excessive financial burden and induce a greater chance of developing geographic atrophy which can lead to marked loss of visual acuity and function [51].

5. Treatment Options for Eyes with VMA and Neovascular AMD

5.1. Vitrectomy. Ikeda et al. first performed vitrectomy for 12 eyes of 11 patients with VMA and neovascular AMD. After 6 months, CNV regressed in six eyes (50%) and completely disappeared in two eyes (17%). Moreover, visual acuity improved in four eyes, was maintained in four eyes, and decreased in four eyes [52]. Mojana et al. performed vitrectomy in five eyes with VMT, and four of the five eyes showed an improvement in visual acuity and a decrease in central foveal thickness on OCT [7]. Furthermore, two case series reported that vitrectomy can induce CNV regression in patients with VMT and neovascular AMD [53, 54]. Sakamoto et al. showed that CNV can regress or disappear after vitrectomy (40/54 eyes) and CNV settled more significantly in eyes with PVD than in eyes without PVD [55]. Schramm et al. investigated the efficacy and safety of a core vitrectomy in patients with neovascular AMD treated with anti-VEGF therapy and they concluded that core vitrectomy might produce similar functional outcomes with respect to decreasing the number of intravitreal ranibizumab injections required over 48 weeks, even though it can induce more CNV bleeding [56].

All of these studies demonstrate that vitrectomy can improve functional and anatomical outcomes or reduce the number of anti-VEGF injections in eyes with VMA and neovascular AMD. Benefits of vitrectomy can be achieved by increasing oxygen diffusion from the anterior chamber to the vitreous cavity and diffusion of VEGF and other proangiogenic cytokines that are trapped between the posterior vitreous and ILM [7]. Furthermore, in vitrectomized eyes, the passage of anti-VEGF from the vitreous to subretinal space is not disturbed by the posterior vitreous cortex during anti-VEGF treatment. However, prospective studies are necessary to confirm the role of vitrectomy in AMD pathogenesis and progression.

5.2. Pharmacologic Vitreolysis. Vitreolytic agents are classified into (1) interfactants that can weaken VMA (e.g., dispase), (2) liquefactants that can induce vitreous liquefaction (e.g., hyaluronidase), or (3) a combination of both (e.g., plasmin, ocriplasmin, and tissue plasminogen activator) [57]. Of these agents, plasmin acts on glycoproteins, including fibronectin and laminin, without damaging the retina and has been widely studied. However, plasmin's use is limited in patients owing to its rapid autolytic properties and the fact that it requires activation by proenzymes and plasminogen, which are not commercially available.

Ocriplasmin (JETREA, ThromboGenics Inc., Iselin, NJ, USA) is an alternative to plasmin that was recently approved for the treatment of symptomatic VMA in the USA and European Union [58]. Ocriplasmin is a human serine protease that contains the catalytic domain of plasmin. Ocriplasmin is more stable than plasmin and can induce vitreous liquefaction and cleave the vitreoretinal interface by degrading "glue" proteins, including fibronectin and laminin [57–59].

The microplasmin for intravitreous injection-traction release without surgical treatment (MIVI-TRUST) study group showed that VMA was resolved in 26.5% of eyes treated by a single injection of ocriplasmin (125 μg in 0.10 mL), compared with 10.1% of eyes in the sham injection group within 28 days [59]. VMA resolution can be achieved more often in younger patients (<65 years), patients with focal VMA (adhesion diameter $\leq$ 1500 μm), phakic patients, and patients without epiretinal membranes. Moreover, visual acuity improvement was better in younger patients (<65 years) and patients with lower baseline visual acuity (Snellen equivalent < 20/50) [60].

Recently, a phase II clinical trial evaluating the safety and efficacy of ocriplasmin in eyes with VMA and neovascular AMD was performed [61]. Their data showed that VMA was released in 24.3% (18/74) of the eyes in the ocriplasmin injection group compared with 12.0% (3/25) of eyes in the sham injection group at day 28 after injection. In addition, the ocriplasmin injection group received fewer anti-VEGF injections compared with the sham injection group during the 12-month study period (4.4 injections versus 6.1 injections). However, their study showed no significant differences in VMA resolution or injection numbers between ocriplasmin and sham injection groups owing to the limited sample size.

It is hypothesized that ocriplasmin can release VMA and reduce the number of anti-VEGF injections required in neovascular AMD, but additional studies with larger sample sizes should be performed to confirm the efficacy of ocriplasmin in patients with VMA and neovascular AMD.

5.3. Gas Injection. Gross-Jendroska et al. found that perfluoropropane (C_3F_8) gas injection improved pigment epithelial detachment caused by AMD [62]. Kim et al. reported that all four patients achieved VMA release in neovascular AMD when intravitreal perfluoropropane gas was injected [63]. Moreover, there were no adverse events, such as endophthalmitis, cataract progression, increased intraocular pressure, intraocular hemorrhage, or retinal detachment, during follow-up. Rodrigues et al. reported that VMA was released in 40% of eyes (6/14) within 1 month and 60% of eyes (9/14) within 6 months by pure perfluoropropane injection [64]. Another case series also reported that pure perfluoropropane injection induced PVD without serious adverse effects [65]. Therefore, pure perfluoropropane injection can be an option for releasing VMA in neovascular AMD.

5.4. Intravitreal Injection. In the MIVI-TRUST study, sham injections with 0.10 mL saline were performed in the placebo group, and spontaneous resolution of VMA occurred in 10.1% of eyes 28 days after injection [59, 60]. This means that

the sham injection itself can affect VMI via mechanical force, without the enzymatic activity of ocriplasmin. There are many studies that speculate that the intravitreal injection itself can alter intraocular structures, including the vitreous, retina, and anterior chamber, by mechanical force and other unknown mechanisms [66, 67].

In eyes with neovascular AMD, multiple anti-VEGF injections are necessary to maintain visual outcome. As a result of multiple intravitreal injections, more eyes achieve VMA resolution during the injection period. In the EXCITE study, about half of the eyes with VMA experienced release at 12 months (29/54 in the quarterly injection group, 19/31 in the monthly injection group) [47]. Despite the fact that this sample included some cases in which spontaneous resolution occurred in eyes with VMA during the treatment period, multiple injections can affect the release of VMA in eyes with neovascular AMD.

5.5. Combined Therapy (Anti-VEGF Plus Photodynamic Therapy). One study compared the effects of anti-VEGF monotherapy and anti-VEGF plus photodynamic therapy (PDT) in eyes with VMA of neovascular AMD. The study concluded that compared to anti-VEGF monotherapy, anti-VEGF plus PDT helped reduce the number of injections in eyes with VMA. The anti-VEGF plus PDT group also showed a trend of superior visual outcome, but this was not clinically significant [49]. Even if PDT did not relieve the VMA in neovascular AMD directly, it can reduce the number of injections, thereby ameliorating the financial burden and serious adverse events.

6. Conclusion

Clinical data shows that the probability of having VMA is twice great in eyes with neovascular AMD than in normal eyes [47]. VMA can affect neovascular AMD by (1) inducing inflammation and oxidative stress, (2) formation of macular detachment, retinoschisis, and macular edema, (3) decreasing of vitreous oxygenation, (4) trapping VEGF and proangiogenic cytokines in front of the macula, and (5) mechanical stress induced VEGF production. As eyes with VMA and neovascular AMD have a tendency to generate a poorer response to routine PRN anti-VEGF injection protocols, more aggressive and continuous anti-VEGF injections might be required to achieve favorable visual outcomes in this cohort.

VMA release can improve responsiveness to anti-VEGF treatments, and the required number of anti-VEGF treatments decreases as a result. Release of VMA can be achieved by (1) vitrectomy, (2) ocriplasmin injection, (3) gas injection, or (4) the repeated injection procedure itself. To decrease the number of injections, combination therapy (PRN plus PDT) should be considered.

Conflict of Interests

Hyoung Jun Koh was a consultant/advisor for Allergan, Bayer, and Novartis Pharmaceuticals Corporation. Eui Chun Kang has no financial interests to disclose. The funding organizations had no role in the design or conduct of this paper.

References

[1] R. Klein, T. Peto, A. Bird, and M. R. Vannewkirk, "The epidemiology of age-related macular degeneration," *American Journal of Ophthalmology*, vol. 137, no. 3, pp. 486–495, 2004.

[2] W. L. Wong, X. Su, X. Li et al., "Global prevalence of age-related macular degeneration and disease burden projection for 2020 and 2040: a systematic review and meta-analysis," *The Lancet Global Health*, vol. 2, no. 2, pp. e106–e116, 2014.

[3] L. K. Cheung and A. Eaton, "Age-related macular degeneration," *Pharmacotherapy*, vol. 33, no. 8, pp. 838–855, 2013.

[4] J. S. Penn, A. Madan, R. B. Caldwell, M. Bartoli, R. W. Caldwell, and M. E. Hartnett, "Vascular endothelial growth factor in eye disease," *Progress in Retinal and Eye Research*, vol. 27, no. 4, pp. 331–371, 2008.

[5] S. Velilla, J. J. García-Medina, A. García-Layana et al., "Smoking and age-related macular degeneration: review and update," *Journal of Ophthalmology*, vol. 2013, Article ID 895147, 11 pages, 2013.

[6] I. Krebs, W. Brannath, C. Glittenberg, F. Zeiler, J. Sebag, and S. Binder, "Posterior vitreomacular adhesion: a potential risk factor for exudative age-related macular degeneration?" *American Journal of Ophthalmology*, vol. 144, no. 5, pp. 741–746, 2007.

[7] F. Mojana, L. Cheng, D.-U. G. Bartsch et al., "The role of abnormal vitreomacular adhesion in age-related macular degeneration: spectral optical coherence tomography and surgical results," *American Journal of Ophthalmology*, vol. 146, no. 2, pp. 218–227, 2008.

[8] S. J. Lee, C. S. Lee, and H. J. Koh, "Posterior vitreomacular adhesion and risk of exudative age-related macular degeneration: paired eye study," *The American Journal of Ophthalmology*, vol. 147, no. 4, pp. 621.e1–626.e1, 2009.

[9] A. B. Roller, V. B. Mahajan, H. C. Boldt, M. D. Abramoff, S. R. Russell, and J. C. Folk, "Effects of vitrectomy on age-related macular degeneration," *Ophthalmology*, vol. 117, no. 7, pp. 1381–1386, 2010.

[10] P. Fernández-Robredo, A. Sancho, S. Johnen et al., "Current treatment limitations in age-related macular degeneration and future approaches based on cell therapy and tissue engineering," *Journal of Ophthalmology*, vol. 2014, Article ID 510285, 13 pages, 2014.

[11] F. G. Holz, W. Amoaku, J. Donate et al., "Safety and efficacy of a flexible dosing regimen of ranibizumab in neovascular age-related macular degeneration: the SUSTAIN study," *Ophthalmology*, vol. 118, no. 4, pp. 663–671, 2011.

[12] A. Lux, H. Llacer, F. M. A. Heussen, and A. M. Joussen, "Non-responders to bevacizumab (Avastin) therapy of choroidal neovascular lesions," *The British Journal of Ophthalmology*, vol. 91, no. 10, pp. 1318–1322, 2007.

[13] S. J. Lee and H. J. Koh, "Effects of vitreomacular adhesion on anti-vascular endothelial growth factor treatment for exudative age-related macular degeneration," *Ophthalmology*, vol. 118, no. 1, pp. 101–110, 2011.

[14] G. Ö. Üney, N. Ünlü, M. A. Acar et al., "Role of posterior vitreous detachment on outcome of anti-vascular endothelial growth factor treatment in age-related macular degeneration," *Retina*, vol. 34, no. 1, pp. 32–37, 2014.

[15] Y. Nomura, H. Takahashi, X. Tan, S. Fujimura, R. Obata, and Y. Yanagi, "Effects of vitreomacular adhesion on ranibizumab treatment in Japanese patients with age-related macular degeneration," *Japanese Journal of Ophthalmology*, vol. 58, no. 5, pp. 443–447, 2014.

[16] J. Sebag, "Vitreous: the resplendent enigma," *The British Journal of Ophthalmology*, vol. 93, no. 8, pp. 989–991, 2009.

[17] P. N. Bishop, "Structural macromolecules and supramolecular organisation of the vitreous gel," *Progress in Retinal and Eye Research*, vol. 19, no. 3, pp. 323–344, 2000.

[18] M. M. Le Goff and P. N. Bishop, "Adult vitreous structure and postnatal changes," *Eye*, vol. 22, no. 10, pp. 1214–1222, 2008.

[19] E. Uchino, A. Uemura, and N. Ohba, "Initial stages of posterior vitreous detachment in healthy eyes of older persons evaluated by optical coherence tomography," *Archives of Ophthalmology*, vol. 119, no. 10, pp. 1475–1479, 2001.

[20] J. S. Duker, P. K. Kaiser, S. Binder et al., "The international vitreomacular traction study group classification of vitreomacular adhesion, traction, and macular hole," *Ophthalmology*, vol. 120, no. 12, pp. 2611–2619, 2013.

[21] A. R. H. Simpson, R. Petrarca, and T. L. Jackson, "Vitreomacular adhesion and neovascular age-related macular degeneration," *Survey of Ophthalmology*, vol. 57, no. 6, pp. 498–509, 2012.

[22] M. Chen, J. V. Forrester, and H. Xu, "Dysregulation in retinal para-inflammation and age-related retinal degeneration in CCL2 or CCR2 deficient mice," *PLoS ONE*, vol. 6, no. 8, Article ID e22818, 2011.

[23] R. Cascella, M. Ragazzo, C. Strafella et al., "Age-related macular degeneration: insights into inflammatory genes," *Journal of Ophthalmology*, vol. 2014, Article ID 582842, 9 pages, 2014.

[24] G. K. Hansson, P. Libby, U. Schönbeck, and Z.-Q. Yan, "Innate and adaptive immunity in the pathogenesis of atherosclerosis," *Circulation Research*, vol. 91, no. 4, pp. 281–291, 2002.

[25] D.-Y. Yu, P. K. Yu, S. J. Cringle, M. H. Kang, and E.-N. Su, "Functional and morphological characteristics of the retinal and choroidal vasculature," *Progress in Retinal and Eye Research*, vol. 40, pp. 53–93, 2014.

[26] M. T. Wong-Riley, "Energy metabolism of the visual system," *Eye and Brain*, vol. 2, pp. 99–116, 2010.

[27] F. Roth, A. Bindewald, and F. G. Holz, "Keypathophysiologic pathways in age-related macular disease," *Graefe's Archive for Clinical and Experimental Ophthalmology*, vol. 242, no. 8, pp. 710–716, 2004.

[28] J. Fowles and E. Dybing, "Application of toxicological risk assessment principles to the chemical constituents of cigarette smoke," *Tobacco Control*, vol. 12, no. 4, pp. 424–430, 2003.

[29] E. Stefánsson, "Physiology of vitreous surgery," *Graefe's Archive for Clinical and Experimental Ophthalmology*, vol. 247, no. 2, pp. 147–163, 2009.

[30] P. K. Kaiser, C. D. Riemann, J. E. Sears, and H. Lewis, "Macular traction detachment and diabetic macular edema associated with posterior hyaloidal traction," *American Journal of Ophthalmology*, vol. 131, no. 1, pp. 44–49, 2001.

[31] D. L. Nickla and J. Wallman, "The multifunctional choroid," *Progress in Retinal and Eye Research*, vol. 29, no. 2, pp. 144–168, 2010.

[32] N. P. Blair, T. Liu, K. A. Warren et al., "Ocular oxygen consumption: estimates using vitreoperfusion in the cat," *Retina*, vol. 24, no. 1, pp. 120–131, 2004.

[33] C. A. Wilson, J. D. Benner, B. A. Berkowitz, C. B. Chapman, and R. M. Peshock, "Transcorneal oxygenation of the preretinal vitreous," *Archives of Ophthalmology*, vol. 112, no. 6, pp. 839–845, 1994.

[34] M. Šín, I. Šínová, O. Chrapek et al., "The effect of pars plan vitrectomy on oxygen saturation in retinal vessels—a pilot study," *Acta Ophthalmologica*, vol. 92, no. 4, pp. 328–331, 2014.

[35] I. A. Barbazetto, J. Liang, S. Chang, L. Zheng, A. Spector, and J. P. Dillon, "Oxygen tension in the rabbit lens and vitreous before and after vitrectomy," *Experimental Eye Research*, vol. 78, no. 5, pp. 917–924, 2004.

[36] A. R. H. Simpson, N. G. Dowell, T. L. Jackson, P. S. Tofts, and E. H. Hughes, "Measuring the effect of pars plana vitrectomy on vitreous oxygenation using magnetic resonance imaging," *Investigative Ophthalmology & Visual Science*, vol. 54, no. 3, pp. 2028–2034, 2013.

[37] P. A. Quiram, V. R. Leverenz, R. M. Baker, L. Dang, F. J. Giblin, and M. T. Trese, "Microplasmin-induced posterior vitreous detachment affects vitreous oxygen levels," *Retina*, vol. 27, no. 8, pp. 1090–1096, 2007.

[38] I. Krebs, C. Glittenberg, F. Zeiler, and S. Binder, "Spectral domain optical coherence tomography for higher precision in the evaluation of vitreoretinal adhesions in exudative age-related macular degeneration," *The British Journal of Ophthalmology*, vol. 95, no. 10, pp. 1415–1418, 2011.

[39] D. F. Martin, M. G. Maguire, G.-S. Ying, J. E. Grunwald, S. L. Fine, and G. J. Jaffe, "Ranibizumab and bevacizumab for neovascular age-related macular degeneration," *The New England Journal of Medicine*, vol. 364, no. 20, pp. 1897–1908, 2011.

[40] T. L. Jackson, R. P. Danis, M. Goldbaum et al., "Retinal vascular abnormalities in neovascular age-related macular degeneration," *Retina*, vol. 34, no. 3, pp. 568–575, 2014.

[41] L. P. Aiello, R. L. Avery, P. G. Arrigg et al., "Vascular endothelial growth factor in ocular fluid of patients with diabetic retinopathy and other retinal disorders," *The New England Journal of Medicine*, vol. 331, no. 22, pp. 1480–1487, 1994.

[42] P. N. Bishop, D. F. Holmes, K. E. Kadler, D. McLeod, and K. J. Bos, "Age-related changes on the surface of vitreous collagen fibrils," *Investigative Ophthalmology & Visual Science*, vol. 45, no. 4, pp. 1041–1046, 2004.

[43] A. B. Reese, I. S. Jones, and W. C. Cooper, "Macular changes secondary to vitreous traction," *American Journal of Ophthalmology*, vol. 64, no. 3, pp. 544–549, 1967.

[44] I. Suzuma, Y. Hata, A. Clermont et al., "Cyclic stretch and hypertension induce retinal expression of vascular endothelial growth factor and vascular endothelial growth factor receptor-2: potential mechanisms for exacerbation of diabetic retinopathy by hypertension," *Diabetes*, vol. 50, no. 2, pp. 444–454, 2001.

[45] H. Kinoshita, K. Suzuma, T. Maki et al., "Cyclic stretch and hypertension increase retinal succinate: potential mechanisms for exacerbation of ocular neovascularization by mechanical stress," *Investigative Ophthalmology & Visual Science*, vol. 55, no. 7, pp. 4320–4326, 2014.

[46] I. Suzuma, K. Suzuma, K. Ueki et al., "Stretch-induced retinal vascular endothelial growth factor expression is mediated by phosphatidylinositol 3-kinase and protein kinase C (PKC)-ζ but not by stretch-induced ERK1/2, Akt, Ras, or classical/novel PKC pathways," *The Journal of Biological Chemistry*, vol. 277, no. 2, pp. 1047–1057, 2002.

[47] T. L. Jackson, E. Nicod, A. Angelis et al., "Vitreous attachment in age-related macular degeneration, diabetic macular edema, and retinal vein occlusion: a systematic review and metaanalysis," *Retina*, vol. 33, no. 6, pp. 1099–1108, 2013.

[48] U. Mayr-Sponer, S. M. Waldstein, M. Kundi et al., "Influence of the vitreomacular interface on outcomes of ranibizumab therapy in neovascular age-related macular degeneration," *Ophthalmology*, vol. 120, no. 12, pp. 2620–2629, 2013.

[49] S. M. Waldstein, M. Ritter, C. Simader, U. Mayr-Sponer, M. Kundi, and U. Schmidt-Erfurth, "Impact of vitreomacular

adhesion on ranibizumab mono- and combination therapy for neovascular age-related macular degeneration," *American Journal of Ophthalmology*, vol. 158, no. 2, pp. 328.e1–336.e1, 2014.

[50] T. A. Cuilla, G. S. Ying, M. G. Maguire et al., "Influence of the vitreomacular interface on treatment outcomes in the comparison of age-related macular degeneration treatments trials," *Ophthalmology*, vol. 122, no. 6, pp. 1203–1211, 2015.

[51] U. Chakravarthy, S. P. Harding, C. A. Rogers et al., "Alternative treatments to inhibit VEGF in age-related choroidal neovascularisation: 2-year findings of the IVAN randomised controlled trial," *The Lancet*, vol. 382, no. 9900, pp. 1258–1267, 2013.

[52] T. Ikeda, H. Sawa, K. Koizumi, T. Yasuhara, and T. Yamasaki, "Pars plana vitrectomy for regression of choroidal neovascularization with agerelated macular degeneration," *Acta Ophthalmologica Scandinavica*, vol. 78, no. 4, pp. 460–464, 2000.

[53] Y.-L. Liu, C.-P. Lin, and C.-M. Yang, "Transient regression of choroidal neovascularization membrane after vitrectomy in age-related macular degeneration with vitreomacular traction syndrome," *Acta Ophthalmologica*, vol. 89, no. 3, pp. e291–e293, 2011.

[54] S. U. Shah and J. A. Haller, "Vitreomacular traction in a case of exudative age-related macular degeneration resistant to anti-VEGF therapy," *Acta Ophthalmologica*, vol. 90, no. 7, pp. e569–e570, 2012.

[55] T. Sakamoto, S.-J. Sheu, N. Arimura et al., "Vitrectomy for exudative age-related macular degeneration with vitreous hemorrhage," *Retina*, vol. 30, no. 6, pp. 856–864, 2010.

[56] K. Schramm, M. Mueller, F. H. Koch, P. Singh, T. Kohnen, and M. J. Koss, "Effects of core vitrectomy in the treatment of age-related macular degeneration," *Acta Ophthalmologica*, vol. 92, no. 5, pp. 465–472, 2014.

[57] E. W. Schneider and M. W. Johnson, "Emerging nonsurgical methods for the treatment of vitreomacular adhesion: a review," *Clinical Ophthalmology*, vol. 5, no. 1, pp. 1151–1165, 2011.

[58] Y. Y. Syed and S. Dhillon, "Ocriplasmin: a review of its use in patients with symptomatic vitreomacular adhesion," *Drugs*, vol. 73, no. 14, pp. 1617–1625, 2013.

[59] P. Stalmans, M. S. Benz, A. Gandorfer et al., "Enzymatic vitreolysis with ocriplasmin for vitreomacular traction and macular holes," *The New England Journal of Medicine*, vol. 367, no. 7, pp. 606–615, 2012.

[60] J. A. Haller, P. Stalmans, M. S. Benz et al., "Efficacy of intravitreal ocriplasmin for treatment of vitreomacular adhesion: subgroup analyses from two randomized trials," *Ophthalmology*, vol. 122, no. 1, pp. 117–122, 2015.

[61] R. L. Novack, G. Staurenghi, A. Girach, N. Narendran, and M. Tolentino, "Safety of intravitreal ocriplasmin for focal vitreomacular adhesion in patients with exudative age-related macular degeneration," *Ophthalmology*, vol. 122, no. 4, pp. 796–802, 2015.

[62] M. Gross-Jendroska, C. J. Flaxel, S. D. Schwartz et al., "Treatment of pigment epithelial detachments due to age-related macular degeneration with intra-ocular C3F8 injection," *Australian and New Zealand Journal of Ophthalmology*, vol. 26, no. 4, pp. 311–317, 1998.

[63] Y. M. Kim, S. J. Lee, and H. J. Koh, "Gas-assisted release of vitreomacular adhesion in wet age-related macular degeneration," *Retina*, vol. 31, no. 10, pp. 2123–2124, 2011.

[64] I. A. Rodrigues, A. N. Stangos, D. A. McHugh, and T. L. Jackson, "Intravitreal injection of expansile perfluoropropane (c(3)f(8)) for the treatment of vitreomacular traction," *The American Journal of Ophthalmology*, vol. 155, no. 2, pp. 270.e2–276.e2, 2013.

[65] D. McHugh, B. Gupta, and M. Saeed, "Intravitreal gas injection for the treatment of diabetic macular edema," *Clinical Ophthalmology*, vol. 5, no. 1, pp. 1543–1548, 2011.

[66] G. Seymenoglu, O. Kayikcioglu, and B. O. Sahin, "Resolution of vitreomacular traction following intravitreal triamcinolone acetonide injection in an eye with branch retinal vein occlusion," *Clinical Ophthalmology (Auckland, N.Z.)*, vol. 6, pp. 1239–1243, 2012.

[67] H. Kerimoglu, B. T. Ozturk, B. Bozkurt, M. Okka, and S. Okudan, "Does lens status affect the course of early intraocular pressure and anterior chamber changes after intravitreal injection?" *Acta Ophthalmologica*, vol. 89, no. 2, pp. 138–142, 2011.

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Review Article

Complications of Macular Peeling

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Macular peeling refers to the surgical technique for the removal of preretinal tissue or the internal limiting membrane (ILM) in the macula for several retinal disorders, ranging from epiretinal membranes (primary or secondary to diabetic retinopathy, retinal detachment...) to full-thickness macular holes, macular edema, foveal retinoschisis, and others. The technique has evolved in the last two decades, and the different instrumentations and adjuncts have progressively advanced turning into a safer, easier, and more useful tool for the vitreoretinal surgeon. Here, we describe the main milestones of macular peeling, drawing attention to its associated complications.

1. Introduction

Macular peeling generally refers to the surgical technique for the correction of a hole or epiretinal membrane (ERM) in the macula, or other reasons that involve the removal of the internal limiting membrane (ILM) in the central retina. Removal of preretinal macular fibrosis [1] begun shortly after the development of closed pars plana vitreoretinal surgery by Machemer and colleagues [2]. Then, bimanual surgical techniques, first used in eyes with complicated proliferative diabetic retinopathy and retinal detachments [3, 4], also permitted the resection of abnormal glial tissue from the superficial retina. The first to remove localized epiretinal membranes that were covering or distorting the macula in the absence of other primary conditions was Machemer [5], but it was popularized by many authors, who named differently such anomalies as epimacular proliferation or macular pucker [6–8].

The ILM was first named by Pacini in 1845 and represents the boundary between the retina and the vitreous body [9]. It is a periodic acid Schiff- (PAS-) positive basement membrane, formed by astrocytes and the end feet of Müller cells and composed of collagen fibers, glycosaminoglycans, laminin, and fibronectin [10] (Figure 1).

The close association between ILM and the Müller cells suggests that it derives from these cells [10]. The macula, the parafoveal, and peripapillary regions of ILM are the thickest, measuring an average of 2.5 μm in thickness, and progressively thinning to 0.5 μm at the vitreous base [11].

Histological and clinical studies demonstrated that the ILM acts as a scaffold for cellular proliferation of Müller cells, thus allowing the survival of ganglion cells [12], and for migration of glial cells, creating a tangential contractile force on the macular surface and posterior vitreous cortex, sometimes with subclinical manifestations, only detected by OCT, and others leading to the formation of tight, thickened, refringent premacular posterior membranes [13]. It seems that ILM may have its main function only during early embryogenesis, and its removal would not have negative effects in the aged human eye [12].

2. Surgical Techniques, Instrumentations, and Adjuncts

The ILM was not clinically relevant until surgical removal of ERM by means of vitrectomy in the 80's identified small fragments of ILM adherent to the surgical specimens [14]. Posteriorly, a technique for repairing sub-ILM macular

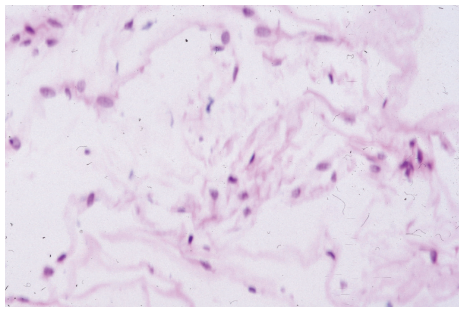

Figure 1: Hematoxylin and eosin 40x showing a paucicellular basement membrane composed of collagen fibers, glycosaminoglycans, laminin, fibronectin, and some astrocytes.

hemorrhages in patients with Terson syndrome with intentional ILM extraction was presented at the Annual Meeting of the American Academy of Ophthalmology in 1990, with excellent results which guided the authors to consider the technique of ILM removal in all forms of tractional maculopathy [15]. After the 90's, the technique became widely extended until accepted today because not only it releases these contractile forces, but also it guarantees complete separation of the posterior hyaloid from the macular surface [16] and also decreases the risk of postoperative ERM formation [17].

The ILM peeling can be achieved after a standard pars plana vitrectomy (PPV), in which a careful detachment and remotion of the posterior hyaloid intend to avoid any possible scaffolding for cellular proliferation and subsequent retinal traction [18]. To detach the posterior hyaloid, there are 2 widespread maneuvers [19]: (1) by means of suction close to the optic disk with the help of the extrusion needle or vitrector tip and control pressure of up to 150 mmHg or (2) by means of mechanical elevation of the posterior hyaloid with a membrane pick or microvitreoretinal blade (MVR). Then, the macular peeling can be performed: the first step is to create an initial flap in the ILM with a sharp instrument such as pick forceps, bent MVR, or vitreoretinal forceps. Once the flap is created, the desired area of ILM is removed with the vitreoretinal forceps using circular movements around the fovea similar to a capsulorhexis and in parallel to the retinal surface [13]. The extent of ILM to be peeled varies from approximately 1 disk area centered at the fovea [20, 21] to an area extending from the superotemporal to the inferotemporal vascular arcades [22–24]. The confirmation of tissue removed during surgery can be obtained with histopathologic studies [25], but postoperatively it is clinically difficult to ascertain the area of retina denuded. Monochromatic images, obtained using the scanning laser ophthalmoscope (SLO) at wavelengths of 488 and 514 nm, were superior to color and red-free photographs [26].

3. Vital Dyes in Macular Surgery

Because the ILM is thin and transparent, surgical remotion can become technically challenging even for experienced surgeons especially in difficult cases such as myopic macular hole or foveoschisis. Staining of the ILM with adjuvant dyes can make the procedure easier to perform and more effective, reducing also the operating time and the mechanical trauma to the retina [27].

Several authors have reported the use of indocyanine green (ICG) and trypan blue for assisted ILM peeling in macular hole (MH) surgery, but concerns soon appeared when evidence from several clinical reports and in vitro toxicity showed worse visual outcomes with both dyes [28, 29].

4. ICG

ICG has been widely used since 1970 for choroidal angiography [30]. Then, anterior segment surgeons described techniques for the intraocular use of ICG dye to facilitate visualization of the endothelial cells [31] and the anterior capsule of the crystalline lens [32], but it was popularized in the very beginning of our century in several reports for vitreoretinal surgery [33–38]. ICG is highly soluble in water but poorly soluble in saline solution and must be diluted in water or in glucose 5% to prevent later precipitation in the balanced salt solution of the eye. The concentration, volume infusion, exposure time, and osmolarity of the final solution used both for ILM and ERM removal have been varied between different authors, and the staining can be done in a fully filled eye with the infusion stopped [28, 34, 35, 39–48], or after complete fluid-air exchange [41, 42]. In order to minimize the side effects of ICG on the retina, several techniques have been emerging: (1) to inject small amounts and concentrations with the infusion on and immediate suction of remains to wash the dye out rapidly [49, 50], (2) to bind remnants by placing autologous serum [51] over the area of retina lacking ILM, knowing that ICG has high affinity to lipoproteins, and (3) to prevent the access of ICG into the subretinal space in eyes with MH by using a drop of perfluorocarbon liquid [52, 53] or viscoelastic materials [54, 55]. Though several reports showed favourable anatomical and visual results with the use of ICG staining, the latest suspicions on its safety forced surgeons to compare functional outcomes with and without the use of the dye. In this respect, numerous studies reported poorer visual results when ICG was used to stain both ILM and ERM [44, 56, 57]. In spite of the fact that ICG could induce a rigidness and detachment of the ILM and facilitate its removal with staining, Gandorfer and Haritoglou found on histopathologic studies fragments of Müller cells and other undetermined retinal structures adherent to the retinal side of the ILM, suggesting that intravitreal application of ICG may cause retinal damage by altering the cleavage plane to the innermost retinal layers [28, 58, 59]. These structural findings were confirmed in a donor human eye [60] and in nonhuman eyes [61].

Others suggested unusual atrophic changes in the retinal pigment epithelium (RPE) on the site of the previous macular hole or in the area where the ICG solution would have had direct access to the bare RPE cells [39, 47, 62]. In experimental models, it was demonstrated that subretinal delivery of ICG was able to induce as much RPE as photoreceptor and outer nuclear layer damage [63, 64], especially if the eye was air

filled [65]. It has been hypothesized that the RPE damage could be related to direct toxicity of the dye to these cells [66]. Some authors attributed an enhanced toxic effect of ICG staining with intense light exposure [67, 68], so that Ho and colleagues proposed to remove the sodium from the solvent for the dye preparation in order to reduce the cytotoxicity [69].

Phototoxicity alone has been studied as a possible cause for RPE cells damage induced by ICG, due to its absorption spectrum (700–800 nm) in front of the emission spectrum of current light sources employed in PPV (380–760 nm) [70, 71]. This deleterious effect could be reduced through the intake of 10 mg/day of oral lutein several days before surgery, according to Wu and colleagues [66].

There also have been described visual field defects with the use of ICG staining: from small nasal scotomas to nasal hemianopsia, whose mechanism of production is not yet well understood [28, 56, 72, 73]. Slimming of the retinal nerve fiber layer [74] or damage to the retinal ganglion cells (RGC) with high concentrations of ICG has been hypothesized [75]. Persistence of the dye seen as fluorescence at the optic disk has been detected in eyes in which ICG was employed up to 2 years after the macular surgery [76–80]; this finding could be related to an uptake of ICG by RPE cells through the hole in cases of MH [77]. Other authors have detected a reduction of the b-wave in experimental electroretinograms after the exposure to ICG, suggesting some degree of inner retinal damage [81].

In spite of the fact that there are many reports suggesting the possibility of ICG toxicity to the retina and RPE, experimental toxicity may not correlate exactly with actual clinical application of ICG, in which the intraoperative conditions can be much different. There is notable laboratory experimentation to the contrary demonstrating that even at high concentrations followed by maximum power illumination for 3 minutes ICG caused no histologically detectable damage [82]. Taking into account the differences in species and in vivo-ex vivo studies, this raises the possibility that either the ICG instillation or the infusion [83] or fluid-air exchange [84, 85] might have hydrodissected the ILM from the underlying retina and injured the retinal nerve fiber layer. Indeed, if ICG instillation hydrodissected the ILM from the retina, the ICG solution would have had direct access to the retinal tissue, which might help to explain their reported photodynamic effects [86].

5. Infracyanine Green

Infracyanine green (IFCG), unlike ICG, does not contain iodine, and it needs glucose 5% to solve in water, but it is isoosmolar, which would reduce the potential for retinal toxicity, compared to ICG [87], and hypoosmolar related to vitreous humor. IFCG has been used to stain both ILM and ERM without serious clinical adverse events [88–92]. In histopathologic studies of ILM specimens obtained from MH and diabetic macular edema (DME) eyes, 80% contained remnants of Müller cells footplates, neural cells, and ganglion cells [93, 94], suggesting would create the same cleavage plane of the ILM as ICG. Nevertheless, no evidence of acute or delayed permanent damage to the RPE at different concentrations of IFCG or in combination with endoillumination was found [95]. In spite of its apparent safety, its use is not very widespread.

6. Trypan Blue

Trypan blue (TB) has been widely used in anterior segment surgery to stain corneal endothelial cells [96] and lens capsule [97]. In vitreoretinal surgery, it has been used to stain the posterior hyaloid, the ERM, and the ILM [98–105]. The mixture with glucose 10% allows adequate staining for both ERM and ILM without detectable toxic side effects [98–101, 103–108], but some authors established that, due to the cellular affinity of TB, the dye would not stain properly the acellular ILM [109] and would need to be used under air for a longer time to improve staining of ILM [110]. Reports comparing TB with ICG found better visual outcomes with trypan blue assisted ILM peeling [111], and no clinical [107, 112] or experimental acute damage was observed [108, 113], although some authors detected some retinal disorganization at concentrations of more than 0.15% [81, 108, 114], or exposure times of more than 2 minutes [115].

7. Other Dyes

Triamcinolone acetonide (TA) was first used by Tano intravitreally in 1980 [116], after being used in ophthalmology to treat many ophthalmic diseases. This water-insoluble steroid aids in the visualization of vitreous, upon the insoluble nature of the white crystals and the integration into loosely organized collagen matrices [117–120]. An extension of this mechanism is thought to be responsible for the staining of the superficial portions of an ILM [121–127] and ERM [120]. The drug is commercially available in an aqueous suspension and has been administered with or without the removal of its solvent in the second case in order to avoid possible toxic effects [117, 120, 122, 123, 127]. Different methods such as sedimentation or filtration techniques and centrifugation [128] are usually used to eliminate the solvent, usually benzyl alcohol, from the preparations. Lately, new products based on TA have appeared that can be injected directly into the eye. Other possible adverse events of TA are increase in intraocular pressure [122, 124, 125, 127, 129, 130], generally transient and controlled medically, cataract progression [129, 130], or, in some cases, endophthalmitis that has been described as infectious (more delayed and painless than usual) or noninfectious (more acute, in which hypopyon may represent the TA material itself or a sterile inflammatory reaction) [131].

Brilliant Blue G (BBG), also known as acid blue 90 or Coomassie BBG, was first reported in vitreoretinal surgery by Enaida et al. and has been used specifically for the staining of the ILM [132] with good morphological and functional results [133–135]. The dye stains badly the ERM, but some authors performed double BBG staining and double peeling for both ERM and ILM in order to prevent ERM recurrence [136]. Recently, a mixture of TB and BBG solution for staining both the ERM and ILM simultaneously avoided the need for fluid-air exchange [137, 138].

Patent blue is another blue dye which was first used in cataract surgery for anterior lens capsule staining [81]. It has been used posteriorly for both ERM and ILM removal with mild staining [139] and without clinical adverse events at 6-month follow-up in small series [140], although more studies are needed to evaluate the efficacy and the safety of the drug. Novel promising vital dyes are under investigation in an in vitro and in vivo models that may be useful for vitreoretinal surgery like lutein and zeaxanthin-based natural solutions.

8. Indications for Macular Peeling

In idiopathic MH, ILM peeling relieves foveal traction from the retinal surface [141–143] by complete removal of any epiretinal tissues and by stimulation of gliosis [61], therefore shortening the face-down period in the post-op and the need for the use of long-acting gas [144–146], with better anatomical closure rates but not better visual improvement [147]. In myopic FTMH, the mechanism of hole formation is more complex and involves not only tangential and/or anteroposterior traction, some authors suggested that the ILM could have a role in the development of foveal retinoschisis that frequently accompanies these cases [148]. Several reports support this reasoning with better visual results and higher definitive closure rates when ILM peeling was performed [149–151]. When FTMH is secondary to trauma and does not resolve by itself (which occurs in up to 44.4% [152]), PPV with removal of posterior hyaloid, ILM peeling, and gas tamponade can obtain the best anatomic success over other techniques [23, 153].

Epiretinal membranes began to be routinely removed by PPV from 1978 [14]. Surgery is recommended in both idiopathic and secondary membranes in eyes whose vision is significantly reduced by the ERM, although secondary ERMs showed a greater amount of improvement than idiopathic ones [154, 155]. Also, as ILM may act as a scaffold for reproliferation, ILM peeling can not only prevent a recurrent postoperative formation of ERM [37, 147, 156–158] but also reduce the preoperative cystoid macular edema associated with ERMs [159].

ILM peeling has been used in some cases of refractory diabetic macular edema (DME) after failed intravitreal injections of anti-VEGF, steroids, and/or laser photocoagulation, with decrease in foveal thickness but with no improvement of visual acuity postoperatively [160–163]. In branch and central retinal vein occlusion-associated macular edema, there are few series of selected cases that show improvement in visual acuity after PPV with the removal of preretinal hyaloid and peeling of the ILM [164–166]. As in DME, PPV alone can provide better retinal oxygenation [167], but ILM peeling could help in pumping blood and fluid from the retina into the vitreous cavity [164] and could also reduce the recurrence rate of both macular edema and ERM compared to PPV alone [168–171].

Other possible applications of macular peeling are optic disk maculopathy [172], vitreomacular traction syndrome [173], Terson's syndrome [174], and prevention of ERM formation in retinal detachment surgery [175, 176]. Dithmar also reports a case of soft confluent drusen absorption after ILM peeling [177].

9. Complications of Macular Peeling

There are some complications after macular peeling that are common to other vitreoretinal procedures, probably more related to PPV than peeling maneuvers, even in the era of microincision surgery [178, 179], like cataract progression [86, 147, 180–182], intraocular pressure increase [46, 182–184], visual fields defects [28, 181, 185–187], retinal tears [22, 86, 151, 182, 188–190], retinal detachment [46, 73, 86, 150, 151, 181, 188, 191–193], vitreous hemorrhage [46, 194], ocular hypotony [195], dislocation of the intraocular lens in pseudophakic eyes [86, 192], macular phototoxicity [188], RPE changes [20, 39, 193], and endophthalmitis [191, 196, 197].

There are other complications directly attributable to macular peeling, including focal retinal hemorrhages and edema, which generally resolves spontaneously without the need of treatment [20, 23, 188, 198]. Paracentral scotomas and visual field defects, usually asymptomatic, have also been reported but not directly correlated with the removal of the ILM and could result from adjuvant stain or mechanical trauma to the nerve fiber layer (RNFL) [20, 44, 74, 198–200]. There are also few reports about retinoschisis [199] and macular edema after macular peeling [20, 201]. Karacorlu described small punctate lesions of the RPE and choriocapillaris attributed to ILM grasping during the surgery that do not appear to affect the surgical outcome [202].

The earliest change in the macula is postoperative swelling of the arcuate RNFL, which disappears within 3 months. It appears as hypoautofluorescent arcuate striae in the macular region on infrared and autofluorescence imaging, with corresponding hyperreflectant swelling demonstrated on spectral-domain optical coherence tomography (OCT) [200]. This is followed by dissociated optic nerve fiber layer (DONFL), now detectable on fundus examination with blue filters in half of the eyes, as arcuate dark striae along the course of the RNFL [203, 204], or as concentric macular dark spots on the en-face OCT [205]. The correspondent image on OCT is seen as "dimples" in the inner retinal layers that seem to be the result of an interplay between trauma and healing processes constrained by nerve fiber layer [206] and it is not associated with adverse effects on the visual function, as detected by visual acuity and scanning laser ophthalmoscopy microperimetry [203, 204, 207, 208]. Postoperative foveal displacement toward the optic disc has been also described after both ERM and ILM peeling [209, 210] and it might be responsible for the stretching and thinning of the retinal parenchyma in the temporal subfield with the thickening of the nasal macula. This is probably secondary to axonal transport and contractility alterations in the RNFL, due to apoptotic and atrophic degeneration on the peripapillary area [200]. Ganglion cells do not seem to be affected by ILM peeling, although some authors detected a reduction in the inner plexiform layer thickness by OCT imaging at 6 months after BBG-assisted surgery, because of trauma to the Müller cells contained in the ganglion cell layer [211]. It is not consistent with other retrospective study that found up

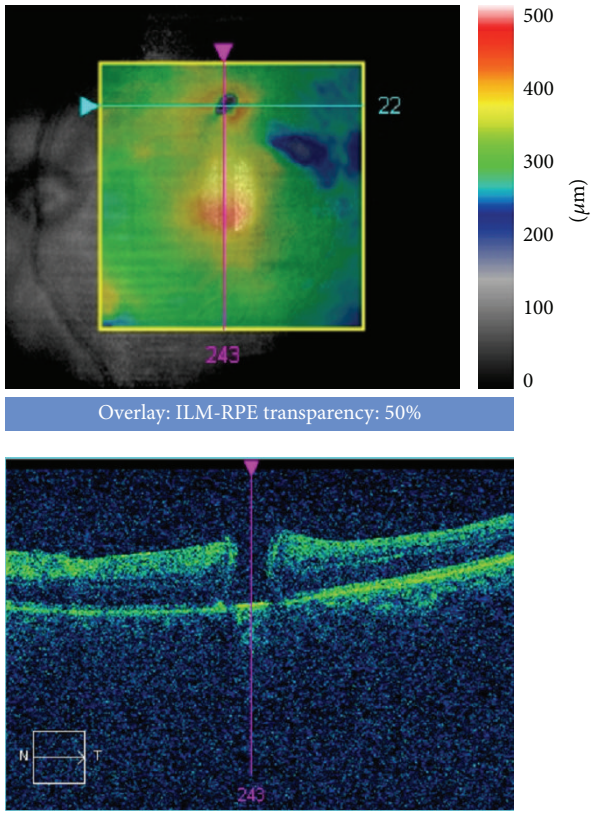

Figure 2: Parafoveal iatrogenic macular hole 1 week after ILM peeling for a full-thickness macular hole (FTMH).

to 46.7% of optic nerve atrophy 6 months after ICG-assisted surgery, which caused irreversible peripheral nasal visual field defect, so that would need longer follow-up investigation [72].

Iatrogenic eccentric full-thickness retinal breaks have been documented after ERM and ILM removal in idiopathic FTMH and DME [204–207], with an average incidence of 0.6% [212]. Usually, they present bright fluorescence on autofluorescence imaging and as flat full-thickness holes on OCT (Figure 2).

Sandali and colleagues. did not found iatrogenic macular holes or choroidal neovascularization in any of the retrospective series of 909 patients with a mean follow-up of two years, but proximity to the fovea correlated well with a worse visual prognosis [212]. It is believed that the location of the holes represents the initial or the end site of ILM elevation, or the result of a weakening in the glial structure of the retina [90, 212, 213]. Some authors propose a modification of the peeling avoiding the foveolar ILM in order to prevent retinal inner changes and probably achieving better final visual outcomes [214].

There are some reports of retained intraretinal emulsified silicone oil and gas bubble after ILM removal and endotamponade with these agents that contributed to the surgery failure [215, 216].

Microtrauma to the RPE and defects in Bruch's membrane are thought to be the origin of rare complications reported like choroidal neovascularization or formation of RAP-like lesions [217–219], and it seems that prior age or trauma-related changes and surgical trauma are predisposing factors for its development.

Uemoto described 2 cases of an epimacular proliferative response after ILM peeling, related to the injury but not progressing after 2 years [143].

Subretinal hemorrhage and subsequent vitreous hemorrhage are other complications that can occur after ILM removal for FTMH [220]. The latter can occur even in the absence of retinal hemorrhage in hypertensive patients [221].

10. Discussion

Comparing series with and without ILM peeling, all but one study [14] reported statistically significant improved outcomes if the ILM was peeled. Internal limiting membrane removal appears to be especially beneficial in eyes with primary surgical failure or reopened/large/chronic holes [14]. A literature meta-analysis, reviewing 31 studies involving 1,654 eyes undergoing macular hole surgery, compared three different surgical techniques: no adjuvant, no ILM peeling; adjuvant, no ILM peeling; and no adjuvant, ILM peeling. There was no statistically significant difference between the first two methods, but ILM removal resulted in statistically significant ($P < 0.0001$) better anatomical and functional outcomes over both the other techniques [222]. In a prospective multicenter randomized controlled trial with 141 patients, although there was no evidence of a better distance visual acuity after the ILM peeling versus no ILM peeling techniques, a benefit in favor of no ILM peeling was ruled out, but it seemed to be the treatment of choice for idiopathic stages 2 to 3 FTMH [223]. It must be taken into account that ILM peeling can be a traumatic procedure that has acute adverse effects on the underlying retinal layers and even in the RPE and choriocapillaris. Further investigation of these subclinical changes may assist in aiding the development and improvement of minimally traumatic techniques for ILM removal.

11. Conclusions

The combined ERM-ILM peeling for the correction of macular ERM and the ILM peeling for the correction of MH and its variations are useful techniques in the new era of microvitreoretinal sugery, usually with good anatomical and functional outcomes, but they can have a little proportion of complications (toxic or mechanical, transient, or irreversible), even in hands of experienced surgeons, which must be taken into consideration in order to achieve the best results.

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

References

[1] G. N. Wise, "Relationship of idiopathic preretinal macular fibrosis to posterior vitreous detachment," *The American Journal of Ophthalmology*, vol. 79, no. 3, pp. 358–362, 1975.

[2] R. Machemer, J.-M. Parel, and H. Buettner, "A new concept for vitreous surgery. I. Instrumentation," *The American Journal of Ophthalmology*, vol. 73, no. 1, pp. 1–7, 1972.

[3] R. Machemer, "Vitrectomy in diabetic retinopathy: removal of preretinal proliferations," *Transactions of the American Academy of Ophthalmology and Otolaryngology*, vol. 80, no. 2, pp. 394–395, 1975.

[4] R. G. Michels and H. D. Gilbert, "Surgical management of macular pucker after retinal reattachment surgery," *American Journal of Ophthalmology*, vol. 88, no. 5, pp. 925–929, 1979.

[5] R. Machemer, "The surgical removal of epiretinal macular membranes (macular puckers)," *Klinische Monatsblatter fur Augenheilkunde*, vol. 173, no. 1, pp. 36–42, 1978.

[6] M. Shea, "The surgical management of macular pucker," *Canadian Journal of Ophthalmology*, vol. 14, no. 2, pp. 110–113, 1979.

[7] S. Charles, "Epimacular proliferation," in *Vitreous Microsurgery*, W. S. Schachet, Ed., chapter 8, pp. 131–133, Williams & Wilkins, Baltimore, Md, USA, 1981.

[8] A. R. Margheiro, D. P. Nachazel, P. L. Murphy et al., "The surgical management of epiretinal membranes, scientific exhibit, American Academy of Ophthalmology Annual Meeting, 1981," *Ophthalmology*, vol. 88, supplement, article 82, 1981.

[9] G. Wollensak, E. Spoerl, G. Grosse, and C. Wirbelauer, "Biomechanical significance of the human internal limiting lamina," *Retina*, vol. 26, no. 8, pp. 965–968, 2006.

[10] B. S. Fine, "Limiting membranes of the sensory retina and pigment epithelium. An electron microscopic study," *Archives of Ophthalmology*, vol. 66, pp. 847–860, 1961.

[11] R. Y. Foos, "Vitreoretinal juncture: topographical variations," *Investigative ophthalmology*, vol. 11, no. 10, pp. 801–808, 1972.

[12] W. Halfter, M. Willem, and U. Mayer, "Basement membrane-dependent survival of retinal ganglion cells," *Investigative Opthalmology & Visual Science*, vol. 46, no. 3, 2005.

[13] A. Almony, E. Nudleman, G. K. Shah et al., "Techniques, rationale, and outcomes of internal limiting membrane peeling," *Retina*, vol. 32, no. 5, pp. 877–891, 2012.

[14] F. Kuhn, "Point: to peel or not to peel, that is the question," *Ophthalmology*, vol. 109, no. 1, pp. 9–11, 2002.

[15] R. Morris, F. Kuhn, and C. D. Witherspoon, "Hemorrhagic macular cysts," *Ophthalmology*, vol. 101, article 1, 1994.

[16] F. M. Recchia, A. J. Ruby, and C. A. Carvalho Recchia, "Pars plana vitrectomy with removal of the internal limiting membrane in the treatment of persistent diabetic macular edema," *American Journal of Ophthalmology*, vol. 139, no. 3, pp. 447–454, 2005.

[17] N. Matsunaga, H. Ozeki, Y. Hirabayashi, S. Shimada, and Y. Ogura, "Histopathologic evaluation of the internal limiting membrane surgically excised from eyes with diabetic maculopathy," *Retina*, vol. 25, no. 3, pp. 311–316, 2005.

[18] E. Abdelkader and N. Lois, "Internal limiting membrane peeling in vitreo-retinal surgery," *Survey of Ophthalmology*, vol. 53, no. 4, pp. 368–396, 2008.

[19] D. P. Han, G. W. Abrams, and T. M. Aaberg, "Surgical excision of the attached posterior hyaloid," *Archives of Ophthalmology*, vol. 106, no. 7, pp. 998–1000, 1988.

[20] C. Haritoglou, C. A. Gass, M. Schaumberger, O. Ehrt, A. Gandorfer, and A. Kampik, "Macular changes after peeling of the internal limiting membrane in macular hole surgery," *The American Journal of Ophthalmology*, vol. 132, no. 3, pp. 363–368, 2001.

[21] A. Hirata, Y. Inomata, T. Kawaji, and H. Tanihara, "Persistent subretinal indocyanine green induces retinal pigment epithelium atrophy," *American Journal of Ophthalmology*, vol. 136, no. 2, pp. 353–355, 2003.

[22] A. P. Da Mata, S. E. Burk, C. D. Riemann et al., "Indocyanine green-assisted peeling of the retinal internal limiting membrane during vitrectomy surgery for macular hole repair," *Ophthalmology*, vol. 108, no. 7, pp. 1187–1192, 2001.

[23] F. Kuhn, R. Morris, V. Mester, and C. D. Witherspoon, "Internal limiting membrane removal for traumatic macular holes," *Ophthalmic Surgery and Lasers*, vol. 32, no. 4, pp. 308–315, 2001.

[24] M. Landolfi, M. A. Zarbin, and N. Bhagat, "Macular holes," *Ophthalmology Clinics of North America*, vol. 15, no. 4, pp. 565–572, 2002.

[25] S. Heegard, O. A. Jensen, and J. U. Prause, "Structure and composition of the inner limiting membrane of the retina," *Graefe's Archive for Clinical and Experimental Ophthalmology*, vol. 224, no. 4, pp. 355–360, 1986.

[26] M. Miura, A. E. Elsner, M. Osako et al., "Spectral imaging of the area of internal limiting membrane peeling," *Retina*, vol. 25, no. 4, pp. 468–472, 2005.

[27] E. B. Rodrigues, C. H. Meyer, M. E. Farah, and P. Kroll, "Intravitreal staining of the internal limiting membrane using indocyanine green in the treatment of macular holes," *Ophthalmologica*, vol. 219, no. 5, pp. 251–262, 2005.

[28] C. Haritoglou, A. Gandorfer, C. A. Gass, M. Schaumberger, M. W. Ulbig, and A. Kampik, "Indocyanine green-assisted peeling of the internal limiting membrane in macular hole surgery affects visual outcome: a clinicopathologic correlation," *American Journal of Ophthalmology*, vol. 134, no. 6, pp. 836–841, 2002.

[29] E. Mavrofrides, W. E. Smiddy, J. W. Kitchens, A. Salicone, and W. Feuer, "Indocyanine green-assisted internal limiting membrane peeling for macular holes: toxicity?" *Retina*, vol. 26, no. 6, pp. 637–644, 2006.

[30] K. Kogure, N. J. David, U. Yamanouchi, and E. Choromokos, "Infrared absorption angiography of the fundus circulation," *Archives of Ophthalmology*, vol. 83, no. 2, pp. 209–214, 1970.

[31] J. K. McEnerney and G. A. Peyman, "Indocyanine green: a new vital stain for use before penetrating keratoplasty," *Archives of Ophthalmology*, vol. 96, no. 8, pp. 1445–1447, 1978.

[32] M. Horiguchi, K. Miyahe, I. Ohta, and Y. Ito, "Staining of the lens capsule for circular continuous capsulorrhexis in eyes with white cataract," *Archives of Ophthalmology*, vol. 116, no. 4, pp. 535–537, 1998.

[33] S. E. Burk, A. P. Da Mata, M. E. Snyder, R. H. Rosa Jr., and R. E. Foster, "Indocyanine green-assisted peeling of the retinal internal limiting membrane," *Ophthalmology*, vol. 107, no. 11, pp. 2010–2014, 2000.

[34] K. Kadonosono, N. Itoh, E. Uchio, S. Nakamura, and S. Ohno, "Staining of internal limiting membrane in macular hole surgery," *Archives of Ophthalmology*, vol. 118, no. 8, pp. 1116–1118, 2000.

[35] A. P. Da Mata, S. E. Burk, C. D. Riemann et al., "Indocyanine green-assisted peeling of the retinal internal limiting membrane during vitrectomy surgery for macular hole repair," *Ophthalmology*, vol. 108, no. 7, pp. 1187–1192, 2001.

[36] A. Gandorfer, E. M. Messmer, M. W. Ulbig, and A. Kampik, "Indocyanine green selectively stains the internal limiting membrane," *The American Journal of Ophthalmology*, vol. 131, no. 3, pp. 387–388, 2001.

[37] M. W. Johnson, "Improvements in the understanding and treatment of macular hole," *Current Opinion in Ophthalmology*, vol. 13, no. 3, pp. 152–160, 2002.

[38] A. K. H. Kwok, Y. S. Yeung, V. Y. W. Lee, and T. H. Wong, "ICG-assisted peeling of the retinal ILM," *Ophthalmology*, vol. 109, no. 6, pp. 1039–1040, 2002.

[39] N. E. Engelbrecht, J. Freeman, P. Sternberg Jr. et al., "Retinal pigment epithelial changes after macular hole surgery with indocyanine green-assisted internal limiting membrane peeling," *The American Journal of Ophthalmology*, vol. 133, no. 1, pp. 89–94, 2002.

[40] A. Kumar, G. Prakash, and R. P. Singh, "Indocyanine green enhanced maculorhexis in macular hole surgery," *Indian Journal of Ophthalmology*, vol. 50, no. 2, pp. 123–126, 2002.

[41] A. W. A. Weinberger, B. Schlossmacher, C. Dahlke, M. Hermel, B. Kirchhof, and N. F. Schrage, "Indocyanine-green-assisted internal limiting membrane peeling in macular hole surgery—a follow-up study," *Graefe's Archive for Clinical and Experimental Ophthalmology*, vol. 240, no. 11, pp. 913–917, 2002.

[42] A. K. H. Kwok, T. Y. Y. Lai, D. T. W. Yew, and W. W. Y. Li, "Internal limiting membrane staining with various concentrations of indocyanine green dye under air in macular surgeries," *American Journal of Ophthalmology*, vol. 136, no. 2, pp. 223–230, 2003.

[43] H. Sakamoto, I. Yamanaka, T. Kubota, and T. Ishibashi, "Indocyanine green-assisted peeling of the epiretinal membrane in proliferative vitreoretinopathy," *Graefe's Archive for Clinical and Experimental Ophthalmology*, vol. 241, no. 3, pp. 204–207, 2003.

[44] F. Ando, K. Sasano, F. Suzuki, and N. Ohba, "Indocyanine green-assisted ILM peeling in macular hole surgery revisited," *The American Journal of Ophthalmology*, vol. 138, no. 5, pp. 886–887, 2004.

[45] A. K. H. Kwok, T. Y. Y. Lai, W. W. Y. Li, D. C. F. Woo, and N. R. Chan, "Indocyanine green-assisted internal limiting membrane removal in epiretinal membrane surgery: a clinical and histologic study," *American Journal of Ophthalmology*, vol. 138, no. 2, pp. 194–199, 2004.

[46] J. Lochhead, E. Jones, D. Chui et al., "Outcome of ICG-assisted ILM peel in macular hole surgery," *Eye*, vol. 18, no. 8, pp. 804–808, 2004.

[47] M. Maia, J. A. Haller, D. J. Pieramici et al., "Retinal pigment epithelial abnormalities after internal limiting membrane peeling guided by indocyanine green staining," *Retina*, vol. 24, no. 1, pp. 157–160, 2004.

[48] K. Kumagai, M. Furukawa, N. Ogino, A. Uemura, and E. Larson, "Long-term outcomes of internal limiting membrane peeling with and without indocyanine green in macular hole surgery," *Retina*, vol. 26, no. 6, pp. 613–617, 2006.

[49] E. H. Bovey, T. J. Wolfensberger, and M. Gonvers, "Staining of internal limiting membrane in vitreomacular surgery: a simplified technique," *Retina*, vol. 22, no. 4, pp. 498–499, 2002.

[50] J. C. Schmidt, E. B. Rodrigues, C. H. Meyer, S. Hoerle, and P. Kroll, "A modified technique to stain the internal limiting membrane with indocyanine green," *Ophthalmologica*, vol. 218, no. 3, pp. 176–179, 2004.

[51] H. Nakamura, K. Hayakawa, S. Sawaguchi, and T. Gaja, "Removal of retinal indocyanine green dye by autologous serum irrigation in macular hole surgery," *Retina*, vol. 25, no. 6, pp. 736–741, 2005.

[52] M. Facino, B. Mochi, S. Lai, and R. Terrile, "A simple way to prevent indocyanine green from entering the subretinal space during vitrectomy for retinal detachment due to myopic macular hole," *European Journal of Ophthalmology*, vol. 14, no. 3, pp. 269–271, 2004.

[53] J. L. Olson, A. V. On, and N. Mandava, "Protecting the retinal pigment epithelium during macular hole surgery," *Clinical and Experimental Ophthalmology*, vol. 33, no. 6, pp. 576–577, 2005.

[54] M. Cacciatori, M. Azzolini, M. Sborgia, M. Coppola, and V. de Molfetta, "Sodium hyaluronate 2.3% prevents contact between indocyanine green and retinal pigment epithelium during vitrectomy for highly myopic macular hole retinal detachment," *Retina*, vol. 24, no. 1, pp. 160–161, 2004.

[55] S. Kusaka, T. Oshita, M. Ohji, and Y. Tano, "Reduction of the toxic effect of indocyanine green on retinal pigment epithelium during macular hole surgery," *Retina*, vol. 23, no. 5, pp. 733–734, 2003.

[56] C. A. Gass, C. Haritoglou, M. Schaumberger, and A. Kampik, "Functional outcome of macular hole surgery with and without indocyanine green-assisted peeling of the internal limiting membrane," *Graefe's Archive for Clinical and Experimental Ophthalmology*, vol. 241, no. 9, pp. 716–720, 2003.

[57] N. Horio and M. Horiguchi, "Effect on visual outcome after macular hole surgery when staining the internal limiting membrane with indocyanine green dye," *Archives of Ophthalmology*, vol. 122, no. 7, pp. 992–996, 2004.

[58] H. Enaida, T. Sakamoto, T. Hisatomi, Y. Goto, and T. Ishibashi, "Morphological and functional damage of the retina caused by intravitreous indocyanine green in rat eyes," *Graefe's Archive for Clinical and Experimental Ophthalmology*, vol. 240, no. 3, pp. 209–213, 2002.

[59] C. Haritoglou, A. Gandorfer, C. A. Gass, and A. Kampik, "Histology of the vitreoretinal interface after staining of the internal limiting membrane using glucose 5% diluted indocyanine and infracyanine green," *American Journal of Ophthalmology*, vol. 137, no. 2, pp. 345–348, 2004.

[60] S. Wolf, U. Schnurbusch, P. Wiedemann, J. Grosche, A. Reichenbach, and H. Wolburg, "Peeling of the basal membrane in the human retina: ultrastructural effects," *Ophthalmology*, vol. 111, no. 2, pp. 238–243, 2004.

[61] T. Nakamura, T. Murata, T. Hisatomi et al., "Ultrastructure of the vitreoretinal interface following the removal of the internal limiting membrane using indocyanine green," *Current Eye Research*, vol. 27, no. 6, pp. 395–399, 2003.

[62] T. Sakamoto, K. Itaya, Y. Noda, and T. Ishibashi, "Retinal pigment epithelial changes after indocyanine green-assisted vitrectomy," *Retina*, vol. 22, no. 6, pp. 794–796, 2002.

[63] T. Kawaji, A. Hirata, Y. Inomata, T. Koga, and H. Tanihara, "Morphological damage in rabbit retina caused by subretinal injection of indocyanine green," *Graefe's Archive for Clinical and Experimental Ophthalmology*, vol. 242, no. 2, pp. 158–164, 2004.

[64] M. Maia, L. Kellner, E. de Juan Jr. et al., "Effects of indocyanine green injection on the retinal surface and into the subretinal space in rabbits," *Retina*, vol. 24, no. 1, pp. 80–91, 2004.

[65] M. P. Czajka, B. W. McCuen II, T. J. Cummings, H. Nguyen, S. Stinnett, and F. Wong, "Effects of indocyanine green on the retina and retinal pigment epithelium in a porcine model of retinal hole," *Retina*, vol. 24, no. 2, pp. 275–282, 2004.

[66] W.-C. Wu, D.-N. Hu, and J. E. Roberts, "Phototoxicity of indocyanine green on human retinal pigment epithelium in vitro and its reduction by lutein," *Photochemistry and Photobiology*, vol. 81, no. 3, pp. 537–540, 2005.

[67] A. Gandorfer, C. Haritoglou, A. Gandorfer, and A. Kampik, "Retinal damage from indocyanine green in experimental macular surgery," *Investigative Ophthalmology and Visual Science*, vol. 44, no. 1, pp. 316–323, 2003.

[68] H.-F. Yam, A. K.-H. Kwok, K.-P. Chan et al., "Effect of indocyanine green and illumination on gene expression in human retinal pigment epithelial cells," *Investigative Ophthalmology & Visual Science*, vol. 44, no. 1, pp. 370–377, 2003.

[69] J.-D. Ho, H.-C. Chen, S.-N. Chen, and R. J.-F. Tsai, "Reduction of indocyanine green-associated photosensitizing toxicity in retinal pigment epithelium by sodium elimination," *Archives of Ophthalmology*, vol. 122, no. 6, pp. 871–878, 2004.

[70] C. Haritoglou, A. Gandorfer, M. Schaumberger, R. Tadayoni, A. Gandorfer, and A. Kampik, "Light-absorbing properties and osmolarity of indocyanine-green depending on concentration and solvent medium," *Investigative Ophthalmology and Visual Science*, vol. 44, no. 6, pp. 2722–2729, 2003.

[71] C. Haritoglou, S. Priglinger, A. Gandorfer, U. Welge-Lussen, and A. Kampik, "Histology of the vitreoretinal interface after indocyanine green staining of the ILM, with illumination using a halogen and xenon light source," *Investigative Ophthalmology & Visual Science*, vol. 46, no. 4, pp. 1468–1472, 2005.

[72] F. Ando, O. Yasui, H. Hirose, and N. Ohba, "Optic nerve atrophy after vitrectomy with indocyanine green-assisted internal limiting membrane peeling in diffuse diabetic macular edema," *Graefe's Archive for Clinical and Experimental Ophthalmology*, vol. 242, no. 12, pp. 995–999, 2004.

[73] C. Haritoglou, A. Gandorfer, C. A. Gass, M. Schaumberger, M. W. Ulbig, and A. Kampik, "The effect of indocyanine-green on functional outcome of macular pucker surgery," *American Journal of Ophthalmology*, vol. 135, no. 3, pp. 328–337, 2003.

[74] T. Yamashita, A. Uemura, H. Kita, and T. Sakamoto, "Analysis of the retinal nerve fiber layer after indocyanine green-assisted vitrectomy for idiopathic macular holes," *Ophthalmology*, vol. 113, no. 2, pp. 280–284, 2006.

[75] A. Iriyama, S. Uchida, Y. Yanagi et al., "Effects of indocyanine green on retinal ganglion cells," *Investigative Ophthalmology & Visual Science*, vol. 45, no. 3, pp. 943–947, 2004.

[76] A. W. A. Weinberger, B. Kirchhof, B. E. Mazinani, and N. F. Schrage, "Persistent indocyanine green (ICG) fluorescence 6 weeks after intraocular ICG administration for macular hole surgery," *Graefe's Archive for Clinical and Experimental Ophthalmology*, vol. 239, no. 5, pp. 388–390, 2001.

[77] A. P. Ciardella, W. Schiff, G. Barile et al., "Persistent indocyanine green fluorescence after vitrectomy for macular hole," *The American Journal of Ophthalmology*, vol. 136, no. 1, pp. 174–177, 2003.

[78] J. Zhang, L. Lu, Y. Li, S. Li, and X. Huang, "Observation of persistent fundus autofluorescence after internal limiting membrane peeling assisted by indocyanine green solution of different concentrations," *Eye Science*, vol. 26, no. 1, pp. 44–47, 2011.

[79] T. L. Kersey, A. Bolton, and C. K. Patel, "Serial autofluorescence imaging over two years following indocyanine green-assisted internal limiting membrane peel for macular hole," *Clinical & Experimental Ophthalmology*, vol. 33, no. 5, pp. 538–539, 2005.

[80] H. Nakamura, K. Hayakawa, A. Imaizumi, M. Sakai, and S. Sawaguchi, "Persistence of retinal indocyanine green dye following vitreous surgery," *Ophthalmic Surgery Lasers and Imaging*, vol. 36, no. 1, pp. 37–45, 2005.

[81] C. Lüke, M. Lüke, T. S. Dietlein et al., "Retinal tolerance to dyes," *British Journal of Ophthalmology*, vol. 89, no. 9, pp. 1188–1191, 2005.

[82] S. Grisanti, P. Szurman, F. Gelisken, S. Aisenbrey, J. Oficjalska-Mlynczak, and K. U. Bartz-Schmidt, "Histological findings in experimental macular surgery with indocyanine green," *Investigative Ophthalmology & Visual Science*, vol. 45, no. 1, pp. 282–286, 2004.

[83] A. Hirata, N. Yonemura, T. Hasumura, Y. Murata, and A. Negi, "Effect of infusion air pressure on visual field defects after macular hole surgery," *American Journal of Ophthalmology*, vol. 130, no. 5, pp. 611–616, 2000.

[84] H. C. Boldt, P. M. Munden, J. C. Folk, and M. G. Mehaffey, "Visual field defects after macular hole surgery," *The American Journal of Ophthalmology*, vol. 122, no. 3, pp. 371–381, 1996.

[85] T. Hasumura, N. Yonemura, A. Hirata, Y. Murata, and A. Negi, "Retinal damage by air infusion during vitrectomy in rabbit eyes," *Investigative Ophthalmology & Visual Science*, vol. 41, no. 13, pp. 4300–4304, 2000.

[86] A. P. Da Mata, S. E. Burk, R. E. Foster et al., "Long-term follow-up of indocyanine green-assisted peeling of the retinal internal limiting membrane during vitrectomy surgery for idiopathic macular hole repair," *Ophthalmology*, vol. 111, no. 12, pp. 2246–2253, 2004.

[87] P. Stalmans, E. H. van Aken, M. Veckeneer, E. J. Feron, and I. Stalmans, "Toxic effect of indocyanine green on retinal pigment epithelium related to osmotic effects of the solvent," *American Journal of Ophthalmology*, vol. 134, no. 2, pp. 282–285, 2002.

[88] M. Ullern, S. Roman, J.-F. Dhalluin et al., "Contribution of intravitreal infracyanine green to macular hole and epimacular membrane surgery: preliminary study," *Journal Français d'Ophtalmologie*, vol. 25, no. 9, pp. 915–920, 2002.

[89] K. Rivett, L. Kruger, and S. Radloff, "Infracyanine-assisted internal limiting membrane peeling in macular hole repair: does it make a difference?" *Graefe's Archive for Clinical and Experimental Ophthalmology*, vol. 242, no. 5, pp. 393–396, 2004.

[90] A. van de Moere and P. Stalmans, "Anatomical and visual outcome of macular hole surgery with infracyanine green-assisted peeling of the internal limiting membrane, endodrainage, and silicone oil tamponade," *American Journal of Ophthalmology*, vol. 136, no. 5, pp. 879–887, 2003.

[91] P. Lanzetta, A. Polito, M. Del Borrello et al., "Idiopathic macular hole surgery with low-concentration infracyanine green-assisted peeling of the internal limiting membrane," *American Journal of Ophthalmology*, vol. 142, no. 5, pp. 771.e2–776.e2, 2006.

[92] A. Husson-Danan, A. Glacet-Bernard, G. Soubrane, and G. Coscas, "Clinical evaluation of the use of indocyanine green for peeling the internal limiting membrane in macular hole surgery," *Graefe's Archive for Clinical and Experimental Ophthalmology*, vol. 244, no. 3, pp. 291–297, 2006.

[93] E. C. La Heij, S. C. Dieudonné, C. M. Mooy et al., "Immunohistochemical analysis of the internal limiting membrane peeled with infracyanine green," *American Journal of Ophthalmology*, vol. 140, no. 6, pp. 1123–1125, 2005.

[94] C. Haritoglou, S. Priglinger, A. Gandorfer, U. Welge-Lussen, and A. Kampik, "Histology of the vitreoretinal interface after indocyanine green staining of the ILM, with illumination using a halogen and xenon light source," *Investigative Ophthalmology and Visual Science*, vol. 46, no. 4, pp. 1468–1472, 2005.

[95] T. L. Jackson, B. Vote, B. C. Knight, A. El-Amir, M. R. Stanford, and J. Marshall, "Safety testing of infracyanine green using

retinal pigment epithelium and glial cell cultures," *Investigative Ophthalmology and Visual Science*, vol. 45, no. 10, pp. 3697–3703, 2004.

[96] M. S. Norn, "Vital staining of corneal endothelium in cataract extraction," *Acta Ophthalmologica*, vol. 49, no. 5, pp. 725–733, 1971.

[97] G. R. J. Melles, P. W. T. de Waard, J. H. Pameyer, and W. H. Beekhuis, "Trypan blue capsule staining to visualize the capsulorhexis in cataract surgery," *Journal of Cataract and Refractive Surgery*, vol. 25, no. 1, pp. 7–9, 1999.

[98] F. A. Teba, A. Mohr, C. Eckardt et al., "Trypan blue staining in vitreoretinal surgery," *Ophthalmology*, vol. 110, no. 12, pp. 2409–2412, 2003.

[99] A. Gandorfer, C. Haritoglou, and A. Kampik, "Staining of the ILM in macular surgery," *British Journal of Ophthalmology*, vol. 87, no. 12, article 1530, 2003.

[100] C. Haritoglou, K. Eibl, M. Schaumberger et al., "Functional outcome after trypan blue-assisted vitrectomy for macular pucker: a prospective, randomized, comparative trial," *American Journal of Ophthalmology*, vol. 138, no. 1, pp. 1–5, 2004.

[101] A. K. H. Kwok, T. Y. Y. Lai, W. W. Y. Li, D. T. W. Yew, and V. W. Y. Wong, "Trypan blue- and indocyanine green-assisted epiretinal membrane surgery: clinical and histopathological studies," *Eye*, vol. 18, no. 9, pp. 882–888, 2004.

[102] S. Balayre, M. Boissonnot, L. Curutchet, and P. Dighiero, "Role of trypan blue in epiretinal membrane surgery," *Journal Francais d'Ophtalmologie*, vol. 28, no. 3, pp. 290–297, 2005.

[103] K. Li, D. Wong, P. Hiscott, P. Stanga, C. Groenewald, and J. McGalliard, "Trypan blue staining of internal limiting membrane and epiretinal membrane during vitrectomy: visual results and histopathological findings," *British Journal of Ophthalmology*, vol. 87, no. 2, pp. 216–219, 2003.

[104] E. Pel-Przybyszewska, E. Szkudlarek, A. Szkudlarek, and J. Nawrocki, "Trypan blue staining in treatment of macular hole," *Klinika Oczna*, vol. 106, supplement 3, pp. 503–505, 2004.

[105] K. L. Lee, S. Dean, and S. Guest, "A comparison of outcomes after indocyanine green and trypan blue assisted internal limiting membrane peeling during macular hole surgery," *British Journal of Ophthalmology*, vol. 89, no. 4, pp. 420–424, 2005.

[106] E. J. Feron, M. Veckeneer, R. Parys-Van Ginderdeuren, A. Van Lommel, G. R. J. Melles, and P. Stalmans, "Trypan blue staining of epiretinal membranes in proliferative vitreoretinopathy," *Archives of Ophthalmology*, vol. 120, no. 2, pp. 141–144, 2002.

[107] S. Balayre, M. Boissonnot, J. Paquereau, and P. Dighiero, "Evaluation of trypan blue toxicity in idiopathic epiretinal membrane surgery with macular function test using multifocal electroretinography: seven prospective case studies," *Journal Français d'Ophtalmologie*, vol. 28, no. 2, pp. 169–176, 2005.

[108] C. Haritoglou, A. Gandorfer, M. Schaumberger et al., "Trypan blue in macular pucker surgery: an evaluation of histology and functional outcome," *Retina*, vol. 24, no. 4, pp. 582–590, 2004.

[109] N. Yamamoto, N. Ozaki, and K. Murakami, "Double visualization using triamcinolone acetonide and trypan blue during stage 3 macular hole surgery," *Ophthalmologica*, vol. 218, no. 5, pp. 297–305, 2004.

[110] E. B. Rodrigues, C. H. Meyer, J. C. Schmidt, and P. Kroll, "Trypan blue stains the epiretinal membrane but not the internal limiting membrane," *British Journal of Ophthalmology*, vol. 87, no. 11, pp. 1431–1432, 2003.

[111] D. Shukla, J. Kalliath, N. Neelakantan, K. B. Naresh, and K. Ramasamy, "A comparison of brilliant blue G, trypan blue, and indocyanine green dyes to assist internal limiting membrane peeling during macular hole surgery," *Retina*, vol. 31, no. 10, pp. 2021–2025, 2011.

[112] G. Rebolleda, F. J. Munoz Negrete, and M. Suarez-Figueroa, "Trypan blue staining in vitreoretinal surgery," *Ophthalmology*, vol. 111, pp. 1622–1623, 2004.

[113] L. Kodjikian, T. Richter, M. Halberstadt et al., "Toxic effects of indocyanine green, infracyanine green, and trypan blue on the human retinal pigmented epithelium," *Graefe's Archive for Clinical and Experimental Ophthalmology*, vol. 243, no. 9, pp. 917–925, 2005.

[114] M. Veckeneer, K. Van Overdam, J. Monzer et al., "Ocular toxicity study of trypan blue injected into the vitreous cavity of rabbit eyes," *Graefe's Archive for Clinical and Experimental Ophthalmology*, vol. 239, no. 9, pp. 698–704, 2001.

[115] Y. Jin, S. Uchida, Y. Yanagi, M. Aihara, and M. Araie, "Neurotoxic effects of trypan blue on rat retinal ganglion cells," *Experimental Eye Research*, vol. 81, no. 4, pp. 395–400, 2005.

[116] Y. Tano, D. Chandler, and R. Machemer, "Treatment of intraocular proliferation with intravitreal injection of triamcinolone acetonide," *American Journal of Ophthalmology*, vol. 90, no. 6, pp. 810–816, 1980.

[117] G. A. Peyman, R. Cheema, M. D. Conway, and T. Fang, "Triamcinolone acetonide as an aid to visualization of the vitreous and the posterior hyaloid during pars plana vitrectomy," *Retina*, vol. 20, no. 5, pp. 554–555, 2000.

[118] T. Sakamoto, M. Miyazaki, T. Hisatomi et al., "Triamcinolone-assisted pars plana vitrectomy improves the surgical procedures and decreases the postoperative blood-ocular barrier breakdown," *Graefe's Archive for Clinical and Experimental Ophthalmology*, vol. 240, no. 6, pp. 423–429, 2002.

[119] S. E. Burk, A. P. Da Mata, M. E. Snyder, S. Schneider, R. H. Osher, and R. J. Cionni, "Visualizing vitreous using Kenalog suspension," *Journal of Cataract and Refractive Surgery*, vol. 29, no. 4, pp. 645–651, 2003.

[120] N. Yamamoto, N. Ozaki, and K. Murakami, "Triamcinolone acetonide facilitates removal of the epiretinal membrane and separation of the residual vitreous cortex in highly myopic eyes with retinal detachment due to a macular hole," *Ophthalmologica*, vol. 218, no. 4, pp. 248–256, 2004.

[121] E. A. Fraser, R. A. Cheema, and M. A. Roberts, "Triamcinolone acetonide-assisted peeling of retinal internal limiting membrane for macular surgery," *Retina*, vol. 23, no. 6, pp. 883–884, 2003.

[122] N. Horio, M. Horiguchi, and N. Yamamoto, "Triamcinolone-assisted internal limiting membrane peeling during idiopathic macular hole surgery," *Archives of Ophthalmology*, vol. 123, no. 1, pp. 96–99, 2005.

[123] C. Haritoglou and A. Kampik, "Staining techniques in macula surgery," *Ophthalmologe*, vol. 103, no. 11, pp. 927–934, 2006.

[124] M. Karacorlu, H. Ozdemir, and S. A. Karacorlu, "Does intravitreal triamcinolone acetonide-assisted peeling of the internal limiting membrane effect the outcome of macular hole surgery?" *Graefe's Archive for Clinical and Experimental Ophthalmology*, vol. 243, no. 8, pp. 754–757, 2005.

[125] G. K. Shah, B. J. Rosenblatt, and M. Smith, "Internal limiting membrane peeling using triamcinolone acetonide: histopathologic confirmation," *American Journal of Ophthalmology*, vol. 138, no. 4, pp. 656–657, 2004.

[126] S. M. Couch and S. Bakri, "Use of triamcinolone during vitrectomy surgery to visualize membranes and vitreous," *Clinical Ophthalmology*, vol. 2, no. 4, pp. 891–896, 2008.

[127] D. Tognetto, S. Zenoni, G. Sanguinetti, C. Haritoglou, and G. Ravalico, "Staining of the internal limiting membrane with intravitreal triamcinolone acetonide," *Retina*, vol. 25, no. 4, pp. 462–467, 2005.

[128] J. García-Arumí, A. Boixadera, J. Giralt et al., "Comparison of different techniques for purification of triamcinolone acetonide suspension for intravitreal use," *British Journal of Ophthalmology*, vol. 89, no. 9, pp. 1112–1114, 2005.

[129] J. K. Challa, M. C. Gillies, P. L. Penfold, J. F. Gyory, A. B. L. Hunyor, and F. A. Billson, "Exudative macular degeneration and intravitreal triamcinolone: 18 month follow up," *Australian and New Zealand Journal of Ophthalmology*, vol. 26, no. 4, pp. 277–281, 1998.

[130] S. Young, G. Larkin, M. Branley, and S. Lightman, "Safety and efficacy of intravitreal triamcinolone for cystoid macular oedema in uveitis," *Clinical and Experimental Ophthalmology*, vol. 29, no. 1, pp. 2–6, 2001.

[131] M. S. Benz, T. G. Murray, S. R. Dubovy, R. S. Katz, and C. W. G. Eifrig, "Endophthalmitis caused by mycobacterium chelonae abscessus after intravitreal injection of triamcinolone," *Archives of Ophthalmology*, vol. 121, no. 2, pp. 271–273, 2003.

[132] H. Enaida, T. Hisatomi, Y. Hata et al., "Brilliant blue G selectively stains the internal limiting membrane/brilliant blue G-assisted membrane peeling," *Retina*, vol. 26, no. 6, pp. 631–636, 2006.

[133] J. Lüke, I. Lüdeke, A. Acksteiner et al., "Morphological and functional outcome after brilliant blue G-assisted macular hole surgery," *Ophthalmologica*, vol. 230, no. 2, pp. 81–86, 2013.

[134] M. Remy, S. Thaler, R. G. Schumann et al., "An in vivo evaluation of Brilliant Blue G in animals and humans," *British Journal of Ophthalmology*, vol. 92, no. 8, pp. 1142–1147, 2008.

[135] D. E. Pelayes, F. Kuhn, A. M. Folgar et al., "Staining of the internal limiting membrane with the use of heavy brilliant blue G," *Ophthalmic Research*, vol. 48, supplement 1, pp. 21–25, 2012.

[136] H. Shimada, H. Nakashizuka, T. Hattori, R. Mori, Y. Mizutani, and M. Yuzawa, "Double staining with brilliant blue G and double peeling for epiretinal membranes," *Ophthalmology*, vol. 116, no. 7, pp. 1370–1376, 2009.

[137] A. Mohr, M. Bruinsma, S. Oellerich, H. Frank, D. Gabel, and G. R. J. Melles, "Dyes for eyes: hydrodynamics, biocompatibility and efficacy of 'Heavy' (dual) dyes for chromovitrectomy," *Ophthalmologica*, vol. 230, no. 2, pp. 51–58, 2013.

[138] M. Veckeneer, A. Mohr, E. Alharthi et al., "Novel 'heavy' dyes for retinal membrane staining during macular surgery: multicenter clinical assessment," *Acta Ophthalmologica*, vol. 92, no. 4, pp. 339–344, 2014.

[139] S. Mennel, C. H. Meyer, J. C. Schmidt, S. Kaempf, and G. Thumann, "Trityl dyes patent blue V and brilliant blue G—clinical relevance and in vitro analysis of the function of the outer blood-retinal barrier," *Developments in Ophthalmology*, vol. 42, pp. 101–114, 2008.

[140] S. Mennel, C. H. Meyer, A. Tietjen, E. B. Rodrigues, and J. C. Schmidt, "Patent blue: a novel vital dye in vitreoretinal surgery," *Ophthalmologica*, vol. 220, no. 3, pp. 190–193, 2006.

[141] S. A. Madreperla, G. L. Geiger, M. Funata, Z. De la Cruz, and W. R. Green, "Clinicopathologic correlation of a macular hole treated by cortical vitreous peeling and gas tamponade," *Ophthalmology*, vol. 101, no. 4, pp. 682–686, 1994.

[142] J. D. M. Gass, "Reappraisal of biomicroscopic classification of stages of development of a macular hole," *American Journal of Ophthalmology*, vol. 119, no. 6, pp. 752–759, 1995.

[143] R. Uemoto, S. Yamamoto, and S. Takeuchi, "Epimacular proliferative response following internal limiting membrane peeling for idiopathic macular holes," *Graefe's Archive for Clinical and Experimental Ophthalmology*, vol. 242, no. 2, pp. 177–180, 2004.

[144] M. Lai, S. Tang, J. Li, X. Liu, Y. Ling, and X. Zheng, "Observation of early closure of idiopathic macular hole after vitrectomy surgery with internal limiting membrane peeling," *Yan Ke Xue Bao*, vol. 20, no. 2, pp. 93–97, 2004.

[145] R. Tadayoni, A. Gaudric, B. Haouchine, and P. Massin, "Relationship between macular hole size and the potential benefit of internal limiting membrane peeling," *British Journal of Ophthalmology*, vol. 90, no. 10, pp. 1239–1241, 2006.

[146] J. C. Wickens and G. K. Shah, "Outcomes of macular hole surgery and shortened face down positioning," *Retina*, vol. 26, no. 8, pp. 902–904, 2006.

[147] K. Spiteri Cornish, N. Lois, N. Scott et al., "Vitrectomy with internal limiting membrane (ILM) peeling versus vitrectomy with no peeling for idiopathic full-thickness macular hole (FTMH)," *The Cochrane Database of Systematic Reviews*, vol. 6, Article ID CD009306, 2013.

[148] K. Sayanagi, Y. Ikuno, and Y. Tano, "Tractional internal limiting membrane detachment in highly myopic eyes," *The American Journal of Ophthalmology*, vol. 142, no. 5, pp. 850–852, 2006.

[149] J. García-Arumí, V. Martinez, J. Puig, and B. Corcostegui, "The role of vitreoretinal surgery in the management of myopic macular hole without retinal detachment," *Retina*, vol. 21, no. 4, pp. 332–338, 2001.

[150] K. Kadonosono, F. Yazama, N. Itoh et al., "Treatment of retinal detachment resulting from myopic macular hole with internal limiting membrane removal," *The American Journal of Ophthalmology*, vol. 131, no. 2, pp. 203–207, 2001.

[151] K. K. W. Li, E. W. H. Tang, P. S. H. Li, and D. Wong, "Double peel using triamcinolone acetonide and trypan blue in the management of myopic macular hole with retinal detachment: a case-control study," *Clinical & Experimental Ophthalmology*, vol. 38, no. 7, pp. 664–668, 2010.

[152] M. M. Lai, M. M. Joshi, and M. T. Trese, "Spontaneous resolution of traumatic macular hole-related retinal detachment," *American Journal of Ophthalmology*, vol. 141, no. 6, pp. 1148–1151, 2006.

[153] J. Wachtlin, C. Jandeck, S. Potthöfer, U. Kellner, and M. H. Foerster, "Long-term results following pars plana vitrectomy with platelet concentrate in pediatric patients with traumatic macular hole," *The American Journal of Ophthalmology*, vol. 136, no. 1, pp. 197–199, 2003.

[154] U. Mester and R. Grewing, "Vitrectomy in the treatment of epimacular membranes (macular pucker)," *Klinika Oczna*, vol. 92, no. 1-2, pp. 1–2, 1990.

[155] C. J. Pournaras, G. Donati, P. D. Brazitikos, A. D. Kapetanios, D. L. Dereklis, and N. T. Stangos, "Macular epiretinal membranes," *Seminars in Ophthalmology*, vol. 15, no. 2, pp. 100–107, 2000.

[156] R. Grewing and U. Mester, "Results of surgery for epiretinal membranes and their recurrences," *British Journal of Ophthalmology*, vol. 80, no. 4, pp. 323–326, 1996.

[157] R. G. Schumann, A. Gandorfer, K. H. Eibl, P. B. Henrich, A. Kampik, and C. Haritoglou, "Sequential epiretinal membrane removal with internal limiting membrane peeling in brilliant blue G-assisted macular surgery," *British Journal of Ophthalmology*, vol. 94, no. 10, pp. 1369–1372, 2010.

[158] A. K. H. Kwok, T. Y. Y. Lai, and K. S. C. Yuen, "Epiretinal membrane surgery with or without internal limiting membrane

peeling," *Clinical and Experimental Ophthalmology*, vol. 33, no. 4, pp. 379–385, 2005.

[159] L. Geerts, G. Pertile, W. van de Sompel, T. Moreels, and C. Claes, "Vitrectomy for epiretinal membranes: visual outcome and prognostic criteria," *Bulletin de la Societe Belge d'Ophtalmologie*, no. 293, pp. 7–15, 2004.

[160] T. Aboutable, "Is removal of internal limiting membrane always necessary during surgery for refractory diffuse diabetic macular edema without evident epimacular proliferation?" *Klinische Monatsblatter fur Augenheilkunde*, vol. 223, no. 8, pp. 681–686, 2006.

[161] C. H. Meyer, "Current treatment approaches in diabetic macular edema," *Ophthalmologica*, vol. 221, no. 2, pp. 118–131, 2007.

[162] K. L. Hartley, W. E. Smiddy, H. W. Flynn Jr., and T. G. Murray, "Pars plana vitrectomy with internal limiting membrane peeling for diabetic macular edema," *Retina*, vol. 28, no. 3, pp. 410–419, 2008.

[163] M.-H. Dehghan, M. Salehipour, J. Naghib, M. Babaeian, S. Karimi, and M. Yaseri, "Pars plana vitrectomy with internal limiting membrane peeling for refractory diffuse diabetic macular edema," *Journal of Ophthalmic and Vision Research*, vol. 5, no. 3, pp. 162–167, 2010.

[164] M. S. Mandelcorn and R. K. Nrusimhadevara, "Internal limiting membrane peeling for decompression of macular edema in retinal vein occlusion: a report of 14 cases," *Retina*, vol. 24, no. 3, pp. 348–355, 2004.

[165] D. H. Park and I. T. Kim, "Long-term effects of vitrectomy and internal limiting membrane peeling for macular edema secondary to central retinal vein occlusion and hemiretinal vein occlusion," *Retina*, vol. 30, no. 1, pp. 117–124, 2010.

[166] M. Raszewska-Steglinska, P. Gozdek, S. Cisiecki, Z. Michalewska, J. Michalewski, and J. Nawrocki, "Pars plana vitrectomy with ILM peeling for macular edema secondary to retinal vein occlusion," *European Journal of Ophthalmology*, vol. 19, no. 6, pp. 1055–1062, 2009.

[167] E. Stefánsson, "Ocular oxygenation and the treatment of diabetic retinopathy," *Survey of Ophthalmology*, vol. 51, no. 4, pp. 364–380, 2006.

[168] S. D. Pendergast, "Vitrectomy for diabetic macular edema associated with a taut premacular posterior hyaloid," *Current Opinion in Ophthalmology*, vol. 9, no. 3, pp. 71–75, 1998.

[169] T. Yamamoto, K. Hitani, Y. Sato, H. Yamashita, and S. Takeuchi, "Vitrectomy for diabetic macular edema with and without internal limiting membrane removal," *Ophthalmologica*, vol. 219, no. 4, pp. 206–213, 2005.

[170] Z. Michalewska, M. Bednarski, J. Michalewski, and N. Jerzy, "The role of ILM peeling in vitreous surgery for proliferative diabetic retinopathy complications," *Ophthalmic Surgery Lasers and Imaging Retina*, vol. 44, no. 3, pp. 238–242, 2013.

[171] A. Gandorfer and A. Kampik, "Pars plana vitrectomy with and without peeling of the inner limiting membrane (ILM) for diabetic macular edema," *Retina*, vol. 28, no. 1, pp. 187–189, 2008.

[172] K. Ishikawa, H. Terasaki, M. Mori, K. Sugita, and Y. Miyake, "Optical coherence tomography before and after vitrectomy with internal limiting membrane removal in a child with optic disc pit maculopathy," *Japanese Journal of Ophthalmology*, vol. 49, no. 5, pp. 411–413, 2005.

[173] A. Gandorfer, M. Rohleder, and A. Kampik, "Epiretinal pathology of vitreomacular traction syndrome," *British Journal of Ophthalmology*, vol. 86, no. 8, pp. 902–909, 2002.

[174] F. Kuhn, R. Morris, C. D. Witherspoon, and V. Mester, "Terson syndrome: results of vitrectomy and the significance of vitreous hemorrhage in patients with subarachnoid hemorrhage," *Ophthalmology*, vol. 105, no. 3, pp. 472–477, 1998.

[175] C. Aras, C. Arici, S. Akar et al., "Peeling of internal limiting membrane during vitrectomy for complicated retinal detachment prevents epimacular membrane formation," *Graefe's Archive for Clinical and Experimental Ophthalmology*, vol. 247, no. 5, pp. 619–623, 2009.

[176] F. Höhn, F. T. A. Kretz, and M. Pavlidis, "Primary vitrectomy with peeling of the internal limiting membrane under decaline: a promising surgical maneuver for treatment of total and subtotal retinal detachment," *Ophthalmologe*, vol. 111, no. 9, pp. 882–886, 2014.

[177] S. Dithmar, S. Pollithy, and T. Ach, "Disappearance of central confluent soft drusen following vitrectomy and ILM peeling," *Eye*, vol. 27, no. 6, pp. 779–781, 2013.

[178] R. G. Michels and S. J. Ryan Jr., "Results and complications of 100 consecutive cases of pars plana vitrectomy," *American Journal of Ophthalmology*, vol. 80, no. 1, pp. 24–29, 1975.

[179] A. Pielen, N. I. P. Guerra, D. Böhringer et al., "Intra- and postoperative risks and complications of small-gauge (23-G) versus conventional (20-G) vitrectomy for macular surgery," *European Journal of Ophthalmology*, vol. 24, no. 5, pp. 778–785, 2014.

[180] C. C. Gottlieb and J. A. Martin, "Phacovitrectomy with internal limiting membrane peeling for idiopathic macular hole," *Canadian Journal of Ophthalmology*, vol. 37, no. 5, pp. 277–282, 2002.

[181] C. Haritoglou, I. W. Reiniger, M. Schaumberger, C. A. Gass, S. G. Priglinger, and A. Kampik, "Five-year follow-up of macular hole surgery with peeling of the internal limiting membrane: update of a prospective study," *Retina*, vol. 26, no. 6, pp. 618–622, 2006.

[182] T. G. Sheidow, K. J. Blinder, N. Holekamp et al., "Outcome results in macular hole surgery: an evaluation of internal limiting membrane peeling with and without indocyanine green," *Ophthalmology*, vol. 110, no. 9, pp. 1697–1701, 2003.

[183] Y. Hasegawa, F. Okamoto, Y. Sugiura, Y. Okamoto, T. Hiraoka, and T. Oshika, "Intraocular pressure elevation after vitrectomy for various vitreoretinal disorders," *European Journal of Ophthalmology*, vol. 24, no. 2, pp. 235–241, 2013.

[184] A. P. Costarides, P. Alabata, and C. Bergstrom, "Elevated intraocular pressure following vitreoretinal surgery," *Ophthalmology Clinics of North America*, vol. 17, no. 4, pp. 507–512, 2004.

[185] R. H. Roe, H. R. McDonald, A. D. Fu et al., "Unexplained vision loss following removal of epiretinal membrane," *British Journal of Ophthalmology*, vol. 94, no. 8, pp. 1033–1039, 2010.

[186] C. A. Gass, C. Haritoglou, E. M. Messmer, M. Schaumberger, and A. Kampik, "Peripheral visual field defects after macular hole surgery: a complication with decreasing incidence," *British Journal of Ophthalmology*, vol. 85, no. 5, pp. 549–551, 2001.

[187] G. T. Kokame, "Visual field defects after vitrectomy with fluid-air exchange," *The American Journal of Ophthalmology*, vol. 130, no. 5, pp. 653–654, 2000.

[188] D. W. Park, J. O. Sipperley, S. R. Sneed, P. U. Dugel, and J. Jacobsen, "Macular hole surgery with internal-limiting membrane peeling and intravitreous air," *Ophthalmology*, vol. 106, no. 7, pp. 1392–1398, 1999.

[189] Y. Sato and T. Isomae, "Macular hole surgery with internal limiting membrane removal, air tamponade, and 1-day prone positioning," *Japanese Journal of Ophthalmology*, vol. 47, no. 5, pp. 503–506, 2003.

[190] A. Van De Moere and P. Stalmans, "Anatomical and visual outcome of macular hole surgery with infracyanine green-assisted peeling of the internal limiting membrane, endodrainage, and silicone oil tamponade," *The American Journal of Ophthalmology*, vol. 136, no. 5, pp. 879–887, 2003.

[191] A. K. H. Kwok and T. Y. Y. Lai, "Internal limiting membrane removal in macular hole surgery for severely myopic eyes: a case-control study," *British Journal of Ophthalmology*, vol. 87, no. 7, pp. 885–889, 2003.

[192] K. Purtskhvanidze, F. Treumer, O. Junge, J. Hedderich, J. Roider, and J. Hillenkamp, "The long-term course of functional and anatomical recovery after macular hole surgery," *Investigative Ophthalmology and Visual Science*, vol. 54, no. 7, pp. 4882–4891, 2013.

[193] A. S. Banker, W. R. Freeman, J. W. Kim et al., "Vision-threatening complications of surgery for full-thickness macular holes," *Ophthalmology*, vol. 104, no. 9, pp. 1442–1453, 1997.

[194] A. Gandorfer, E. M. Messmer, M. W. Ulbig, and A. Kampik, "Resolution of diabetic macular edema after surgical removal of the posterior hyaloid and the inner limiting membrane," *Retina*, vol. 20, no. 2, pp. 126–133, 2000.

[195] C. Framme, S. Klotz, U. E. K. Wolf-Schnurrbusch, P. Wiedemann, and S. Wolf, "Intraocular pressure changes following 20G pars-plana vitrectomy," *Acta Ophthalmologica*, vol. 90, no. 8, pp. 744–749, 2012.

[196] P. C. Ho and F. I. Tolentino, "Bacterial endophthalmitis after closed vitrectomy," *Archives of Ophthalmology*, vol. 102, no. 2, pp. 207–210, 1984.

[197] V. P. Dave, A. Pathengay, S. G. Schwartz, and H. W. Flynn, "Endophthalmitis following pars plana vitrectomy: a literature review of incidence, causative organisms, and treatment outcomes," *Clinical Ophthalmology*, vol. 8, pp. 2183–2188, 2014.

[198] N. Nagai, S. Ishida, K. Shinoda, Y. Imamura, K. Noda, and M. Inoue, "Surgical effects and complications of indocyanine green-assisted internal limiting membrane peeling for idiopathic macular hole," *Acta Ophthalmologica Scandinavica*, vol. 85, no. 8, pp. 883–889, 2007.

[199] H. S. Walia, G. K. Shah, and S. M. Hariprasad, "ILM peeling a vital intervention for many vitreoretinal disorders," *Ophthalmic Surgery Lasers and Imaging Retina*, vol. 45, no. 2, pp. 92–96, 2014.

[200] F. Pichi, A. Lembo, M. Morara et al., "Early and late inner retinal changes after inner limiting membrane peeling," *International Ophthalmology*, vol. 34, no. 2, pp. 437–446, 2014.

[201] D. Tognetto, C. Haritoglou, A. Kampik, and G. Ravalico, "Macular edema and visual loss after macular pucker surgery with ICG-assisted internal limiting membrane peeling," *European Journal of Ophthalmology*, vol. 15, no. 2, pp. 289–291, 2005.

[202] M. Karacorlu, S. Karacorlu, and H. Ozdemir, "Iatrogenic punctate chorioretinopathy after internal limiting membrane peeling," *American Journal of Ophthalmology*, vol. 135, no. 2, pp. 178–182, 2003.

[203] R. Tadayoni, M. Paques, P. Massin, S. Mouki-Benani, J. Mikol, and A. Gaudric, "Dissociated optic nerve fiber layer appearance of the fundus after idiopathic epiretinal membrane removal," *Ophthalmology*, vol. 108, no. 12, pp. 2279–2283, 2001.

[204] H. Imai and K. Ohta, "Microperimetric determination of retinal sensitivity in areas of dissociated optic nerve fiber layer following internal limiting membrane peeling," *Japanese Journal of Ophthalmology*, vol. 54, no. 5, pp. 435–440, 2010.

[205] M. Alkabes, C. Salinas, L. Vitale, A. Burés-Jelstrup, P. Nucci, and C. Mateo, "En face optical coherence tomography of inner retinal defects after internal limiting membrane peeling for idiopathic macular hole," *Investigative Ophthalmology and Visual Science*, vol. 52, no. 11, pp. 8349–8355, 2011.

[206] R. F. Spaide, ""Dissociated optic nerve fiber layer appearance" after internal limiting membrane removal is inner retinal dimpling," *Retina*, vol. 32, no. 9, pp. 1719–1726, 2012.

[207] D. H. W. Steel, C. Dinah, M. Habib, and K. White, "ILM peeling technique influences the degree of a dissociated optic nerve fibre layer appearance after macular hole surgery," *Graefe's Archive for Clinical and Experimental Ophthalmology*, vol. 253, no. 5, pp. 691–698, 2015.

[208] Y. Mitamura and K. Ohtsuka, "Relationship of dissociated optic nerve fiber layer appearance to internal limiting membrane peeling," *Ophthalmology*, vol. 112, no. 10, pp. 1766–1770, 2005.

[209] D. Weinberger, H. Stiebel-Kalish, E. Priel, D. Barash, R. Axer-Siegel, and Y. Yassur, "Digital red-free photography for the evaluation of retinal blood vessel displacement in epiretinal membrane," *Ophthalmology*, vol. 106, no. 7, pp. 1380–1383, 1999.

[210] K. Kawano, Y. Ito, M. Kondo et al., "Displacement of foveal area toward optic disc after macular hole surgery with internal limiting membrane peeling," *Eye*, vol. 27, no. 7, pp. 871–877, 2013.

[211] A. L. Sabater, Á. Velázquez-Villoria, M. A. Zapata et al., "Evaluation of macular retinal ganglion cell-inner plexiform layer thickness after vitrectomy with internal limiting membrane peeling for idiopathic macular holes," *BioMed Research International*, vol. 2014, Article ID 458631, 8 pages, 2014.

[212] O. Sandali, M. El Sanharawi, E. Basli et al., "Paracentral retinal holes occurring after macular surgery: incidence, clinical features, and evolution," *Graefe's Archive for Clinical and Experimental Ophthalmology*, vol. 250, no. 8, pp. 1137–1142, 2012.

[213] A. Rubinstein, R. Bates, L. Benjamin, and A. Shaikh, "Iatrogenic eccentric full thickness macular holes following vitrectomy with ILM peeling for idiopathic macular holes," *Eye*, vol. 19, no. 12, pp. 1333–1335, 2005.

[214] T. C. Ho, C. M. Yang, J. S. Huang, C. H. Yang, and M. S. Chen, "Foveola nonpeeling internal limiting membrane surgery to prevent inner retinal damages in early stage 2 idiopathic macula hole," *Graefe's Archive for Clinical and Experimental Ophthalmology*, vol. 252, no. 10, pp. 1553–1560, 2014.

[215] J. Chung and R. Spaide, "Intraretinal silicone oil vacuoles after macular hole surgery with internal limiting membrane peeling," *The American Journal of Ophthalmology*, vol. 136, no. 4, pp. 766–767, 2003.

[216] S. Tatlipinar and N. M. Yenerel, "Microbubble in the hole: a rare cause of failed macular hole surgery?" *Retinal Cases and Brief Reports*, vol. 7, no. 2, pp. 150–151, 2013.

[217] S. Natarajan, H. B. Mehta, S. K. Mahapatra, and S. Sharma, "A rare case of choroidal neovascularization following macular hole surgery," *Graefe's Archive for Clinical and Experimental Ophthalmology*, vol. 244, no. 2, pp. 271–273, 2006.

[218] P. Rishi, M. Dhupper, and E. Rishi, "Can retinal microtrauma by internal limiting membrane peeling cause retinal angiomatosis proliferans?" *Oman Journal of Ophthalmology*, vol. 4, no. 3, pp. 144–146, 2011.

[219] H. Tabandeh and W. E. Smiddy, "Choroidal neovascularization following macular hole surgery," *Retina*, vol. 19, no. 5, pp. 414–417, 1999.

[220] K. Nakata, M. Ohji, Y. Ikuno, S. Kusaka, F. Gomi, and Y. Tano, "Sub-retinal hemorrhage during internal limiting membrane peeling for a macular hole," *Graefe's Archive for Clinical and Experimental Ophthalmology*, vol. 241, no. 7, pp. 582–584, 2003.

[221] A. K. H. Kwok, D. Y. L. Leung, C. Hon, and D. S. C. Lam, "Vision threatening vitreous haemorrhage after internal limiting membrane peeling in macular surgeries," *British Journal of Ophthalmology*, vol. 86, no. 12, pp. 1449–1450, 2002.

[222] V. Mester and F. Kuhn, "Internal limiting membrane removal in the management of full-thickness macular holes," *The American Journal of Ophthalmology*, vol. 129, no. 6, pp. 769–777, 2000.

[223] N. Lois, J. Burr, J. Norrie et al., "Internal limiting membrane peeling versus no peeling for idiopathic full-thickness macular hole: a pragmatic randomized controlled trial," *Investigative Ophthalmology and Visual Science*, vol. 52, no. 3, pp. 1586–1592, 2011.

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Clinical Study

Functional and Morphological Correlations before and after Video-Documented 23-Gauge Pars Plana Vitrectomy with Membrane and ILM Peeling in Patients with Macular Pucker

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Purpose. To assess functional and morphological alterations following video-documented surgery for epiretinal membranes. *Methods*. Forty-two patients underwent video-documented 23-gauge vitrectomy with peeling of epiretinal (ERM) and inner limiting membrane (ILM). Patient assessment was performed before and 3 and 6 months including best corrected visual acuity (BCVA), slit lamp biomicroscopy, SD-OCT, and central 2° and 18° microperimetry. In addition, all video-documented areas of peeling on the retinal surface were evaluated postoperatively using an additional focal 2° microperimetry. Retinal sensitivity and BCVA were correlated with morphological changes (EZ and ELM) in the foveal region and in regions of membrane peeling. *Results*. Overall, BCVA increased from 0.6 (±0.2) to 0.2 (±0.2) logMAR after 6 months with an increase in retinal sensitivity (17.9 ± 2.7 dB to 26.8 ± 3.1 dB, $p < 0.01$). We observed a significant correlation between the integrity of the EZ but not of the ELM and the retinal sensitivity, overall and in peeling areas ($p < 0.05$). However, no significant correlation between alterations in the area of peeling and overall retinal sensitivity regarding visual acuity gain could be observed after 6 months ($p > 0.05$). In contrast, overall postoperative retinal sensitivity was significantly decreased in patients with a visual acuity gain lower than 2 lines ($p < 0.05$) correlating with EZ defects seen in OCT. *Conclusions*. Mechanical trauma of epiretinal membrane and ILM peeling due to the use of intraocular forceps may affect the outer retinal structure. Nevertheless, these changes seem to have no significant impact on postoperative functional outcome.

1. Introduction

Epiretinal membrane (ERM) formation reflects a number of pathological changes occurring in vitreoretinal junctions. Retinal glial cells, fibrous astrocytes, and Müller cells proliferate and migrate from neurosensory retina, through surface and breaks of the internal limiting membrane (ILM). In most cases, the disease is idiopathic but it can also be seen in eyes following retinal surgery, like vitrectomy or extracapsular lens extraction, in uveitic eyes or following vascular retinal diseases [1–4]. The epiretinal membrane itself is defined as a fine, semitranslucent, nonvascular, fibrocellular membrane on the inner retinal surface along the ILM [1, 2, 5]. Affected patients may present with variable degrees of decrease in visual acuity (VA) and disturbing metamorphopsia or micropsia.

Pars plana vitrectomy with membrane peeling is the current standard treatment for surgical removal of ERM, with reported rates of visual improvement ranging between 67% and 82%. In addition, removing the ILM has been suggested as a measure to prevent cellular reproliferation. Furthermore, a number of recent reports are dealing with an interesting correlation of macular function and morphology using SD-OCT and microperimetry. Disruptions of the photoreceptor inner and outer segment band seem to be a potential predictor for poor visual recovery in eyes having undergone

macular surgery and some patients also seem to have paracentral microscotomas after membrane and ILM peeling. These findings were postulated to range between 16.6% and 56.2% [6–10].

However, the induction of a potential mechanical trauma by using end-gripping forceps in areas of epiretinal membrane and ILM peeling resulting in potential functional or morphological damage has not yet been addressed.

The aim of the present study was to analyze the correlation between morphological changes of the outer retina, such as EZ (ellipsoid zone) and ELM (external limiting membrane), and functional parameters, such as retinal sensitivity and visual acuity in the fovea and in the area of ERM and ILM peeling, whether the manual peeling using forceps during surgery has an influence on postoperative functional outcome or not. In order to be able to identify these specific areas all operations were video-documented.

2. Methods

2.1. Study Population and Surgical Approach. In this prospective, observational nonrandomized study, 42 eyes of 42 patients who were diagnosed with epiretinal membranes, but no other retinal diseases, were included. In all subjects 23-gauge pars plana vitrectomy with peeling of the ERM and ILM was performed at the Department of Ophthalmology, Ludwig Maximilians University of Munich, Germany, between July and December 2013. Patients were informed about the use of their data for this study prior to surgery. All patients suffered from a decrease in best corrected visual acuity (BCVA) below 20/30 Snellen. Furthermore, all patients suffered from visual symptoms like disturbing metamorphopsia and/or micropsia. Patients with severe refractive medium opacity, proliferative diabetic retinopathy, age related maculopathy, advanced glaucoma, history of uveitis, previous retinal surgery, and intravitreal injections were excluded. Standard 23-gauge pars plana vitrectomy was performed by two highly trained vitreoretinal surgeons (Anselm Kampik and Christos Haritoglou). In all cases heavy brilliant blue solution (Fluoron GmbH, Neu-Ulm, Germany) was applied for visualization of the ILM before or after ERM removal. The tissue was removed using end-gripping forceps.

Patients with relevant lens opacification (LOCS III with grade >3 of nuclear and/or cortical and/or posterior subcapsular opacification) underwent a combined surgery with cataract extraction and intraocular lens implantation. The surgery was documented on video in order to be able to postoperatively identify areas where peeling using end-gripping forceps was applied.

2.2. Patient Examination. All patients were assessed before surgery and 3 and 6 months after the intervention. Preoperatively, a complete medical and ophthalmic history was obtained. A detailed eye examination including measurement of BCVA, intraocular pressure, and slit lamp examination of the anterior segment, with documentation of lens opacities using the Lens Opacities Classification System III, thorough fundus examination by indirect binocular ophthalmoscopy, spectral-domain volume scan OCT (Heidelberg Engineering SD-OCT, Heidelberg, Germany) and central 2-degree and 18-degree microperimetry (MAIA, Ellex Medical Lasers Ltd., Adelaide, Australia) was performed at every visit. In addition, all video-documented areas of manipulation on the retinal surface using forceps were postoperatively evaluated using a focal 2° microperimetry at these areas (Figure 1). Morphological changes in the outer retina such as EZ and ELM were scored using a grading system (grades 0–2) already published in the literature [6, 11] and mean retinal thickness was analyzed with SD-OCT pre- and postoperatively. Briefly, in OCT measurements grade 0 was defined as an intact EZ/ELM junction, as seen by a continuous hyperreflective line, grade 1 showed a focal disruption of the EZ/ELM junction <200 microns in length, and grade 2 was documented as a disruption of the EZ/ELM junction of >200 microns in length. These morphological changes were then correlated with functional results, such as BCVA, expressed as a gain in lines, and mean retinal sensitivity measured by microperimetry.

The macular area was divided into 5 sectors as published previously (modified EDTRS grid) [6] in order to allow a reliable standardized examination and correlation of findings. Sector 1 was defined as the foveal area while the parafoveal area was divided into 4 quadrants labeled sectors 2–5.

Microperimetry was performed with the MAIA machine, which is a near-infrared, line scanning laser ophthalmoscope that incorporates a high frequency eye tracker and an automated macular perimeter to determine threshold sensitivity and fixation characteristics. The automated eye tracker locks onto the entire fundus image and captures fixation changes 25 times per second during testing. The system is using a 4-2-1-staircase strategy with a Goldmann III stimulus. Preoperatively we performed two tests, a 25-stimulus test covering two degrees of the foveal area and a 68-stimulus test covering 18 degrees of the whole macular center field. These two regions were reassessed 3 and 6 months postoperatively. In brief, a fundus image is taken every time a new baseline test is performed with the MAIA machine. A follow-up exam then repeats the baseline expert test by accurately remeasuring the same points while comparing anatomical significant landmarks to the baseline test. In addition, we performed a 25-stimulus test covering two degrees of all video-documented peeling areas to observe any changes in functional sensitivity in these areas during follow-up. Background luminance was set at 4 asb, the stimulus dynamic range was set up to 30 dB, and maximum luminance was 1000 asb.

For the SD-OCT analyses, a volume scan was performed in each observational time step. Five horizontal scans of the fovea and 22 horizontal scans of each parafoveal quadrant with a single scan distance of 11 microns were obtained and separately evaluated in the modified EDTRS grid to cover the areas where peeling of membranes was performed during surgery.

2.3. Statistical Analysis. BCVA was measured using a Snellen chart and converted to the logarithm of minimum angle of resolution (logMAR). The Mann-Whitney test was used to compare the statistical distribution of evaluated parameters. Fisher's exact test was used for categorical variable

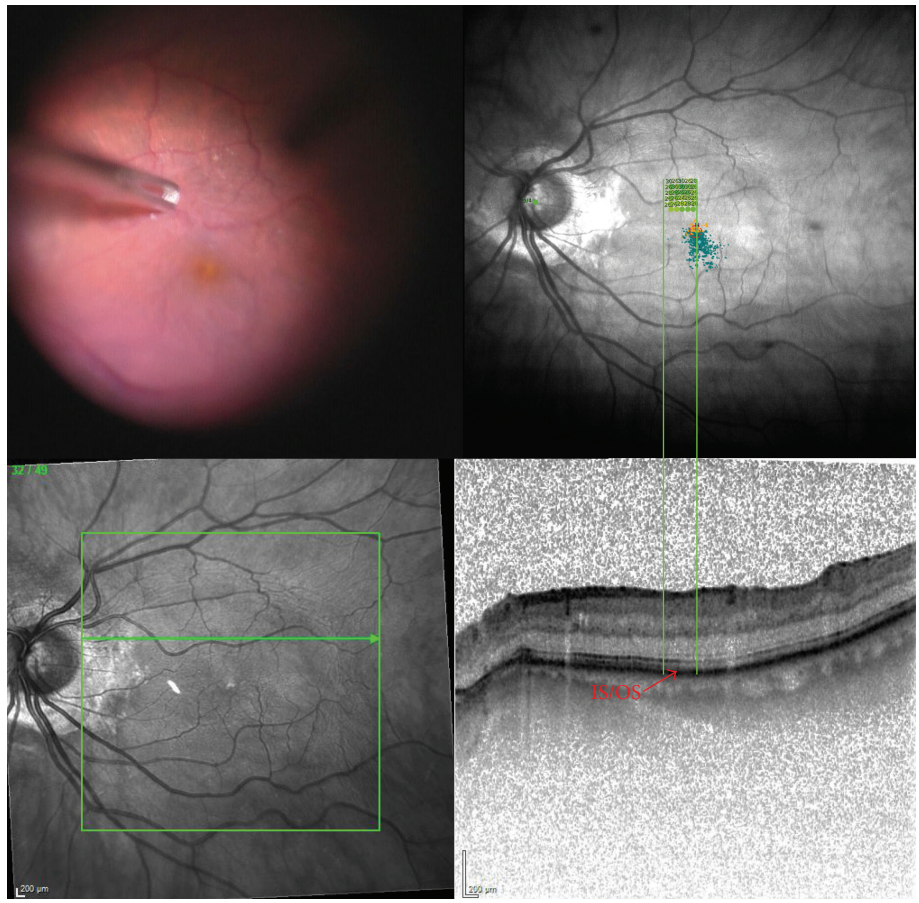

Figure 1: Example for a postoperative evaluation of a peeling area using microperimetry analysis and a matching SD-OCT scan: the integrated photoreceptor junction (IS/OS/ellipsoid zone, bottom right) correlates with a stable retinal sensitivity in this area (green microperimetry field, top right).

comparison. A change of BCVA of at least 2 Snellen lines was considered statistically significant. The mean retinal sensitivity of the fovea, overall and in areas of peeling, was correlated with mean SD-OCT grading (0–2). All analyses were conducted using SPSS statistics software (SPSS, Inc., Chicago, IL, USA). A p value < 0.05 was considered statistically significant. The impact of lens opacities on BCVA was analyzed using Lens Opacities Classification System III.

3. Results

The study population consisted of 20 males and 22 females with a mean age of 71 years (range of 45–86 years). In all eyes, epiretinal membranes were successfully removed. In 24 eyes with relevant lens opacification using LOCS III grading we performed combined cataract surgery and vitrectomy; 18 eyes were already pseudophakic. However, impact of lens opacity on BCVA was not significant between the combined surgery group and preoperative pseudophakic group ($p = 0.12$). The video documentation of all surgical procedures revealed that the surgeon made 3 to 8 (mean of 5.3) grasps with the end-gripping forceps at the retinal surface to remove epiretinal membranes and the ILM.

3.1. Overall Best Corrected Visual Acuity and Microperimetry Changes. The median preoperative BCVA was 0.6 (±0.2) logMAR. We encountered no postoperative complications in any of the cases, that is, endophthalmitis, retinal detachment, macular edema, or persisting or recurring ERM formation. Overall, 30 out of 42 patients showed an increase of more than two lines 6 months postoperatively. Mean overall macular sensitivity increased from preoperative 17.9 (±2.7) dB to postoperative 24.9 (±3.0) dB after 3 months and to 26.8 (±3.1) dB after 6 months. Mean macular sensitivity increased from preoperative 21.9 (±3.9) dB to postoperative 23.6 (±4.4) dB after 3 months and to 28.4 (±1.6) dB after 6 months in all areas where peeling was initiated (Table 1). Fixation stability increased from 79 (±10.1) percent to postoperative 89.5 (±9.2) percent after 3 months and 97.0 (±11.9) percent after 6 months (Table 1).

Patients with at least 2 Snellen lines BCVA improvement ($n = 30$) showed an increase of retinal sensitivity in microperimetry in all areas where peeling using end-gripping forceps was initiated during surgery, which was not statistically significant compared to retinal sensitivity in general ($p = 0.08$, Figure 2).

Table 1: Overall data assessment during 6-month follow-up.

Parameters ($n = 42$)	Baseline	3 months	6 months
BCVA (logMAR)	0.6 (±0.2)	0.3 (±0.3)	0.2 (±0.2)
Central retinal thickness (μm)	455.7 (±104.3)	379.1 (±53.3)	332.3 (±51.1)
Ellipsoid zone, foveal (grading, 0–2)	0.5 (±0.7)	0.3 (±0.5)	0.3 (±0.5)
Ellipsoid zone, area of peeling (grading, 0–2)	0.3 (±0.5)	0.1 (±0.4)	0.1 (±0.3)
Retinal sensitivity, foveal (dB, max. 30)	21.2 (±3.7)	22.5 (±2.6)	23.2 (±2.7)
Retinal sensitivity, overall (dB, max. 30)	17.9 (±2.7)	24.9 (±3.0)	26.8 (±3.1)
Retinal sensitivity, area of peeling (dB, max. 30)	21.9 (±3.9)	23.6 (±4.4)	28.4 (±1.6)
Fixation (%)	79 (±10.1)	89.5 (±9.2)	97.0 (±11.9)

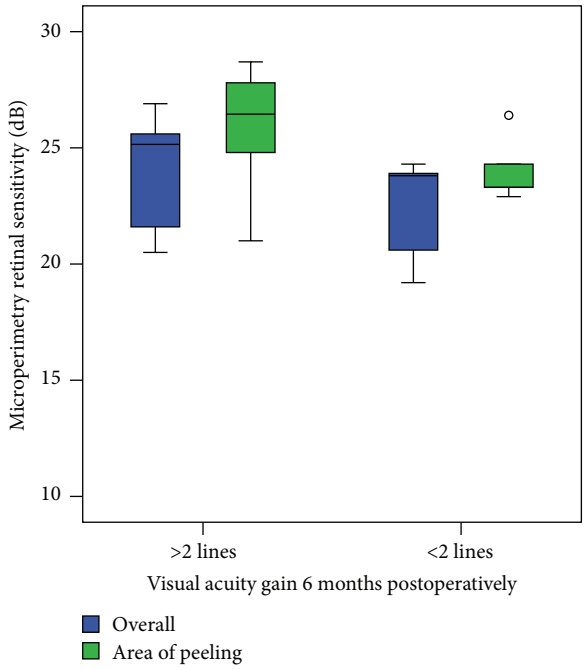

Figure 2: Mean retinal sensitivity in microperimetry measurements overall (18°, blue box) and areas of peeling (2°, green box) based on visual acuity gain 6 months postoperatively. No significant correlation between retinal sensitivity in areas of peeling and overall measurements ($p = 0.08$).

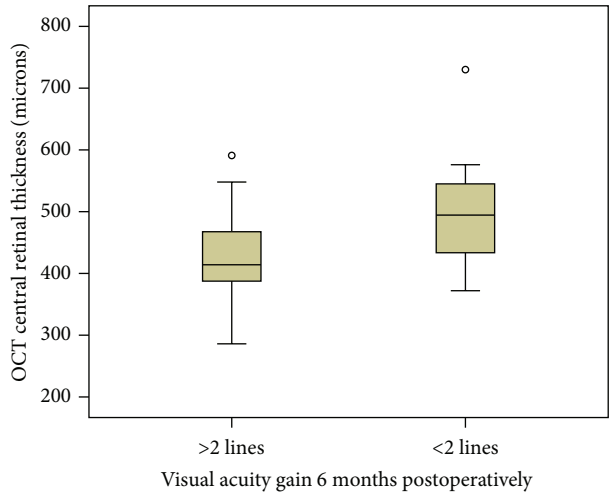

Figure 3: Comparison of preoperative mean central retinal thickness between patients with more than 2 lines ($n = 30$) and patients with less ($n = 12$) than 2 lines of visual acuity gain ($p < 0.05$).

3.2. OCT Findings. Central retinal thickness decreased from 455.7 (±104.3) microns to postoperative 379.1 (±53.3) microns after 3 months and to 332.3 (±51.1) microns after 6 months. We observed a significant correlation between preoperative central retinal thickness and the increase of BCVA. Patients with an increase of at least 2 Snellen lines ($n = 30$) had a significant thinner preoperative central retinal thickness ($p < 0.02$, Figure 3).

Eyes with a preoperative intact ellipsoid zone junction (grade 0) showed a greater improvement in BCVA compared to eyes with an irregular ellipsoid zone junction (grade 1) or disrupted ellipsoid zone junction (grade 2). However, this difference was not statistically significant, for both the foveal region and areas of documented peeling. Quite similar results were obtained for the ELM (Figures 4(a), 4(b), 5(a), and 5(b)).

We observed a significant correlation between EZ integrity and mean retinal sensitivity postoperatively, both overall and in areas where peeling using end-gripping forceps was initiated ($p < 0.05$, Figure 6). However, alterations in areas of peeling had no significant influence on gain in visual acuity ($p > 0.05$).

Furthermore, investigated OCT measurements in areas of peeling showed no worsening of preexisting outer retinal structure defects or new defects in a preexisting normal EZ and ELM band after surgical intervention.

4. Discussion

The current approach of correlating morphological alterations with functional ones in various macular diseases is to compare OCT scans with microperimetry patterns, not only in the foveal but also in the parafoveal area. Due to advances of newer OCT machines (high resolution, eye tracker, and fast scan mode) it is possible to evaluate the vitreomacular interface and outer retinal structures in more detail. Specifically, the EZ, formerly IS/OS, and the ELM have been thought to be of prognostic nature in case of

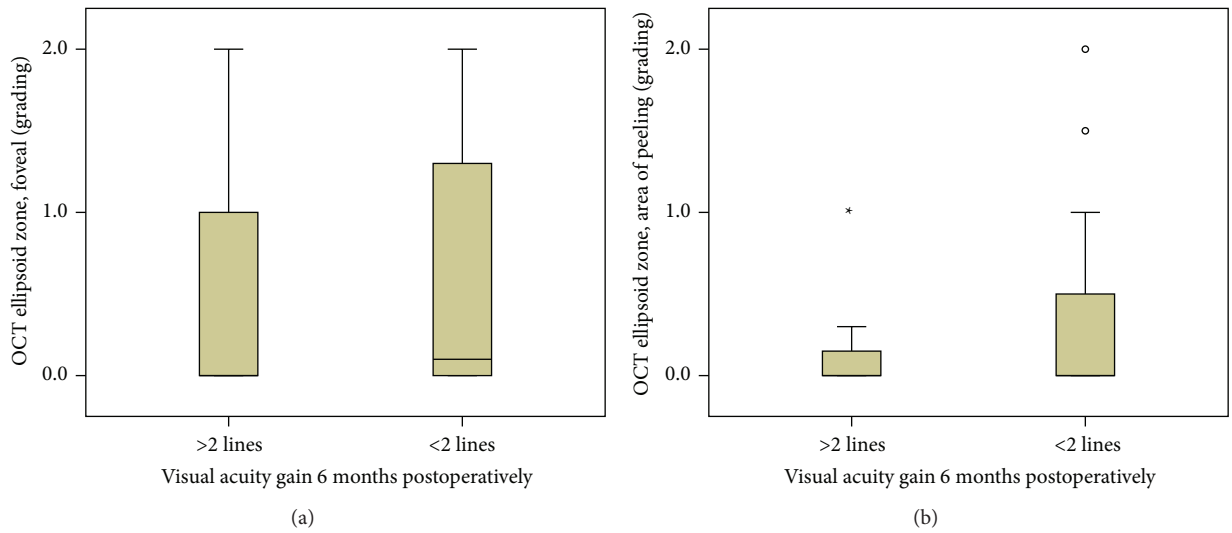

Figure 4: (a) Correlation of preoperative foveal EZ grading and gain of visual acuity 6 months postoperatively. No significant difference between groups ($p > 0.05$). (b) Correlation of preoperative EZ grading in areas of peeling and gain of visual acuity 6 months postoperatively. No significant difference between groups ($p > 0.05$).

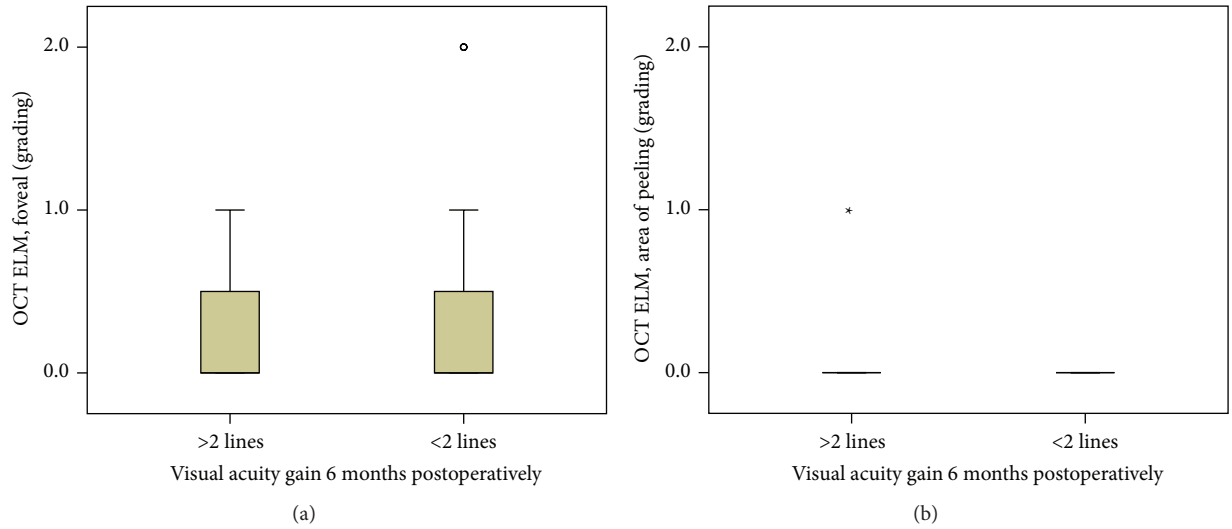

Figure 5: (a) Correlation of preoperative foveal ELM grading and gain of visual acuity 6 months postoperatively. No significant difference between groups ($p > 0.05$). (b) Correlation of preoperative ELM grading in areas of peeling and gain of visual acuity 6 months postoperatively. No significant difference between groups ($p > 0.05$).

pathological alterations or surgical intervention like pars plana vitrectomy with membrane peeling [6, 8, 9, 11–13].

The formation of ERM is a pathology of the vitreoretinal interface and the cellular proliferation is very likely related to an incomplete posterior vitreous detachment in idiopathic cases but can secondly occur after different retinal diseases or interventions such as retinal breaks, laser or cryotherapy, inflammatory diseases, or retinal detachment. As a first step tractional forces lead to morphological disorganization of the inner retina [14–16] followed by changes in the outer retinal layers as the disease progresses. The extent and localization of outer retinal changes in eyes with ERM formation may be very variable and correlate with the size of the membrane and the focus where tractional forces are most pronounced. These morphological alterations are often associated with a decrease of visual acuity and disturbing metamorphopsia, which are the main indications for surgical intervention [17–20].

However, in some cases the functional result obtained postoperatively is not satisfying for both the surgeon and the patient despite clinically visible anatomic success. The reason for this discrepancy is correlated with alterations of the outer retinal layers, which can be depicted with high resolution imaging OCT [7, 12, 20–22]. Furthermore, our study group recently showed that not only foveal but also

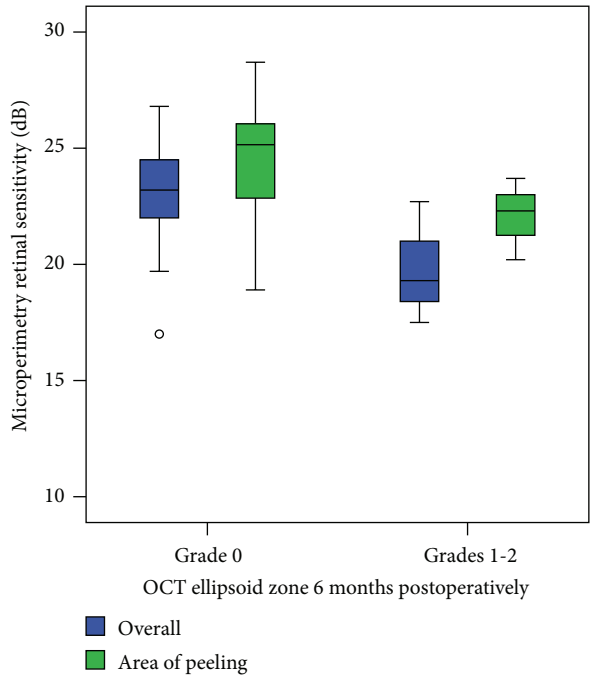

Figure 6: Mean retinal sensitivity based on EZ grading in OCT measurements 6 months postoperatively. A significant difference between intact EZ zone (grade 0) and retinal sensitivity compared to disrupted (grades 1-2) EZ zone in both OCT measurements overall and in areas of peeling could be demonstrated ($p < 0.05$).

parafoveal alterations in photoreceptor junction influence postoperative outcome [6]. In addition to a positive correlation between outer segment restoration and functional results after macular surgery, Itoh and associates observed that a recovery of the foveal cone microstructure may be seen as late as 12 months after anatomically successful surgery and that intact cone outer segment tips after ERM surgery correlate with BCVA [12, 21]. The influence of the used tamponade in the end of ERM surgery (air or balanced salt solution) has also been discussed [23].

However, so far published studies investigating the role of the outer retinal layers and their impact on functional recovery focused mainly on foveal sections obtained during OCT examinations and did not include the area surrounding the fovea [7, 8, 10, 13, 17, 18, 24–27]. The present investigation systematically analyzed both the foveal and the parafoveal region and established a correlation between morphological abnormalities detected in OCT images and retinal function in these specific areas as measured by microperimetry and BCVA after a surgical intervention.

Despite a successful surgical intervention some patients still complain about decreased visual acuity and/or microscotoma postoperatively. To exclude a mechanical injury to the retina by using end-gripping forceps we analyzed in detail the areas of peeling using OCT and microperimetry to compare morphological alterations in the outer retina with functional ones. In our study we could find a significant correlation of decreased retinal sensitivity and EZ or ELM interruptions in OCT measurements both overall and in areas of peeling. However, patients with more than two lines of visual acuity gain showed no significant improvement in retinal sensitivity compared to patients with a visual acuity gain below 2 lines.

Our results indicate that EZ integrity on SD-OCT is a statistically significant predictor of visual acuity in patients with ERM formation, and statistical analysis illustrates that EZ disruption, in contrast to ELM disruption, increases the predictive power of OCT measurements. Furthermore, the present study indicates that the standard surgical approach of ILM and ERM peeling using forceps has no significant negative influence on postoperative retinal sensitivity outcome, even if preexisting outer retinal alterations exist.

A limitation of our study is related to the limited number of patients included and the evaluation of only outer retinal structure alterations.

As we have already shown in our previous study [6], the present work confirms that morphological and functional tests (SD-OCT and microperimetry) in patients with ERM formation should not be focused on the foveal region alone but should also cover the parafoveal area. In addition, the surgical approach using manual forceps for membrane peeling in a highly trained surgeon setting does not influence functional outcome. Therefore, standard 23-gauge vitrectomy with membrane peeling is a safe and efficient approach to treat ERM formation.

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

Authors' Contribution

Wolfgang J. Mayer and Clara Fazekas contributed equally as first authors.

References

[1] R. G. Schumann, A. Gandorfer, J. Ziada et al., "Hyalocytes in idiopathic epiretinal membranes: a correlative light and electron microscopic study," *Graefe's Archive for Clinical and Experimental Ophthalmology*, vol. 252, no. 12, pp. 1887–1894, 2014.

[2] F. Zhao, A. Gandorfer, C. Haritoglou et al., "Epiretinal cell proliferation in macular pucker and vitreomacular traction syndrome: analysis of flat-mounted internal limiting membrane specimens," *Retina*, vol. 33, no. 1, pp. 77–88, 2013.

[3] C. E. Jahn, V. Minich, S. Moldaschel et al., "Epiretinal membranes after extracapsular cataract surgery(1)," *Journal of Cataract and Refractive Surgery*, vol. 27, no. 5, pp. 753–760, 2001.

[4] K. G. Nobel and R. E. Carr, "Idiopathic preretinal gliosis," *Ophthalmology*, vol. 89, no. 5, pp. 521–523, 1982.

[5] J. Sebag, "The vitreoretinal interface and its role in the pathogenesis of vitreomaculopathies," *Ophthalmologe*, vol. 112, no. 1, pp. 10–19, 2015.

[6] W. J. Mayer, M. Vogel, A. Neubauer et al., "Pars plana vitrectomy and internal limiting membrane peeling in epimacular membranes: correlation of function and morphology across the macula," *Ophthalmologica*, vol. 230, no. 1, pp. 9–17, 2013.

[7] M. Inoue, S. Morita, Y. Watanabe et al., "Preoperative inner segment/outer segment junction in spectral-domain optical coherence tomography as a prognostic factor in epiretinal membrane surgery," *Retina*, vol. 31, no. 7, pp. 1366–1372, 2011.

[8] S. F. Oster, F. Mojana, M. Brar, R. M. S. Yuson, L. Cheng, and W. R. Freeman, "Disruption of the photoreceptor inner segment/outer segment layer on spectral domain-optical coherence tomography is a predictor of poor visual acuity in patients with epiretinal membranes," *Retina*, vol. 30, no. 5, pp. 713–718, 2010.

[9] M. Inoue, S. Morita, Y. Watanabe et al., "Inner segment/outer segment junction assessed by spectral-domain optical coherence tomography in patients with idiopathic epiretinal membrane," *American Journal of Ophthalmology*, vol. 150, no. 6, pp. 834–839, 2010.

[10] Y. Mitamura, K. Hirano, T. Baba, and S. Yamamoto, "Correlation of visual recovery with presence of photoreceptor inner/outer segment junction in optical coherence images after epiretinal membrane surgery," *British Journal of Ophthalmology*, vol. 93, no. 2, pp. 171–175, 2009.

[11] R. G. Schumann, D. Compera, M. M. Schaumberger et al., "Epiretinal membrane characteristics correlate with photoreceptor layer defects in lamellar macular holes and macular pseudoholes," *Retina*, vol. 35, no. 4, pp. 727–735, 2015.

[12] Y. Itoh, M. Inoue, T. Rii, T. Hiraoka, and A. Hirakata, "Significant correlation between visual acuity and recovery of foveal cone microstructures after macular hole surgery," *American Journal of Ophthalmology*, vol. 153, no. 1, pp. 111–119, 2012.

[13] M. H. Suh, J. M. Seo, K. H. Park, and H. G. Yu, "Associations between macular findings by optical coherence tomography and visual outcomes after epiretinal membrane removal," *American Journal of Ophthalmology*, vol. 147, no. 3, pp. 473.e3–480.e3, 2009.

[14] O. Sandali, E. Basli, V. Borderie, L. Laroche, and C. Monin, "Recurrence of an idiopathic vasocentric epiretinal membrane: clinical and surgical particularities," *Journal Français d'Ophtalmologie*, vol. 35, no. 1, pp. 48.e1–48.e5, 2012.

[15] T. Yagi, K. Sakata, H. Funatsu, H. Noma, K. Yamamoto, and S. Hori, "Macular microcirculation in patients with epiretinal membrane before and after surgery," *Graefe's Archive for Clinical and Experimental Ophthalmology*, vol. 250, no. 6, pp. 931–934, 2012.

[16] J. Zhou, W. Liu, Q. Li, X. Li, J. Hao, and X.-L. Wang, "A comparative study of macular thickness and function before and after idiopathic macular epiretinal membrane surgery," *Zhonghua Yan Ke Za Zhi*, vol. 48, no. 2, pp. 119–123, 2012.

[17] T. Niwa, H. Terasaki, M. Kondo, C.-H. Piao, T. Suzuki, and Y. Miyake, "Function and morphology of macula before and after removal of idiopathic epiretinal membrane," *Investigative Ophthalmology and Visual Science*, vol. 44, no. 4, pp. 1652–1656, 2003.

[18] D. Odrobina, Z. Michalewska, J. Michalewski, K. Dzięgielewski, and J. Nawrocki, "Long-term evaluation of vitreomacular traction disorder in spectral-domain optical coherence tomography," *Retina*, vol. 31, no. 2, pp. 324–331, 2011.

[19] H. J. Kim, J.-W. Kang, H. Chung, and H. C. Kim, "Correlation of foveal photoreceptor integrity with visual outcome in idiopathic epiretinal membrane," *Current Eye Research*, vol. 39, no. 6, pp. 626–633, 2014.

[20] J. H. Kim, Y. M. Kim, E. J. Chung, S. Y. Lee, and H. J. Koh, "Structural and functional predictors of visual outcome of epiretinal membrane surgery," *The American Journal of Ophthalmology*, vol. 153, no. 1, pp. 103.e1–110.e1, 2012.

[21] T. Rii, Y. Itoh, M. Inoue, K. Hirota, and A. Hirakata, "Outer retinal morphological changes and visual function after removal of epiretinal membrane," *Canadian Journal of Ophthalmology*, vol. 49, no. 5, pp. 436–442, 2014.

[22] A. Shiono, J. Kogo, G. Klose et al., "Photoreceptor outer segment length: a prognostic factor for idiopathic epiretinal membrane surgery," *Ophthalmology*, vol. 120, no. 4, pp. 788–794, 2013.

[23] M. A. Leitritz, F. Ziemssen, B. Voykov et al., "Early postoperative changes of the foveal surface in epiretinal membranes: comparison of 23-gauge macular surgery with air vs. balanced salt solution," *Graefe's Archive for Clinical and Experimental Ophthalmology*, vol. 252, no. 8, pp. 1213–1219, 2014.

[24] S. Arichika, M. Hangai, and N. Yoshimura, "Correlation between thickening of the inner and outer retina and visual acuity in patients with epiretinal membrane," *Retina*, vol. 30, no. 3, pp. 503–508, 2010.

[25] C. I. Falkner-Radler, C. Glittenberg, S. Hagen, T. Benesch, and S. Binder, "Spectral-domain optical coherence tomography for monitoring epiretinal membrane surgery," *Ophthalmology*, vol. 117, no. 4, pp. 798–805, 2010.

[26] H. C. Koo, W. Rhim, and E. K. Lee, "Morphologic and functional association of retinal layers beneath the epiretinal membrane with spectral-domain optical coherence tomography in eyes without photoreceptor abnormality," *Graefe's Archive for Clinical and Experimental Ophthalmology*, vol. 250, no. 4, pp. 491–498, 2012.

[27] J. Michalewski, Z. Michalewska, S. Cisiecki, and J. Nawrocki, "Morphologically functional correlations of macular pathology connected with epiretinal membrane formation in spectral optical coherence tomography (SOCT)," *Graefe's Archive for Clinical and Experimental Ophthalmology*, vol. 245, no. 11, pp. 1623–1631, 2007.

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Review Article

Current Trends about Inner Limiting Membrane Peeling in Surgery for Epiretinal Membranes

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The inner limiting membrane (ILM) is the basement membrane of the Müller cells and can act as a scaffold for cellular proliferation in the pathophysiology of disorders affecting the vitreomacular interface. The atraumatic removal of the macular ILM has been proposed for treating various forms of tractional maculopathy in particular for macular pucker. In the last decade, the removal of ILM has become a routine practice in the surgery of the epiretinal membranes (ERMs), with good anatomical results. However many recent studies showed that ILM peeling is a procedure that can cause immediate traumatic effects and progressive modification on the underlying inner retinal layers. Moreover, it is unclear whether ILM peeling is helpful to improve vision after surgery for ERM. In this review, we describe the current understanding about ILM peeling and highlight the beneficial and adverse effects associated with this surgical procedure.

1. Introduction

Macular distortion and macular edema with the resultant macular dysfunction are the sequelae of epimacular proliferation.

Such proliferation of surface cells is associated with the distortion of both the inner limiting membrane (ILM) and sometimes the outer retinal layers.

The ILM is the basement membrane of Müller cells and is stiffer than the underlying neuroretina that is easily bent or changed in shape.

The ILM provides a support surface to contractile cells acting as a rigid scaffold that transmits the distortion on the underlying retina. Thus, the ILM is closely involved in the pathophysiology of disorders affecting the vitreomacular interface.

The analysis of specimens of ERM after vitrectomy often contains ILM fragments that have been unintentionally removed to treat traction maculopathy [1].

The ILM is the basement membrane between the neuroretina and the vitreous and can act as a scaffold for cellular proliferation in the pathophysiology of disorders affecting the vitreomacular interface.

When ILM is spontaneously separated from the retina in Terson's syndrome, the macula displays no significant reparative fibrosis and maintains excellent visual function during long-term follow-up [2, 3]. These observations showed that removing the ILM is compatible with good visual function, and many surgeons have speculated that the removal of the ILM, which increases the elasticity of the denuded macula, could be exploited in the treatment of diseases that distort the posterior pole [4].

The intentional removal of the macular ILM has indeed greatly improved the anatomical success rate of the surgical treatment of macular hole, and it is a cost-effective option for the treatment of this disease [5, 6]. Therefore, atraumatic ILM peeling has been proposed in the treatment of all forms of traction maculopathy such as ERM, macular hole, vitreomacular traction, myopic foveoschisis, and some forms of chronic diabetic macular edema [7]. However, although the anatomical outcomes are better after ILM peeling, this procedure may potentially cause adverse effects that could affect functional recovery in the medium or long term after surgery.

The introduction of modern Optical Coherence Tomography (OCT) instruments has allowed the identification of anatomical changes that occur months after macular ILM peeling. The formation of irregularities and indentations on the inner surface of the retina, the thinning of the temporal retina, and the thickening of the nasal retina are often evident on OCT frames several months after ILM peeling.

Other aspects like the inner retinal dimpling, firstly called "dissociated optic nerve fiber layer" (DONFL) appearance, may be visible a few weeks after surgery without the use of any sophisticated tools [8].

Finally, the appearance of a transient reduction of the retinal differential light threshold is more marked in cases of ILM removal than in cases in which the ILM is left in place.

Actually, it is not known whether these morphological and functional changes reflect potentially progressive retinal damage.

For most vitreoretinal surgeons, the surgical procedure for treating ERM is well established; however, whether ILM removal is always safe or if it is better to limit this procedure to selected patients remains controversial.

In this review are analyzed the pathogenesis and the treatment of ERM focusing primarily on positive and negative consequences related to ILM peeling.

2. Pathophysiology of Müller Cells and ILM

The ILM is a transparent structure that defines the boundary between the retina and the vitreous body. It is composed of the internal expansions of Müller cells and by a meshwork of collagen fibers, glycosaminoglycans, laminin, and fibronectin called the cuticular layer [9].

The ultrastructural analysis of the human retina shows that the ILM appears as a 10 μm thick, homogeneous, periodic acid-Schiff- (PAS-) positive basement membrane; its vitreal surface is smooth and its retinal surface is markedly irregular. The latter surface is made up of Müller cell footplates. An outer dense fibrillar meshwork, the Müller cells basal membrane, and a loose net of fibrils form the cuticular layer [1, 10, 11].

Proceeding from peripheral to central macular retina, the ILM thickness increases up from 0.4 μm to about 1.4 μm.

The ILM is the site of adhesion between the cortical vitreous gel and the retina and is crucial in the pathogenesis of several eye diseases such as idiopathic macular holes, epiretinal macular membrane, and tractional diabetic macular edema.

In physiological retinal processes, Müller cells are able to modulate the concentration of retinal ions through voltage-gated channels, participate in acid-base balance through bicarbonate ions, limit excitatory signals through specific glutamate receptor by a specific reuptake, and provide an adjuvant for metabolic functions (e.g., glycolysis, glycogen metabolism, and oxidative metabolism) of the inner neurosensory retina [12].

Virtually any damage or stimulation on Müller cells can alter retinal function. Every disease of the retina is associated with reactive Müller cell gliosis. Müller cell gliosis is a generic term that reflects the capacity of Müller cells to increase their volume (i.e., hypertrophy) and to proliferate with the aim of supporting the survival of retinal neurons. This reactivity may have deleterious effects on vision, for example, causing intraretinal fibrosis that modifies neuroretinal connections and photoreceptor metabolism and epiretinal fibrosis because the ILM offers a scaffold that permits the adhesion and subsequent proliferation of glial cells [12–14].

Müller cells are the primary support that confers resistance to mechanical stimulation of the retina. Müller cell extensions that blend between the ILM and the external limiting membrane (ELM) exert a major contribution to the biomechanical strength of the retina [15, 16].

The Müller cell footplates that constitute the outer portion of the ILM in the center of the macula form an inverted cone-shaped zone that forms the base of the foveola [17, 18]. This cone acts as a punch, which is the primary point of adhesion between the ILM and ELM over the external segment of foveal cones; this gives the characteristic navel configuration of the fovea. The Müller cells also maintain the nerve fiber bundles of the inner layer of the retina close to each other.

3. Composition of Epiretinal Membranes

Epiretinal membranes (ERMs) growing over the macula can result from several pathogenic mechanisms in response to age-related changes such as synchysis and liquefaction in the vitreous humor. They represent a very frequent ocular disease of the elderly. ERMs develop at the vitreomacular interface and are determined by the proliferation of a different type of cells that produce collagen and migrate onto the ILM. These cells gradually form a transparent hypocellular avascular layer and, like all scar tissue, tighten to create tension on the retina, which may bulge and pucker or even cause swelling or macular edema.

The most common form of ERM is idiopathic, which forms in elderly healthy eyes without any other apparent diseases. However, retinal breaks, retinopexy, photocoagulation, inflammation, retinal detachment, and vascular disease (e.g., longstanding central vein occlusion) can also lead to secondary ERM formation.

ERMs are composed of an extracellular matrix (consisting of collagen, laminin, vitronectin, tenascin, thrombospondin, and fibronectin) and of cells. A polymorphous cell population has been found in the membranes: glial cells (e.g., Müller cells, microglia, and fibrous astrocytes); epithelial cells from the retinal pigment epithelium and ciliary body; blood-borne immune cells (e.g., lymphocytes, macrophages, and

neutrophils); cells from vitreous fibrocytes (i.e., hyalocytes); and myofibrocytes. Retinal pigment epithelial (RPE) cells also contribute to the formation of ERM in cases of macular holes, retinal tears, and retinal detachment [19–21].

The origin of the epiretinal cells in idiopathic ERM has recently been the subject of numerous studies. The morphologic and histological criteria that were used in the past to classify the cell population of ERM have recently proven to be inadequate because the cells in the vitreous have the capability to undergo striking morphologic changes [22].

The cell population in idiopathic ERM possesses a great variability of immunocytochemical properties because of transdifferentiation in the vitreous [12]. The cells lose contact inhibition and are modified according to the evolutionary phases of the membrane. They are characterized at first to some markers during proliferation and then exposed to other markers during maturation and contraction of the membrane.

Recent studies using proteomic techniques and immunocytochemistry suggest that a large proportion of cells that make up idiopathic ERM is constituted by Müller cells and hyalocytes that undergo transdifferentiation into cells with different characteristics [23–25].

In idiopathic ERM, a large percentage of cells are positive in immunomarkers for Müller cells such as glial fibrillary acid protein (GFAP), cellular retinaldehyde binding protein, vimentin, and Kir4.1; by contrast, immunostaining for pancytokeratin is often negative, which predicts little, if any, role of RPE cells in idiopathic ERM [23, 26–28]. Secondary ERM may be formed by RPE cells, fibroblasts, fibrous astrocytes, and cells of blood origin [29].

Müller cells transdifferentiation is characterized by a reduction in cell-specific proteins such as GFAPs and cytokeratins, whereas proteins (e.g., α-smooth muscle actin (which is normally not expressed by the cells)) that are involved in motility and proliferation are upregulated. The GFAP content in epiretinal tissues is inversely correlated with clinical contractility [30], which suggests that the transdifferentiation to myofibroblasts increases the capacity of glial cells to generate tractional forces. In addition idiopathic ERMs are positive for immunomarkers typical of Müller cells and hyalocytes.

In addition, the immunomarkers for hyalocytes are positive in ERM. Hyalocytes are of macrophage lineage and have phagocytosis activity and may collaborate with Müller cells as scavengers of debris and apoptotic cells in the pathogenesis of ERM [23, 31]. What activates these cells in idiopathic ERM is not yet known. An important role is probably provided by the mechanical stimulation of the movement of the liquefied vitreous on the retina that results in an immune system response to protect the retina.

The histopathological analysis of surgically removed ERM generally shows two primary types of epimacular proliferation. In type 1, the ERM is in direct contact with the ILM; in type 2, the ERM is laid on a layer of collagen fibers of vitreal origin [23, 32, 33].

This finding underlines two possible theories about ERM pathogenesis. The first and oldest theory is that ERM develops after a cleft in the ILM is created by dynamic vitreous traction on the focal area of adhesion. Through this, Müller cells or other glial cells grow outward from the retina to the inner retinal surface. Müller cell proliferation is aimed at healing the retina (i.e., to heal the ILM break) and at protecting the neuroretinal layers from mechanical stimuli. These reactions create a "conservative gliosis" [34] to protect photoreceptors from apoptosis induced by traction and to resist from the passive movements of the retina [35–37].

This theory seems to be supported by the fact that a group of ERMs, called type II ERMs, are composed of a layer of cells that proliferate directly over the ILM without the interposition of collagen type II [38]. During the peeling of this type of membrane, it is common to simultaneously remove the ILM or its fragments that remain tenaciously adherent to the ERM. However, the presence of an ILM break was never directly demonstrated, even if it could have healed, and this makes it difficult to find a break later in the specimens [39].

The second pattern of ERM, termed type I ERM, is characterized by a layer of collagen between the ILM and the proliferating cells. This pattern seems to underlie a second possibility for ERM formation: a subtle layer of vitreous remains attached to the retina after PVD and this remnant provides a medium for the proliferation of glial cells and hyalocytes [40].

In favor of this hypothesis is the finding of the presence of a premacular oval defect in the detached hyaloid of many patients affected by ERM, which confirms that the rear part of the hyaloid can tear while remaining adherent to the macula [41, 42].

4. Etiology and Pathogenesis of Epiretinal Membranes

Posterior vitreous detachment (PVD) is associated with 75–93% of ERMs; it is widely accepted that an anomaly in this process is the primary cause of ERM formation [43, 44]. The modification of the vitreoretinal relationships in aging individuals appears somewhat correlated with a disturbance in collagen metabolism. Posterior vitreous detachment occurs in the same age group that is affected by ERM, and it may precede the onset of ERM symptoms by months or years.

Posterior vitreous detachment commonly occurs bilaterally; the same occurs with ERM, which occurs bilaterally in 20–31% of patients. The unaffected eye has a 2.5 times higher possibility of developing an ERM. This suggests a systemic predisposition to develop an ERM that is probably related to a disturbance of collagen metabolism that is accentuated by age, myopia, and diabetes [45].

Vitreous liquefaction occurs progressively in all eyes with age, and it occurs earlier in myopic eyes than in normal eyes. It appears to be accompanied by a reduced concentration of collagen type IX, which causes the collapse of collagen type II that constitutes the ordinate scaffold of the normal vitreous gel [46, 47]. This significantly reduces the gel volume and increases the liquid volume that creates PVD or posterior vitreoschisis [48]. During eye movement, the shear retinal stress exerted by the vitreous movement on the posterior pole may cause a proliferative cellular reaction and lead to the formation of epiretinal membranes [49–51].

The posterior hyaloid normally adheres to the major superficial retinal vessels, the optic disc, and the macula [52].

At the sites of vitreoretinal attachment, the ILM can become thin and vitreous fibers can adhere directly to Müller cells that support the underlying macular structure and confer the normal shape of the fovea.

Under normal conditions, vitreous fibers exert traction evenly to numerous Müller cells. However, in cases of incomplete PVDs or vitreous shrinkage, a limited area of few Müller cells must support most of the vitreous traction. This may result in chronic mechanical stimulation of the Müller cells and in the local release of inflammatory factors that induce Müller cell gliosis and the breakdown of the blood-retinal barrier [52].

A breakdown of blood-ocular barriers occurs also in cases of ocular inflammation, ischemia, and trauma, all situations associated with ERM formation [52–54]. Vitreous hemorrhage, which sometimes happens in PVD, can be another causative factor that results in the activation of glial cells. In the human vitreous, the presence of biologically active quantities of serum-derived and blood cell-derived cytokines and growth factors, derived by inflammatory blood-borne cells or cell debris, is probably the primary stimulus that triggers and regulates Müller cell process extension and proliferation [55, 56].

The ILM is a reservoir of cytokines. Growth factors regulate the growth and contraction of the ERM. The analysis of human specimens of the ILM and the vitreous associated with a macular hole and the ERM shows several proteins: some, like cytokines and growth factors, are expressed in low abundance; others, such as the heavy and light chains of immunoglobulin G, serum albumin, transferrin, antithrombin III, α_1-antichymotrypsin, hemopexin, α_1-antitrypsin, α_2-HS-glycoprotein, apolipoprotein A-1, transthyretin, apolipoprotein J, fibrinogen γ chain, and haptoglobin-1, are expressed in high abundance [57, 58]. Possible mediators for ERM proliferation are basic fibroblast growth factor, nerve growth factor, and glial cell line-derived neurotrophic factor, fibrinogen A, platelet derived growth factors, transforming growth factor β1, VEGF (although there are no blood vessels in an ERM), and tumor necrosis factor [59–65].

The contraction of the ERM generates a mechanical stimulus over the ILM that induces further hypertrophy of Müller cells within the retina, thereby causing edema and creating a progressive partially irreversible retinal thickening and photoreceptor disruption. The percentage of loosened photoreceptors can be estimated by the evaluation of the reflectivity of the ELM, the ellipsoid and cone interdigitation zones by OCT. It is a predictive factor for visual acuity recovery after ERM surgery [66, 67].

Even after ERM removal, the total reduction in retinal thickening is not completely possible in longstanding cases of glial scar. Long-term vitreoretinal traction, especially if it disrupts the blood-brain barrier and causes macular edema, is more likely to create significant intraretinal Müller cell proliferation and irreversible functional and structural disruption of the neural retina that does not permit good visual recovery after surgery.

A suggestive theory to clarify the pathogenesis of tractional macular diseases has been proposed by Sebag [68]. He suggested that the phenomenon of vitreoschisis is the basis of most tractional diseases of the macula. According to this theory, PVD is a physiological phenomenon of aging caused by two main changes in the vitreous humor: the liquefaction of the central part of the vitreous and the weakening of adhesions between the retina and the posterior hyaloid. In most patients, PVD occurs in a physiological manner with complete separation of the posterior hyaloid from the retina without collagen remnants on the ILM surface. In pathological PVD, the weakening of the adhesion between the posterior hyaloid and the retina does not occur. The liquefaction of the central vitreous creates a dynamic traction on the fibers of the cortical vitreous adherent to the posterior hyaloid that are arranged in layers like onion bracts. This causes a cleft in the thickness of the cortical vitreous and creates vitreoschisis, in which the most peripheral layer of the posterior hyaloid remains attached to the retina and separates from the other layers [69].

Hyalocytes within the vitreous cortex remnants remain on the inner retinal surface after PVD. In this situation, an unknown stimulus induces the hyalocytes to stimulate the intraretinal Müller cells to proliferate on a layer of vitreal collagen fibers. Epiretinal membranes, once formed, tend to progress even when the original inciting stimuli are decreased or eliminated, because the cells within the membranes can produce growth factors and cytokines that recruit other cells and stimulate their proliferation.

It has been suggested that a primary mechanism that leads to ERM enlargement is phagocytosis of blood-borne substances and cell debris, which adhere to the vitreal surface of the retina by Müller cell processes that extend through holes in the basement membrane of the ILM [19]. The proliferation of these cells may paste the ILM to the vitreous and to the ERM. In this situation, ERM removal cannot be performed without removing the ILM at the same time.

Müller cells and hyalocytes can proliferate on the layer of vitreous fibers that remain on the retina and form the ERM; they also can colonize all areas where there is a vitreous-liquid interface [70].

When the vitreomacular traction is stronger than the mechanical resistance of the center of the foveola, foveal integrity may be damaged by vitreous movement or by surgery. This harmful event can occur during surgery, vitreofoveal traction, or myopic traction maculopathy and lead to the formation of a macular hole [71].

The thickness and the size of the area of adhesion between the retina and the hyaloid explain why different tractional macular pathologies exist. If the area of vitreomacular traction is focal and anteroposterior, it may result in vitreofoveal or vitreomacular traction syndrome; if the area of traction is focal and centered on the edge of the foveola, it may form a macular hole; and if the area of traction is wide and spreads across the macula, it may form a macular pucker.

In high myopia, PVD is often complicated by large sheets of residual cortical vitreous that remain attached over the inner surface of the retina and may subsequently contract,

thereby giving rise to tractional vitreoretinal diseases. If the thickness of the vitreous that remains adherent to the retina is remarkable, this may result in myopic vitreous macular traction syndrome, which is also called "myopic foveoschisis."

Finally retinal breaks, retinopexy, photocoagulation, inflammation, retinal detachment, vascular disease, and, more rarely, retinitis pigmentosa (over the peripapillary retina), hemorrhagic glaucoma, Terson's syndrome, Eales disease, and Coats disease may cause secondary ERM [53, 72–76].

5. Epidemiology and Treatment of Epiretinal Membranes

ERMs are also called "cellophane maculopathy," "macular puckers," "surface-wrinkling retinopathy," "epiretinal gliosis," and "premacular fibrosis." The prevalence of idiopathic ERM depends primarily on the age of patients: they may occur in 2% of people under 60 years of age, but the prevalence increases to 12–20% after the age of 70 years [45] and is bilateral in 10–20% of patients [77].

Approximately 30 years ago, Machemer introduced vitrectomy for the treatment of macular pucker. Since it was first proposed, the technique of removing the ERM as a single piece has not changed significantly, and the removal of the pucker is always performed without the ILM peeling with substantially favorable results [78–80].

Surgery is recommended if the blurred vision or the distortions are severe enough to interfere with binocular vision or daily living. Many case reports achieved good results simply by removing the ERM and reduced metamorphopsia and improved visual acuity in 70–90% of patients with a mean improvement in vision by 2 or more Snellen lines [38, 81–84]. The visual acuity improvement continued for the next 6–8 months and the best final visual acuity may be obtained after 1 year [80].

Surgery for macular pucker allows the recovery of approximately one-half of the visual acuity that had been lost, and visual recovery is greater if the preoperative visual acuity is lower. However, the probability to regain vision after surgery is increased in patients with a preoperative visual acuity of 0.25 or better; patients with better baseline visual acuity can get a full visual recovery [85].

Complete recovery of vision is rare in patients with longstanding ERMs, and retinal thickness and the macular profile rarely return to normal. Thus, early surgery is likely to decrease the risk of developing irreversible macular damage [86].

Despite seemingly adequate and complete removal of the ERM, some patients continue afterwards to complain of blurred vision, slight metamorphopsia, or distortion [87]. Furthermore, ERMs may form again months after apparently successful epimacular proliferation removal; it is estimated that up to 16.5% of patients may have ERM recurrence after surgery. This phenomenon requires a repetition of the surgery for the pucker in 3–6% of patients [79, 80, 88]. Patients affected by secondary ERM and young patients have more recurrences and, in this category of patients, final visual outcome is usually less satisfactory [89].

6. ILM Peeling in Surgery of Epiretinal Membranes

Until 1990, the ILM was considered an integral part of the retina, and vitreoretinal surgeons did not think that it could be removed without causing damage to vision.

The reports of cases of spontaneous separation of the ILM in Terson's syndrome, which resulted in no significant reparative fibrosis and good visual prognosis after surgery, have attracted the attention of vitreoretinal surgeons; this phenomenon showed the possibility of removing the ILM to release vitreoretinal tractions [2, 3]. Furthermore, the histological examination of the removed ERM shows that, in 40–60% of patients, the ILM and ERM are so adherent they are often removed together at the same time, thereby confirming the hypothesis that these 2 membranes are strictly linked in causing epiretinal puckering [90, 91].

On the other hand, the ultrastructural examination of ILM specimens, which were removed after ERM peeling, demonstrates the presence of microscopic ERM remnants that persist over the ILM in almost one-half of the patients [92–94]. These observations highlight that the conventional way of peeling the ERM leaves fragments of cells behind on the ILM and that these residual tissues could form the islands of reproliferation [91].

ILM removal provides the certainty of having removed all cells that produce collagen above the retina, thereby eliminating the scaffold for proliferative cells such as transdifferentiated Müller cells and myofibroblasts, which are the prevailing type of cells in recurrent ERM [95]. In addition, this procedure ensures that all adhesions that corrugate the inner retina have been released, because the ILM can stiffen and thicken in the process of ERM formation. Thus, in the early 90s the first studies appeared in which the ILM was removed during ERM surgery [96].

The simultaneous separation of ERM and ILM apparently does not cause adverse effects on vision. In some studies, the visual acuity indeed appeared better in patients in whom large portions of the ILM were removed with the ERM [97]. For example, Bovey et al., in their prospective case-control trial, reported a final visual gain, at 21 months of follow-up, of 3.1 lines when ILM peeling is performed and 0.9 lines when ILM is not removed. However, in one retrospective study conducted on 41 patients, the ILM removal was reportedly correlated with worse visual functionality [98].

In 2000, the introduction of vital dyes in vitreoretinal surgery revealed other findings that previously had not been noticed. The simple removal of the ERM may also partially separate the ILM from the retina that after several months may contract again causing residual traction and retinal striae. By performing ILM peeling, the retinal striae are more likely to disappear or flatten [96].

In 2003, a randomized pilot study showed that peeling of the ILM during ERM surgery may not have a deleterious effect [99]. ILM peeling was also found superior in resolving cystoid macular edema due to epiretinal traction, which disappeared in 90% of patients, compared to 44% of patients who had undergone removal of the ERM only [86].

Thus, the simultaneous removal of ERM, followed by ILM peeling, has become a widely approved procedure in vitreoretinal surgery. In a few years, the number of surgeons routinely performing this procedure has widely risen.

Numerous studies confirmed that ILM removal during surgery for ERM is associated with better anatomical improvement, better final vision, and a lower risk of recurrent epimacular membranes [86, 94, 97, 99–104].

From a surgical point of view, the peeling of this ERM type I is easier because a cleavage plane exists that is a collagenous layer interspersed between the ILM and the cells. However, by removing only the first membrane, a certain amount of collagen and cells remains over the ILM. A histological study has verified that the removal of only the ERM can leave on the ILM surface up to 20% of the cells that compose epimacular proliferation in two-thirds of patients [33].

Thus, a second membrane, made by the ILM with residues of collagen, should be removed to ensure eliminating all tangential traction over the retina and to avoid ERM recurrence [91].

In type II ERM, ILM and ERM are so adherent that they often are separated at the same time during surgery [88, 90, 91]. The release of the epiretinal traction inhibits the stimulus for hypertrophy of Müller cells within the retina but appears to not completely inhibit the growth of these cells onto the surface of the ILM where they can reform a new glial scar [36].

The omission of the removal of the ILM could not inhibit the growth of glial cells above and below the ILM where they can reform a new macular pucker. Thus, ILM and ERM are considered of the same pathology and should be removed together [105, 106].

7. Vital Dyes to Highlight the ILM

The difficulty of distinguishing the ILM from underlying structures makes ILM peeling a challenging maneuver. Failing to distinguish details of ILM can lead the surgeon to cause damage to the nerve fibers, extend the time of surgery, and lead to increased inflammation with subsequent responsive macular edema. To facilitate ILM clear identification the use of vital dyes has been introduced since 2000 and is currently used by the vast majority of vitreoretinal surgeons.

The first among these dyes was indocyanine green (ICG) that at the concentration of 5 mg/mL (0.5%) provides a stark contrast between the stained and the unstained ILM [107–109].

Early clinical studies with the use of ICG have reported good anatomical and functional results [110–113].

However, subsequent studies have found that intraocular ICG can cause toxic effects to both the neuroretina and pigmented epithelium [114, 115] and this could compromise the functional success of the surgery [116].

A direct toxicity on retinal glial, EPR, and ganglion cells has been highlighted in in vivo and in vitro studies [114, 115, 117, 118].

The morphological examination of samples of ILM after the use of ICG demonstrated that the cleavage plane of the membrane is deepened and its removal also removes layers of Müller cells [119]. Far more cellular debris on the retinal side of the ILM were seen in the ICG-stained in comparison with the unstained specimens. ICG seems to be toxic also for the hypoosmolarity of the injected solution and for a phototoxic effect triggered by natural light or by the endoilluminator [117, 118].

It was also discovered that ICG could persist on the inner retina for many months after surgery so the phototoxic effect could last a long time [120].

Other vital dyes were later introduced to replace the ICG: Trypan Blue 0.15%, Brilliant Blue, triamcinolone acetonide, and very recently Acid Violet 17.

Trypan Blue is not specific for the ILM but stains sufficiently the inner retinal surface and allows a useful contrast between the colored surface and the underlying unstained layers.

It appears to be less toxic than ICG, as shown by studies that highlight the best functional results and the lower incidence of central scotoma in groups of patients that were treated by vitrectomy with ILM peeling and stained with Trypan Blue versus ICG [121].

Brilliant Blue G is another vital dye that has been introduced after the Trypan Blue. It has a good safety profile, provides significant anatomical and functional postoperative results [122], and has the peculiar characteristic of staining specifically the ILM and not the rest of the retina as well as ICG.

Triamcinolone acetonide (TA) is a synthetic glucocorticoid that can be formulated to intraocular use. It has the consistency of a whitish powder that forms a deposit on the retinal surface. It can be used to distinguish the epiretinal membranes and the posterior hyaloid from the inner retina and the ILM from the underlying retinal layers. It has the major drawback of dirtying the tip of the instruments and being absolutely a nonselective dye.

TA is considered safe [123]; however, studies exist that highlight long-term toxicity when it is used in high concentrations like transient but consistent intraocular pressure elevation and in very few cases acute endophthalmitis [124]. In animal species, some toxic effects have been shown on RPE cells, retinal Müller glial cells, and retinal neurosensory cells [125].

Finally, very recently the use of another vital dye has been introduced: the Acid Violet 17 that is specific to the ILM and allows its clear intraoperative visualization. Acid Violet 17 was safe for the retinal tissue at concentrations of 0.25 and 0.50 g/L after intravitreous injection; however further studies are required to investigate its long-term safety [126].

8. Concerns about ILM Peeling in Epiretinal Membrane Surgery

After ERM surgery retinal thickness as well as the macular profile rarely returns to normal.

The partial recovery of macular morphology is due to the chronic deformation exerted by the ERM that caused hypertrophy of Müller cells whose ramifications tend to fill all the empty spaces previously occupied by other degenerated neurons. Also the intraretinal edema creates an irreversible

alteration of the retinal structure and probably of the retinal function [79, 80, 88].

Similarly, complete recovery of vision is rare and mostly dependent on visual acuity before surgery. ERM surgery allows recovery of approximately one-half of the visual acuity that has been lost [96].

Mechanical injury to the neurosensory retina during ERM and ILM peeling could have a role in partial postsurgical recovery of vision.

Cystoid macular edema is a disappointing and relatively common complication. Surgical traction on Müller cells may induce damage to their function and gliosis of the ELM with subsequent accumulation of proteins and material over its inner side, thereby causing the cystoid macular edema [98, 127].

A recent study showed that the glial proliferation involves also the retina under the ILM [128]. The authors observed that ILM removal is more difficult during ERM surgery than in macular hole. They detected glial and/or neuronal cells on the retinal surface of the ILM in 32% of the macular hole-ILM specimens and in 65% of the ILMs peeled after ERM removal; this difference was significant. These findings suggest that ERM may be associated with sub-ILM fibrosis that alters the plane of separation during ILM peeling and that a possible loss of superficial nerve fibers is to be expected after ILM peeling in some patients. In fact, OCT examination shows a thinning of the retinal nerve fiber layer (RNFL) after surgery.

The ERM may have a significant intraretinal component under the ILM. This indicates that this disease may affect the entire thickness of the retina, not just the inner layer. The proliferation of these cells may paste the inner retinal layers to the ERM; in that case, ERM removal cannot be performed without ILM removal at the same time.

When this adhesion is particularly strong, the center of the foveola may be damaged by surgery. This event may be harmful in case of small but tenacious adherence of the ERM to the center of the macula. If the macula is thickened, that is, in case of vitreofoveal tractions or in myopic traction maculopathies, the surgical traction may cause the formation of a macular hole [71].

ILM removal may also result in glial apoptosis due to removal of Müller cell plates and may be responsible of weakening of the retina, thereby leading to eccentric retinal hole development. The etiology of these holes may be due by contracture of the remaining epiretinal proliferation, thereby causing expansion of a previously undetectable iatrogenic defect [129]. After ERM combined with ILM peeling, the foveal depression rarely forms again.

Thickening of macula without foveal depression has been found in 84.2% of patients of ILM-peeled eyes, compared to 42.9% of patients with unpeeled eyes; a normal foveal contour with a foveal depression has been found in only 15.8% of ILM-peeled eyes, compared to 57.1% of unpeeled eyes [105]. ILM peeling could damage the Müller cell footplates that form the inverted cone scaffold that gives the navel shape to the fovea. The fovea remains virtually without any lateral structural support. Thus, some authors recommend leaving the ILM just above the fovea [18].

Visual recovery after surgery ERM can also be achieved without combining ILM peeling. Many works of comparison found no functional difference between the groups in combination and without with ILM peeling [88, 130].

Tadayoni et al. first reported anatomical damage after ILM peeling and first described a peculiar macular appearance, called "dissociated optic nerve fiber layer" (DONFL), which appeared 1–3 months after ERM surgery [8].

Blue light autofluorescence and infrared reflectance imaging may also provide evidence for arcuate striae formed by nerve fibers that radiated from the macula to the papilla in an arcuate fashion. Their appearance reflects a swelling of nerve fiber bundles and is visible as early as 1 week until 1 month postoperatively and disappears after 2 months [131]. In fact, the retinal nerve fiber layer (RNFL) appearance with the OCT is thickened in the first month after surgery [132]. After a short period, the RNFL displays a tendency to decrease from the third month and become progressively more apparent many months postoperatively. The RNFL decreases especially in the temporal quadrant and becomes thinner than before surgery [132–134]. At last, the appearance of the macula after 3–6 months has often nicks and dimples in the inner surface [132, 135].

At first, the use of ICG was held responsible for toxic and mechanical damage to the inner retina leading to the thinning of the RNFL [114, 115]. However, even with the use of other vital dyes such as Trypan Blue, the reduction of RNFL thickness as well as the phenomenon of DONFL and arcuate swelling of the nerve fiber layer occurs [136].

Finally, a possible side effect that may be related to ILM peeling surgical procedure is an ipo/atrophic modification in macular region. Baba et al. reported a partial macular hypotrophy with a reduction in the thicknesses of the inner retina and ganglion cell complex [135].

In most cases, however, with the tools available today there is not obvious demonstrable functional damage caused by these anatomical macular modifications.

Most patients do not show any symptomatic visual field defect, and most patients after ILM peeling have an improvement in their vision and reading speed [137, 138].

9. Discussion and Conclusions

The ILM is the boundary that establishes the contact and communication point of two compartments: the retina and vitreous. The inner part of ILM has a living boundary formed by the footplate processes of Müller cells. These glial cells regulate retinal homeostasis and functionality; however, they also constitute a scaffold for the correct positioning of all neural cells with a particular importance in maintaining the shape of the fovea.

Thus, the ILM is the pivot on which vitreal tractions spread throughout the retina. The tractions from the inner surface of the retina are transmitted to the whole retina through the Müller cell network and through the ELM, which then stretches the photoreceptors. The shear stress generated by the movement of the liquefied vitreous on abnormal vitreomacular adherence triggers specific natural inflammatory

reactions. The expression of contractile proteins by these cells transforms Müller cells into microfibroblasts.

Müller cells react to mechanical and hypoxic stimuli by hypertrophy to resist and protect the neuroretinal layers from traction (i.e., passive movements induced by traction) and to protect photoreceptors from apoptosis. The Müller cells reaction however is self-maintained by a vicious circle in which hypertrophy is followed by transdifferentiation, proliferation, and contraction. The vitreous initiates the pathology that the retinal cells worsen. Epiretinal membranes, once formed, tend to progress, even when the original inciting stimuli are decreased or eliminated, because the cells within the membranes can produce growth factors and cytokines that recruit other cells and stimulate their proliferation.

Pathological vitreoretinal adhesion on the ILM offers different surfaces on which transdifferentiated glial cells migrate and thereby configures different aspects of traction maculopathies.

Vitrectomy is performed to release the pathological influence of the vitreous on the retina and is useful in restoring the normal anatomical shape of the macula and improving visual acuity. The removal of the ILM has been the major advance in vitrectomy in the past 15 years. On the other hand, the surgical technique of ILM peeling may unintentionally injure the underlying retina. It often depends on the degree of adherence of the epiretinal membrane.

Traction during ILM peeling could lead to a retinoschisis or to accidental interruption of the intraretinal neural network or the nerve fiber bundle. In addition to the damage closely associated with the surgical technique, recent findings have revealed adverse effects related only to the peeling of the ILM, including damage to the tropism of the Müller cells, a decrease in foveal retinal sensitivity, and alteration of the b-wave of electroretinograms [139, 140].

In conclusion, it is not possible with the present knowledge to confidently choose whether peeling the ILM in ERM surgery is associated with an improvement in vision.

No sufficiently large randomized clinical trials (RCTs) on this topic are available. Further studies are desirable to increase our knowledge on the physiology of Müller cells, which are closely related to the physiology of the ILM.

Studies are underway on supplying astrocytes as a strategy that will inhibit the exaggerated response of glial cells to mechanical and ischemic stimuli in order to restore the physiological network of capillaries in avascular retina areas. In addition, the delivery of recombinant pigment epithelium-derived factor may allow the recovery of Müller cells and thus creates favorable conditions for the survival of retinal cells in the loss of their homeostasis [141].

Moreover, the mechanism and the severity of the traction on the inner retina can vary from patient to patient, depending on the amount of cells in the ERM (i.e., sparse cellular proliferation or dense cellular proliferation). The latter group (i.e., patients with dense cellular proliferation) may be associated with a higher chance of surgical difficulty during ILM peeling.

Surgeons using vital dyes must assess the presence of cortical vitreous on the ILM after having first removed the ERM. If there is residual vitreous and it is not possible to remove it, peeling of the ILM is indicated. Surgeons must also consider whether the ILM is intact or damaged after ERM removal. If the ILM is not damaged, the surgeon may decide to leave it; if it is damaged or responsible for retinal striae, probably it should be removed [142]. The surgeon must preserve the eye from ILM removal in cases of retinal thinning for circulatory or metabolic disorders and in case of glaucoma. Additional surgical experiences and further functional studies must be conducted to determine if it is safe to leave a portion of the ILM in front of the fovea.

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

References

[1] H.-S. Yoon, H. L. Brooks Jr., A. Capone, N. L. L'Hernault, and H. E. Grossniklaus, "Ultrastructural features of tissue removed during idiopathic macular hole surgery," *American Journal of Ophthalmology*, vol. 122, no. 1, pp. 67–75, 1996.

[2] R. Morris, F. Kuhn, C. D. Witherspoon, V. Mester, and J. Dooner, "Hemorrhagic macular cysts in Terson's syndrome and its implications for macular surgery," *Developments in Ophthalmology*, vol. 29, pp. 44–54, 1997.

[3] F. Kuhn, R. Morris, C. D. Witherspoon, and V. Mester, "Terson syndrome: results of vitrectomy and the significance of vitreous hemorrhage in patients with subarachnoid hemorrhage," *Ophthalmology*, vol. 105, no. 3, pp. 472–477, 1998.

[4] V. Mester and F. Kuhn, "Internal limiting membrane removal in the management of full-thickness macular holes," *American Journal of Ophthalmology*, vol. 129, no. 6, pp. 769–777, 2000.

[5] N. Lois, J. Burr, J. Norrie et al., "Internal limiting membrane peeling versus no peeling for idiopathic full-thickness macular hole: a pragmatic randomized controlled trial," *Investigative Ophthalmology and Visual Science*, vol. 52, no. 3, pp. 1586–1592, 2011.

[6] L. Ternent, L. Vale, C. Boachie, J. M. Burr, and N. Lois, "Cost-effectiveness of internal limiting membrane peeling versus no peeling for patients with an idiopathic full-thickness macular hole: results from a randomised controlled trial," *British Journal of Ophthalmology*, vol. 96, no. 3, pp. 438–443, 2012.

[7] T. Yamamoto, N. Akabane, and S. Takeuchi, "Vitrectomy for diabetic macular edema: the role of posterior vitreous detachment and epimacular membrane," *American Journal of Ophthalmology*, vol. 132, no. 3, pp. 369–377, 2001.

[8] R. Tadayoni, M. Paques, P. Massin, S. Mouki-Benani, J. Mikol, and A. Gaudric, "Dissociated optic nerve fiber layer appearance of the fundus after idiopathic epiretinal membrane removal," *Ophthalmology*, vol. 108, no. 12, pp. 2279–2283, 2001.

[9] J. Sebag, "The vitreous," in *Adler's Physiology of the Eye*, W. M. Hart, Ed., pp. 268–347, Mosby-Year Book, Baltimore, Md, USA, 9th edition, 1992.

[10] B. S. Fine, "Limiting membranes of the sensory retina and pigment epithelium. An electron microscopic study," *Archives of Ophthalmology*, vol. 66, pp. 847–860, 1961.

[11] E. C. La Heij, S. C. Dieudonné, C. M. Mooy et al., "Immunohistochemical analysis of the internal limiting membrane peeled with infracyanine green," *American Journal of Ophthalmology*, vol. 140, no. 6, pp. 1123–1125, 2005.

[12] C. Guidry, "The role of Müller cells in fibrocontractive retinal disorders," *Progress in Retinal and Eye Research*, vol. 24, no. 1, pp. 75–86, 2005.

[13] F. Morescalchi, S. Duse, E. Gambicorti, M. R. Romano, C. Costagliola, and F. Semeraro, "Proliferative vitreoretinopathy after eye injuries: an overexpression of growth factors and cytokines leading to a retinal keloid," *Mediators of Inflammation*, vol. 2013, Article ID 269787, 12 pages, 2013.

[14] I. Iandiev, O. Uckermann, T. Pannicke et al., "Glial cell reactivity in a porcine model of retinal detachment," *Investigative Ophthalmology and Visual Science*, vol. 47, no. 5, pp. 2161–2171, 2006.

[15] G. Wollensak and E. Spoerl, "Biomechanical characteristics of retina," *Retina*, vol. 24, no. 6, pp. 967–970, 2004.

[16] G. Wollensak, E. Spoerl, G. Grosse, and C. Wirbelauer, "Biomechanical significance of the human internal limiting lamina," *Retina*, vol. 26, no. 8, pp. 965–968, 2006.

[17] E. Yamada, "Some structural features of the fovea centralis in the human retina," *Archives of Ophthalmology*, vol. 82, no. 2, pp. 151–159, 1969.

[18] J. D. M. Gass, "Müller cell cone, an overlooked part of the anatomy of the fovea centralis: hypotheses concerning its role in the pathogenesis of macular hole and foveomacular retinoschisis," *Archives of Ophthalmology*, vol. 117, no. 6, pp. 821–823, 1999.

[19] B. Miller, "Epiretinal macular membranes: pathogenesis and treatment," *Developments in ophthalmology*, vol. 29, pp. 61–63, 1997.

[20] Y.-N. Hui, R. Goodnight, X.-J. Zhang, N. Sorgente, and S. J. Ryan, "Glial epiretinal membranes and contraction. Immunohistochemical and morphological studies," *Archives of Ophthalmology*, vol. 106, no. 9, pp. 1280–1285, 1988.

[21] T. Kono, T. Kohno, and H. Inomata, "Epiretinal membrane formation: light and electron microscopic study in an experimental rabbit model," *Archives of Ophthalmology*, vol. 113, no. 3, pp. 359–363, 1995.

[22] S. A. Vinores, P. A. Campochiaro, R. McGehee, W. Orman, S. F. Hackett, and L. M. Hjelmeland, "Ultrastructural and immunocytochemical changes in retinal pigment epithelium, retinal glia, and fibroblasts in vitreous culture," *Investigative Ophthalmology & Visual Science*, vol. 31, no. 12, pp. 2529–2545, 1990.

[23] F. Zhao, A. Gandorfer, C. Haritoglou et al., "Epiretinal cell proliferation in macular pucker and vitreomacular traction syndrome: analysis of flat-mounted internal limiting membrane specimens," *Retina*, vol. 33, no. 1, pp. 77–88, 2013.

[24] S.-C. Bu, R. Kuijer, R. J. van der Worp et al., "Glial cells and collagens in epiretinal membranes associated with idiopathic macular holes," *Retina*, vol. 34, no. 5, pp. 897–906, 2014.

[25] E. O. Johnsen, R. C. Frøen, R. Albert et al., "Activation of neural progenitor cells in human eyes with proliferative vitreoretinopathy," *Experimental Eye Research*, vol. 98, no. 5, pp. 28–36, 2012.

[26] R. G. Schumann, K. H. Eibl, F. Zhao et al., "Immunocytochemical and ultrastructural evidence of glial cells and hyalocytes in internal limiting membrane specimens of idiopathic macular holes," *Investigative Ophthalmology and Visual Science*, vol. 52, no. 11, pp. 7822–7834, 2011.

[27] S. Kase, W. Saito, M. Yokoi et al., "Expression of glutamine synthetase and cell proliferation in human idiopatnic epiretinal membrane," *British Journal of Ophthalmology*, vol. 90, no. 1, pp. 96–98, 2006.

[28] H. Higashimori and H. Sontheimer, "Role of Kir4.1 channels in growth control of glia," *Glia*, vol. 55, no. 16, pp. 1668–1679, 2007.

[29] D. R. J. Snead, S. James, and M. P. Snead, "Pathological changes in the vitreoretinal junction 1: epiretinal membrane formation," *Eye*, vol. 22, no. 10, pp. 1310–1317, 2008.

[30] S. J. Sramek, I. H. Wallow, T. S. Stevens, and T. M. Nork, "Immunostaining of preretinal membranes for actin, fibronectin, and glial fibrillary acidic protein," *Ophthalmology*, vol. 96, no. 6, pp. 835–841, 1989.

[31] R.-I. Kohno, Y. Hata, S. Kawahara et al., "Possible contribution of hyalocytes to idiopathic epiretinal membrane formation and its contraction," *British Journal of Ophthalmology*, vol. 93, no. 8, pp. 1020–1026, 2009.

[32] A. Kampik, "Pathology of epiretinal membrane, idiopathic macular hole, and vitreomacular traction syndrome," *Retina*, vol. 32, supplement 2, pp. S194–S199, 2012.

[33] A. Gandorfer, C. Haritoglou, R. Scheler, R. Schumann, F. Zhao, and A. Kampik, "Residual cellular proliferation on the internal limiting membrane in macular pucker surgery," *Retina*, vol. 32, no. 3, pp. 477–485, 2012.

[34] A. Bringmann and A. Reichenbach, "Role of Müller cells in retinal degenerations," *Front Biosci*, vol. 6, pp. E72–E92, 2001.

[35] B. Cook, G. P. Lewis, S. K. Fisher, and R. Adler, "Apoptotic photoreceptor degeneration in experimental retinal detachment," *Investigative Ophthalmology & Visual Science*, vol. 36, no. 6, pp. 990–996, 1995.

[36] S. Nagar, V. Krishnamoorthy, P. Cherukuri, V. Jain, and N. K. Dhingra, "Early remodeling in an inducible animal model of retinal degeneration," *Neuroscience*, vol. 160, no. 2, pp. 517–529, 2009.

[37] S. K. Fisher and G. P. Lewis, "Müller cell and neuronal remodeling in retinal detachment and reattachment and their potential consequences for visual recovery: a review and reconsideration of recent data," *Vision Research*, vol. 43, no. 8, pp. 887–897, 2003.

[38] S. de Bustros, J. T. Thompson, R. G. Michels, T. A. Rice, and B. M. Glaser, "Vitrectomy for idiopathic epiretinal membranes causing macular pucker," *British Journal of Ophthalmology*, vol. 72, no. 9, pp. 692–695, 1988.

[39] R. Y. Foos, "Vitreoretinal juncture: simple epiretinal membranes," *Albrecht von Graefes Archiv fur Klinische und Experimentelle Ophthalmologie*, vol. 189, no. 4, pp. 231–250, 1974.

[40] S. Kishi, C. Demaria, and K. Shimizu, "Vitreous cortex remnants at the fovea after spontaneous vitreous detachment," *International Ophthalmology*, vol. 9, no. 4, pp. 253–260, 1986.

[41] S. Kishi and K. Shimizu, "Posterior precortical vitreous pocket," *Archives of Ophthalmology*, vol. 108, no. 7, pp. 979–982, 1990.

[42] T. Hikichi, M. Takahashi, C. L. Trempe, and C. L. Schepens, "Relationship between premacular cortical vitreous defects and idiopathic premacular fibrosis," *Retina*, vol. 15, no. 5, pp. 413–416, 1995.

[43] M. W. Johnson, "Posterior vitreous detachment: evolution and complications of its early stages," *American Journal of Ophthalmology*, vol. 149, no. 3, pp. 371–382.e1, 2010.

[44] S. Fraser-Bell, M. Guzowski, E. Rochtchina, J. J. Wang, and P. Mitchell, "Five-year cumulative incidence and progression of epiretinal membranes: the Blue Mountains Eye Study," *Ophthalmology*, vol. 110, no. 1, pp. 34–40, 2003.

[45] P. Mitchell, W. Smith, T. Chey, and A. Chang, "Prevalence and associations of epiretinal membranes: the blue mountains eye study, Australia," *Ophthalmology*, vol. 104, no. 6, pp. 1033–1040, 1997.

[46] J. Sebag, "Age-related changes in human vitreous structure," *Graefe's Archive for Clinical and Experimental Ophthalmology*, vol. 225, no. 2, pp. 89–93, 1987.

[47] M. Angi, H. Kalirai, S. E. Coupland, B. E. Damato, F. Semeraro, and M. R. Romano, "Proteomic analyses of the vitreous humour," *Mediators of Inflammation*, vol. 2012, Article ID 148039, 7 pages, 2012.

[48] J. Sebag, "Vitreoschisis," *Graefe's Archive for Clinical and Experimental Ophthalmology*, vol. 246, no. 3, pp. 329–332, 2008.

[49] J. Meskauskas, R. Repetto, and J. H. Siggers, "Shape change of the vitreous chamber influences retinal detachment and reattachment processes: is mechanical stress during eye rotations a factor?" *Investigative Ophthalmology & Visual Science*, vol. 53, no. 10, pp. 6271–6281, 2012.

[50] T. David, S. Smye, T. Dabbs, and T. James, "A model for the fluid motion of vitreous humour of the human eye during saccadic movement," *Physics in Medicine and Biology*, vol. 43, no. 6, pp. 1385–1399, 1998.

[51] R. Repetto, J. H. Siggers, and A. Stocchino, "Mathematical model of flow in the vitreous humor induced by saccadic eye rotations: effect of geometry," *Biomechanics and Modeling in Mechanobiology*, vol. 9, no. 1, pp. 65–76, 2010.

[52] H. D. Schubert, "Cystoid macular edema: the apparent role of mechanical factors," *Progress in Clinical and Biological Research*, vol. 312, pp. 277–291, 1989.

[53] D. McLeod, P. S. Hiscott, and I. Grierson, "Age-related cellular proliferation at the vitreoretinal juncture," *Eye*, vol. 1, no. 2, pp. 263–281, 1987.

[54] C. J. Pournaras, "Retinal oxygen distribution. Its role in the physiopathology of vasoproliferative microangiopathies," *Retina*, vol. 15, no. 4, pp. 332–347, 1995.

[55] M. Ehrenberg, R. J. Thresher, and R. Machemer, "Vitreous hemorrhage nontoxic to retina as a stimulator of glial and fibrous proliferation," *American Journal of Ophthalmology*, vol. 97, no. 5, pp. 611–626, 1984.

[56] T. Kono, H. Kato, and K. Oshima, "Immunohistochemical study of retinal muller cell response in experimental epiretinal membrane formation," *Journal of Japanese Ophthalmological Society*, vol. 102, no. 1, pp. 22–27, 1998.

[57] M. García-Ramírez, F. Canals, C. Hernández et al., "Proteomic analysis of human vitreous fluid by fluorescence-based difference gel electrophoresis (DIGE): a new strategy for identifying potential candidates in the pathogenesis of proliferative diabetic retinopathy," *Diabetologia*, vol. 50, no. 6, pp. 1294–1303, 2007.

[58] N. Mandal, M. Kofod, H. Vorum et al., "Proteomic analysis of human vitreous associated with idiopathic epiretinal membrane," *Acta Ophthalmologica*, vol. 91, no. 4, pp. e333–e334, 2013.

[59] T. Harada, C. Harada, Y. Mitamura et al., "Neurotrophic factor receptors in epiretinal membranes after human diabetic retinopathy," *Diabetes Care*, vol. 25, no. 6, pp. 1060–1065, 2002.

[60] C. Harada, Y. Mitamura, and T. Harada, "The role of cytokines and trophic factors in epiretinal membranes: involvement of signal transduction in glial cells," *Progress in Retinal and Eye Research*, vol. 25, no. 2, pp. 149–164, 2006.

[61] M. Hollborn, M. Francke, I. Iandiev et al., "Early activation of inflammation- and immune response-related genes after experimental detachment of the porcine retina," *Investigative Ophthalmology & Visual Science*, vol. 49, no. 3, pp. 1262–1273, 2008.

[62] T. Nakazawa, A. Matsubara, K. Noda et al., "Characterization of cytokine responses to retinal detachment in rats," *Molecular Vision*, vol. 12, pp. 867–878, 2006.

[63] G. Velez, A. R. Weingarden, B. A. Tucker, H. Lei, A. Kazlauskas, and M. J. Young, "Retinal pigment epithelium and müller progenitor cell interaction increase müller progenitor cell expression of PDGFR α and ability to induce proliferative vitreoretinopathy in a rabbit model," *Stem Cells International*, vol. 2012, Article ID 106486, 6 pages, 2012.

[64] Y. Hata, K. Nakagawa, K. Sueishi, T. Ishibashi, H. Inomata, and H. Ueno, "Hypoxia-induced expression of vascular endothelial growth factor by retinal glial cells promotes in vitro angiogenesis," *Virchows Archiv*, vol. 426, no. 5, pp. 479–486, 1995.

[65] E. Mandelcorn, Y. Khan, L. Javorska, J. Cohen, D. Howarth, and M. Mandelcorn, "Idiopathic epiretinal membranes: cell type, growth factor expression, and fluorescein angiographic and retinal photographic correlations," *Canadian Journal of Ophthalmology*, vol. 38, no. 6, pp. 457–463, 2003.

[66] M. H. Suh, J. M. Seo, K. H. Park, and H. G. Yu, "Associations between macular findings by optical coherence tomography and visual outcomes after epiretinal membrane removal," *American Journal of Ophthalmology*, vol. 147, no. 3, pp. 473.e3–480.e3, 2009.

[67] S. F. Oster, F. Mojana, M. Brar, R. M. S. Yuson, L. Cheng, and W. R. Freeman, "Disruption of the photoreceptor inner segment/outer segment layer on spectral domain-optical coherence tomography is a predictor of poor visual acuity in patients with epiretinal membranes," *Retina*, vol. 30, no. 5, pp. 713–718, 2010.

[68] J. Sebag, "Anomalous posterior vitreous detachment: a unifying concept in vitreo-retinal disease," *Graefe's Archive for Clinical and Experimental Ophthalmology*, vol. 242, no. 8, pp. 690–698, 2004.

[69] S. Lei and W. B. Wei, "Vitreomacular traction syndrome," *Chinese Medical Journal*, vol. 127, no. 8, pp. 1566–1571, 2014.

[70] M. W. Johnson, "Perifoveal vitreous detachment and its macular complications," *Transactions of the American Ophthalmological Society*, vol. 103, pp. 537–567, 2005.

[71] R. F. Spaide and Y. Fisher, "Removal of adherent cortical vitreous plaques without removing the internal limiting membrane in the repair of macular detachments in highly myopic eyes," *Retina*, vol. 25, no. 3, pp. 290–295, 2005.

[72] M. Spitznas and R. Leuenberger, "Primary epiretinal gliosis," *Klinische Monatsblatter fur Augenheilkunde*, vol. 171, no. 3, pp. 410–420, 1977.

[73] F. J. Rentsch, "The ultrastructure of preretinal macular fibrosis," *Albrecht von Graefes Archiv für Klinische und Experimentelle Ophthalmologie*, vol. 203, no. 3-4, pp. 321–337, 1977.

[74] R. B. Szamier, "Ultrastructure of the preretinal membrane in retinitis pigmentosa," *Investigative Ophthalmology and Visual Science*, vol. 21, no. 2, pp. 227–236, 1981.

[75] J. Garcia-Arumi, B. Corcostegui, N. Tallada, and F. Salvador, "Epiretinal membranes in Tersons syndrome: a clinicopathologic study," *Retina*, vol. 14, no. 4, pp. 351–355, 1994.

[76] H. P. Heidenkummer and A. Kampik, "Morphologic analysis of epiretinal membranes in surgically treated idiopathic macular foramina. Results of light and electron microscopy," *Ophthalmologe*, vol. 93, pp. 675–679, 1996.

[77] A. D. Pearlstone, "The incidence of idiopathic preretinal macular gliosis," *Annals of Ophthalmology*, vol. 17, no. 6, pp. 378–380, 1985.

[78] F. S. M. Ting and A. K. H. Kwok, "Treatment of epiretinal membrane: an update," *Hong Kong Medical Journal*, vol. 11, no. 6, pp. 496–502, 2005.

[79] R. Grewing and U. Mester, "Results of surgery for epiretinal membranes and their recurrences," *British Journal of Ophthalmology*, vol. 80, no. 4, pp. 323–326, 1996.

[80] S. R. Pesin, R. J. Olk, M. G. Grand et al., "Vitrectomy for premacular fibroplasia: prognostic factors, long-term follow-up, and time course of visual improvement," *Ophthalmology*, vol. 98, no. 7, pp. 1109–1114, 1991.

[81] R. G. Michels, "Vitreous surgery for macular pucker," *American Journal of Ophthalmology*, vol. 92, no. 5, pp. 628–639, 1981.

[82] R. R. Margherio, M. S. Cox Jr., M. T. Trese, P. L. Murphy, J. Johnson, and L. A. Minor, "Removal of epimacular membranes," *Ophthalmology*, vol. 92, no. 8, pp. 1075–1083, 1985.

[83] L. S. Poliner, R. J. Olk, M. G. Grand, R. F. Escoffery, E. Okun, and I. Boniuk, "Surgical management of premacular fibroplasia," *Archives of Ophthalmology*, vol. 106, no. 6, pp. 761–764, 1988.

[84] G. Donati, A. D. Kapetanios, and C. J. Pournaras, "Complications of surgery for epiretinal membranes," *Graefe's Archive for Clinical and Experimental Ophthalmology*, vol. 236, no. 10, pp. 739–746, 1998.

[85] T. A. Rice, S. de Bustros, R. G. Michels, J. T. Thompson, S. M. Debanne, and D. Y. Rowland, "Prognostic factors in vitrectomy for epiretinal membranes of the macula," *Ophthalmology*, vol. 93, no. 5, pp. 602–610, 1986.

[86] L. Geerts, G. Pertile, W. van de Sompel, T. Moreels, and C. Claes, "Vitrectomy for epiretinal membranes: visual outcome and prognostic criteria," *Bulletin de la Societe belge d'ophtalmologie*, no. 293, pp. 7–15, 2004.

[87] P. Massin, C. Allouch, B. Haouchine et al., "Optical coherence tomography of idiopathic macular epiretinal membranes before and after surgery," *American Journal of Ophthalmology*, vol. 130, no. 6, pp. 732–739, 2000.

[88] H. Shimada, H. Nakashizuka, T. Hattori, R. Mori, Y. Mizutani, and M. Yuzawa, "Double staining with brilliant blue G and double peeling for epiretinal membranes," *Ophthalmology*, vol. 116, no. 7, pp. 1370–1376, 2009.

[89] M. J. Banach, T. S. Hassan, M. S. Cox et al., "Clinical course and surgical treatment of macular epiretinal membranes in young subjects," *Ophthalmology*, vol. 108, no. 1, pp. 23–26, 2001.

[90] F. Kuhn, "Point: to peel or not to peel, that is the question," *Ophthalmology*, vol. 109, no. 1, pp. 9–11, 2002.

[91] S. K. Gibran, B. Flemming, T. Stappler et al., "Peel and peel again," *British Journal of Ophthalmology*, vol. 92, no. 3, pp. 373–377, 2008.

[92] A. K. H. Kwok, T. Y. Y. Lai, W. W. Y. Li, D. C. F. Woo, and N. R. Chan, "Indocyanine green-assisted internal limiting membrane removal in epiretinal membrane surgery: a clinical and histologic study," *American Journal of Ophthalmology*, vol. 138, no. 2, pp. 194–199, 2004.

[93] A. K. H. Kwok, T. Y. Y. Lai, W. W. Y. Li, D. T. W. Yew, and V. W. Y. Wong, "Trypan blue- and indocyanine green-assisted epiretinal membrane surgery: clinical and histopathological studies," *Eye*, vol. 18, no. 9, pp. 882–888, 2004.

[94] A. K. H. Kwok, T. Y. Y. Lai, and K. S. C. Yuen, "Epiretinal membrane surgery with or without internal limiting membrane peeling," *Clinical and Experimental Ophthalmology*, vol. 33, no. 4, pp. 379–385, 2005.

[95] A. M. Maguire, W. E. Smiddy, S. K. Nanda, R. G. Michels, Z. de la Cruz, and W. R. Green, "Clinicopathologic correlation of recurrent epiretinal membranes after previous surgical removal," *Retina*, vol. 10, no. 3, pp. 213–222, 1990.

[96] A. Gaudric, C. Fardeau, M. Goberville et al., "Ablation of the internal limiting membrane, macular unfolding and visual outcome in surgery of idiopathic epimacular membranes," *Journal Français d'Ophtalmologie*, vol. 16, no. 11, pp. 571–576, 1993.

[97] E. H. Bovey, S. Uffer, and F. Achache, "Surgery for epimacular membrane: impact of retinal internal limiting membrane removal on functional outcome," *Retina*, vol. 24, no. 5, pp. 728–735, 2004.

[98] A. Sivalingam, R. C. Eagle Jr., J. S. Duker et al., "Visual prognosis correlated with the presence of internal-limiting membrane in histopathologic specimens obtained from epiretinal membrane surgery," *Ophthalmology*, vol. 97, no. 11, pp. 1549–1552, 1990.

[99] D. W. Park, P. U. Dugel, J. Garda et al., "Macular pucker removal with and without internal limiting membrane peeling: pilot study," *Ophthalmology*, vol. 110, no. 1, pp. 62–64, 2003.

[100] C. Haritoglou, A. Gandorfer, C. A. Gass, M. Schaumberger, M. W. Ulbig, and A. Kampik, "The effect of indocyanine-green on functional outcome of macular pucker surgery," *American Journal of Ophthalmology*, vol. 135, no. 3, pp. 328–337, 2003.

[101] C. Haritoglou, K. Eibl, M. Schaumberger et al., "Functional outcome after trypan blue-assisted vitrectomy for macular pucker: A prospective, randomized, comparative trial," *American Journal of Ophthalmology*, vol. 138, no. 1, pp. 1–5, 2004.

[102] T. Hasegawa, K. Emi, T. Ikeda, M. Watanabe, and G. Takaoka, "Long-term prognosis of internal limiting membrane peeling for idiopathic epiretinal membrane," *Nippon Ganka Gakkai zasshi*, vol. 108, no. 3, pp. 150–156, 2004.

[103] S. Rizzo, F. Genovesi-Ebert, S. Murri et al., "25-gauge, sutureless vitrectomy and standard 20-gauge pars plana vitrectomy in idiopathic epiretinal membrane surgery: a comparative pilot study," *Graefe's Archive for Clinical and Experimental Ophthalmology*, vol. 244, no. 4, pp. 472–479, 2006.

[104] R. Sorcinelli, "Surgical management of epiretinal membrane with indocyanine-green-assisted peeling," *Ophthalmologica*, vol. 217, no. 2, pp. 107–110, 2003.

[105] J. W. Lee and I. T. Kim, "Outcomes of idiopathic macular epiretinal membrane removal with and without internal limiting membrane peeling: a comparative study," *Japanese Journal of Ophthalmology*, vol. 54, no. 2, pp. 129–134, 2010.

[106] C. J. Pournaras, A. Emarah, and I. K. Petropoulos, "Idiopathic macular epiretinal membrane surgery and ILM peeling: anatomical and functional outcomes," *Seminars in Ophthalmology*, vol. 26, no. 2, pp. 42–46, 2011.

[107] K. Kadonosono, N. Itoh, E. Uchio, S. Nakamura, and S. Ohno, "Staining of internal limiting membrane in macular hole surgery," *Archives of Ophthalmology*, vol. 118, no. 8, pp. 1116–1118, 2000.

[108] S. E. Burk, A. P. Da Mata, M. E. Snyder, R. H. Rosa Jr., and R. E. Foster, "Indocyanine green-assisted peeling of the retinal internal limiting membrane," *Ophthalmology*, vol. 107, no. 11, pp. 2010–2014, 2000.

[109] A. P. da Mata, S. E. Burk, C. D. Riemann et al., "Indocyanine green-assisted peeling of the retinal internal limiting membrane during vitrectomy surgery for macular hole repair," *Ophthalmology*, vol. 108, no. 7, pp. 1187–1192, 2001.

[110] A. P. da Mata, S. E. Burk, R. E. Foster et al., "Long-term follow-up of indocyanine green-assisted peeling of the retinal internal limiting membrane during vitrectomy surgery for idiopathic macular hole repair," *Ophthalmology*, vol. 111, no. 12, pp. 2246–2253, 2004.

[111] A. W. A. Weinberger, B. Schlossmacher, C. Dahlke, M. Hermel, B. Kirchhof, and N. F. Schrage, "Indocyanine-green-assisted internal limiting membrane peeling in macular hole surgery—a follow-up study," *Graefe's Archive for Clinical and Experimental Ophthalmology*, vol. 240, no. 11, pp. 913–917, 2002.

[112] P. Stalmans, R. Parys-Vanginderdeuren, R. De Vos, and E. J. Feron, "ICG staining of the inner limiting membrane facilitates its removal during surgery for macular holes and puckers," *Bulletin de la Societe Belge d'Ophtalmologie*, vol. 281, pp. 21–26, 2001.

[113] J. Hillenkamp, P. Saikia, W. A. Herrmann, C. Framme, V.-P. Gabel, and H. G. Sachs, "Surgical removal of idiopathic epiretinal membrane with or without the assistance of indocyanine green: a randomised controlled clinical trial," *Graefe's Archive for Clinical and Experimental Ophthalmology*, vol. 245, no. 7, pp. 973–979, 2007.

[114] A. Gandorfer, C. Haritoglou, C. A. Gass, M. W. Ulbig, and A. Kampik, "Indocyanine green-assisted peeling of the internal limiting membrane may cause retinal damage," *American Journal of Ophthalmology*, vol. 132, no. 3, pp. 431–433, 2001.

[115] A. W. A. Weinberger, B. Kirchhof, B. E. Mazinani, and N. F. Schrage, "Persistent indocyanine green (ICG) fluorescence 6 weeks after intraocular ICG administration for macular hole surgery," *Graefe's Archive for Clinical and Experimental Ophthalmology*, vol. 239, no. 5, pp. 388–390, 2001.

[116] A. Gandorfer, C. Haritoglou, and A. Kampik, "Toxicity of indocyanine green in vitreoretinal surgery," *Developments in Ophthalmology*, vol. 42, pp. 69–81, 2008.

[117] E. B. Rodrigues, C. H. Meyer, S. Mennel, and M. E. Farah, "Mechanisms of intravitreal toxicity of indocyanine green dye: implications for chromovitrectomy," *Retina*, vol. 27, no. 7, pp. 958–970, 2007.

[118] N. E. Engelbrecht, J. Freeman, P. Sternberg Jr. et al., "Retinal pigment epithelial changes after macular hole surgery with indocyanine green-assisted internal limiting membrane peeling," *American Journal of Ophthalmology*, vol. 133, no. 1, pp. 89–94, 2002.

[119] S. Wolf, U. Schnurbusch, P. Wiedemann, J. Grosche, A. Reichenbach, and H. Wolburg, "Peeling of the basal membrane in the human retina: ultrastructural effects," *Ophthalmology*, vol. 111, no. 2, pp. 238–243, 2004.

[120] T. L. Kersey, A. Bolton, and C. K. Patel, "Serial autofluorescence imaging over two years following indocyanine green-assisted internal limiting membrane peel for macular hole," *Clinical and Experimental Ophthalmology*, vol. 33, no. 5, pp. 538–539, 2005.

[121] D. Shukla, J. Kalliath, N. Neelakantan, K. B. Naresh, and K. Ramasamy, "A comparison of brilliant blue g, trypan blue, and indocyanine green dyes to assist internal limiting membrane peeling during macular hole surgery," *Retina*, vol. 31, no. 10, pp. 2021–2025, 2011.

[122] M. Remy, S. Thaler, R. G. Schumann et al., "An in vivo evaluation of Brilliant Blue G in animals and humans," *British Journal of Ophthalmology*, vol. 92, no. 8, pp. 1142–1147, 2008.

[123] L. H. M. El-Shazly, A. A. El-Gohary, and G. G. El-Hossary, "Safety of intravitreal triamcinolone acetonide: an electrophysiologic and histopathological study in rabbits," *International Journal of Ophthalmology*, vol. 6, no. 6, pp. 790–795, 2013.

[124] T. Sakamoto and T. Ishibashi, "Visualizing vitreous in vitrectomy by triamcinolone," *Graefe's Archive for Clinical and Experimental Ophthalmology*, vol. 247, no. 9, pp. 1153–1163, 2009.

[125] S.-Y. Yu, F. M. Damico, F. Viola, D. J. D'Amico, and L. H. Young, "Retinal toxicity of intravitreal triamcinolone acetonide: a morphological study," *Retina*, vol. 26, no. 5, pp. 531–536, 2006.

[126] E. B. Cardoso, M. Moraes-Filho, E. B. Rodrigues et al., "Investigation of the retinal biocompatibility of acid violet for chromovitrectomy," *Graefe's Archive for Clinical and Experimental Ophthalmology*, vol. 251, no. 4, pp. 1115–1121, 2013.

[127] M. F. Marmor, "Mechanisms of fluid accumulation in retinal edema," *Documenta Ophthalmologica*, vol. 97, no. 3-4, pp. 239–249, 1999.

[128] N. Kenawy, D. Wong, T. Stappler et al., "Does the presence of an epiretinal membrane alter the cleavage plane during internal limiting membrane peeling?" *Ophthalmology*, vol. 117, no. 2, pp. 320–323.e1, 2010.

[129] M. Abo EL Enin, H. El-Toukhy, and A. Swelam, "Non-foveal macular holes after PPV for macular pucker," *Middle East African Journal of Ophthalmology*, vol. 17, no. 3, p. 254, 2010.

[130] H. N. Oh, J. E. Lee, H. W. Kim, and I. H. Yun, "Clinical outcomes of double staining and additional ILM peeling during ERM surgery," *Korean Journal of Ophthalmology*, vol. 27, no. 4, pp. 256–260, 2013.

[131] A. Clark, N. Balducci, F. Pichi et al., "Swelling of the arcuate nerve fiber layer after internal limiting membrane peeling," *Retina*, vol. 32, no. 8, pp. 1608–1613, 2012.

[132] S. B. Lee, Y. I. Shin, Y. J. Jo, and J. Y. Kim, "Longitudinal changes in retinal nerve fiber layer thickness after vitrectomy for epiretinal membrane," *Investigative Ophthalmology & Visual Science*, vol. 55, no. 10, pp. 6607–6611, 2014.

[133] Y. Mitamura and K. Ohtsuka, "Relationship of dissociated optic nerve fiber layer appearance to internal limiting membrane peeling," *Ophthalmology*, vol. 112, no. 10, pp. 1766–1770, 2005.

[134] N. Balducci, M. Morara, C. Veronese, C. Torrazza, F. Pichi, and A. P. Ciardella, "Retinal nerve fiber layer thickness modification after internal limiting membrane peeling," *Retina*, vol. 34, no. 4, pp. 655–663, 2014.

[135] T. Baba, S. Yamamoto, R. Kimoto, T. Oshitari, and E. Sato, "Reduction of thickness of ganglion cell complex after internal limiting membrane peeling during vitrectomy for idiopathic macular hole," *Eye*, vol. 26, no. 9, pp. 1173–1180, 2012.

[136] U. C. Christensen, K. Krøyer, B. Sander et al., "Value of internal limiting membrane peeling in surgery for idiopathic macular hole stage 2 and 3: a randomised clinical trial," *British Journal of Ophthalmology*, vol. 93, no. 8, pp. 1005–1015, 2009.

[137] E. Cappello, G. Virgili, L. Tollot, M. D. Borrello, U. Menchini, and M. Zemella, "Reading ability and retinal sensitivity after surgery for macular hole and macular pucker," *Retina*, vol. 29, no. 8, pp. 1111–1118, 2009.

[138] K. Tamura, Y. Matsui, T. Sugimoto et al., "Longterm course of indings simulating dissociated optic nerve fiber layer following peeling of internal limiting membrane," *Rinsho Ganka*, vol. 58, pp. 381–385, 2004.

[139] H. Terasaki, Y. Miyake, R. Nomura et al., "Focal macular ERGs in eyes after removal of macular ILM during macular hole surgery," *Investigative Ophthalmology & Visual Science*, vol. 42, no. 1, pp. 229–234, 2001.

[140] R. Jacek, C. Katarzyna, F. Małgorzata, W. Joanna, and S. Andrzej, "Müller glial cells—the mediators of vascular disorders with vitreomacular interface pathology in diabetic maculopathy," *Klinika Oczna*, vol. 112, no. 10–12, pp. 328–332, 2010.

[141] J. Robaszkiewicz, K. Chmielewska, M. Figurska, J. Wierzbowska, and A. Stankiewicz, "Müller glial cells—the mediators of vascular disorders with vitreomacular interface pathology in diabetic maculopathy," *Klinika Oczna*, vol. 112, no. 10–12, pp. 328–332, 2010.

[142] C. Carpentier, M. Zanolli, L. Wu et al., "Residual internal limiting membrane after epiretinal membrane peeling: results of the Pan-American Collaborative Retina Study Group," *Retina*, vol. 33, no. 10, pp. 2026–2031, 2013.

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Research Article

Correlative Microscopy of Lamellar Hole-Associated Epiretinal Proliferation

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Purpose. To describe morphology of lamellar hole-associated epiretinal proliferation (LHEP) removed from eyes with lamellar macular holes (LMH). *Methods*. Based on optical coherence tomography data, 10 specimens of LHEP were removed from 10 eyes with LMH during standard vitrectomy. Specimens were prepared for correlative light and electron microscopy (CLEM) using an immunonanogold particle of 1.4 nm diameter that was combined with a fluorescein moiety, both having been attached to a single antibody fragment. As primary antibodies, we used antiglial fibrillary acidic protein (GFAP), anti-CD45, anti-CD64, anti-α-smooth muscle actin (α-SMA), and anticollagen type I and type II. *Results*. In LHEP, GFAP-positive cells possess ultrastructural characteristics of fibroblasts and hyalocytes. They represent the major cell types and were densely packed in cell agglomerations on vitreous collagen strands. Epiretinal cells of LHEP rarely demonstrated contractive properties as α-SMA-positive myofibroblasts were an infrequent finding. *Conclusion*. CLEM indicates that epiretinal cells in LHEP might originate from the vitreous and that remodelling processes of vitreous collagen may play an important role in pathogenesis of eyes with LMH.

1. Introduction

Recently, the term of lamellar hole-associated epiretinal proliferation (LHEP) was introduced by Pang and colleagues to characterize a thick homogenous layer of unusual material on the epiretinal surface in eyes with lamellar macular holes (LMH) [1, 2]. High-resolution optical coherence tomography (OCT) studies have demonstrated that eyes with LMH frequently show this epiretinal proliferation presenting as a highly reflective line with moderately reflective material filling the space between the inner border of the epiretinal proliferation and the retinal nerve fibre layer [3–7].

However, pathogenesis, morphology, and clinical course of eyes with LHEP are poorly understood. By recent OCT studies, the presence of LHEP was shown to be related to the presence of photoreceptor layer defects and poor visual acuity compared to eyes with LMH without LHEP [1, 2, 8]. On OCT examination, LHEP does not appear to have contractive properties [1, 2, 5, 8]. In general, traction forces by conventional ERM become visible as retinal folds that are usually not seen in retinal layers covered by LHEP.

Since there is little detail on cell and collagen composition of LHEP, the aim of this study was to describe morphologic characteristics of LHEP in eyes with LMH by correlative microscopy. Correlative light and electron microscopy (CLEM) was recently proposed using immunonanogold particles of 1.4 nm diameter combined with a fluorescein moiety that both are attached to a single antibody fragment [9–11]. In this study, we used CLEM for improved visualization of cells and extracellular matrix of LHEP [12].

2. Materials and Methods

2.1. Patient Samples. Surgically excised specimens of LHEP were consecutively harvested from 10 eyes of 10 patients with lamellar macular holes during vitrectomy. All patients required surgery due to the severity of clinical symptoms such as progressive visual loss. Patients' records were reviewed for age, gender, previous ocular surgery, and preoperative

history such as trauma. All specimens were obtained from patients who were part of a recent retrospective OCT study reporting on clinical course of 112 operated and nonoperated eyes with lamellar macular holes and macular pseudoholes [8]. Clinical data of patients and volume B-scans of high-resolution OCT examinations (Spectralis OCT, Heidelberg Engineering, Heidelberg, Germany) were reevaluated in order to exclusively include eyes with presence of LHEP. This study was approved by the Institutional Review Board and Ethics Committee and was conducted according to the tenets of the Declaration of Helsinki. Informed consent was obtained from all patients before surgery.

2.2. Surgical Procedure. Patients underwent a standard 23-gauge vitrectomy. Surgery was recommended if BCVA decreased to LogMAR 0.3 or more, if BCVA decreased 2 Snellen lines or more during the preoperative follow-up period, and if the patient experienced a significant impairment of the quality of life. If necessary, a posterior vitreous detachment (PVD) was induced by suction with the vitrectomy probe around the optic nerve head. The posterior hyaloid was detached from the retina and PVD was extended to the periphery with the vitreous being removed at least up to the equator. For removal of LHEP, intraocular end-gripping forceps were used. For ILM peeling, a 0.25 mg/mL solution of Brilliant Blue (Brilliant Peel, Fluoron GmbH, Neu-Ulm, Germany) was used. The vitreous cavity was then filled with a tamponade of either 15% hexafluoroethane (C2F6) gas-air mixture, or air, or balanced salt solution. Infrequently, patients were instructed to keep a face-down position for at least 2 days.

2.3. Specimen Preparation. For fixation, specimens were placed into 2% paraformaldehyde solution. Indirect immunocytochemistry was performed for all specimens after flat-mount preparation following interference and phase contrast microscopy. If necessary, large specimens were divided into pieces in accordance with their size in order to label excised tissue of each patient with all antibodies. Specimens were incubated with 0.1% pepsin and normal donkey serum. Primary antibodies for glial and retinal cells (antiglial fibrillary acidic protein (anti-GFAP), DAKO, Hamburg, Germany); for hyalocytes (anti-CD45 and anti-CD64, Santa Cruz Biotechnology, Heidelberg, Germany); for myofibroblasts (anti-α-smooth muscle actin (anti-α-SMA), Santa Cruz Biotechnology, Heidelberg, Germany); and for extracellular matrix (anticollagen type I (anti-col-I), Santa Cruz Biotechnology, Heidelberg, Germany; anticollagen type II (anti-col-II), Biotrend, Cologne, Germany) were added and incubated over night at room temperature. As second antibody, FluoroNanogold (Fab′-fragments, Nanoprobes, Yaphank, NY, USA) was incubated for two hours at room temperature. Postfixation with 2% glutaraldehyde was following.

Preparing negative controls, specimens with large area and multilayered cell proliferation were cut into half in order to use one part for labelling procedures and the other part for negative control preparation. The primary antibody was substituted with both diluent and isotype controls (IgG2a monoclonal mouse antibodies, X0934, DAKO, Hamburg, Germany; M5409, Sigma-Aldrich, Taufkirchen, Germany). All other procedures were identical to the procedures illustrated above.

Flat-mount preparation of LHEP specimens was performed as recently reported [12]. Following fluorescence microscopic analysis (Leica DM 2500, Wetzlar, Germany) at magnifications between ×50 and ×400, specimens were processed for transmission electron microscopy. Specimens were incubated with gold enhancement solution. Postfixation in osmium tetroxide 2% and uranyl acetate as well as dehydration and embedding in Epon 812 was following. Ultrathin sections of 60 nm were obtained by series-sectioning and were contrasted with uranyl acetate and lead citrate. Analysis and imaging of 5 grids (each with 6–9 ultrathin sections) per specimen were performed using a transmission electron microscope Zeiss EM 9 S-2 (Zeiss, Jena, Germany).

3. Results

3.1. Clinical Data Analysis. This is a series of 10 surgically excised specimens of LHEP obtained during vitrectomy from eyes with lamellar macular holes. Patients' mean age was 70 ± 6 years (median, 70 years; range, 63–82 years). We included four women and six men.

Preoperatively median BCVA of eyes with LMH was LogMAR 0.40 (mean 0.41 ± 0.13 SD) and increased postoperatively to median BCVA of LogMAR 0.30 (mean 0.34 ± 0.19 SD) during a mean follow-up period of 8.6 months (median 10 months; range, 3–15 months). The difference was not statistically significant (Wilcoxon test, $p > 0.05$). In detail, 6 of 10 patients improved visual acuity, whereas 3 of 10 patients lost vision, and in one patient BCVA remained unchanged. From the eyes with LHEP only, 4 of 5 eyes improved BCVA, whereas one of 5 patients lost vision acuity. Considering eyes with a combination of both LHEP and an extrafoveal conventional ERM, 2 of 5 patients improved vision acuity. Two of 5 patients lost BCVA and one patient was stable.

At time of surgery, 8 of 10 eyes were phakic and 2 eyes were pseudophakic. All of the phakic eyes underwent combined vitrectomy with cataract extraction and intraocular lens implantation. Regarding the presence of posterior vitreous detachment (PVD), a complete PVD was seen in 4 of 10 eyes as intraoperatively assessed by the surgeon. A partial PVD was documented in 4 of 10 eyes, and an attached posterior vitreous was found in 2 of 10 eyes. Postoperatively, none of the eyes developed a full-thickness macular hole and no persistent macular edema was noted.

In SD-OCT examinations, LHEP was directly located at the macular defect (Figures 1(a) and 1(b)). In half of all eyes, a combination of both LHEP and a conventional ERM with contractive properties was seen. If present, conventional ERM was found extrafoveal with some distance to the foveal defect (Figure 1(c)). Preoperatively, defects of the ellipsoid zone were detected in 8 of 10 eyes (Table 1). In 2 eyes, defects of the external limiting membrane (ELM) were documented.

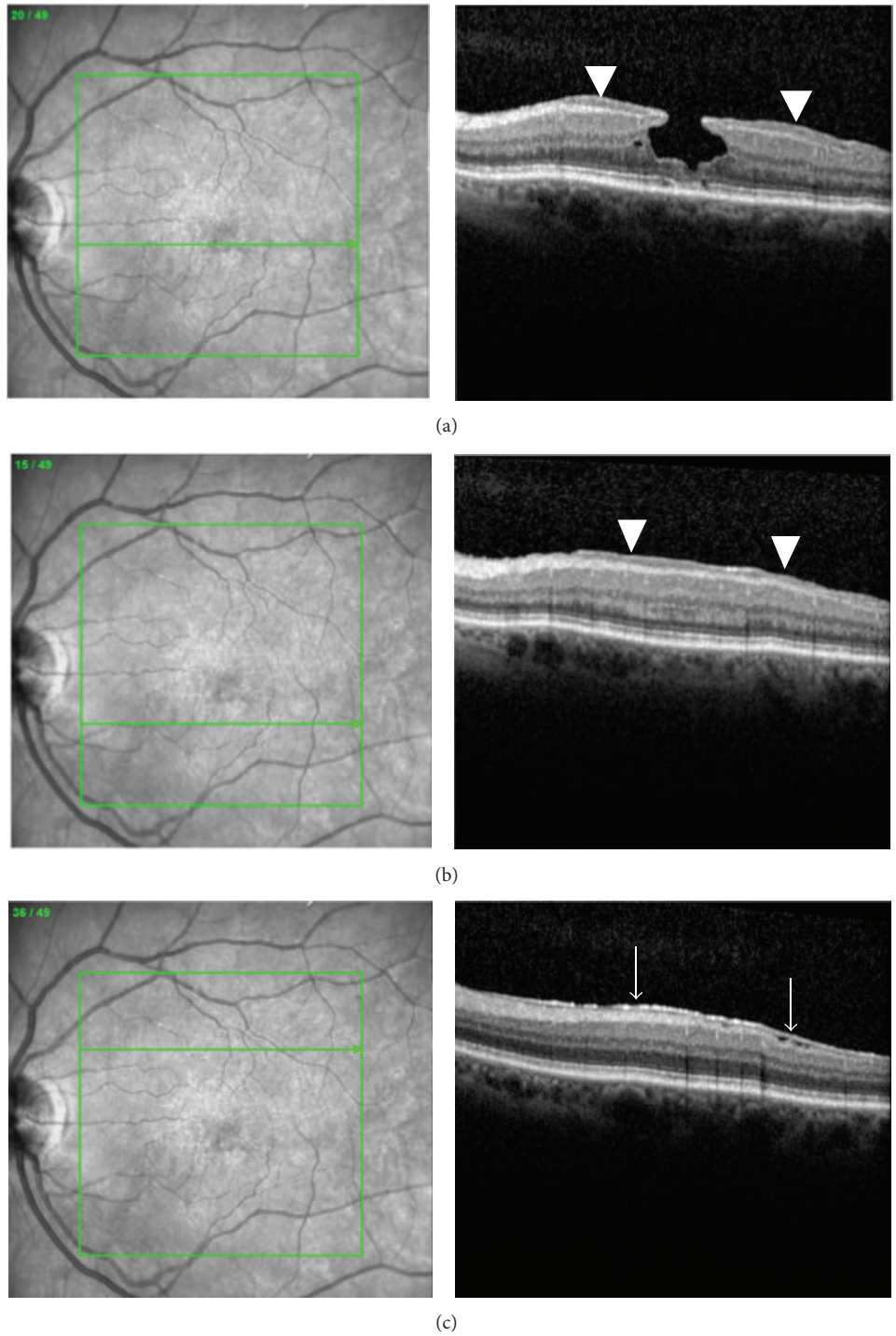

Figure 1: Spectral-domain optical coherence tomography images of a 73-year-old female with lamellar macular hole and lamellar hole-associated epiretinal proliferation (arrowheads) seen (a) at the macular defect and (b) in the parafoveal area. (c) A conventional epiretinal membrane (arrows) was found extrafoveal with some distance to the foveal defect.

At last follow-up, defects of the ellipsoid zone were seen in 7 of 10 eyes. Discontinuity of the ELM was seen in one eye.

3.2. Correlative Light and Electron Microscopy. Analysing flat-mounted specimens, positive immunostaining for anti-GFAP and for the hyalocyte cell markers anti-CD45 and anti-CD64 was seen in all eyes with LHEP (Table 1, Figure 2). Anticollagen type I was often positive as well as immunolabelling for anticollagen type II. Moreover, a colocalisation of anti-GFAP with anti-CD64 as well as anticollagen type I was seen in several specimens. In negative control specimens, no specific positive immunostaining was observed.

Table 1: Analysis of spectral-domain optical coherence tomography (SD-OCT) and immunocytochemistry of lamellar hole-associated proliferation (LHEP) removed from eyes with lamellar macular holes (LMH).

ID number	LHEP	ERM	SD-OCT analysis				Immunocytochemistry					
			Preop defect of ellipsoid zone	Preop defect of ELM	Postop defect of ellipsoid zone	Postop defect of ELM	Anti-GFAP	Anti-CD45	Anti-CD64	Anti-α-SMA	Anticollagen type I	Anticollagen type II
1	+	+	+	−	+	−	+	+	+	(+)	(+)	+
2	+	+	+	+	+	−	+	+	+	+	+	+
3	+	−	+	−	+	−	++	+	+	(+)	(+)	+
4	+	+	−	−	−	−	+	+	+	+	(+)	+
5	+	−	+	−	−	−	+	(+)	+	−	+	(+)
6	+	−	+	−	+	−	++	+	(+)	(+)	+	+
7	+	+	+	+	+	+	+	+	+	−	+	+
8	+	−	+	−	+	−	++	+	+	−	+	(+)
9	+	−	+	−	+	−	+	+	(+)	−	+	+
10	+	+	−	−	−	−	++	+	+	(+)	+	+

ERM: epiretinal membrane; extrafoveal location with contractive properties; ELM: external limiting membrane; GFAP: glial fibrillary acidic protein; α-SMA: α-smooth muscle actin.

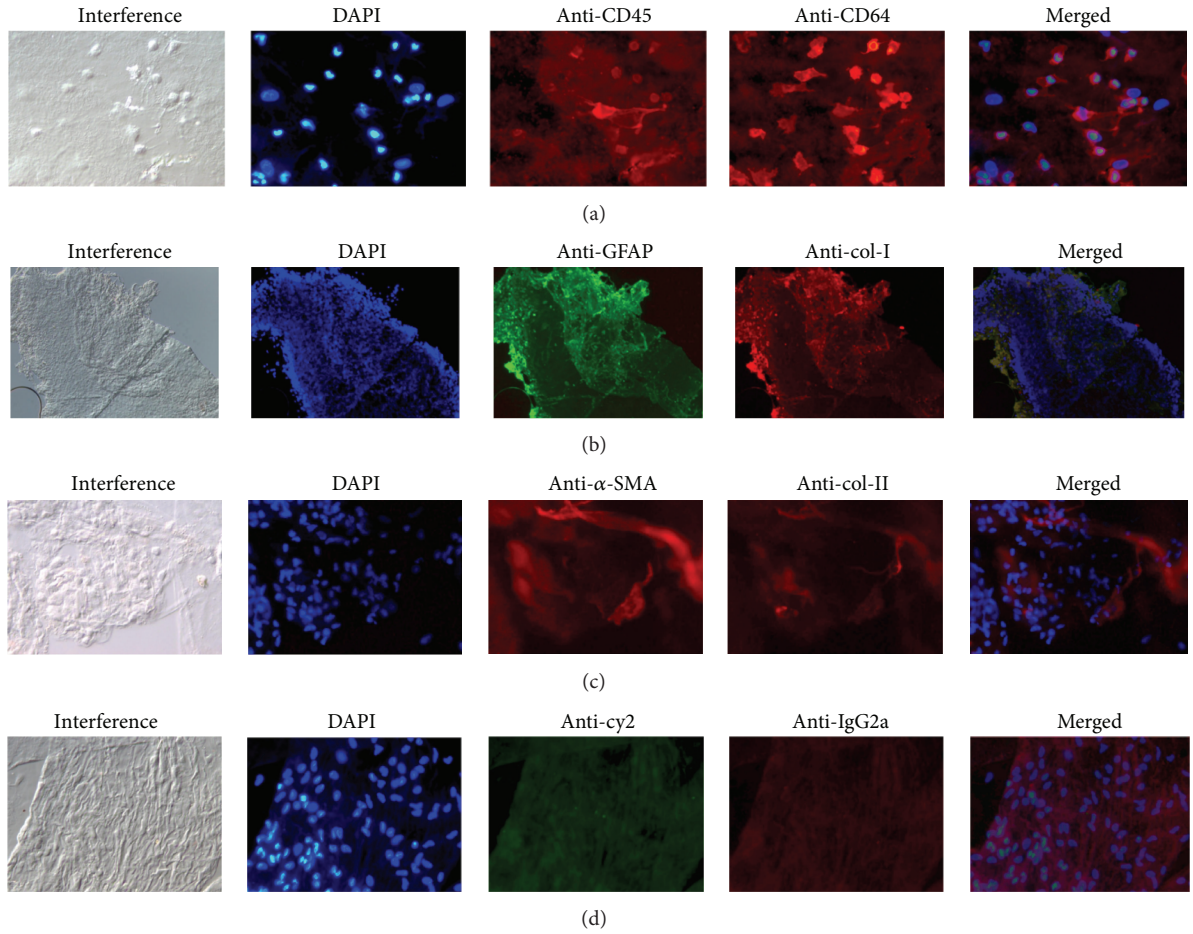

FIGURE 2: Interference microscopy, cell nuclei staining with 4′,6-diamidino-2-phenylindole, DAPI (blue), and immunocytochemical staining of lamellar hole-associated epiretinal proliferation removed from eyes with lamellar macular holes (LMH). (a) Epiretinal cells show positive immunolabelling with anti-CD45 (red) and anti-CD64 (red) in specimen removed from eyes with LMH. (b) Immunostaining of epiretinal cells seen as a thick homogenous layer positively labelled with anti-GFAP (green) and anticollagen type I (anti-col-I) (red). (c) Immunolabelling with anti-α-smooth muscle actin (α-SMA) (red) and anticollagen type II (anti-col-II) (red). (d) Negative control specimen with positive cell nuclei staining but no specific immunoreactivity of cell proliferation. (Original magnification: (a) ×400; (b) ×100; (c-d) ×400).

By transmission electron microscopy, the ILM was characterized by its undulated retinal side and the smooth vitreal side. The ILM was noted in 8 of 10 specimens removed from eyes with LMH. The ILM was clearly differentiated from thick collagen strands.

In epiretinal cell proliferation, fibroblasts and hyalocytes were the predominant cell types (Figure 3). Fibroblasts were characterized by their abundant rough endoplasmatic reticulum, prominent golgi complex, and a fusiform shape of the cell body and nucleus. Hyalocytes were distinguished by their lobulated cell nuclei, intracellular vacuoles, vesicles, and mitochondria as well as long cell fibers. Myofibroblasts containing cell fibers with contractile forces were rarely found. In the collagen matrix, native vitreous collagen (NVC) was predominant and identified as major type of collagen. It is characterized by a regular arrangement of fibrils with a collagen fibril diameter of less than 16 nm. Newly formed collagen (NFC) with irregular fibril arrangement and fibril diameter of more than 16 nm was seen as well. In NVC, fibrous long spacing collagen (FLSC) was frequently found.

Negative controls did show neither specific labelling of cellular structures nor extracellular components by immunonanogold labelling.

4. Conclusions

This is the first correlative light and electron microscopic study presenting histopathologic data of LHEP by using application of immunonanogold. Correlative light and electron microscopy was recently reported to improve visualization of cells and extracellular matrix in epiretinal membranes by using FluoroNanogold as secondary antibody. It composes an immunonanogold particle of 1.4 nm diameter that is combined with a fluorescein moiety and a single antibody Fab-fragment [9–12]. By application of immunonanogold particles, we were able to analyse the same cellular and

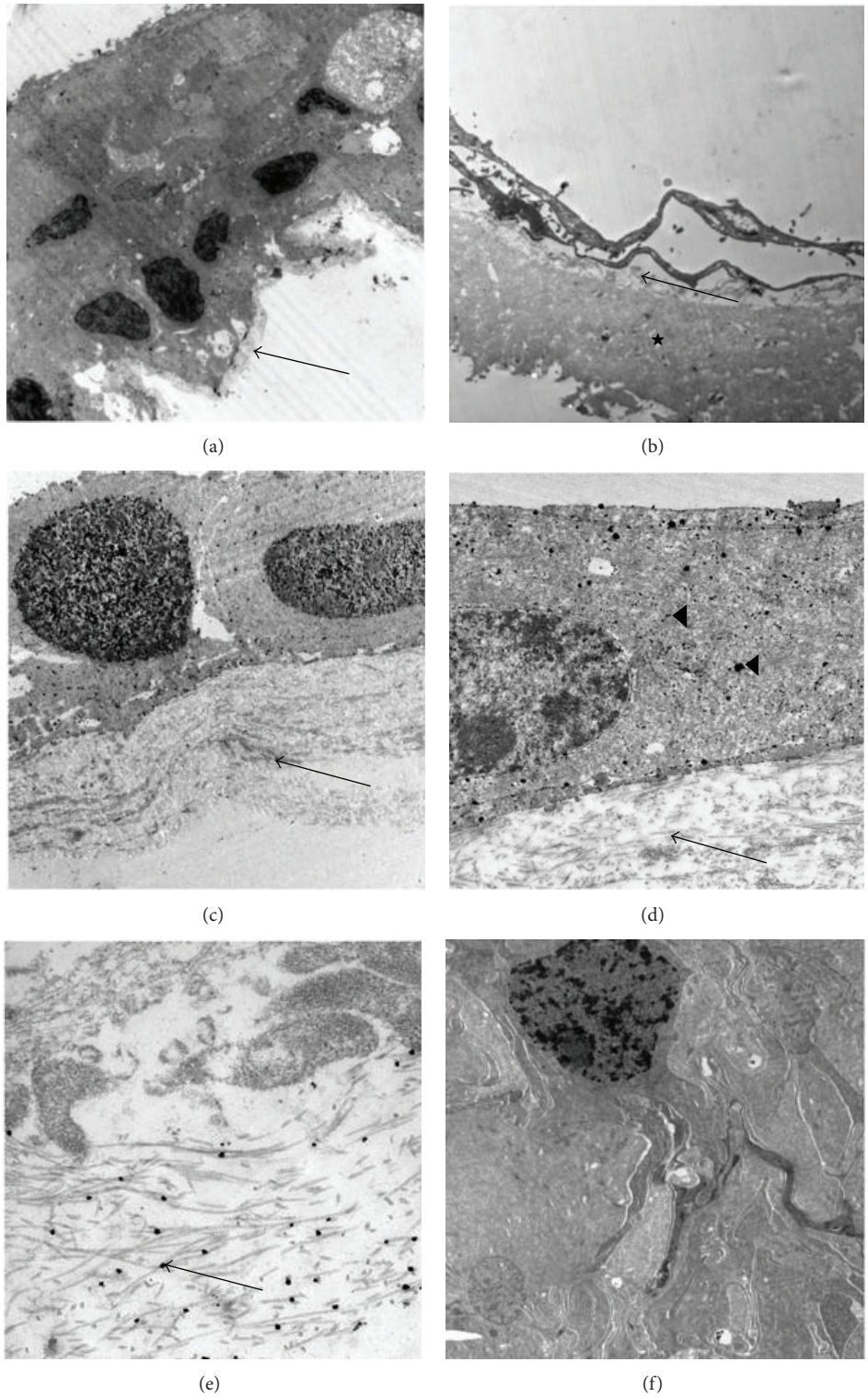

Figure 3: Transmission electron micrographs of lamellar hole-associated epiretinal proliferation (LHEP) with immunonanogold application following gold enhancement preparation procedures. (a) Densely packed cell agglomeration of fibroblasts and hyalocytes situated on a thin strand of vitreous collagen (arrow). (b) Internal limiting membrane (big star) with small vitreous collagen deposits (arrow) and fine cellular processes on the vitreal side. (c, d) Native vitreous collagen (arrow) with GFAP-positive fibroblasts as demonstrated by immunonanogold staining (arrowhead). (e) Small black dots (arrow) represent immunonanogold particles staining collagen type II of vitreous cortex collagen. (f) Negative control specimen with typical dense epiretinal cell proliferation seen as cell agglomeration of fibroblast-like cells. (Original magnification: (a) ×3,000; (b) ×4,400; (c, f) ×7,500; (d) ×18,000; (e) ×55,000).

extracellular components of LHEP by fluorescence and electron microscopy.

Lamellar hole-associated epiretinal proliferation was recently suggested to be primarily driven by a proliferation of Müller cells onto the inner retina originating from the middle layers of the retina [1, 2]. In this study, we demonstrated GFAP-positive cells in LHEP. This finding is in accordance with immunohistological results of Parolini and colleagues, who also presented cells with positive immunostaining of anti-GFAP [5]. In the majority of studies, immunoreactivity for GFAP in epiretinal membranes was usually interpreted as an indicator for the presence of glial cells [13]. However, electron microscopy revealed fibroblasts as predominant cell type in this analysis. Hyalocytes were seen as well.

More recent studies demonstrated positive GFAP staining in other cell populations than glia. Of note, fibroblasts and hyalocytes were occasionally described to be GFAP-positive [14–18]. Several species were found to present GFAP-positive hyalocytes, including porcine, pectineal, and bovine hyalocyte cell lines. Therefore, we hypothesize that vitreous derived cells rather than cells of glial origin may play a major role in pathogenesis of LMH with LHEP. In this series, fibroblasts were often seen densely packed in cell agglomerations, mostly situated on vitreous collagen strands. These cell agglomerations did not show signs of contraction. In contrast, myofibroblast-like cells with contractive properties were a rare finding. Our observations are in accordance with SD-OCT examinations demonstrating a thick homogenous layer of unusual material on the epiretinal surface in eyes with lamellar macular holes that does not show contraction signs [1, 2].

Predominance of vitreous collagen in specimens of LHEP was reported by Parolini et al. and has been confirmed by this study [5]. Native vitreous collagen fibrils were arranged as thick collagen strands often dispersed with fibrous long spacing collagen that is known to represent a remodelling process of vitreous collagen [18, 19]. Thus, LHEP appears to primarily consist of vitreous derived cells proliferating on vitreous collagen strands that are marked by degradation and remodelling of collagen components.

In this study, the majority of eyes with LHEP showed defects of the ellipsoid zone in preoperative SD-OCT examinations, which is in accordance with previous reports on disruptions of the outer photoreceptor layer in LMH [2, 8]. Furthermore, recent studies demonstrated that the presence of LHEP correlated with defects of the ellipsoid zone and the ELM layer [8, 20, 21]. However, it is still unknown why eyes with LMH do not respond to ERM/ILM peeling as positively as expected [6, 22–24]. Differences in contractive properties of epiretinal cell proliferation might partly explain these postoperative findings and should be taken into consideration when recommending surgical intervention in eyes with LMH. In this study, half of all eyes with LHEP were accompanied by eccentric foci of conventional ERM. In these cases of LMH, macular surgery might be indicated and surgical outcome of these eyes should be addressed in further studies.

Conflict of Interests

The authors have no proprietary interest in any aspect of this study.

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References

[1] C. E. Pang, R. F. Spaide, and K. B. Freund, "Epiretinal proliferation seen in association with lamellar macular holes: a distinct clinical entity," *Retina*, vol. 34, pp. 1513–1523, 2014.

[2] C. E. Pang, R. F. Spaide, and K. B. Freund, "Comparing functional and morphologic characteristics of lamellar macular holes with and without lamellar hole-associated epiretinal proliferation," *Retina*, vol. 35, pp. 720–726, 2015.

[3] B. Haouchine, P. Massin, R. Tadayoni, A. Erginay, and A. Gaudric, "Diagnosis of macular pseudoholes and lamellar macular holes by optical coherence tomography," *American Journal of Ophthalmology*, vol. 138, no. 5, pp. 732–739, 2004.

[4] A. J. Witkin, T. H. Ko, J. G. Fujimoto et al., "Redefining lamellar holes and the vitreomacular interface: an ultrahigh-resolution optical coherence tomography study," *Ophthalmology*, vol. 113, no. 3, pp. 388–397, 2006.

[5] B. Parolini, R. G. Schumann, M. G. Cereda, C. Haritoglou, and G. Pertile, "Lamellar macular hole: a clinicopathologic correlation of surgically excised epiretinal membranes," *Investigative Ophthalmology and Visual Science*, vol. 52, no. 12, pp. 9074–9083, 2011.

[6] Z. Michalewska, J. Michalewski, D. Odrobina, and J. Nawrocki, "Non-full-thickness macular holes reassessed with spectral domain optical coherence tomography," *Retina*, vol. 32, no. 5, pp. 922–929, 2012.

[7] F. Bottoni, A. P. Deiro, A. Giani, C. Orini, M. Cigada, and G. Staurenghi, "The natural history of lamellar macular holes: a spectral domain optical coherence tomography study," *Graefe's Archive for Clinical and Experimental Ophthalmology*, vol. 251, no. 2, pp. 467–475, 2013.

[8] R. G. Schumann, D. Compera, M. M. Schaumberger et al., "Epiretinal membrane characteristics correlate with photoreceptor layer defects in lamellar macular holes and macular pseudoholes," *Retina*, vol. 35, no. 4, pp. 727–735, 2015.

[9] J. M. Robinson and T. Takizawa, "Correlative fluorescence and electron microscopy in tissues: immunocytochemistry," *Journal of Microscopy*, vol. 235, no. 3, pp. 259–272, 2009.

[10] T. Takizawa and J. M. Robinson, "Ultrathin cryosections: an important tool for immunofluorescence and correlative microscopy," *Journal of Histochemistry and Cytochemistry*, vol. 51, no. 6, pp. 707–714, 2003.

[11] H. Asakawa, Y. Hiraoka, and T. Haraguchi, "A method of correlative light and electron microscopy for yeast cells," *Micron*, vol. 61, pp. 53–61, 2014.

[12] R. G. Schumann, A. Gandorfer, J. Ziada et al., "Hyalocytes in idiopathic epiretinal membranes: a correlative light and electron microscopic study," *Graefe's Archive for Clinical and Experimental Ophthalmology*, vol. 252, no. 12, pp. 1887–1894, 2014.

[13] P. S. Hiscott, I. Grierson, C. J. Trombetta, A. H. Rahi, J. Marshall, and D. McLeod, "Retinal and epiretinal glia—an immunohistochemical study," *British Journal of Ophthalmology*, vol. 68, no. 10, pp. 698–707, 1984.

[14] J. A. Hainfellner, T. Voigtländer, T. Ströbel et al., "Fibroblasts can express glial fibrillary acidic protein (GFAP) in vivo," *Journal of Neuropathology and Experimental Neurology*, vol. 60, no. 5, pp. 449–461, 2001.

[15] K. Nishitsuka, Y. Kashiwagi, N. Tojo et al., "Hyaluronan production regulation from porcine hyalocyte cell line by cytokines," *Experimental Eye Research*, vol. 85, no. 4, pp. 539–545, 2007.

[16] C. Llombart, V. Nacher, D. Ramos et al., "Morphological characterization of pecteneal hyalocytes in the developing quail retina," *Journal of Anatomy*, vol. 215, no. 3, pp. 280–291, 2009.

[17] R.-I. Kohno, Y. Hata, S. Kawahara et al., "Possible contribution of hyalocytes to idiopathic epiretinal membrane formation and its contraction," *British Journal of Ophthalmology*, vol. 93, no. 8, pp. 1020–1026, 2009.

[18] R. G. Schumann, K. H. Eibl, F. Zhao et al., "Immunocytochemical and ultrastructural evidence of glial cells and hyalocytes in internal limiting membrane specimens of idiopathic macular holes," *Investigative Ophthalmology and Visual Science*, vol. 52, no. 11, pp. 7822–7834, 2011.

[19] F. Zhao, A. Gandorfer, C. Haritoglou et al., "Epiretinal cell proliferation in macular pucker and vitreomacular traction syndrome: analysis of flat-mounted internal limiting membrane specimens," *Retina*, vol. 33, no. 1, pp. 77–88, 2013.

[20] M. Parravano, F. Oddone, B. Boccassini et al., "Functional and structural assessment of lamellar macular holes," *British Journal of Ophthalmology*, vol. 97, no. 3, pp. 291–296, 2013.

[21] M. Reibaldi, M. Parravano, M. Varano et al., "Foveal microstructure and functional parameters in lamellar macular hole," *American Journal of Ophthalmology*, vol. 154, no. 6, pp. 974–980, 2012.

[22] B. R. Garretson, J. S. Pollack, A. J. Ruby, K. A. Drenser, G. A. Williams, and R. Sarrafizadeh, "Vitrectomy for a symptomatic lamellar macular hole," *Ophthalmology*, vol. 115, no. 5, pp. 884.e1–886.e1, 2008.

[23] S. Androudi, A. Stangos, and P. D. Brazitikos, "Lamellar macular holes: tomographic features and surgical outcome," *American Journal of Ophthalmology*, vol. 148, no. 3, pp. 420–426, 2009.

[24] J. P. Sun, S. N. Chen, C. C. Chuang et al., "Surgical treatment of lamellar macular hole secondary to epiretinal membrane," *Graefe's Archive for Clinical and Experimental Ophthalmology*, vol. 251, no. 12, pp. 2681–2688, 2013.

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Review Article

Retinal Damage Induced by Internal Limiting Membrane Removal

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The internal limiting membrane (ILM), the basement membrane of the Müller cells, serves as the interface between the vitreous body and the retinal nerve fiber layer. It has a fundamental role in the development, structure, and function of the retina, although it also is a pathologic component in the various vitreoretinal disorders, most notably in macular holes. It was not until understanding of the evolution of idiopathic macular holes and the advent of idiopathic macular hole surgery that the idea of adjuvant ILM peeling in the treatment of tractional maculopathies was explored. Today intentional ILM peeling is a commonly applied surgical technique among vitreoretinal surgeons as it has been found to increase the rate of successful macular hole closure and improve surgical outcomes in other vitreoretinal diseases. Though ILM peeling has refined surgery for tractional maculopathies, like all surgical procedures it is not immune to perioperative risk. The essential role of the ILM to the integrity of the retina and risk of trauma to retinal tissue spurs suspicion with regard to its routine removal. Several authors have investigated the retinal damage induced by ILM peeling and these complications have been manifested across many different diagnostic studies.

1. Introduction

The internal limiting membrane (ILM) is the basal lamina of the inner retina that is formed by the footplates of Müller cells. It is the structural interface between the retina and the vitreous and is composed of collagen fibers, glycosaminoglycans, laminin, and fibronectin. The ILM is 1.5 μm thick in the peripheral foveal area and is thickest in this region [1]. The ILM serves as a scaffold for cellular proliferation of myofibroblasts, fibrocytes, and retinal pigment epithelium (RPE) cells [2]. Experimental studies on embryonic mouse and chick eyes have shown that the ILM is a critical component of retinal histogenesis and optic axonal growth and navigation to the optic disc. Halfter et al. demonstrated that the absence of the ILM caused permanent retraction of the endfeet of neuroepithelial cells from the vitreal surface of the retina and the formation of a disorganized and abnormally thickened ganglion cell layer [3]. Despite its essential role in early retinal and optic nerve development, in pathologic conditions cellular proliferation on the ILM is strongly correlated with tractional forces on the retina; this association coupled with the tendency of the ILM to thicken with age makes ILM removal mandatory to relieve the contractile forces in tractional maculopathies. Furthermore, since ILM removal has also been found to decrease the risk of epiretinal membrane development postoperatively, the indications for its application are broadened to include several vitreoretinal conditions [4].

ILM peeling is now a widely recognized technique used routinely for traction maculopathies, but what are the possible complications of this intervention? It is a technique that requires additional intraoperative agents, instruments, and surgical time. No studies or reports to date have shown adverse visual outcomes in patients status after an ILM peel, but there has yet to be a large enough randomized control trial assessing side effects of ILM removal, and therefore the question remains: Does the ILM have a function vital to the integrity of the retina that would render it damage upon ILM removal? If so, what type of retinal damage can this surgical technique induce?

2. The History of ILM Peeling

ILM peeling is a surgical technique commonly used today to treat various vitreoretinal disorders including macular holes, macular puckers, epiretinal membranes, diabetic macular edema, retinal detachment, retinal vein occlusions, vitreomacular traction, optic pit maculopathy, and Terson syndrome [4]. It was not until the late 1980s when the possibility of ILM peeling was even considered to be a surgical option in the treatment of vitreoretinal disorders; in a 1989 pilot study, Kelly and Wendel performed vitrectomy and removal of the posterior cortical vitreous to relieve traction over the macula, shedding light on ILM peeling as a possible therapy in the treatment of full thickness macular holes. Prior to this, idiopathic macular holes were considered an untreatable condition [9]. Shortly following the pilot study, in the 1990s Morris et al. reported promising results of intentional ILM peeling in the treatment of hemorrhagic macular cysts due to Terson syndrome. Specifically, 83% of the study subjects' eyes had a visual acuity of 20/25 or better without development of observable reproliferation. With these favorable results, Morris et al. postulated ILM removal as a surgical technique that could be used for other tractional types of maculopathies [10].

3. Technique

ILM peeling begins with pars plana vitrectomy and posterior hyaloid removal. Following these steps, adjuvant dyes are used to stain the translucent ILM to improve visualization and ensure complete removal in a technique called chromovitrectomy. The most commonly used dyes are indocyanine green (ICG), infracyanine green (IfCG), trypan blue, brilliant blue, and triamcinolone acetonide. Following dye injection, the ILM is grasped directly with forceps or a flap of the ILM is created and vitreoretinal forceps are used to grasp the flap (Figure 1, [5]). Pulling with the forceps in a circular motion parallel to the retinal surface, the ILM flap is extended, peeled from the retinal surface, and removed.

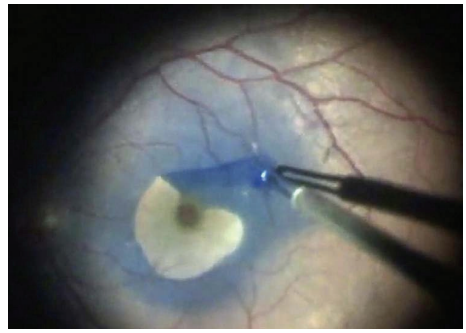

Figure 1: ILM peeling after staining with brilliant blue dye [5].

4. Common Indications

4.1. Macular Hole Repair. Macular holes are full thickness defects through the fovea centralis causing loss of central visual acuity, central scotoma, and metamorphopsia in affected eyes. Most of these holes are idiopathic, though trauma, inflammation, and high myopia are less common causes.

As Gass eloquently classified the progression of macular holes and, later, demonstrated with optical coherence tomography (OCT), idiopathic macular holes begin with the development of tangential traction of the prefoveal vitreous cortex [11]. This initially causes dehiscence of the outer retina in the foveal region and subsequently progresses to separation of the retinal structures and ultimately a full thickness hole at the fovea (Figure 2(a)). In a study analyzing the ultrastructure of vitreomacular interface, Schumann et al. found that fibrocellular proliferation on the vitreal side of the ILM (when present) was composed of fibrous astrocytes, myofibroblasts, fibroblasts, RPE cells, and macrophages, that collagen was invariably associated with this proliferation, and that the process was actually a secondary event in this condition [12]. Stages II–IV macular holes require closure for the best possible outcome, but it was not until 1991 that Kelly and Wendel suggested the use of surgical repair as a treatment option [9]. The literature suggests that removal of the ILM increases rates of successful hole closure by relieving prefoveal traction as well as inducing gliosis via surgical trauma [7]. Success rates in primary anatomic macular hole closure have been reported to range from 90 to 100% when vitreoretinal surgery included ILM peeling versus 60–90% when it did not include ILM peeling [1, 13–15]. Though universal better visual outcomes have been more difficult to demonstrate with adjuvant ILM peeling in macular hole surgery compared to without, a greater than 2-line improvement in vision has been reported in 60–85% of eyes [14, 15]. OCT, the gold standard diagnostic tool for retinal diseases, is tremendously useful for evaluation of macular holes preoperatively and the surgical outcomes postoperatively. Focusing on short-term follow-up, Christensen et al. analyzed data from the Copenhagen Macular Hole Study and found that 3 months after macular hole surgery OCT illustrates 3 distinct patterns in closure type, though these results were found to be the same between eyes that underwent ILM removal and those that did not (Figure 2(b), [1]). Concerning the long-term results, in a large retrospective study comparing results of surgery with and without ILM peeling after a follow-up of 18–84 months (mean 44.5 months), Brooks reported functional and visual outcomes with ILM peeling to be better than without peeling for stages II, III, and IV macular holes, acute and chronic. He reported primary hole closure without reopenings in 100% of ILM-peeled eyes and a mean postoperative vision of 20/40. The rate of reopening after primary hole closure without adjuvant ILM peeling was 25%, increasing to 100% with reoperation to include ILM peeling; mean vision remained unchanged or improved postoperatively in 78% of these reoperated eyes [13].

In a large prospective study focusing on the long-term outcomes of ILM peeling for macular holes after at least 12 months, Haritoglou et al. described promising results. The authors reported anatomic closure in 87% after 1 surgery, closure in 96% of reoperated eyes, and a median best-corrected

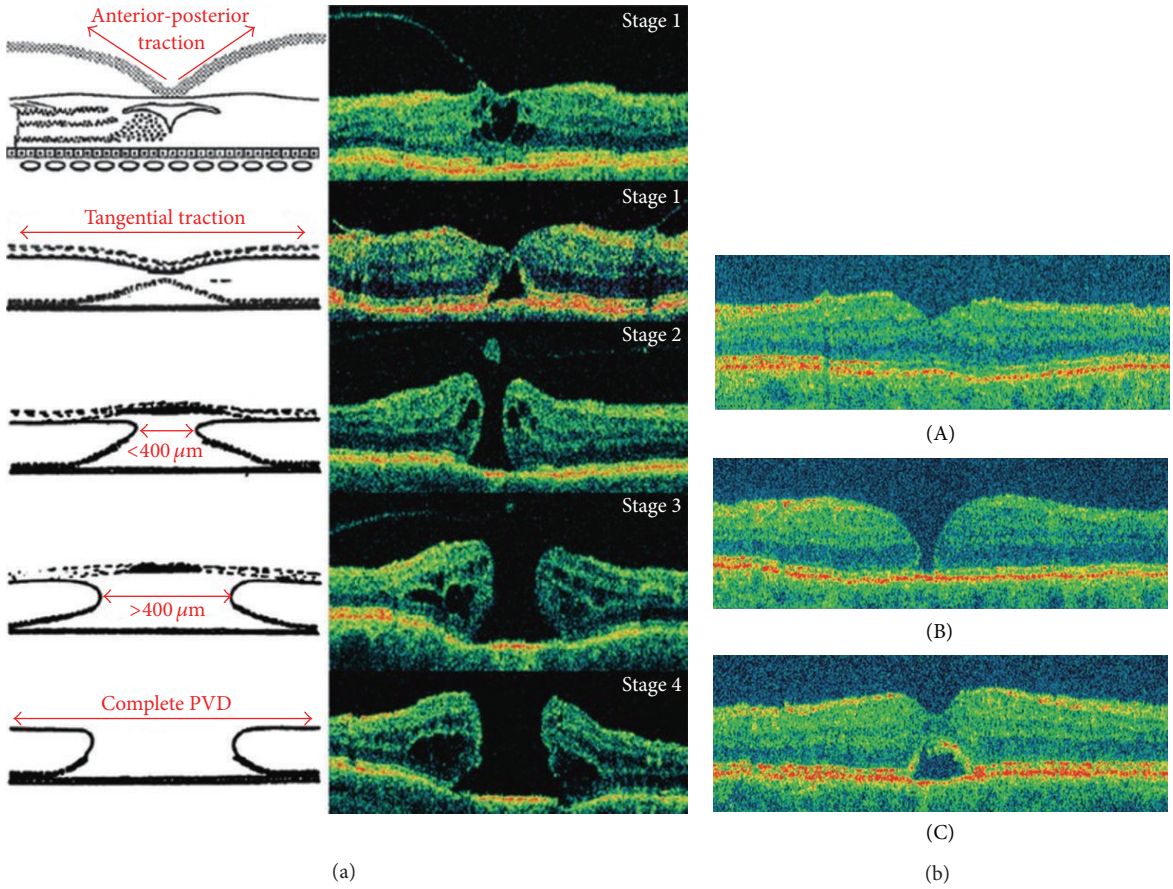

Figure 2: (a) Schematic and OCT representation of macular hole formation [1]. (b) Optical coherence tomography images 3 months after macular hole surgery. (A) Normal gross anatomic features with an attached fovea. (B) Flat edges with persistent neurosensory defect. (C) Contiguous foveal surface with persistent subfoveal fluid [1].

visual acuity improvement from a median of 20/100 preoperatively to 20/40 postoperatively in 94% [16]. Following primary hole closure they did not encounter any reopenings in eyes that underwent ILM peeling as compared to variable frequencies of reopenings in eyes that did not undergo ILM peeling [17, 18]. Furthermore, the authors found that though over half of the patients developed paracentral scotomata after surgery with ILM peeling, they were subclinical in the majority of subjects and the size, shape, and density of the scotomata were unchanging in all cases [16].

As several sources have displayed favorable anatomic and functional outcomes with ILM peeling, this technique has become part of the standard of practice for vitreoretinal surgeons repairing full thickness macular holes.

4.2. Macular Thickness Reduction in Diabetic Macular Edema. Diabetic macular edema (DME), caused by intraretinal fluid accumulation in the macula, is the most common cause of visual impairment in diabetic patients and a major cause of legal blindness in the United States. The pathogenesis is multifactorial and includes breakdown of the blood-retinal barrier (BRB) secondary to weakened capillary intercellular tight junctions, loss of pericytes, and leukostasis in the retinal vessels and vasoactive factors such as vascular endothelial growth factor-A (VEGF-A), various growth factors, and matrix metalloproteinases. Abnormalities at the vitreoretinal interface (the posterior vitreous cortex and ILM) have also been found to promote DME. Specifically, the hyaloid becomes taut and thickened with induced cellular proliferation and production of cytokines. The fovea and the vitreous base, where the ILM is thinnest, are the points at which the posterior vitreous cortex and the ILM have the strongest attachment. Advanced Glycation End-Products (AGEs), accumulated in the posterior vitreous cortex, increase cross-linking of collagen fibrils and induce structural changes in the posterior hyaloid that strengthen vitreomacular adhesions between the posterior hyaloid and ILM. This is further aggravated by AGE receptors (RAGEs), which are attached to the footplates of the Müller cells and extend to the external limiting membrane (ELM). RAGE activation by the binding of AGEs stimulates VEGF upregulation and retinal vessel permeability, further exacerbating DME [19].

Laser photocoagulation is the standard treatment for clinically significant macular edema (CSME) as established by the Early Treatment Diabetic Retinopathy Study (ETDRS), but not uncommonly DME persists despite laser treatment [20].

Several studies have shown favorable results of pars plana vitrectomy (PPV) to address the tractional forces involved in DME [21–24], and though the role that the ILM plays in macular edema is not entirely understood, some authors have found its removal with PPV to be more beneficial than PPV alone. In an ongoing prospective study investigating the structural and visual outcomes of PPV and ILM removal in eyes with diffuse DME, Recchia et al. reported improvement in visual acuity (1 Snellen line in 100% of studied eyes) and macular thickness (20% decrease in 80% of eyes). The authors state that ILM removal ensures complete posterior hyaloid separation when PPV gives the false appearance of full separation in the event of vitreoschisis, which commonly occurs. They also suggest that as the ILM serves as a scaffold for cellular proliferation, its absence may prevent the formation of an epiretinal membrane that might otherwise occur [20].

4.3. Epiretinal Membrane Removal. Epiretinal membrane (ERM) is a disease of the vitreomacular interface characterized by cellular proliferation on the inner retinal surface. It is classified as either idiopathic in nature or secondary to an independent ocular pathology such as inflammation, trauma, retinal vascular disease, and surgery. Regardless of the underlying etiology, it is the contractile properties of ERM elements that have the potential to create vitreomacular traction, distort foveal morphology, and promote retinal thickening, producing symptoms of decreased visual acuity or metamorphopsia. Though ERM is relatively common among older persons, most are asymptomatic and can be managed conservatively with observation; however, development of visual disturbances or deterioration of vision warrants surgical intervention [25, 26].

The standard surgical technique for treating ERM has been established since the 1970s and entails pars plana vitrectomy with ERM removal. In general, this approach has proven to have good outcomes with the potential for few associated complications. ERM recurrence is one such complication and though uncommon, reported by Grewing and Mester to occur in approximately 12% of cases, reoperation may be indicated in cases of symptom exacerbation [27]. One reason for recurrence is thought to be secondary to incomplete removal of microscopic ERM elements, not visible with staining, that use the ILM as a scaffold for cellular proliferation. The pilot study conducted by Park et al. demonstrated that PPV for macular pucker with additional ILM peeling resulted in 0% recurrence versus 21% recurrence in those without ILM removal [28]. Shimada et al. reproduced similar results in a prospective case series aimed at determining ERM recurrence in eyes that underwent either single peeling of ERM or double peeling of ERM and ILM. The authors reported 0% recurrence rate in double-peeled eyes versus 16.3% in single-peeled eyes. Though overall there was no difference in postoperative visual acuity between the two groups, 1/3 of eyes with ERM recurrence required reoperation for impaired visual acuity, all of which confirmed via histopathologic examination the ILM to be the source of fibroblast proliferation [29].

Additional ILM peeling in surgery for ERM removal does not eliminate the potential for future ERM development, but, according to a retrospective study of 440 eyes, the recurring membrane is thin and asymptomatic. ERM does not recur often, and the need for reoperation is rare, but as of yet ILM peeling is the only measure proven to be preventative; therefore, though not a necessary component of every operation for ERM, in select cases ILM removal is invaluable in maximizing postoperative visual potential [30].

4.4. Myopic Macular Retinoschisis. Macular retinoschisis is a traction-induced maculopathy common among highly myopic eyes with posterior staphyloma, with manifestations including retinal thickening, formation of cystoid spaces, foveal detachment (termed myopic foveoschisis), and lamellar or full thickness macular hole. With the advent of OCT, such retinal anomalies, previously difficult to diagnose, were better characterized and discovered to be present in up to one-third of highly myopic eyes with staphylomata [31, 32].

Vitreous traction is pivotal in the pathogenesis of macular retinoschisis in highly myopic eyes, but the source of this traction is variable with etiologies including ERM, remnant cortical vitreous plaques following posterior vitreous detachment (PVD), perifoveal PVD, and a taut ILM [32–38]. Macular retinoschisis associated with vitreomacular traction increases the risk of macular hole formation and retinal detachment and necessitates surgical intervention [33, 36–38]. Several case series have reported different surgical procedures, namely, PPV, with or without gas tamponade and prone positioning, with our without ILM peeling, to be effective in promoting postoperative anatomic resolution, or retinal flattening, and improving visual acuity [32, 34, 37–39]. The specific role of the ILM in the pathogenesis continues to be investigated, but, according to VanderBeek and Johnson, there are several reports in the literature of myopic macular retinoschisis in which macular traction is not secondary to a preretinal source but rather to a taut, highly elastic ILM inducing noncompliance of the inner retina. In such cases, ILM peeling is elemental in the management of macular retinoschisis [35], but as the inciting etiology for vitreomacular traction is variable among highly myopic eyes, so too is the best surgical approach in its management.

5. The Complications

5.1. Chromophore Toxicity. Retinal toxicity can occur secondary to the specific dye used during chromovitrectomy. Indocyanine green (ICG), introduced in 2000, is a chromophore that stains the ILM secondary to its affinity for laminin and collagen type IV. Several authors have reported side effects observed with ICG use, the most common being visual field defects, reduced retinal nerve fiber layer thickness on OCT, and RPE or ganglion cell changes that manifest as abnormalities on multifocal electroretinography (mfERG), light and transmission electron microscopies, and reduced enzymatic activity [40–43]. The mechanism of injury is unclear, but the adverse effects could be related to the dose of the dye, its osmolarity, or the photooxidative qualities

causing cellular damage. In an interventional consecutive case series, Tsuiki et al. postulated that postoperative visual field defects are caused by ICG toxicity via photochemical effects, that is, illumination induced chromophore excitation [44]. Based on OCT analysis, Yamashita et al. suggest ICG directly damages the retinal nerve fiber layer and is associated with postoperative visual field defects; they found a significant decrease in the measured nerve fiber layer thickness in eyes with visual field defects after ICG-assisted macular hole surgery compared to eyes without visual field defects [45]. Lai et al. assessed retinal function via mfERG performed before and after epiretinal membrane (ERM) surgery with ILM peeling using different ICG concentrations. Patients were randomized prior to surgery to receive either 0.5 mg/mL or 1.25 mg/mL of ICG staining and mfERGs done preoperatively, 3 months postoperatively, and 6 months postoperatively were compared between the 2 groups. At 3 months cone photoreceptor function, corresponding to the first negative peak (N1 or a-wave), and bipolar and Müller cell function, corresponding to the first positive peak (P1 or b-wave), were found to be significantly reduced in the group of eyes in which a higher ICG concentration was used compared to the group of eyes in which a lower concentration was used, though at 6 months no significant changes were observed in these amplitudes. The authors proposed that though there were no abnormalities of visual acuity or visual field noted, lower concentrations of ICG should be used [46].

Trypan blue (TB) is a dye that stains damaged cell membranes often used in epiretinal membrane removal in addition to ILM peeling. The formulations used in vitreoretinal surgery are low concentrations, but experimental studies have shown TB induces neurotoxic effects on retinal ganglion cells in a dose- and time-dependent manner [47, 48].

Triamcinolone acetonide (TA) is used to identify the posterior vitreous cortex, epiretinal membranes, and the ILM during vitrectomy. Conflicting evidence makes it difficult to definitively say if TA is toxic to the retina, though there are published reports of its use producing similar adverse effects to ICG. Crystal deposition secondary to TA, which aids in ILM removal, has been proposed to delay the healing process and affect macular hole closure [49]; however, in a large case series of patients who underwent idiopathic macular hole surgery with the use of adjuvant TA for ILM removal, the authors reported favorable visual outcomes and anatomical closures at a rate comparable to studies in the literature using different agents for staining [50].

Brilliant blue G (BBG) selectively binds to and stains ILM similarly to ICG and IfCG, optimizing ILM peeling. Historically found to have good clinical outcomes without evidence of toxicity on mfERG, it has widely been accepted as a good alternative dye, though its safety profile is still a matter of controversy [51]. In a case report recently published in January 2015, BBG 0.05% was used for chromovitrectomy during a PPV with ERM and ILM peeling for a patient with ERM. Following BBG injection and removal, the dye was observed to have accidentally migrated into the subretinal space in the macula, presumably through a retinal break that was not visible during the operation. Postoperative complications included cystoid macular edema observed on OCT, staining on fluorescein angiography, and amplitude reduction and implicit time increase on mfERG. It cannot definitively be concluded that these functional and anatomic changes were directly caused by macular subretinal migration of the dye, but the case report sheds light on the need for further studies to delineate the harmful effects of BBG on retinal tissue [52].

5.2. Damage to the Müller Cell. Given the close proximity of the ILM to the inner retina and its interdigitation with Müller cell footplates, it is not surprising to find retinal tissue and Müller cell debris on removed ILM specimens (Figure 3, [6] or [53]). Though there are variable amounts and sizes of such debris found on the ILM depending on the underlying disease process, one might reasonably wonder whether loss of inner retinal elements interferes with normal retinal function. Müller cells are specialized cells that contribute to retinal homeostasis [54] and they are an integral component of the ILM, contributing to formation of the b-wave on the electroretinogram (ERG). Terasaki et al. analyzed recordings of focal macular electroretinograms (FMERGs), looking at retinal physiology in the macular region of subjects undergoing ILM removal (Figure 4). The recordings demonstrated a limited and delayed recovery of the b-wave amplitude 6 months after surgery, possibly indicating dysfunction or physiologic changes of the Müller cell, though the authors did not find associated adverse postoperative visual outcomes [7]. In another study, Lim et al. also assessed whether the amount of debris on surgically removed ILM (visible on electron microscopy) affected retinal function. Implicit time (time-to-peak of the b-wave), which is a more sensitive measure of retinal damage than amplitude, was prolonged, indicating Müller cell damage and possibly subtle macular dysfunction, though final visual acuity was unaffected. Though several studies have been performed to determine the effect of Müller cell trauma on retinal function, we cannot definitively say that ILM peeling and subsequent Müller cell impairment has an overall negative outcome [53].

5.3. Paracentral Retinal Holes. In a case series from 2006, Steven et al. reported the formation of paracentral retinal holes following seemingly atraumatic ILM removal, observed with ICG, TB, and TA and when no adjuvant dye was used. They suggested that this postoperative finding might be a consequence of Müller cell damage causing weakening of the glial structures of the retina and ultimately hole formation. Specifically, as Müller cells remove metabolic waste products from retinal neurons, their removal in the process of ILM peeling may induce glial apoptosis and resultant retinal dysfunction. As these secondary paracentral holes always developed in the area of ILM removal, the authors discuss possibly limiting the area of retina that is peeled [55]. Since then, there have been additional reports of formation of paracentral retinal holes associated with ILM removal. A recent study was conducted investigating retinal sensitivity and frequency of paracentral microscotomas in eyes that had undergone ILM peeling compared to eyes that had not. Results of combined scanning laser ophthalmoscope (SLO) microperimetry and

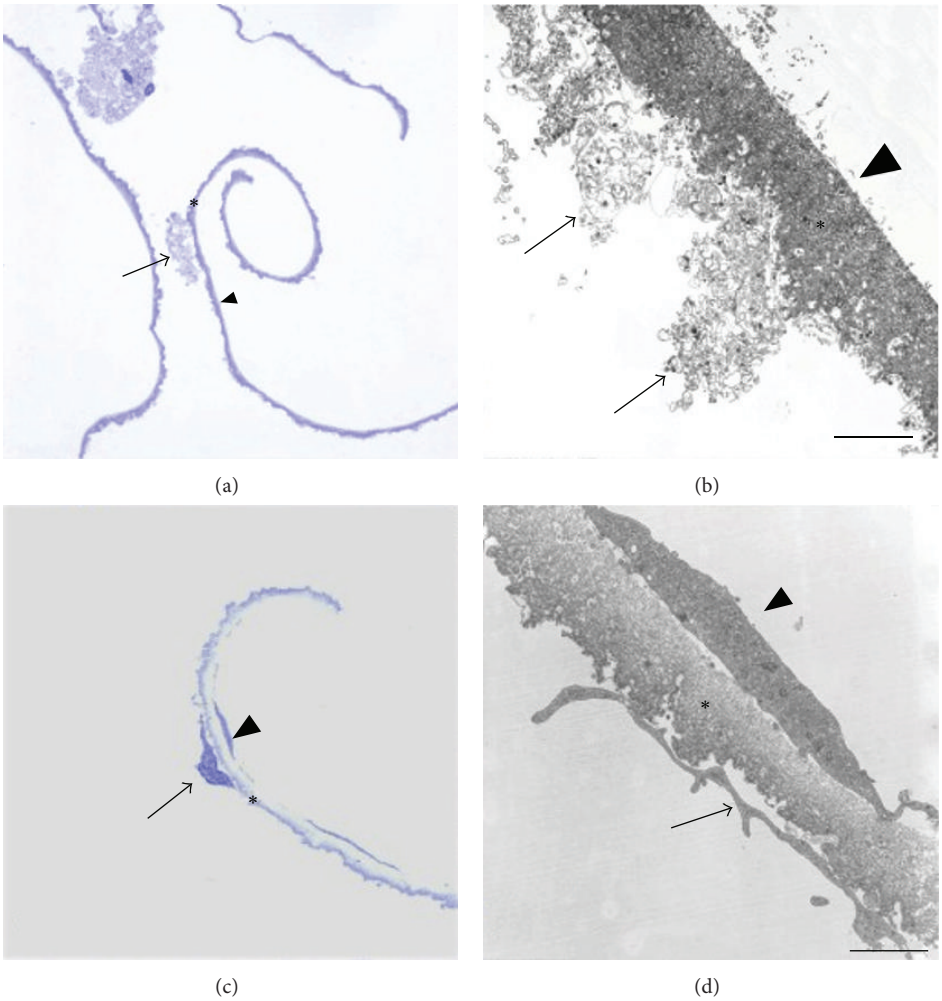

Figure 3: Light micrographs (LM) and transmission electron micrographs (TEM) of the ILM (asterisks) removed from eyes with diabetic macular edema ((a) and (b)) and stage IV idiopathic macular hole ((c) and (d)). The ILM is characterized by an undulated retinal side and a smooth vitreal side. ((a), (b)) Cell membrane fragments (arrow) on the retinal side of the ILM. The vitreal side of the ILM (arrowhead) is devoid of cells and collagen. ((c), (d)) LM shows a cell (arrow) with nucleus on the retinal side of the ILM. EM shows one large cell fragment (arrow) in contact with ILM and a single cell on the vitreal side of the ILM (arrowhead), which is likely a fibrous astrocyte [6].

spectral domain OCT were used to quantify the data and demonstrated a significantly lower mean retinal sensitivity and more frequent postoperative microscotomas in eyes that underwent ILM removal (Figure 5). The exact mechanism was not elucidated, but the authors discuss that it is unlikely to be secondary to forceps-induced trauma or dye-associated toxicity. They explained that the surgeons were highly experienced and accustomed to the procedure; the diminished retinal sensitivity was diffuse and not focal (as would be expected with direct mechanical trauma); and like the previous study [55], 3 different dyes were used, none of which included ICG (the dye most strongly associated with retinal ganglion cell toxicity). Rather, the reduced retinal sensitivity development of microscotomas may be secondary to direct damage to Müller cells [8].

5.4. Dissociated Optic Nerve Fiber Layer. A dissociated optic nerve fiber layer (DONFL) appearance is described as arcuate retinal striae along the optic nerve fibers in the macular region, slightly darker than the surrounding retina. A retrospective case series of 91 eyes with closed idiopathic macular holes, 67 ILM-peeled and 24 non-ILM-peeled, detected a DONFL on color fundus photography in 54% (36 of 67 eyes) of ILM-peeled eyes and 0% of nonpeeled eyes. OCT was performed on 20 of the 36 eyes and all of the nonpeeled eyes and demonstrated focal dehiscence of the optic nerve fiber layer only in the 20 eyes that demonstrated DONFL. Despite these findings and previous reports of DONFL associated with ILM peeling, no functional outcomes were observed; that is, visual acuity, visual field testing, and SLO microperimetry did not show abnormalities. The authors suggest DONFL appearance may be secondary to mere shifting of optic nerve fibers, rather than deterioration, resulting from loss of Müller cell support or postoperative regenerative processes of Müller cells or astrocytes [56, 57].

5.5. Phototoxic Damage. Phototoxic damage to the retina can occur because of photothermal, photomechanical, or

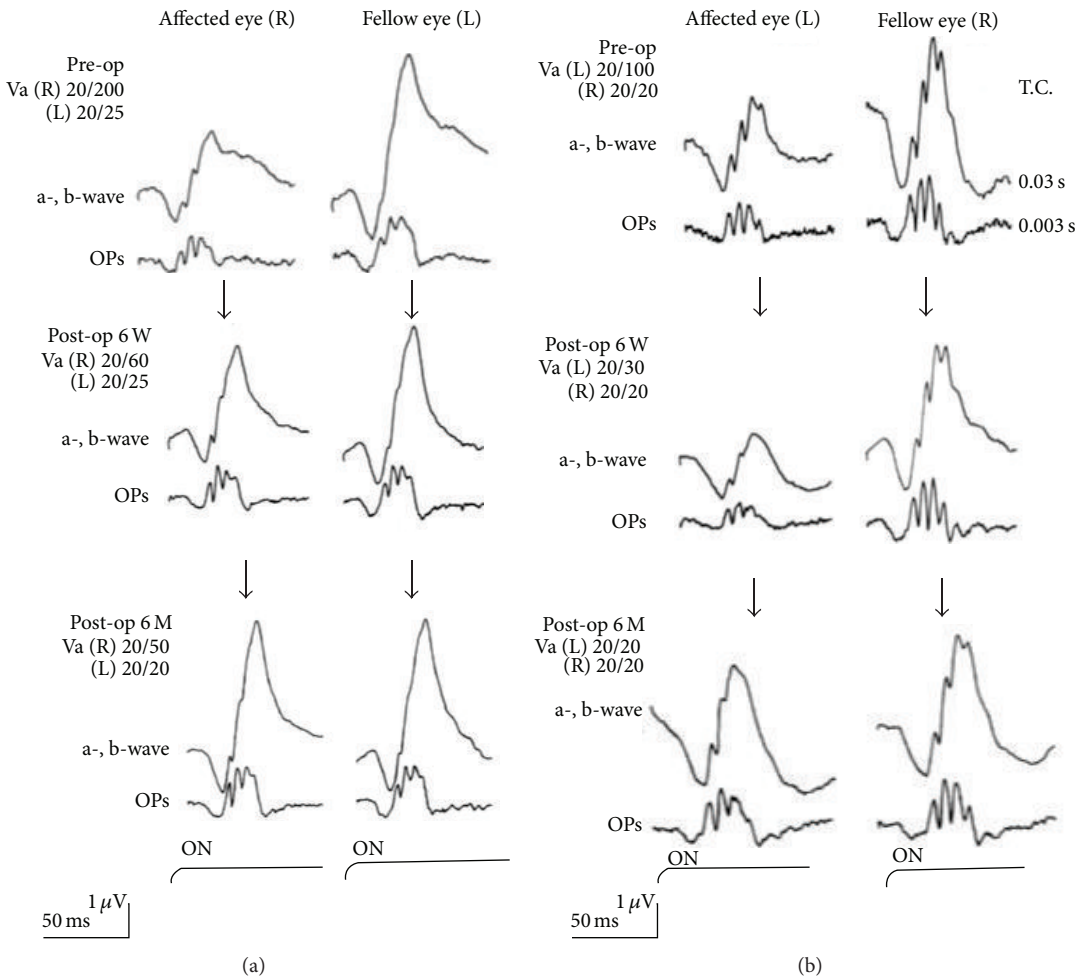

Figure 4: (a) Focal macular ERGs before and 6 weeks and 6 months after IMH surgery without ILM removal and the fellow eye. The b-wave amplitudes increase 6 weeks and even further 6 months after surgery. (b) Focal macular ERGs before and 6 weeks and 6 months after IMH surgery with ILM removal and the fellow eye. The b-wave amplitudes are significantly decreased 6 weeks after surgery but recover 6 months after surgery to the same level as that prior to surgery [7].

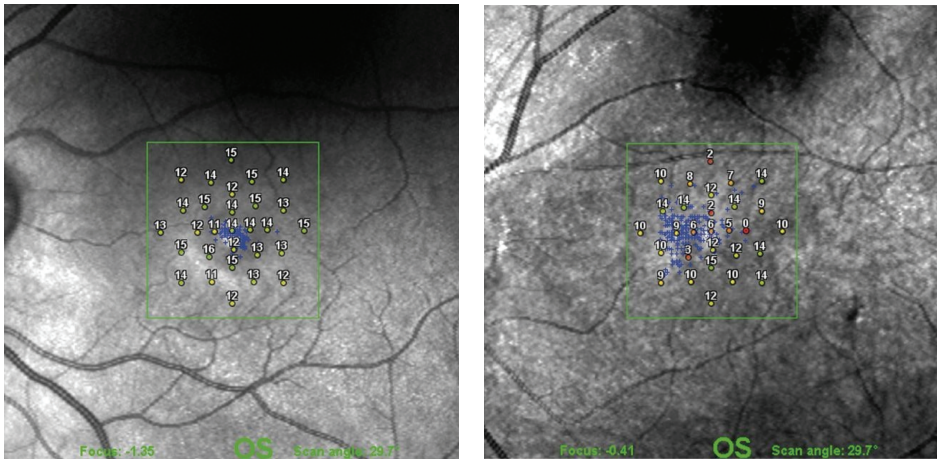

Figure 5: Scanning laser ophthalmoscope microperimetry after idiopathic macular hole surgery. (a) One month after surgery without ILM peeling showing normal retinal sensitivity and no deep microscotomas in the central 9 degrees of the visual field. (b) Two months after surgery with ILM peeling showing decreased mean retinal sensitivity and deep absolute and relative microscotomas in the central 9 degrees of the visual field [8].

photochemical mechanisms. Photothermal damage results from prolonged exposure of the retina to a light source. Photomechanical retinal damage is a possibility if there is physical contact between the light probe and the retina. Photochemical damage results when the visible light excites endogenous or exogenous chromophores. The endogenous chromophores excitable by visible light wavelengths are the photoreceptor pigments, as well as the melanin and lipofuscin of the RPE. ICG is an example of an exogenous chromophore excitable by visible light. Chromophore excitation produces reactive oxygen species, which cause lipid peroxidation and ultimately destroy cell membranes [1].

6. Conclusion

Though the ILM is integral to the histogenesis, structure, metabolism, and function of the retina, its detrimental role in inducing or exacerbating traction in various vitreoretinal diseases has made its removal in the treatment of traction-induced maculopathies logical and absolutely necessary, so much so that its indications have extended from the idiopathic full thickness macular hole from which it was born to include several other conditions that have an element of prefoveal traction. ILM peeling has revolutionized and become a vital component in vitreoretinal surgery as it has repeatedly been shown to be safe and effective in improving anatomic and functional outcomes across a range of retinal diseases, but the technique is not resistant to causing perioperative retinal damage and several authors in the literature have reported objective abnormal findings postoperatively. Despite its widespread acceptance and high safety profile, it is of paramount importance to always be aware of the possible deleterious consequences ILM peeling can impose, because as routine as the technique has become for the field and for the surgeon, it indeed is not routine for the patient.

Conflict of Interests

The authors declare that there is no competing/conflict of interests related to any topic in this paper.

References

[1] U. C. Christensen, "Value of internal limiting membrane peeling in surgery for idiopathic macular hole and the correlation between function and retinal morphology," *Acta Ophthalmologica*, vol. 87, no. 2, pp. 1–23, 2009.

[2] A. Almony, E. Nudleman, G. K. Shah et al., "Techniques, rationale, and outcomes of internal limiting membrane peeling," *Retina*, vol. 32, no. 5, pp. 877–891, 2012.

[3] W. Halfter, S. Dong, M. Balasubramani, and M. E. Bier, "Temporary disruption of the retinal basal lamina and its effect on retinal histogenesis," *Developmental Biology*, vol. 238, no. 1, pp. 79–96, 2001.

[4] H. S. Walia, G. K. Shah, and S. M. Hariprasad, "ILM peeling a vital intervention for many vitreoretinal disorders," *Ophthalmic Surgery Lasers and Imaging Retina*, vol. 45, no. 2, pp. 92–96, 2014.

[5] A. M. Al-Halafi, "Chromovitrectomy: update," *Saudi Journal of Ophthalmology*, vol. 27, no. 4, pp. 271–276, 2013.

[6] R. G. Schumann, Y. Yang, C. Haritoglou et al., "Histopathology of internal limiting membrane peeling in traction induced maculopathies," *Journal of Clinical & Experimental Ophthalmology*, vol. 3, article 224, 2012.

[7] H. Terasaki, Y. Miyake, R. Nomura et al., "Focal macular ERGs in eyes after removal of macular ILM during macular hole surgery," *Investigative Ophthalmology and Visual Science*, vol. 42, no. 1, pp. 229–234, 2001.

[8] R. Tadayoni, I. Svorenova, A. Erginay, A. Gaudric, and P. Massin, "Decreased retinal sensitivity after internal limiting membrane peeling for macular hole surgery," *British Journal of Ophthalmology*, vol. 96, no. 12, pp. 1513–1516, 2012.

[9] N. E. Kelly and R. T. Wendel, "Vitreous surgery for idiopathic macular holes: results of a pilot study," *Archives of Ophthalmology*, vol. 109, no. 5, pp. 654–659, 1991.

[10] R. Morris, F. Kuhn, and C. D. Witherspoon, "Hemorrhagic macular cysts," *Ophthalmology*, vol. 101, article 1, 1994.

[11] J. D. M. Gass, "Idiopathic senile macular hole. Its early stages and pathogenesis," *Archives of Ophthalmology*, vol. 106, no. 5, pp. 629–639, 1988.

[12] R. G. Schumann, M. M. Schaumberger, M. Rohleder, C. Haritoglou, A. Kampik, and A. Gandorfer, "Ultrastructure of the vitreomacular interface in full-thickness idiopathic macular holes: a consecutive analysis of 100 cases," *American Journal of Ophthalmology*, vol. 141, no. 6, pp. 1112–1119, 2006.

[13] H. Brooks, "Macular hole surgery with and without internal limiting membrane peeling," *Ophthalmology*, vol. 107, no. 10, pp. 1939–1948, 2000.

[14] V. Mester and F. Kuhn, "Internal limiting membrane removal in the management of full-thickness macular holes," *The American Journal of Ophthalmology*, vol. 129, no. 6, pp. 769–777, 2000.

[15] D. Tognetto, R. Grandin, G. Sanguinetti et al., "Internal limiting membrane removal during macular hole surgery: results of a multicenter retrospective study," *Ophthalmology*, vol. 113, no. 8, pp. 1401–1410, 2006.

[16] C. Haritoglou, C. A. Gass, M. Schaumberger, A. Gandorfer, M. W. Ulbig, and A. Kampik, "Long-term follow-up after macular hole surgery with internal limiting membrane peeling," *American Journal of Ophthalmology*, vol. 134, no. 5, pp. 661–666, 2002.

[17] N. J. Christmas, W. E. Smiddy, and H. W. Flynn Jr., "Reopening of macular holes after initially successful repair," *Ophthalmology*, vol. 105, no. 10, pp. 1835–1838, 1998.

[18] S. S. Park, D. M. Marcus, J. S. Duker et al., "Posterior segment complications after vitrectomy for macular hole," *Ophthalmology*, vol. 102, no. 5, pp. 775–781, 1995.

[19] N. Bhagat, R. A. Grigorian, A. Tutela, and M. A. Zarbin, "Diabetic macular edema: pathogenesis and treatment," *Survey of Ophthalmology*, vol. 54, no. 1, pp. 1–32, 2009.

[20] F. M. Recchia, A. J. Ruby, and C. A. Carvalho Recchia, "Pars plana vitrectomy with removal of the internal limiting membrane in the treatment of persistent diabetic macular edema," *American Journal of Ophthalmology*, vol. 139, no. 3, pp. 447–454, 2005.

[21] H. Lewis, G. W. Abrams, M. S. Blumenkranz, and R. V. Campo, "Vitrectomy for diabetic macular traction and edema associated with posterior hyaloidal traction," *Ophthalmology*, vol. 99, no. 5, pp. 753–759, 1992.

[22] S. D. Pendergast, T. S. Hassan, G. A. Williams et al., "Vitrectomy for diffuse diabetic macular edema associated with a taut premacular posterior hyaloid," *American Journal of Ophthalmology*, vol. 130, no. 2, pp. 178–186, 2000.

[23] J. W. Harbour, W. E. Smiddy, H. W. Flynn Jr., and P. E. Rubsamen, "Vitrectomy for diabetic macular edema associated with a thickened and taut posterior hyaloid membrane," *American Journal of Ophthalmology*, vol. 121, no. 4, pp. 405–413, 1996.

[24] T. Otani and S. Kishi, "A controlled study of vitrectomy for diabetic macular edema," *American Journal of Ophthalmology*, vol. 134, no. 2, pp. 214–219, 2002.

[25] S. Fraser-Bell, M. Guzowski, E. Rochtchina, J. J. Wang, and P. Mitchell, "Five-year cumulative incidence and progression of epiretinal membranes: the Blue Mountains eye study," *Ophthalmology*, vol. 110, no. 1, pp. 34–40, 2003.

[26] A. L. Levison and P. K. Kaiser, "Vitreomacular interface diseases: diagnosis and management," *Taiwan Journal of Ophthalmology*, vol. 4, no. 2, pp. 63–68, 2014.

[27] R. Grewing and U. Mester, "Results of surgery for epiretinal membranes and their recurrences," *The British Journal of Ophthalmology*, vol. 80, no. 4, pp. 323–326, 1996.

[28] D. W. Park, P. U. Dugel, J. Garda et al., "Macular pucker removal with and without internal limiting membrane peeling: pilot study," *Ophthalmology*, vol. 110, no. 1, pp. 62–64, 2003.

[29] H. Shimada, H. Nakashizuka, T. Hattori, R. Mori, Y. Mizutani, and M. Yuzawa, "Double staining with brilliant blue G and double peeling for epiretinal membranes," *Ophthalmology*, vol. 116, no. 7, pp. 1370–1376, 2009.

[30] O. Sandali, M. El Sanharawi, E. Basli et al., "Epiretinal membrane recurrence: incidence, characteristics, evolution, and preventive and risk factors," *Retina*, vol. 33, no. 10, pp. 2032–2038, 2013.

[31] M. Takano and S. Kishi, "Foveal retinoschisis and retinal detachment in severely myopic eyes with posterior staphyloma," *American Journal of Ophthalmology*, vol. 128, no. 4, pp. 472–476, 1999.

[32] G. Panozzo and A. Mercanti, "Optical coherence tomography findings in myopic traction maculopathy," *Archives of Ophthalmology*, vol. 122, no. 10, pp. 1455–1460, 2004.

[33] D. Gaucher, B. Haouchine, R. Tadayoni et al., "Long-term follow-up of high myopic foveoschisis: natural course and surgical outcome," *The American Journal of Ophthalmology*, vol. 143, no. 3, pp. 455–462, 2007.

[34] R. F. Spaide and Y. Fisher, "Removal of adherent cortical vitreous plaques without removing the internal limiting membrane in the repair of macular detachments in highly myopic eyes," *Retina*, vol. 25, no. 3, pp. 290–295, 2005.

[35] B. L. VanderBeek and M. W. Johnson, "The diversity of traction mechanisms in myopic traction maculopathy," *American Journal of Ophthalmology*, vol. 153, no. 1, pp. 93–102, 2012.

[36] N. Benhamou, P. Massin, B. Haouchine, A. Erginay, and A. Gaudric, "Macular retinoschisis in highly myopic eyes," *American Journal of Ophthalmology*, vol. 133, no. 6, pp. 794–800, 2002.

[37] A. K. H. Kwok, T. Y. Y. Lai, and W. W. K. Yip, "Vitrectomy and gas tamponade without internal limiting membrane peeling for myopic foveoschisis," *The British Journal of Ophthalmology*, vol. 89, no. 9, pp. 1180–1183, 2005.

[38] Y. Ikuno, K. Sayanagi, M. Ohji et al., "Vitrectomy and internal limiting membrane peeling for myopic foveoschisis," *American Journal of Ophthalmology*, vol. 137, no. 4, pp. 719–724, 2004.

[39] H. Kobayashi and S. Kishi, "Vitreous surgery for highly myopic eyes with foveal detachment and retinoschisis," *Ophthalmology*, vol. 110, no. 9, pp. 1702–1707, 2003.

[40] B. D. Sippy, N. E. Engelbrecht, G. B. Hubbard et al., "Indocyanine green effect on cultured human retinal pigment epithelial cells: implication for macular hole surgery," *American Journal of Ophthalmology*, vol. 132, no. 3, pp. 433–435, 2001.

[41] H. Ikagawa, M. Yoneda, M. Iwaki et al., "Chemical toxicity of indocyanine green damages retinal pigment epithelium," *Investigative Ophthalmology and Visual Science*, vol. 46, no. 7, pp. 2531–2539, 2005.

[42] T. Kawaji, A. Hirata, Y. Inomata, T. Koga, and H. Tanihara, "Morphological damage in rabbit retina caused by subretinal injection of indocyanine green," *Graefe's Archive for Clinical and Experimental Ophthalmology*, vol. 242, no. 2, pp. 158–164, 2004.

[43] P. Stalmans, E. H. Van Aken, M. Veckeneer, E. J. Feron, and I. Stalmans, "Toxic effect of indocyanine green on retinal pigment epithelium related to osmotic effects of the solvent," *American Journal of Ophthalmology*, vol. 134, no. 2, pp. 282–285, 2002.

[44] E. Tsuiki, A. Fujikawa, N. Miyamura, K. Yamada, K. Mishima, and T. Kitaoka, "Visual field defects after macular hole surgery with indocyanine green-assisted internal limiting membrane peeling," *American Journal of Ophthalmology*, vol. 143, no. 4, pp. 704–705, 2007.

[45] T. Yamashita, A. Uemura, H. Kita, and T. Sakamoto, "Analysis of the retinal nerve fiber layer after indocyanine green-assisted vitrectomy for idiopathic macular holes," *Ophthalmology*, vol. 113, no. 2, pp. 280–284, 2006.

[46] T. Y. Y. Lai, A. K. H. Kwok, A. W. H. Au, and D. S. C. Lam, "Assessment of macular function by multifocal electroretinography following epiretinal membrane surgery with indocyanine green-assisted internal limiting membrane peeling," *Graefe's Archive for Clinical and Experimental Ophthalmology*, vol. 245, no. 1, pp. 148–154, 2007.

[47] Y. Jin, S. Uchida, Y. Yanagi, M. Aihara, and M. Araie, "Neurotoxic effects of trypan blue on rat retinal ganglion cells," *Experimental Eye Research*, vol. 81, no. 4, pp. 395–400, 2005.

[48] C. Haritoglou, A. Gandorfer, M. Schaumberger et al., "Trypan blue in macular pucker surgery: an evaluation of histology and functional outcome," *Retina*, vol. 24, no. 4, pp. 582–590, 2004.

[49] T. Koto, M. Inoue, K. Shinoda, S. Ishida, and K. Tsubota, "Residual crystals of triamcinolone acetonide in macular hole may prevent complete closure," *Acta Ophthalmologica Scandinavica*, vol. 85, no. 8, pp. 913–914, 2007.

[50] A. Tewari, A. Almony, and G. K. Shah, "Macular hole closure with triamcinolone-assisted internal limiting membrane peeling," *Retina*, vol. 28, no. 9, pp. 1276–1279, 2008.

[51] E. Cervera, M. Díaz-Llopis, D. Salom, P. Udaondo, and L. Amselem, "Internal limiting membrane staining using intravitreal brilliant blue G: good help for vitreo-retinal surgeon in training," *Archivos de la Sociedad Espanola de Oftalmologia*, vol. 82, no. 2, pp. 71–72, 2007.

[52] F. P. P. Almeida, A. C. De Lucca, I. U. Scott, R. Jorge, and A. Messias, "Accidental subretinal brilliant blue G migration during internal limiting membrane peeling surgery," *JAMA Ophthalmology*, vol. 133, no. 1, pp. 85–88, 2015.

[53] J. W. Lim, H. K. Kim, and D. Y. Cho, "Macular function and ultrastructure of the internal limiting membrane removed during surgery for idiopathic epiretinal membrane," *Clinical & Experimental Ophthalmology*, vol. 39, no. 1, pp. 9–14, 2011.

[54] E. A. Newman, D. A. Frambach, and L. L. Odette, "Control of extracellular potassium levels by retinal glial cell K^+ siphoning," *Science*, vol. 225, no. 4667, pp. 1174–1175, 1984.

[55] P. Steven, H. Laqua, D. Wong, and H. Hoerauf, "Secondary paracentral retinal holes following internal limiting membrane removal," *British Journal of Ophthalmology*, vol. 90, no. 3, pp. 293–295, 2006.

[56] Y. Ito, H. Terasaki, A. Takahashi, T. Yamakoshi, M. Kondo, and M. Nakamura, "Dissociated optic nerve fiber layer appearance after internal limiting membrane peeling for idiopathic macular holes," *Ophthalmology*, vol. 112, no. 8, pp. 1415–1420, 2005.

[57] Y. Mitamura, T. Suzuki, T. Kinoshita, N. Miyano, A. Tashimo, and K. Ohtsuka, "Optical coherence tomographic findings of dissociated optic nerve fiber layer appearance," *American Journal of Ophthalmology*, vol. 137, no. 6, pp. 1155–1156, 2004.

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Review Article

Retinal Changes Induced by Epiretinal Tangential Forces

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Two kinds of forces are active in vitreoretinal traction diseases: tangential and anterior-posterior forces. However, tangential forces are less characterized and classified in literature compared to the anterior-posterior ones. Tangential epiretinal forces are mainly due to anomalous posterior vitreous detachment (PVD), vitreoschisis, vitreopapillary adhesion (VPA), and epiretinal membranes (ERMs). Anomalous PVD plays a key role in the formation of the tangential vectorial forces on the retinal surface as consequence of gel liquefaction (synchysis) without sufficient and fast vitreous dehiscence at the vitreoretinal interface. The anomalous and persistent adherence of the posterior hyaloid to the retina can lead to vitreomacular/vitreopapillary adhesion or to a formation of avascular fibrocellular tissue (ERM) resulting from the proliferation and transdifferentiation of hyalocytes resident in the cortical vitreous remnants after vitreoschisis. The right interpretation of the forces involved in the epiretinal tangential tractions helps in a better definition of diagnosis, progression, prognosis, and surgical outcomes of vitreomacular interfaces.

1. Introduction

Two kinds of forces are involved in vitreoretinal traction diseases: tangential and anterior-posterior forces. The formation of these forces is due to the anomalous posterior vitreous detachment. When the posterior hyaloid partially detaches from the posterior pole and macula, keeping a strong attachment at a focal point, the anterior-posterior vector appears. The tangential forces result from vectors that are tangent to the retinal surface. These forces are less characterized and classified in literature compared to anterior-posterior ones, although they are responsible for retinal damages of the inner and outer layers [1]. We will characterize the tangential vectors involved in the retinal changes: (i) anomalous posterior vitreous detachment and vitreoschisis; (ii) epiretinal membranes (ERMs); (iii) vitreopapillary adhesion (VPA).

2. Anomalous Posterior Vitreous Detachment and Vitreoschisis

The vitreous is an extended extracellular matrix that is composed mainly of water (98%); in youth, it is nonetheless a solid gel due to the intricate association of hyaluronan, collagen, and additional molecular components [2]. In youth, this fine structure is strongly adherent to the retina in a fascial (as opposed to focal) manner [3], although the exact processes and cells responsible for the synthesis and adhesion of such macromolecules remain unidentified [4]. The main function of the vitreous, however, is the maintenance of transparency within the eye (Figure 1). This feature minimizes light scattering, allowing the unhindered transmission of photons to the retina for photoreception [5, 6]. During aging, changes in vitreous macromolecular interactions result in the formation of a liquid vitreous that consists primarily of hyaluronan and water as well as collagen fibrils that aggregate

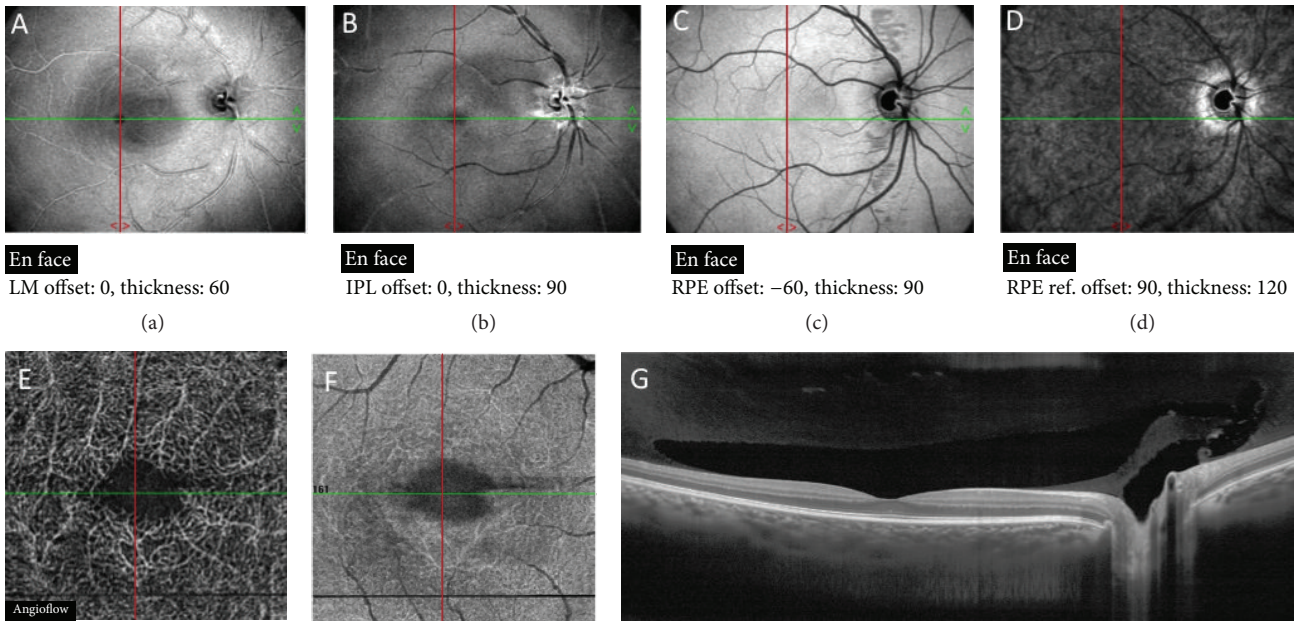


Figure 1: OCT images of normal eye. (a)–(d) En face OCT images at different segmentation thicknesses. (e)-(f) Angio-OCT images of, respectively, superficial and deep retinal plexus. (g) Premacular bursa appears on OCT as boat-shaped lacunae in the macular region.

into bundles of parallel fibers [7]. Moreover, during aging, changes at the interface weaken vitreoretinal adhesion and promote vitreoretinal dehiscence in most individuals. These two processes must occur in concert and simultaneously to result in an innocuous posterior vitreous detachment (PVD) [8]. Posterior vitreous detachment is characterized by synchysis (gel liquefaction) and syneresis (vitreoretinal dehiscence with collapse) of the posterior vitreous away from the retina [4]. The effect of vitreous syneresis varies from negligible to significant, depending on the condition of the vitreoretinal interface [9]. In diseases such as age-related macular degeneration [10] and diabetic retinopathy [11], complete PVD is less frequent, but, if present, it protects against more advanced stages of disease [12].

2.1. The "Anomalous PVD". In a minority of cases, a clean separation of the posterior vitreous cortex (PVC) from the retina does not occur due to the presence of liquefaction without sufficient dehiscence at the vitreoretinal interface. This is known as "anomalous PVD" [13]. Five stages of PVD have been described: stage 0, absence of PVD; stage 1, focal perifoveal PVD, with persistent attachment to the fovea, optic nerve head, and midperipheral retina; stage 2, macular PVD with persistent attachment to the optic disc but without vitreofoveal adhesion; stage 3, near-complete PVD with VPA only; and stage 4, complete PVD [14, 15]. The sequelae of anomalous PVD vary depending on the position of the strongest retinal adherence of the PVC and greatest liquefaction of the gel. In the peripheral fundus, advanced gel liquefaction with firm vitreoretinal adhesion causes retinal detachments and tears [8]. At the optic disc, anomalous PVD can cause different vitreopapillopathies, and it can also play a role in promoting vitreous hemorrhage and neovascularization in ischemic retinopathies [8]. At the macula, anomalous PVD can induce various pathologies, and it is relevant if the PVC that remains adherent to the retina is of partial thickness or full thickness. Peripheral vitreoretinal separation with full-thickness vitreous cortex adherence to the macula can induce vitreomacular traction (VMT). In presence of symptomatic intraretinal changes, this condition is known as vitreomacular traction syndrome (VMTS) [8]. In VMTS, a broad, full-thickness posterior vitreous adhesion occurs to the margin of the fovea (macular adhesion size of ~≥1500 μm) [16]. Meanwhile, a more focal adhesion induces vitreofoveal traction syndrome (foveal adhesion size < 500 μm) [16]. However, the smaller the diameter of the vitreofoveal adhesion is, the greater the tractional force that is exerted is, causing more serious foveal deformation [16]. In these instances, peripheral vitreoretinal separation in the presence of persistent adhesion at the macula is evident. The tractional forces are mainly anteroposterior, causing a central cyst in the vitreofoveal traction and retinal thickening with edema in the VMTS [8].

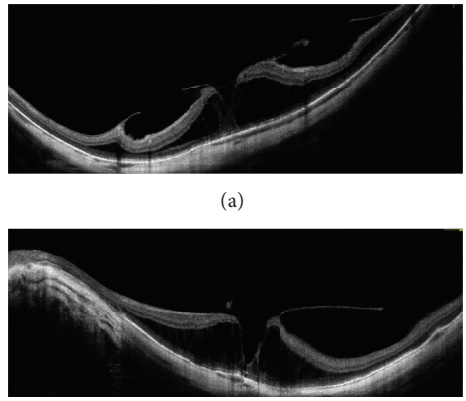
2.2. Vitreoschisis. Vitreoschisis is a consequence of a splitting in the PVC [8]. The PVC has a multilamellar structure, composed of densely packed collagen fibrils that run parallel to the retinal surface. It is comprised mostly of type II collagen, but a hybrid of types V/XI and type IX is also present [13, 17]. The adhesion molecules such as fibronectin, laminin, and heparan sulfate keep these collagen fibers attached to the retina surface and interact with opticin in the vitreous gel [18, 19]. The packed collagen fibrils of the PVC are superficially inserted into the internal limiting membrane (ILM) of the retina [17]. The PVC is 100–300 μm in thickness; it is thinnest at the fovea, where collagen fibrils are more densely

packed [17]. Hyalocytes, resident mononuclear phagocytes, are located in a single layer in the PVC approximately 50 μm from the ILM of the retina [20–22].

Vitreoschisis results from anomalous PVD [13] in presence of a firm vitreomacular adhesion (VMA) that causes a splitting of the PVC during syneresis, in which the outermost vitreous layer remains attached to the macula, while the remaining vitreous collapses forward [8].

Vitreoschisis induces various vitreomacular pathologies [8]. Kakehashi and colleagues detected vitreoschisis in patients with retinovascular diseases by applying clinical biomicroscopy [23]. Studies using ultrasonography [24] and histopathology [25] have also resulted in the diagnosis of vitreoschisis in proliferative diabetic retinopathy. Recently, combined optical coherence tomography/scanning laser ophthalmoscopy (OCT/SLO) led to the clinical diagnosis of vitreoschisis. In vitreoschisis, two membranous layers appear to join into one, forming the shape of the letter "Y" or "lambda" (λ); in other cases, this shape is not observed, but there is visible evidence of a membrane attached to the retina and a separate and distinct second membrane on the posterior side of the detached vitreous [26]. Indeed, studies [27] conducted at the VMR Institute using combined OCT/SLO imaging have identified vitreoschisis in 53% of the patients with macular holes (MHs) and in 43% of the patients with macular pucker (MP). These studies have suggested that it is important whether the split occurs anteriorly or posteriorly to the level of the hyalocytes [20–22]. If the split occurs posteriorly to the layer of hyalocytes, a thin hypocellular membrane remains attached to the macula. If this membrane also maintains its attachment to the optic disc, it may cause an outward (centrifugal) tangential contraction, inducing a MH. If the split occurs anteriorly to the layer of hyalocytes, the remaining layer of vitreous attached to the macula will include the hyalocytes and will be relatively thick, hypercellular, and contractile. As mononuclear phagocytes of the reticuloendothelial cell system, "sentinel" hyalocytes can stimulate the migration of glial cells from the circulation to the retina and monocytes [26]. Contraction of this tissue induces inward (centripetal) tangential traction upon the underlying retina, causing a MP. Recent studies [28] have shown that cytokines can influence hyalocyte metabolism and may also induce further cell proliferation; furthermore, other studies [29] have demonstrated that hyalocytes can cause collagen gel contraction in response to platelet-derived growth factor (PDGF) and other cytokines. Hence, hyalocytes are likely to be important in stimulating cell proliferation and in inducing tangential vitreoretinal contraction.

The hypothesis that the PVC can split into layers is fundamental to the theory of anomalous PVD with vitreoschisis [8]. The collagen fibrils within the PVC have a multilamellar organization, which has been confirmed in studies performed in monkeys [26, 27, 30], and these lamellae constitute a series of potential cleavage planes. The splitting of the PVC can also occur during vitreous surgery. Yamashita et al. were the first investigators to present in vivo intraoperative evidence of the occurrence of vitreoschisis [31]. They noted that 80% of eyes with MP develop vitreoschisis during vitrectomy surgery. Among those eyes in which vitreoschisis occurred intraoperatively, 58% had a visible "hole" in the PVC, while the remaining 42% had no visible hole. This finding suggests that vitreoschisis can occur at various levels within the PVC, consistent with the underlying multilamellar anatomy of the PVC [31]. These results could influence the performance of vitreoretinal surgery. The aggressiveness with which surgeon searches for membranes during membrane peeling can be influenced by the knowledge that vitreoschisis can occur either preoperatively or during surgery. A higher index of suspicion can also be decisive in the choice to use or not to use surgical adjuncts that could function like particulate suspensions, such as triamcinolone, or colored stains, such as trypan blue and indocyanine green.



(a)

(b)

Figure 2: OCT images of myopic eye. Myopic foveoschisis associated with tangential traction due to ERM and vitreoschisis.

2.2.1. Vitreoschisis and ILM in Myopic Eyes. Myopia is associated with vitreous liquefaction excessive in relation to the degree of vitreoretinal adhesion, resulting in anomalous PVD and traction at vitreoretinal interface [13] (Figure 2). In high myopia, the anteroposterior axis is the longest, and the vitreous chamber may be prolate [32]. Meskauskas et al. suggested that elongation and enlargement of the vitreous chamber might increase the vitreous and retinal shear stress exerted by the movement of the eye, playing an important role in the pathogenesis of PVD and retinal detachment (RD) [33]. This shear stress could be the origin of the disintegration of the collagen network and the consequent vitreous liquefaction and PVD. The vitreous, partially liquefied, is more rapidly disrupted in larger eyes than in normal eyes [32]. This process leads to a significant reduction in the gel volume and a consequent increase in the liquid volume, which results in PVD or posterior vitreoschisis, whereas the increased rigidity of the preretinal vitreous might be the cause of undue tangential traction at the vitreoretinal interface either at the posterior pole or in the middle periphery [13, 32]. Furthermore, in highly myopic eyes, when PVD occurs, sheets of residual cortical vitreous often remain attached to the inner surface of the retina. These sheets may contribute to a number of vitreoretinal diseases due to their subsequent contraction [8].

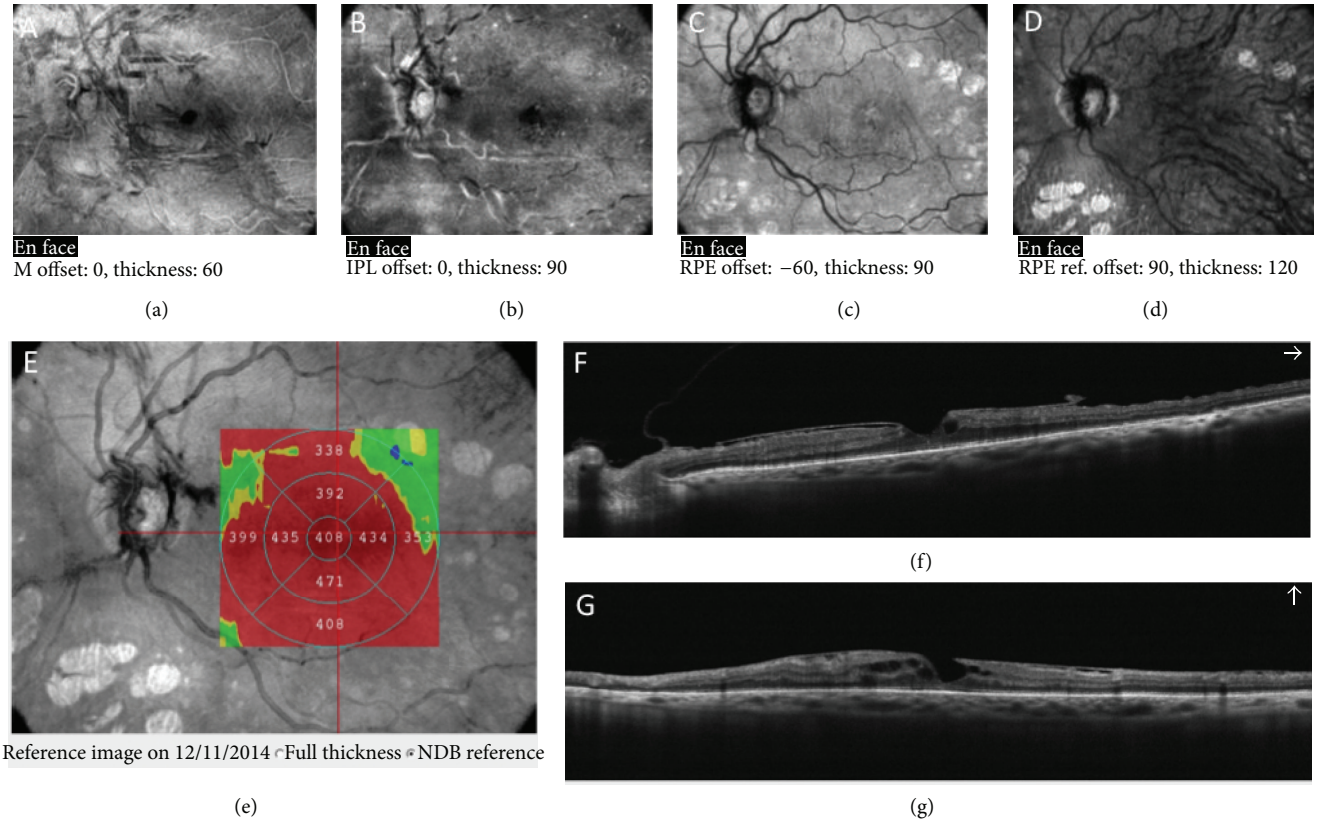


Figure 3: OCT images of diabetic eye. (a)–(d) En face OCT images at different segmentation thicknesses. (e) Increased retinal thickness map. (f)-(g) Vitreoschisis associated with vitreopapillary adhesion. The tangential traction induces wrinkling of ILM and intraretinal cysts.

In addition, in highly myopic eyes, an insufficient flexibility after axial length elongation could cause sclerotic retinal arteriole that determines a not distensible ILM [34]. The rigidity of the ILM seems to be the primary component that generates an inward tangential traction on the retina along the arterioles and may be responsible for the pathogenesis of myopic vitreoretinal diseases, such as foveoschisis, macular hole formation, and paravascular retinal break formation [34–36]. Sayanagi et al. [37] hypothesized that inflexibility of retinal vessels and the consequent tractional force in highly myopic eyes can lead to development of vascular microfolds. Bando et al. [38] identified fibroglial cell debris and collagen fibers on the inner surface of the ILM peeled from eyes with myopic foveoschisis in 70% of cases. The origin of these cells was not exactly determined; however, some cells such as astrocytes, abundant around retinal vessels, might migrate from the retina through small retinal pores in eyes with paravascular lamellar holes, produce collagen fibers, and initiate a proliferative response on the ILM. The rigid ILM, tightly attached to the posterior cortical vitreous, may cause the difficult differentiation between them on OCT images [39].

2.2.2. Vitreoschisis in Diabetic Eyes. The panmetabolic disease of diabetes mellitus (DM) induces structural and biochemical changes in vitreous tissue (Figure 3). The resulting diabetic vitreopathy plays an important role in the pathobiology of proliferative diabetic vitreoretinopathy [13]. Intravitreal glucose levels reflect blood glucose ones and can permit intravitreal nonenzymatic glycation reactions in patients with diabetes [40]: high levels of early glycation products were found in patients with diabetes when compared with patients without diabetes who undergo vitrectomy [41]. Functionally, advanced glycation end (AGE) cross-links in the collagen fibrils of vitreoretinal interface cause reduced solubility, tissue rigidity, a decreased susceptibility of proteins to enzymatic digestion, aggregation of collagen fibers, and dissociation of collagen from hyaluronan, resulting in vitreous destabilization and alterations of PVC and hyalocytes [40, 42]. Stitt et al. [40] suggested that AGE-derived cross-links on the vitreous collagen network may cause earlier age-related vitreous degeneration in patients with diabetes than in those without diabetes and may cause anomalous PVD, vitreoschisis, and vitreoretinal traction [40, 43]. Furthermore, proliferative diabetic retinopathy (PDR) alters the vitreous tissue by inclusion of fibrous tissue and vasogenic cells [43]. Structural changes at the vitreoretinal interface promote migration and proliferation of vasogenic cells in the vitreous and the consequent contraction can produce macular edema and vitreous hemorrhage [43]. Vitreoschisis in diabetics was first described by ultrasound [24] and by histopathology [25] in 80% of eyes with PDR. Spectral OCT-SLO studies [27] have furthermore detected vitreoschisis in half of eyes with macular hole and macular pucker. In a study of DME [44], 13

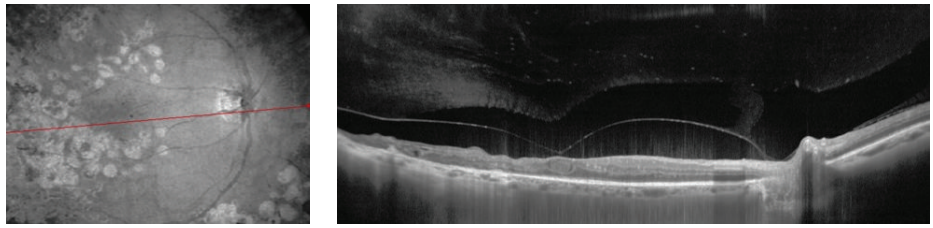


Figure 4: VPA associated with vitreomacular adhesion in diabetic retinopathy. Clear evidence of posterior precortical vitreous pocket at enhanced HD line scan.

(57%) out of the 23 subjects with anomalous PVD had PDR. This is an important consideration, given the high prevalence of vitreoschisis in this group of patients [45]. In eyes with PDR, the cortical vitreous is rarely detached; rather there is a large, anterior, ring-like vitreoschisis, with multiple smaller ones, more posteriorly [46].

2.2.3. Vitreoschisis and Surgical Outcomes. Induced PVD during pars plana vitrectomy (PPV) is a fundamental step to decrease the recurrence rate of RD. If the removal of PVC is incomplete, a thin but very adherent layer of the cortical vitreous remains attached to the retina and postoperative complications such as tractional redetachment and ERM reproliferation may occur. Indeed with an incomplete PVD mobile gel remains in the eye, with more room for it to exert dynamic traction, retinal shear stress, and redetachment; the free fluid enters the original or newly formed break at the point of residual vitreoretinal adhesion [46].

Vitreoschisis represents a convincing explanation for the recurrence of MH and MP after surgery. Indeed, if only the anterior layer or inner wall of the vitreoschisis cavity is removed during surgery, the posterior layer, or outer wall of the vitreoschisis cavity, will remain on the anterior surface of the retina.

In some studies of MH surgery, aggressive chromodissection [22] has been associated with a lower rate of recurrent disease [29, 47], which is likely because aggressive chromodissection of the vitreoretinal interface results in definitive removal of the outer wall of the vitreoschisis cavity. Other studies have reported a more favorable outcome by employing "ILM peeling" in MP surgery in comparison to those without aggressive membrane dissection [48].

Furthermore, Lois et al. in the FILM study have proved that ILM peeling, compared with no-ILM peeling, is more effective in reducing the risk of reoperation in patients with idiopathic stage 2 or 3 full-thickness macular holes (FTMHs), removing completely the potential tangential ILM traction and any residual cortex on ILM. However, they did not find any significant differences in distance visual acuity after the two techniques [49].

Triamcinolone acetonide (TA) is most commonly used as an adjunct to visualize vitreous, posterior hyaloid, preretinal membrane, and ILM during vitrectomy or chromovitrectomy. The granules of TA adhered to the residual posterior hyaloid, making it more visible [50]. This technique can disclose the residual hyaloid cortex pattern after surgical PVD and permit intraoperative visualization of vitreoschisis. Indeed, diffuse posterior hyaloid cortex is frequently found in high myopia and diabetic retinopathy, and an island-like cortex is often left on the macula, which can lead to future macular pucker. TA-assisted vitrectomy facilitated removal of residual island-like cortex, thus ensuring a low reproliferation rate on vitreomacular interface.

Recently, ocriplasmin has showed a proteolytic activity against fibronectin and laminin. The aim of the use of ocriplasmin is to cleave vitreoretinal interface with an intravitreal injection, causing a complete PVD [17]. Recent studies have shown that intravitreal injection of ocriplasmin can induce vitreous liquefaction and its separation from the retina [51–53], leading to closure of macular holes and resolution of VMT without causing serious adverse events [54, 55]. Stalmans et al. [56] conducted two pivotal phase III trials (TG-MV-006 and TG-MV-007) with a single injection dose of 125 μg in patients with symptomatic VMA/VMT. Whereas ocriplasmin was generally well tolerated in these trials, recent studies showed some adverse effects, such as incomplete VMT release, retinal breaks, and visual impairment associated with subretinal fluid [57–59]. It is possible that ocriplasmin may have an enzymatic effect not limited to areas of VMA but diffuse on the retinal pigment epithelium or photoreceptors producing a phenomenon defined as lucency, characterized by the presence of subretinal fluid in macular area. Rod photoreceptors seem to be more susceptible to the effects of ocriplasmin than cone photoreceptors [60]. Some variables may limit the success of ocriplasmin: lens status, broad versus focal vitreomacular attachments, multiple vitreomacular attachments, and patient's age [58].

3. Vitreopapillary Adhesion

Vitreopapillary adhesion is defined as a prominent vitreous membrane attached to the borders of the optic disc [61], associated with the development of PVD [62] (Figure 4). Dynamic VPA, which is associated with PVD stages 1 through 3, is occasionally severe enough to cause visual symptoms and anatomic changes [63, 64]. Affected patients are usually asymptomatic or report transient photopsias and gaze-evoked amaurosis. Visual acuity and automated perimetry are typically normal or almost normal. Rarely, a mild relative afferent pupillary defect may be transient [63, 64]. However, the resolution of symptoms occurs with progression to complete PVD [62]. Biomicroscopic signs often include fullness, elevation, and even subtle whitening of the peripapillary nerve fiber layer, which can simulate nontractional disc

edema. Intrapapillary and peripapillary hemorrhages may occur [65], but they are benign and self-resolving [66]. The most common associated hemorrhages have been reported to be subretinal [67]. Although these hemorrhages can occur at any age, they are commonly associated with partial PVD development in young myopic patients [66].

The strong and persistent adhesion of the posterior hyaloid to the optic nerve head results in traction and tenting of the papillary rim as well as elevation of the optic nerve head, which appears as a pseudopapilledema upon examination of the fundus [1, 68]. The presence of an elevated optic nerve head must be differentiated from several etiologies of disc edema, such as papillitis, papilledema, optic nerve head drusen, optic nerve infiltration, and optic nerve or orbital masses [63, 68, 69].

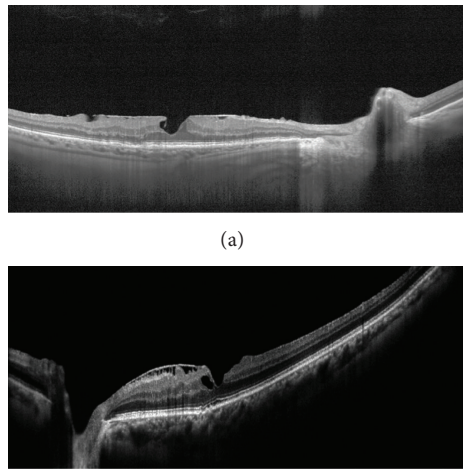
This condition can cause possible optic nerve dysfunction [70]. Indeed, tractional forces elongate the retinal nerve fibers and inflect the central retinal vessels. The stretching, thinning, and consequent deformation of the ganglion cell axons reduce the anterogradely or retrogradely axoplasmatic flow and account for a sensory blockade of neuroretinal signals; the visual evoked potentials can result in alterations. Mechanical restriction and feeding of the central retinal blood vessels also decrease prelaminar blood flow [1]. In addition, optic atrophy might occur with established optic disc traction [1].

VPA is also known to induce epiretinal traction and intraretinal changes such as cysts, MHs, MP, macular edema [71], and age-related macular degeneration (AMD) [70] and to promote retinal and optic disc neovascularization [13].

While anomalous PVD may be the initial event, persistent adherence of the vitreous to the optic disc may influence the vectors of force that are exerted on the macular interface [72]. After anomalous PVD with vitreoschisis [8], the outer layer of the splitted PVC remains attached to the macula. In the absence of VPA, inward (centripetal) tangential traction likely throws the underlying retina into folds, resulting in MP. If the vitreous is still attached to the optic disc, the vectors of force could be changed, resulting in outward (centrifugal) tangential traction that induces central retinal dehiscence, MH [72], and/or ERM [73].

The vectors of force that result from VPA may conceivably contribute to the perifoveal vitreous detachment proposed by Johnson and associates [74] as the primary pathogenic event in the formation of macular holes.

Sebag and colleagues have demonstrated that VPA is significantly more common in FTMHs than in LMHs, MP, dry AMD, and age-matched controls. They also showed that VPA, when present in MHs and/or in MP, is highly associated with intraretinal cystoid spaces. Indeed, in their study, cysts were found in 100% of the eyes with VPA and MH, 80% of the eyes with MP and VPA, 75% of the eyes with LMH and VPA, only 42.9% of the eyes with LMH without VPA, and 4.3% of the eyes with MP without VPA [61]. Therefore, VPA is far more common in MP and MH with cysts as compared to LMHs or MP without cysts [61]. Foveal cysts are believed to be the precursors of either FTMHs or LHs [75, 76]. Wang and colleagues found that 100% of the eyes with MH and VPA were associated with intraretinal cysts. MHs and LMHs may have more cysts compared with MP because the inner retinal layers are severely disrupted by changing fluid dynamics [72]. VPA is also more frequent in LMHs than in the presence of pseudomacular holes (PMHs) [73] (Figure 5).



(a)

(b)

Figure 5: (a)-(b) VPA with pseudomacular hole (PMH).

Van Newkirk and colleagues [77] detected vitreous attachment to the peripapillary retina in 65 of 65 patients with stage 3 MHs. The results of these studies suggest that LMHs represent an intermediate stage in the process of macular hole formation and that foveal pseudocysts with partial PVD become LHs if the base is conserved and become FTMHs if the outer retinal layer is disrupted [75]. These results have been confirmed by Wang et al. who discovered VPA in 87.5% of the eyes with FTMHs as compared with 36.4% of the eyes with LMHs and 17.9% of the eyes with MP [72].

Vitreopapillary traction syndrome has also been described, but it is usually in conjunction with other manifestations of anomalous PVD and includes rhegmatogenous RD retinal detachment, MP, MHs, and proliferative diabetic vitreoretinopathy [63]. Vitreopapillary traction can occur in the absence of other forms of anomalous posterior vitreous detachment in diabetic vitreoretinopathy [63].

The diagnosis of VPA is important because affected patients may inappropriately undergo ancillary testing, such as neuroimaging, or invasive procedures, such as lumbar puncture and referrals for retinal and neuroophthalmic evaluations. B-scan ultrasonography and OCT are valuable diagnostic tools that can be used to confirm the presence of vitreopapillary traction and to distinguish it from other causes of optic nerve elevation [65]. On B-scan ultrasonography, peripapillary vitreoretinal traction appears as a partial separation of the posterior hyaloid [68]. OCT can provide a precise diagnostic evaluation of the underlying etiology that may be challenging to establish with clinical observation and B-scan ultrasonography [78]. OCT image of peripapillary vitreoretinal traction is visualized as a partially detached vitreous band with continuous adherence to the optic nerve, thus causing elevation [69, 78].

3.1. Vitreopapillary Adhesion and Surgical Outcomes. The evaluation of OCT is important not only to determine the prognosis but also to identify the requirement for surgical intervention with PPV. Surgical release of VPA may significantly improve the anatomical and visual outcome [1, 73].

The tangential traction induced by VPA can cause damage to the outer retinal layers and the progression of a LMH. In presence of a LMH, VPA is considered as negative functional prognostic factor [73]. For these reasons, it is necessary to monitor LMHs, especially type 3, with OCT exam. Type 3 LMHs are the consequence of a vitreoschisis posteriorly to the level of hyalocytes and these holes can progress mainly in the presence of VPA.

In presence of preoperative VPA, the induction of PVD during PPV should be performed with caution because removal of the adherent peripapillary membranes or posterior vitreous may lead to iatrogenic excision of axons that compromise visual acuity and the visual field [79]. In addition, the suction for vitreous aspiration can induce iatrogenic retinal breaks [79].

4. Epiretinal Membrane

Epiretinal membrane is a common disease of the vitreoretinal interface. It is more commonly diagnosed in elderly people [80]; indeed, its prevalence is 2% in patients under the age of 60 years and 12% in those over 70 years of age [81]. It has been shown that the prevalence of ERM is lower in the Asians than in Caucasians [80–83]. A recent study demonstrated that ERM is significantly more common in the Chinese compared to Caucasians, Blacks, and Hispanics [84].

The ERM is a sheet of avascular fibrocellular tissue that can be formed on the ILM. This membranous tissue is usually deposited on the macula and then on the retinal periphery. ERM is classified as idiopathic (iERM) when it is not associated with any ocular disease and as secondary when it occurs during ocular processes such as RD, intraocular inflammation, trauma, retinal vascular diseases, and retinal surgery [85].

The term ERM refers to a group of vitreoretinal diseases that includes the following: MP [86], cellophane maculopathy, and epiretinal fibrosis [87]. However, many authors suggest that these diseases correspond to different stages of the same pathology [88]. The difference between the various stages has been noted in terms of the type of collagen and the thickness: collagen type VI characterizes cellophane membrane, which is the thinnest; types I and II characterize epiretinal fibrosis, while type IV and laminin are ubiquitous [88]. In a fundoscopic exam, ERM can appear as a translucent, semitranslucent, or opaque membrane (especially in later stages) that is located on the inner surface of the retina.

ERMs are composed of two main components: extracellular matrix (consisting of collagen, laminin, tenascin, fibronectin, vitronectin, and thrombospondin, among others) and retinal and extraretinal cells. A wide variety of cell types have been found in the membranes: glial cells (including microglia, Müller cells, and fibrous astrocytes), epithelial cells from the retinal pigment epithelium (RPE) and ciliary body, hyalocytes, blood-borne immune cells, fibrocytes, and myofibrocytes [85, 89].

An ERM can be static or it can develop over time. Histologically, two types of ERM can be observed: a simple one and a complex one [17]. The simple type, which grows directly on the ILM, is composed of a monolayer of retinal glial cells that produce type IV collagen (laminocytes) [90]. These cells for the first time described by Foos [91] like accessory glial cells migrating from the nerve fiber layer then were termed laminocytes by Snead et al. in spite of their laminar arrangement, close association with the ILM, and evidence of novel ILM production [90]. Laminocytes of the simple type show positivity to glial fibrillary acidic protein (GFAP), atypical protein of the astroglia, and the cytokeratin marker AE1/AE3 using immunocytochemistry [90]. The expression of GFAP indicates the ability of these cells to proliferate and migrate on the retinal surface. The complex or tractional type contains cells such as fibrous astrocytes, myofibroblasts, fibrocytes, hyalocytes, macrophages, and RPE cells in addition to glial cells [17, 90–93]. This multilayer of cells is separated from the ILM by a layer of native vitreous (type II) collagen that remains after incomplete PVD [92, 93]. The presence of type II collagen positivity in these cells suggests an additional role in secreting collagen into the vitreous gel. Simple ERM is a noncontractile type and is associated with mild to no visual symptoms. However, the contraction of myofibroblasts within the more complex type has been proposed to exert a progressive tangential traction at the vitreoretinal interface, which can result in retinal puckering, radial wrinkles, thickening, folding, or detachment, together with vascular distortion and retinal edema or a pseudohole. Thus, contractile ERM can reduce visual acuity and cause metamorphopsia [93–96].

Zhao et al. [97] stated that Müller cells and hyalocytes constitute the predominant cell type of the macular pucker. Myofibroblasts, the major cell type in complex ERM with glial cells [85], are considered to be derived from the transdifferentiation hyalocytes, REP cells, and glial cells. Indeed, many new studies have demonstrated high levels of nerve growth factor (NGF) and transforming growth factor β1 (TGF β1) in the vitreous. These growth factors can cause fibroblast migration and deposition, differentiation into myofibroblasts, and contraction of the extracellular matrix [85, 98]. The transdifferentiated cells are characterized by a downregulation of GFAP and cytokeratins, while proteins involved in motility and proliferation such as α-smooth muscle actin are upregulated [89]. Therefore, the GFAP content in epiretinal tissues has been shown to correlate inversely with the clinical contractility and directly with tractional forces [89].

The retinal changes induced by tangential traction may appear on the fundus examination as follows: irregular wrinkling, nerve fiber layer dragging, ectopic fovea, winding corkscrew vessels surrounding the overlying ERM, or major vessel straightening and crowding [99]. Fundus photography and, in particular, red-free or blue-reflectance imaging, can highlight the presence of ERM [17]. Fundus autofluorescence shows hyperautofluorescent lines that indicate the original location of the retinal vessels, which have been displaced because of a tractional ERM. These lines are called

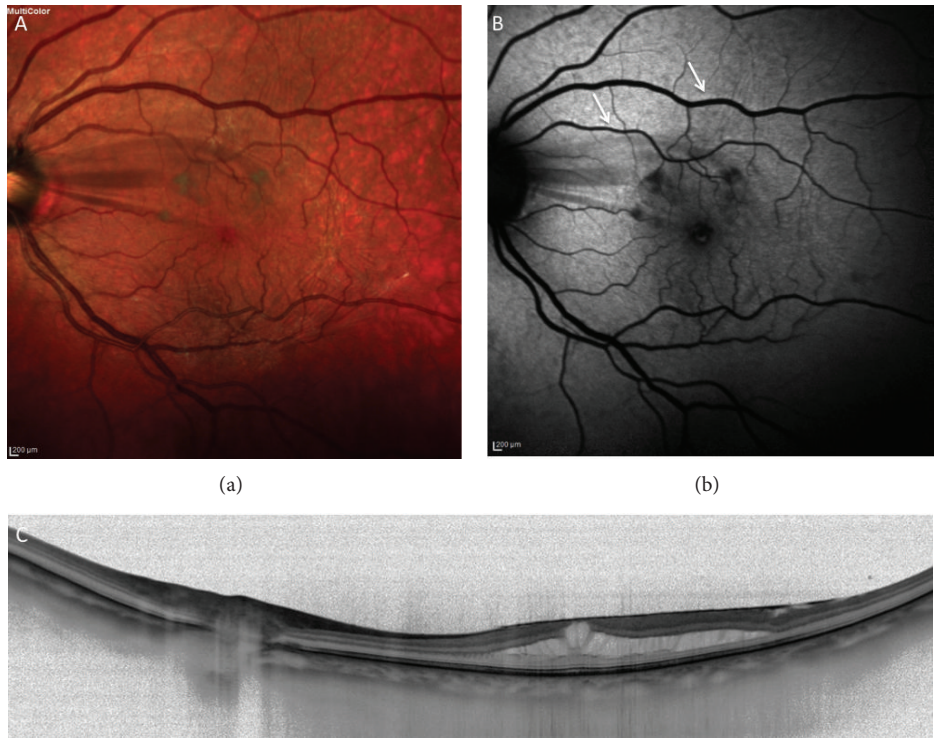


Figure 6: (a) The multicolor fundus photograph shows an iERM (a) with presence of "retinal vessel printings" (b) at fundus autofluorescence induced by tractional forces. The hyperautofluorescent lines (arrows) indicate the original location of the retinal vessels. (c) OCT scan of the same patient shows the cystoid macular edema induced by tractional forces.

"retinal vessel printings" (RVP) and their visualization in eyes with ERM may give useful information about the severity and direction of tangential traction (Figure 6). Recently, Dell'Omo and colleagues proved that the presence of RVP is associated with a higher degree of irregularity of the external limiting membrane (ELM) and the junction between the photoreceptor inner segment and outer segment (IS/OS line) at the fovea and a higher average metamorphopsia score [100].

4.1. Posterior Vitreous Detachment and Epiretinal Membrane. The pathogenesis of iERM remains unknown despite significant progress in the field. The past theories have proposed that PVD certainly plays a critical role in the pathogenesis of this pathology through different possible mechanisms [101]. Among these, transient vitreoretinal traction during the development of PVD may cause breaks in the ILM through which glial cells and RPE cells can migrate and proliferate on the inner retinal surface [85, 102]. In addition, iERM may also result from the proliferation and transdifferentiation of hyalocytes contained within vitreous cortical remnants on the retinal surface following PVD [31, 103] and macrophages from subsequent inflammatory processes [102]. Indeed, partial or complete PVD has been found in 80% to 95% of eyes with idiopathic ERM [96, 101]. Actually, Foos and Bellhorn reported the presence of vitreous collagen fibrils in premacular fibrosis and within the ERM in their studies [91, 104]. Meanwhile, Kishi and Shimizu [101] reported the presence of defects in detached posterior hyaloid membranes of patients with idiopathic preretinal fibrosis. Sebag later clarified the pathogenesis with his concept of "anomalous PVD" [8]. This condition leads to a vitreoschisis and then to an ERM, especially when the split occurs anteriorly to the level of hyalocytes [8, 17, 26]. In this way, hyalocytes attached to the retina stimulate glial cells to proliferate upon an intact ILM to form the scaffolding that allows the uptake of other cells into the membrane [85, 93]. PVD and chronic irritation of glial cells can induce a local release of factors that induce cell gliosis, cellular hypertrophy, and upregulation of GFAP (simple static ERM) [105]. Andjelić et al. found Nestin-1 positivity, marker of progenitor cells of the retina, and Sox2 positivity, marker of epithelial stem cells and of pluripotency potential, to indicate the origin of transdifferentiated cells of ERM. When glial and pigment epithelial cells transdifferentiate to other cells, there is a reduction in cell-specific proteins such as GFAP and cytokeratins [105].

In addition to increasing age and PVD, other risk factors for this pathology are the presence of diabetes and hypercholesterolemia [84].

ERM is only symptomatic if the macular or perimacular area is involved. The initial formation of this epiretinal tissue does not usually cause any clinically important reduction in vision; however, the progression and contraction could be slow. Therefore, advancement of the disease results in significantly reduced visual acuity [106]. Although the cellular mechanism underlying visual impairment in this

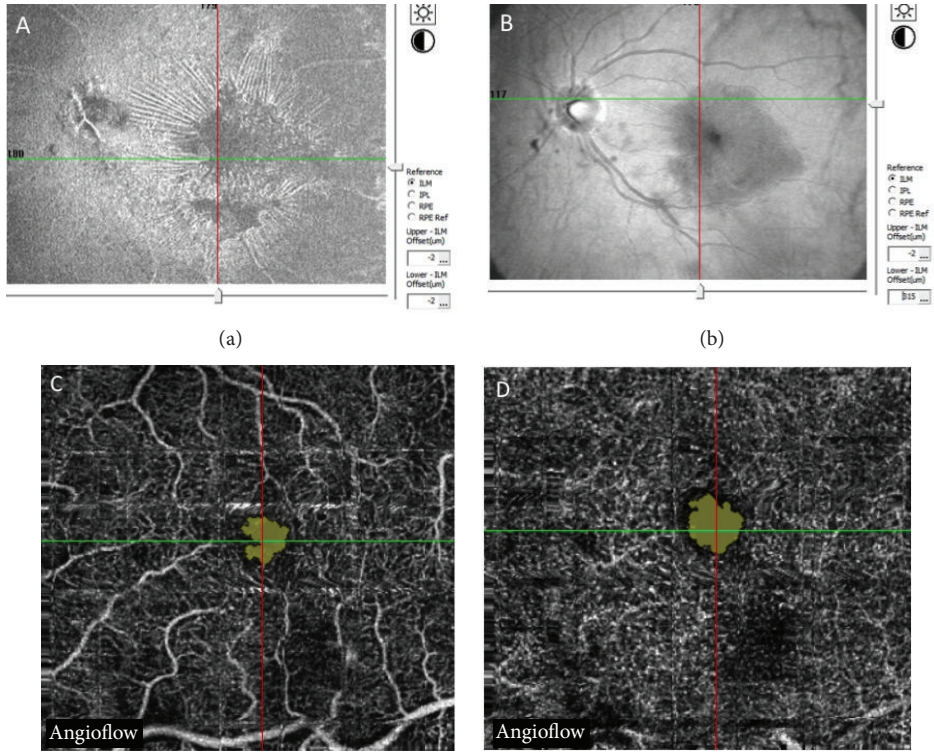


Figure 7: (a)-(b) iERM on en face OCT images at different segmentation thicknesses; at 315 microns offset from ILM the traction disappears (b); (c)-(d) angio-OCT images of retinal superficial plexus (c) and retinal deep plexus (d).

pathology remains unclear, an increasing number of studies have suggested that it is related to abnormalities in macular morphology caused by ERM traction. The contraction affects the outer segments with distortion or detachment of the retina and/or photoreceptors, and it disturbs the spatial arrangement of the cones [107]. Arichika et al. examined retinal changes in iERM and discovered that thickening was greater in the foveal region than in the extrafoveal regions and that the thickening of the external foveal retina to the inner plexiform layer was associated with visual impairment [106].

ERM can occur together with other diseases associated with the vitreoretinal interface.

Tangential centripetal traction on the fovea results in a cleft between the inner retina and outer retina; alternately, it may induce avulsion of the foveal tissue or the roof of a pseudocyst, leading to the formation of lamellar macular defects [108].

The spontaneous separation of ERM is uncommon. Nomoto observed 5 cases of spontaneous separation of iERM in 92 eyes [107].

OCT is very useful in identifying the precise shape and size of ERM [14], in confirming the relationship between PVD and ERM, and in following its natural history [96] (Figure 7). Using OCT, it is quite easy to differentiate the posterior hyaloid, a minimally reflective signal, from an ERM, which is highly reflective [109]. However, so far, we do not have any classification of tangential traction, but only the classification of the morphology changes induced by anteroposterior vectors of traction [110].

OCT could also be shown to discriminate secondary from idiopathic types of abnormalities; in contrast, secondary ERM demonstrates focal adhesion points [111]. The retinal structural changes can be resolved after surgical removal of ERM, and some OCT parameters, such as macular thickness, are associated with the surgical outcome [97]. In recent studies, prolonged macular traction has been shown to cause irreversible photoreceptor cell loss and alignment disruption [112]. Outer retinal structures rarely return to normal after they are impaired, thus indicating a poor visual prognosis [113]. Therefore, prompt surgical intervention would be beneficial to prevent such damage [112].

4.2. Epiretinal Membrane and Surgical Outcomes. Falkner-Radler and colleagues, using spectral-domain OCT, identified the following prognostic factors in the ERM surgery: baseline visual acuity, the IS/OS line integrity of the junction between the photoreceptor inner segment and outer segment, the ILM profile, and foveal contour-like [114].

PPV with membrane peeling using vital dyes is the standard surgical procedure for patients with symptomatic ERM [114]. However, iERMs recur in approximately 10% of cases, and reoperation is required in approximately 3% of cases [115]. Sandali and colleagues showed a recurrence of 5% in 440 patients. They also demonstrated that ILM peeling

seemed to be the only factor preventing ERM recurrence and that the use of staining dyes did not reduce the recurrence rate compared to ILM peeling in the absence of dyes [116].

Kenawy and colleagues have demonstrated that ERMs alter the cleavage plane during ILM peeling. Their study has shown that the formation of ERMs involves epiretinal glial proliferation with neuronal or glial cells on the retinal surface of the ILM and consequent intraretinal displacement. The adhesion of cells to the retinal surface of ILM might lead to focal force transmission into the retina during peeling with consequent retinal breakages and damage of Müller cells [117]. Such iatrogenic retinal damage after ERM-ILM peeling leads in patients with DME prominent cyst characteristics to the "floor effect." Such phenomena consist in the collapse of retinal layers, damage of outer retina, and worsening of visual acuity [118].

Looking through the literature we found a further classification of tangential tractions, on which we are working on, based on the area and the depth of traction, was necessary. These features are better investigated with en face OCT analysis. The right interpretation of the forces involved in the epiretinal tangential tractions helps in a better definition of diagnosis, progression, prognosis, and surgical outcomes of many vitreoretinal diseases.

Conflict of Interests

The authors have no proprietary or commercial interest in any materials described in this paper.

References

[1] C. H. Meyer, J. C. Schmidt, S. Mennel et al., "Anatomical and functional results after macular hole surgery," *Klinische Monatsblätter für Augenheilkunde*, vol. 225, no. 3, pp. 220–226, 2008.

[2] J. Sebag, "Macromolecular structure of the corpus vitreus," *Progress in Polymer Science*, vol. 23, no. 3, pp. 415–446, 1998.

[3] J. Sebag, "Age-related differences in the human vitreoretinal interface," *Archives of Ophthalmology*, vol. 109, no. 7, pp. 966–971, 1991.

[4] J. Sebag, "Vitreous: the resplendent enigma," *British Journal of Ophthalmology*, vol. 93, no. 8, pp. 989–991, 2009.

[5] A. R. Clamp and G. C. Jayson, "The clinical potential of antiangiogenic fragments of extracellular matrix proteins," *British Journal of Cancer*, vol. 93, no. 9, pp. 967–972, 2005.

[6] M. Slevin, J. Krupinski, J. Gaffney et al., "Hyaluronan-mediated angiogenesis in vascular disease: uncovering RHAMM and CD44 receptor signaling pathways," *Matrix Biology*, vol. 26, no. 1, pp. 58–68, 2007.

[7] J. Sebag and E. A. Balazs, "Morphology and ultrastructure of human vitreous fibers," *Investigative Ophthalmology and Visual Science*, vol. 30, no. 8, pp. 1867–1871, 1989.

[8] J. Sebag, "Vitreoschisis," *Graefe's Archive for Clinical and Experimental Ophthalmology*, vol. 246, no. 3, pp. 329–332, 2008.

[9] W. R. Green and J. Sebag, "Vitreous and the vitreo-retinal interface," in *Retina*, S. J. Ryan, Ed., vol. 3, pp. 1882–1960, Mosby, St. Louis, Miss, USA, 2001.

[10] I. Krebs, W. Brannath, C. Glittenberg, F. Zeiler, J. Sebag, and S. Binder, "Posterior vitreomacular adhesion: a potential risk factor for exudative age-related macular degeneration?" *American Journal of Ophthalmology*, vol. 144, no. 5, pp. 741.e1–746.e1, 2007.

[11] J. Akiba, C. W. Arzabe, and C. L. Trempe, "Posterior vitreous detachment and neovascularization in diabetic retinopathy," *Ophthalmology*, vol. 97, no. 7, pp. 889–891, 1990.

[12] M. D. de Smet, A. M. Gad Elkareem, and A. H. Zwinderman, "The vitreous, the retinal interface in ocular health and disease," *Ophthalmologica*, vol. 230, no. 4, pp. 165–178, 2013.

[13] J. Sebag, "Anomalous posterior vitreous detachment: a unifying concept in vitreo-retinal disease," *Graefe's Archive for Clinical and Experimental Ophthalmology*, vol. 242, no. 8, pp. 690–698, 2004.

[14] M. W. Johnson, "Perifoveal vitreous detachment and its macular complications," *Transactions of the American Ophthalmological Society*, vol. 103, pp. 537–567, 2005.

[15] E. Uchino, A. Uemura, and N. Ohba, "Initial stages of posterior vitreous detachment in healthy eyes of older persons evaluated by optical coherence tomography," *Archives of Ophthalmology*, vol. 119, no. 10, pp. 1475–1479, 2001.

[16] J. Bottós, J. Elizalde, E. B. Rodrigues, M. Farah, and M. Maia, "Classifications of vitreomacular traction syndrome: diameter vs morphology," *Eye*, vol. 28, no. 9, pp. 1107–1112, 2014.

[17] D. H. W. Steel and A. J. Lotery, "Idiopathic vitreomacular traction and macular hole: a comprehensive review of pathophysiology, diagnosis, and treatment," *Eye*, vol. 27, no. 10, pp. S1–S21, 2013.

[18] M. M. Le Goff and P. N. Bishop, "Adult vitreous structure and postnatal changes," *Eye*, vol. 22, no. 10, pp. 1214–1222, 2008.

[19] S. Ramesh, R. E. Bonshek, and P. N. Bishop, "Immunolocalisation of opticin in the human eye," *British Journal of Ophthalmology*, vol. 88, no. 5, pp. 697–702, 2004.

[20] H. S. Lazarus and G. S. Hageman, "In situ characterization of the human hyalocyte," *Archives of Ophthalmology*, vol. 112, no. 10, pp. 1356–1362, 1994.

[21] H. Qiao, T. Hisatomi, K.-H. Sonoda et al., "The characterisation of hyalocytes: the origin, phenotype, and turnover," *British Journal of Ophthalmology*, vol. 89, no. 4, pp. 513–517, 2005.

[22] S. R. Bababeygy and J. Sebag, "Chromodissection of the vitreoretinal interface," *Retinal Physician*, vol. 6, pp. 16–21, 2009.

[23] A. Kakehashi, C. L. Schepens, A. de Sousa-Neto, A. E. Jalkh, and C. L. Trempe, "Biomicroscopic findings of posterior vitreoschisis," *Ophthalmic Surgery*, vol. 24, no. 12, pp. 846–850, 1993.

[24] T. G. Chu, P. F. Lopez, M. R. Cano et al., "Posterior vitreoschisis: an echographic finding in proliferative diabetic retinopathy," *Ophthalmology*, vol. 103, no. 2, pp. 315–322, 1996.

[25] S. D. Schwartz, R. Alexander, P. Hiscott, and Z. J. Gregor, "Recognition of vitreoschisis in proliferative diabetic retinopathy. A useful landmark in vitrectomy for diabetic traction retinal detachment," *Ophthalmology*, vol. 103, no. 2, pp. 323–328, 1996.

[26] P. Gupta, K. M. P. Yee, P. Garcia et al., "Vitreoschisis in macular diseases," *British Journal of Ophthalmology*, vol. 95, no. 3, pp. 376–380, 2011.

[27] J. Sebag, P. Gupta, R. R. Rosen, P. Garcia, and A. A. Sadun, "Macular holes and macular pucker: the role of vitreoschisis as imaged by optical coherence tomography/scanning laser ophthalmoscopy," *Transactions of the American Ophthalmological Society*, vol. 105, pp. 121–129, 2007.

[28] K. Nishitsuka, Y. Kashiwagi, N. Tojo et al., "Hyaluronan production regulation from porcine hyalocyte cell line by cytokines," *Experimental Eye Research*, vol. 85, no. 4, pp. 539–545, 2007.

[29] R. Uemoto, S. Yamamoto, T. Aoki, I. Tsukahara, T. Yamamoto, and S. Takeuchi, "Macular configuration determined by optical coherence tomography after idiopathic macular hole surgery with or without internal limiting membrane peeling," *British Journal of Ophthalmology*, vol. 86, no. 11, pp. 1240–1242, 2002.

[30] S. R. Russell and G. S. Hageman, "Optic disc, foveal, and extrafoveal damage due to surgical separation of the vitreous," *Archives of Ophthalmology*, vol. 119, no. 11, pp. 1653–1658, 2001.

[31] T. Yamashita, A. Uemura, and T. Sakamoto, "Intraoperative characteristics of the posterior vitreous cortex in patients with epiretinal membrane," *Graefe's Archive for Clinical and Experimental Ophthalmology*, vol. 246, no. 3, pp. 333–337, 2008.

[32] F. Semeraro, F. Morescalchi, A. Russo, M. R. Romano, and C. Costagliola, "Tamponade or filling effect: changes of forces in myopic eyes," *BioMed Research International*, vol. 2014, Article ID 618382, 15 pages, 2014.

[33] J. Meskauskas, R. Repetto, and J. H. Siggers, "Shape change of the vitreous chamber influences retinal detachment and reattachment processes: is mechanical stress during eye rotations a factor?" *Investigative Ophthalmology and Visual Science*, vol. 53, no. 10, pp. 6271–6281, 2012.

[34] Y. Ikuno, F. Gomi, and Y. Tano, "Potent retinal arteriolar traction as a possible cause of myopic foveoschisis," *The American Journal of Ophthalmology*, vol. 139, no. 3, pp. 462–467, 2005.

[35] R. G. Mirza, M. W. Johnson, and L. M. Jampol, "Optical coherence tomography use in evaluation of the vitreoretinal interface: a review," *Survey of Ophthalmology*, vol. 52, no. 4, pp. 397–421, 2007.

[36] K. Sayanagi, Y. Ikuno, and Y. Tano, "Tractional internal limiting membrane detachment in highly myopic eyes," *American Journal of Ophthalmology*, vol. 142, no. 5, pp. 850–852, 2006.

[37] K. Sayanagi, Y. Ikuno, F. Gomi, and Y. Tano, "Retinal vascular microfolds in highly myopic eyes," *American Journal of Ophthalmology*, vol. 139, no. 4, pp. 658–663, 2005.

[38] H. Bando, Y. Ikuno, J.-S. Choi, Y. Tano, I. Yamanaka, and T. Ishibashi, "Ultrastructure of internal limiting membrane in myopic foveoschisis," *American Journal of Ophthalmology*, vol. 139, no. 1, pp. 197–199, 2005.

[39] H. Faghihi, F. Hajizadeh, and M. Riazi-Esfahani, "Optical coherence tomographic findings in highly myopic eyes," *Journal of Ophthalmic and Vision Research*, vol. 5, no. 2, pp. 110–121, 2010.

[40] A. W. Stitt, J. E. Moore, J. A. Sharkey et al., "Advanced glycation end products in vitreous: structural and functional implications for diabetic vitreopathy," *Investigative Ophthalmology and Visual Science*, vol. 39, no. 13, pp. 2517–2523, 1998.

[41] J. Sebag, S. Nie, K. Reiser, M. A. Charles, and N.-T. Yu, "Raman spectroscopy of human vitreous in proliferative diabetic retinopathy," *Investigative Ophthalmology & Visual Science*, vol. 35, no. 7, pp. 2976–2980, 1994.

[42] J. Sebag, B. Buckingham, M. A. Charles, and K. Reiser, "Biochemical abnormalities in vitreous of humans with proliferative diabetic retinopathy," *Archives of Ophthalmology*, vol. 110, no. 10, pp. 1472–1476, 1992.

[43] A. K. Dubey, P. N. Nagpal, S. Chawla, and B. Dubey, "A proposed new classification for diabetic retinopathy: the concept of primary and secondary vitreopathy," *Indian Journal of Ophthalmology*, vol. 56, no. 1, pp. 23–29, 2008.

[44] A. Ophir and M. R. Martinez, "Epiretinal membranes and incomplete posterior vitreous detachment in diabetic macular edema, detected by spectral-domain optical coherence tomography," *Investigative Ophthalmology and Visual Science*, vol. 52, no. 9, pp. 6414–6420, 2011.

[45] J. Sebag, "Vitreoschisis in diabetic macular edema," *Investigative Ophthalmology and Visual Science*, vol. 52, no. 11, pp. 8455–8456, 2011.

[46] F. Kuhn and B. Aylward, "Rhegmatogenous retinal detachment: a reappraisal of its pathophysiology and treatment," *Ophthalmic Research*, vol. 51, no. 1, pp. 15–31, 2013.

[47] M. Yoshida and S. Kishi, "Pathogenesis of macular hole recurrence and its prevention by internal limiting membrane peeling," *Retina*, vol. 27, no. 2, pp. 169–173, 2007.

[48] D. W. Park, P. U. Dugel, J. Garda et al., "Macular pucker removal with and without internal limiting membrane peeling: pilot study," *Ophthalmology*, vol. 110, no. 1, pp. 62–64, 2003.

[49] N. Lois, J. Burr, J. Norrie et al., "Internal limiting membrane peeling versus no peeling for idiopathic full-thickness macular hole: a pragmatic randomized controlled trial," *Investigative Ophthalmology and Visual Science*, vol. 52, no. 3, pp. 1586–1592, 2011.

[50] X. Fang, X. Zheng, Y. Weng et al., "Anatomical and visual outcome after vitrectomy with triamcinolone acedonide-assisted epiretinal membrane removal in highly myopic eyes with retinal detachment due to macular hole," *Eye*, vol. 23, no. 2, pp. 248–254, 2009.

[51] M. D. de Smet, C. Valmaggia, J. Zarranz-Ventura, and B. Willekens, "Microplasmin: ex vivo characterization of its activity in porcine vitreous," *Investigative Ophthalmology and Visual Science*, vol. 50, no. 2, pp. 814–819, 2009.

[52] A. Gandorfer, M. Rohleder, C. Sethi et al., "Posterior vitreous detachment induced by microplasmin," *Investigative Ophthalmology and Visual Science*, vol. 45, no. 2, pp. 641–647, 2004.

[53] M. D. de Smet, A. Gandorfer, P. Stalmans et al., "Microplasmin intravitreal administration in patients with vitreomacular traction scheduled for vitrectomy: the MIVI I trial," *Ophthalmology*, vol. 116, no. 7, pp. 1349–1355, 2009.

[54] M. S. Benz, K. H. Packo, V. Gonzalez et al., "A placebo-controlled trial of microplasmin intravitreous injection to facilitate posterior vitreous detachment before vitrectomy," *Ophthalmology*, vol. 117, no. 4, pp. 791–797, 2010.

[55] P. Stalmans, C. Delaey, M. D. de Smet, E. Van Dijkman, and S. Pakola, "Intravitreal injection of microplasmin for treatment of vitreomacular adhesion: results of a prospective, randomized, sham-controlled phase II trial (the MIVI-IIT trial)," *Retina*, vol. 30, no. 7, pp. 1122–1127, 2010.

[56] P. Stalmans, M. S. Benz, A. Gandorfer et al., "Enzymatic vitreolysis with ocriplasmin for vitreomacular traction and macular holes," *The New England Journal of Medicine*, vol. 367, no. 7, pp. 606–615, 2012.

[57] J. Moisseiev, I. Moroz, and G. Katz, "Effect of ocriplasmin on the management of macular holes: assessment of the clinical relevance of ocriplasmin," *JAMA Ophthalmology*, vol. 132, no. 6, pp. 709–713, 2014.

[58] E. K. Chin, D. R. Almeida, E. H. Sohn et al., "Incomplete vitreomacular traction release using intravitreal ocriplasmin," *Case Reports in Ophthalmology*, vol. 5, no. 3, pp. 455–462, 2014.

[59] R. A. Silva, D. M. Moshfeghi, and T. Leng, "Retinal breaks due to intravitreal ocriplasmin," *Clinical Ophthalmology*, vol. 8, pp. 1591–1594, 2014.

[60] M. D. Tibbetts, E. Reichel, and A. J. Witkin, "Vision loss after intravitreal ocriplasmin: correlation of spectral-domain optical

coherence tomography and electroretinography," *JAMA Ophthalmology*, vol. 132, no. 4, pp. 487–490, 2014.

[61] J. Sebag, M. Y. Wang, D. Nguyen, and A. A. Sadun, "Vitreopapillary adhesion in macular diseases," *Transactions of the American Ophthalmological Society*, vol. 107, pp. 35–44, 2009.

[62] A. Hixson and S. Reynolds, "Peripapillary vitreoretinal traction," *Optometry*, vol. 82, no. 10, pp. 602–606, 2011.

[63] T. R. Hedges III, N. L. Flattem, and A. Bagga, "Vitreopapillary traction confirmed by optical coherence tomography," *Archives of Ophthalmology*, vol. 124, no. 2, pp. 279–281, 2006.

[64] B. Katz and W. F. Hoyt, "Gaze-evoked amaurosis from vitreopapillary traction," *American Journal of Ophthalmology*, vol. 139, no. 4, pp. 631–637, 2005.

[65] M. W. Johnson, "Posterior vitreous detachment: evolution and complications of its early stages," *The American Journal of Ophthalmology*, vol. 149, no. 3, pp. 371–382, 2010.

[66] P. Sibony, S. Fourman, R. Honkanen, and F. El Baba, "Asymptomatic peripapillary subretinal hemorrhage: a study of 10 cases," *Journal of Neuro-Ophthalmology*, vol. 28, no. 2, pp. 114–119, 2008.

[67] G. T. Kokame, I. Yamamoto, S. Kishi, A. Tamura, and J. H. Drouilhet, "Intrapapillary hemorrhage with adjacent peripapillary subretinal hemorrhage," *Ophthalmology*, vol. 111, no. 5, pp. 926–930, 2004.

[68] B. J. Wisotsky, C. B. Magat-Gordon, and J. E. Puklin, "Vitreopapillary traction as a cause of elevated optic nerve head," *American Journal of Ophthalmology*, vol. 126, no. 1, pp. 137–139, 1998.

[69] S. Cabrera, A. Katz, and E. Margalit, "Vitreopapillary traction: cost-effective diagnosis by optical coherence tomography," *Canadian Journal of Ophthalmology*, vol. 41, no. 6, pp. 763–765, 2006.

[70] J. Sebag, B. J. Wisotsky, C. B. Magat-Gordon, and J. E. Puklin, "Vitreopapillary traction as a cause of elevated optic nerve head," *American Journal of Ophthalmology*, vol. 128, no. 2, pp. 261–267, 1999.

[71] M. Karatas, J. A. Ramirez, and A. Ophir, "Diabetic vitreopapillary traction and macular oedema," *Eye*, vol. 19, no. 6, pp. 676–682, 2005.

[72] M. Y. Wang, D. Nguyen, N. Hindoyan, A. A. Sadun, and J. Sebag, "Vitreo-papillary adhesion in macular hole and macular pucker," *Retina*, vol. 29, no. 5, pp. 644–650, 2009.

[73] M. R. Romano, J. L. Vallejo-Garcia, F. I. Camesasca, P. Vinciguerra, and C. Costagliola, "Vitreo-papillary adhesion as a prognostic factor in pseudo- and lamellar macular holes," *Eye*, vol. 26, no. 6, pp. 810–815, 2012.

[74] M. W. Johnson, M. R. Van Newkirk, and K. A. Meyer, "Perifoveal vitreous detachment is the primary pathogenic event in idiopathic macular hole formation," *Archives of Ophthalmology*, vol. 119, no. 2, pp. 215–222, 2001.

[75] B. Haouchine, P. Massin, and A. Gaudric, "Foveal pseudocyst as the first step in macular hole formation: a prospective study by optical coherence tomography," *Ophthalmology*, vol. 108, no. 1, pp. 15–22, 2001.

[76] A. Gaudric, B. Haouchine, P. Massin, M. Paques, P. Blain, and A. Erginay, "Macular hole formation: new data provided by optical coherence tomography," *Archives of Ophthalmology*, vol. 117, no. 6, pp. 744–751, 1999.

[77] M. R. Van Newkirk, M. W. Johnson, J. R. Hughes, K. A. Meyer, and S. F. Byrne, "B-scan ultrasonographic findings in the stages of idiopathic macular hole," *Transactions of the American Ophthalmological Society*, vol. 98, pp. 163–171, 2000.

[78] S. Rumelt, M. Karatas, J. Pikkel, M. Majlin, and A. Ophir, "Optic disc traction syndrome associated with central retinal vein occlusion," *Archives of Ophthalmology*, vol. 121, no. 8, pp. 1093–1097, 2003.

[79] S. D. Pendergast, D. F. Martin, A. D. Proia, G. J. Jaffe, and B. W. McCuen II, "Removal of optic disc stalks during diabetic vitrectomy," *Retina*, vol. 15, no. 1, pp. 25–28, 1995.

[80] D. J. McCarty, B. N. Mukesh, V. Chikani et al., "Prevalence and associations of epiretinal membranes in the visual impairment project," *The American Journal of Ophthalmology*, vol. 140, no. 2, pp. 288–294, 2005.

[81] P. Mitchell, W. Smith, T. Chey, and A. Chang, "Prevalence and associations of epiretinal membranes. The Blue Mountains Eye Study, Australia," *Ophthalmology*, vol. 104, no. 6, pp. 1033–1040, 1997.

[82] Q. You, L. Xu, and J. B. Jonas, "Prevalence and associations of epiretinal membranes in adult Chinese: the Beijing eye study," *Eye*, vol. 22, no. 7, pp. 874–879, 2008.

[83] X. R. Duan, Y. B. Liang, D. S. Friedman et al., "Prevalence and associations of epiretinal membranes in a rural Chinese adult population: the handan eye study," *Investigative Ophthalmology and Visual Science*, vol. 50, no. 5, pp. 2018–2023, 2009.

[84] C. H. Ng, N. Cheung, J. J. Wang et al., "Prevalence and risk factors for epiretinal membranes in a multi-ethnic United States population," *Ophthalmology*, vol. 118, no. 4, pp. 694–699, 2011.

[85] M. Joshi, S. Agrawal, and J. B. Christoforidis, "Inflammatory mechanisms of idiopathic epiretinal membrane formation," *Mediators of Inflammation*, vol. 2013, Article ID 192582, 6 pages, 2013.

[86] M. Trese, D. B. Chandler, and R. Machemer, "Macular pucker. II. Ultrastructure," *Graefe's Archive for Clinical and Experimental Ophthalmology*, vol. 221, no. 1, pp. 16–26, 1983.

[87] T. A. Ciulla and R. D. Pesavento, "Epiretinal fibrosis," *Ophthalmic Surgery and Lasers*, vol. 28, no. 8, pp. 670–679, 1997.

[88] M. Kritzenberger, B. Junglas, C. Framme et al., "Different collagen types define two types of idiopathic epiretinal membranes," *Histopathology*, vol. 58, no. 6, pp. 953–965, 2011.

[89] A. Bringmann and P. Wiedemann, "Involvement of Müller glial cells in epiretinal membrane formation," *Graefe's Archive for Clinical and Experimental Ophthalmology*, vol. 247, no. 7, pp. 865–883, 2009.

[90] D. R. J. Snead, S. James, and M. P. Snead, "Pathological changes in the vitreoretinal junction 1: epiretinal membrane formation," *Eye*, vol. 22, no. 10, pp. 1310–1317, 2008.

[91] R. Y. Foos, "Vitreoretinal juncture—simple epiretinal membranes," *Graefe's Archive for Clinical and Experimental Ophthalmology*, vol. 189, pp. 231–250, 1974.

[92] L. K. Chang, H. F. Fine, R. F. Spaide, H. Koizumi, and H. E. Grossniklaus, "Ultrastructural correlation of spectral-domain optical coherence tomographic findings in vitreomacular traction syndrome," *The American Journal of Ophthalmology*, vol. 146, no. 1, pp. 121–127, 2008.

[93] A. Kampik, "Pathology of epiretinal membrane, idiopathic macular hole, and vitreomacular traction syndrome," *Retina*, vol. 32, no. 2, pp. S194–S199, 2012.

[94] P. Hiscott, S. Hagan, L. Heathcote et al., "Pathobiology of epiretinal and subretinal membranes: possible roles for the matricellular proteins thrombospondin 1 and osteonectin (SPARC)," *Eye*, vol. 16, no. 4, pp. 393–403, 2002.

[95] P. S. Hiscott, I. Grierson, C. J. Trombetta, A. H. S. Rahi, J. Marshall, and D. Mcleod, "Retinal and epiretinal glia—an

immunohistochemical study," *British Journal of Ophthalmology*, vol. 68, no. 10, pp. 698–707, 1984.

[96] Y. Barak, M. A. Ihnen, and S. Schaal, "Spectral domain optical coherence tomography in the diagnosis and management of vitreoretinal interface pathologies," *Journal of Ophthalmology*, vol. 2012, Article ID 876472, 7 pages, 2012.

[97] F. Zhao, A. Gandorfer, C. Haritoglou et al., "Epiretinal cell proliferation in macular pucker and vitreomacular traction syndrome: analysis of flat-mounted internal limiting membrane specimens," *Retina*, vol. 33, no. 1, pp. 77–88, 2013.

[98] S. Minchiotti, B. Stampachiacchiere, A. Micera et al., "Human idiopathic epiretinal membranes express NGF and NGF receptors," *Retina*, vol. 28, no. 4, pp. 628–637, 2008.

[99] H. K. Yang, S. J. Kim, Y. S. Jung, K. G. Kim, J. H. Kim, and H. G. Yu, "Improvement of horizontal macular contraction after surgical removal of epiretinal membranes," *Eye*, vol. 25, no. 6, pp. 754–761, 2011.

[100] R. Dell'Omo, F. Cifariello, E. Dell'Omo et al., "Influence of retinal vessel printings on metamorphopsia and retinal architectural abnormalities in eyes with idiopathic macular epiretinal membrane," *Investigative Ophthalmology and Visual Science*, vol. 54, no. 12, pp. 7803–7811, 2013.

[101] S. Kishi and K. Shimizu, "Oval defect in detached posterior hyaloid membrane in idiopathic preretinal macular fibrosis," *American Journal of Ophthalmology*, vol. 118, no. 4, pp. 451–456, 1994.

[102] N. Mandal, M. Kofod, H. Vorum et al., "Proteomic analysis of human vitreous associated with idiopathic epiretinal membrane," *Acta Ophthalmologica*, vol. 91, no. 4, pp. 333–334, 2013.

[103] X.-F. Zhu, J.-J. Peng, H.-D. Zou et al., "Prevalence and risk factors of idiopathic epiretinal membranes in Beixinjing blocks, Shanghai, China," *PLoS ONE*, vol. 7, no. 12, Article ID e51445, 2012.

[104] M. B. Bellhorn, A. H. Friedman, G. N. Wise, and P. Henkind, "Ultrastructure and clinicopathologic correlation of idiopathic preretinal macular fibrosis," *American Journal of Ophthalmology*, vol. 79, no. 3, pp. 366–373, 1975.

[105] S. Andjelić, X. Lumi, X. Yan et al., "Characterization of *ex vivo* cultured neuronal- and glial- like cells from human idiopathic epiretinal membranes," *BMC Ophthalmology*, vol. 14, article 165, 2014.

[106] S. Arichika, M. Hangai, and N. Yoshimura, "Correlation between thickening of the inner and outer retina and visual acuity in patients with epiretinal membrane," *Retina*, vol. 30, no. 3, pp. 503–508, 2010.

[107] H. Nomoto, C. Matsumoto, E. Arimura et al., "Quantification of changes in metamorphopsia and retinal contraction in eyes with spontaneous separation of idiopathic epiretinal membrane," *Eye*, vol. 27, no. 8, pp. 924–930, 2013.

[108] J. C. Chen and L. R. Lee, "Clinical spectrum of lamellar macular defects including pseudoholes and pseudocysts defined by optical coherence tomography," *British Journal of Ophthalmology*, vol. 92, no. 10, pp. 1342–1346, 2008.

[109] B. Hajnajeeb, M. Georgopoulos, R. Sayegh, W. Geitzenauer, and U. Schmidt-Erfurth, "The role of the optical coherence tomography in identifying shape and size of idiopathic epiretinal membranes," *British Journal of Ophthalmology*, vol. 96, no. 6, pp. 867–871, 2012.

[110] J. S. Duker, P. K. Kaiser, S. Binder et al., "The international vitreomacular traction study group classification of vitreomacular adhesion, traction, and macular hole," *Ophthalmology*, vol. 120, no. 12, pp. 2611–2619, 2013.

[111] K. Mori, P. L. Gehlbach, A. Sano, T. Deguchi, and S. Yoneya, "Comparison of epiretinal membranes of differing pathogenesis using optical coherence tomography," *Retina*, vol. 24, no. 1, pp. 57–62, 2004.

[112] M. H. Suh, J. M. Seo, K. H. Park, and H. G. Yu, "Associations between macular findings by optical coherence tomography and visual outcomes after epiretinal membrane removal," *The American Journal of Ophthalmology*, vol. 147, no. 3, pp. 473–480, 2009.

[113] T. Niwa, H. Terasaki, M. Kondo, C.-H. Piao, T. Suzuki, and Y. Miyake, "Function and morphology of macula before and after removal of idiopathic epiretinal membrane," *Investigative Ophthalmology and Visual Science*, vol. 44, no. 4, pp. 1652–1656, 2003.

[114] C. I. Falkner-Radler, C. Glittenberg, S. Hagen, T. Benesch, and S. Binder, "Spectral-domain optical coherence tomography for monitoring epiretinal membrane surgery," *Ophthalmology*, vol. 117, no. 4, pp. 798–805, 2010.

[115] G. Donati, A. D. Kapetanios, and C. J. Pournaras, "Complications of surgery for epiretinal membranes," *Graefe's Archive for Clinical and Experimental Ophthalmology*, vol. 236, no. 10, pp. 739–746, 1998.

[116] O. Sandali, M. El Sanharawi, E. Basli et al., "Epiretinal membrane recurrence: incidence, characteristics, evolution, and preventive and risk factors," *Retina*, vol. 33, no. 10, pp. 2032–2038, 2013.

[117] N. Kenawy, D. Wong, T. Stappler et al., "Does the presence of an epiretinal membrane alter the cleavage plane during internal limiting membrane peeling?" *Ophthalmology*, vol. 117, no. 2, pp. 320.e1–323.e1, 2010.

[118] M. R. Romano, V. Romano, J. L. Vallejo-Garcia et al., "Macular hypotrophy after internal limiting membrane removal for diabetic macular edema," *Retina*, vol. 34, no. 6, pp. 1182–1189, 2014.