19 Surgical Management of Diabetic Macular Edema

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19.1 Introduction

Macular edema is an important cause of vision loss in diabetic patients [1]. Diabetic macular edema (DME) develops in approximately 30% of patients who have had diabetes mellitus for more than 20 years and constitutes a major cause of visual impairment worldwide. Identifying treatments that can effectively treat DME is critical to managing this increasing number of patients.

Currently, the first line of treatment of DME is intravitreal pharmacotherapy. All phase III randomized clinical trials (RISE/RIDE, RESTORE, VIVID/VISTA) have demonstrated the superiority of anti-vascular endothelial growth factor (anti-VEGF) agents, such as ranibizumab and aflibercept, over laser photocoagulation and/or surgery. Nevertheless, anti-VEGF agents confer high direct and indirect costs to patients and payers that can exceed those of laser and vitrectomy. In addition, there is a subset of nonresponders who may benefit from alternative therapy.

In 1988, Nasrallah et al. demonstrated a lower prevalence of DME in eyes with a posterior vitreous detachment compared to eyes without [2]. Hikichi et al. similarly showed resolution of macular edema in almost half of the eyes which underwent a posterior vitreous separation [3]. Lewis et al. also reported the improvement of DME in eyes with posterior hyaloid traction who underwent vitrectomy [4]. In 1996, Tachi et al. reported good results after vitrectomy in patients with diffuse edema in the presence of an attached, albeit not thickened hyaloid [5]. In his series, macular edema resolved in 90% of these cases and vision improved in 50% of treated eyes.

19.2 Pathophysiology

We must appreciate the physiology of the diabetic vitreous and its interaction with the retina to understand the role of vitrectomy in the management of DME.

The vitreous cortex adheres tightly to the internal limiting membrane (ILM) through an extracellular matrix of laminin, opticin, fibronectin, and other constituents [6, 7]. In diabetic patients, there is an abnormal cross-linking of fibrils that results in stronger adhesions between

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the posterior vitreous cortex and the ILM. This is the result of the deposition of advanced glycosylation end-products at the sites of vitreoretinal adhesion [7]. The ILM is noted to be pathologically thickened in diabetic patients due to this accumulation of extracellular matrix components (such as collagen type I, III, IV, V, proteoglycans, laminin, and fibronectin), as well as macrophages and fibroblasts [8].

There is sufficient clinicopathologic correlation to suggest that these changes are relevant in the diabetic eye. For example, Hagenau et al. examined specimens from eyes with DME that underwent vitrectomy. All eyes showed pathologic changes at the vitreomacular interface, regardless of the appearance of the retina on prior OCT or clinical examination. They reported trans-differentiation of hyalocytes into myofibroblasts, as well as thickening and remodeling of the vitreous cortex [9]. This thickened posterior hyaloid–ILM complex can impede the outflow of fluids accumulated in the retina and prevents proper diffusion of oxygen into the retina from the vitreous [10].

The vitreous is an important contributor to the development of DME in other ways. Intact vitreous causes traction on Muller cells, resulting in cellular proliferation and leakage [11]. Vascular permeability is increased as traction distorts the retinal vessels and results in disruption of the macular microcirculation [12–16].

19.3 Role of Vitrectomy

There are three main hypothesized methods by which a vitrectomy is thought to improve macular edema in diabetic, non-vitrectomized patients: (1) relief of vitreoretinal traction, (2) increase in retinal and vitreous oxygenation, and (3) reduction of intravitreal VEGF load.

A vitrectomy with detachment of the posterior hyaloid effectively relieves any traction that may contribute to anatomic thickening and/or increased vascular permeability. Independent of the relief of traction, vitrectomy has also been shown to effectively decrease certain growth factors, such as vascular endothelial growth factor (VEGF), interleukin-6 (IL-6), and platelet-derived growth factor (PDGF). These growth factors play an important role in the development and progression of macular edema in diabetic retinopathy and venous occlusive disease [17–20]. Vitrectomy also increases oxygen tension in the posterior segment and allows for increased retinal and, potentially, choroidal oxygenation [21–27].

19.4 Indications for Vitrectomy

19.4.1 Eyes with Clinically Visible Vitreomacular Traction

Vitreomacular interface abnormalities are common in patients with diabetic macular edema. Chang et al. showed that in patients treated with intravitreal anti-VEGF injections, vitreomacular interface abnormalities were present in 6.4% of eyes, and vitreomacular adhesion (VMA) was a predictor of poor baseline vision. Nevertheless, the presence of VMA did not affect response to treatment [28]. This was corroborated in other studies [29]. A spontaneous release of VMA seems to be associated with a positive anatomic response to anti-VEGF treatment with decreased DME.

There is evidence to suggest that in the presence of clinically identifiable vitreomacular traction (VMT), vitrectomy confers some anatomic and functional benefit, with a relatively favorable anatomic success rate and a low rate of complications [30]. Vitrectomy proves to be particularly useful in eyes with diffuse macular edema that present with a taut posterior hyaloid or clinical evidence of VMT by clinical examination and/or on optical coherence tomography (OCT). Whereas focal macular edema generally results from microaneurysmal leakage, diffuse macular edema is associated with widespread breakdown of the blood–retinal barrier and is often associated with a taut posterior hyaloid [31–34]. The posterior hyaloid tends to condense and cause tangential vitreomacular traction, with a subsequent increase in the permeability of the retinal vasculature [31]. All eyes showed pathologic changes at the vitreomacular interface, regardless of the appearance of the retina on prior OCT or clinical examination [35]. They reported trans-differentiation of hyalocytes

into myofibroblasts, as well as thickening and remodeling of the vitreous cortex. This thickened posterior hyaloid–ILM complex is thought to impede the outflow of fluid accumulated in the retina and prevent diffusion of oxygen into the retina from the vitreous.

In the absence of macular ischemia, removing the posterior hyaloid in eyes with traction at the fovea improves macular edema and visual function in up to 90% of eyes, according to some studies [31]. Lewis et al. showed that in eyes with macular edema that did not adequately respond to laser photocoagulation and had biomicroscopic evidence of a taut posterior hyaloid, vitrectomy improves anatomic and functional outcomes. In their study, 9 of 10 vitrectomized eyes showed improvement in macular edema, and vision improved by two or more Snellen lines in 6 eyes [4]. Harbour et al. showed that eyes with a taut posterior hyaloid similarly benefitted from surgery, with vision improving in 4 out of 10 eyes, with the rest remaining stable [33]. Other studies have corroborated these findings [36]. Rosenblatt et al. similarly showed improvements in retinal thickness and vision in a series of 26 eyes with a taut posterior hyaloid [37]. Otani et al. also demonstrated improvement in foveal thickness and vision after vitrectomy [38]. Even in eyes with "massive" exudation, vitrectomy has been shown to be useful in obtaining some functional and/or anatomic improvement [39].

The Diabetic Retinopathy Clinical Research Network (DRCRnet) Vitrectomy Study evaluated the role of vitrectomy in DME in a prospective, data-gathering study of 87 eyes with clinical evidence of VMT, baseline vision of 20/63 to 20/400, and OCT subfield thickness of greater than 300 um [40]. After vitrectomy with or without epiretinal and/or ILM peeling, there was a statistically significant anatomic and functional improvement. Median OCT thickness decreased by 160 um. Vision improved in 38% of eyes, although 22% of eyes showed some loss of visual acuity. There were several pitfalls with this study that should be taken into account which can limit our ability to apply these findings to routine clinical practice. There was no assessment of the degree of macular ischemia in these eyes. Vitreomacular traction was also not universally defined. There was no control group. Surgical technique and indication was left up to the surgeon's discretion. Surgery was performed only if it was deemed that the eye would likely not improve after further sessions of macular laser photocoagulation, thereby selecting patients who were more than likely to present with a poorer functional and anatomic baseline. Despite any controlled and standardized approach to this condition with respect to preoperative macular status, preoperative imaging, timing of intervention, inclusion criteria, surgical technique, and follow-up, the study nevertheless outlined the potentially positive role vitrectomy can have on DME.

Even in the absence of a taut posterior hyaloid on examination or OCT, a clinically identifiable epiretinal membrane (ERM) can also cause underlying macular traction and contribute to DME. Although most studies evaluating the role of surgery in DME have examined eyes with a taut posterior hyaloid, some groups have examined the role of ERM peeling in DME. For example, Yamamoto et al. included a group of DME eyes with a posterior vitreous detachment and ERM that underwent vitrectomy and membrane peeling. Although mean foveal thickness decreased, the difference was not statistically significant. Nevertheless, vision improved in 60% of eyes [41].

19.4.2 Eyes Without Clinically Visible Vitreomacular Traction

As mentioned earlier, most of the earlier studies evaluating the role of vitrectomy for DME focused on eyes with a clinically visible taut posterior hyaloid, and these reports suggest a clear benefit. Nevertheless, this is a small subset of the overall population of eyes with DME. Thomas et al. demonstrated that only 4% of patients with DME had a taut thickened posterior hyaloid that could be definitively identified in the clinical setting [42].

Traction is a significant cause of diffuse retinal leakage in DME that can improve with vitrectomy. If the hyaloid is detached and there is no evidence of VMT, there is less evidence to

suggest surgery is beneficial. Despite some evidence suggesting the efficacy of vitrectomy in these cases, there is still controversy over the criteria used for selecting surgical cases if the clinical examination and/or OCT does not reveal a tractional component.

There is a body of literature that suggests that vitrectomy is only useful in eyes with clinical evidence of traction. In a comparative, prospective case series, Shah et al. demonstrated that vitrectomy was only useful in eyes with OCT signs suggestive of macular traction. Vision only improved in eyes with tractional signs preoperatively [43]. A randomized controlled trial by the same group demonstrated that in eyes previously treated with macular laser, there was no significant improvement in macular thickness in eyes with no macular traction [44]. This result was replicated by Patel et al. [45]. Massin et al. similarly showed that vitrectomy was only beneficial in eyes with prior evidence of vitreomacular traction [46]. Ikeda et al. examined five DME eyes with a posterior vitreous detachment on exam. After vitrectomy, four eyes showed improved macular thickening, and all exhibited some improvement in vision. The authors attributed this to a reduction in pro-inflammatory cytokines in the vitrectomized eye and an increase in oxygen tension [47]. Kumagai et al. followed eyes with non-tractional DME that underwent vitrectomy and reported long-term visual acuity gains in 52.7% of eyes [48]. Le Heij et al. similarly demonstrated visual acuity improvement in eyes without evident VMT. Eyes that had prior macular laser photocoagulation showed a 14% improvement in vision, whereas eyes with no prior macular laser showed a 77% improvement in vision [49]. Michalewska et al. examined a cohort of treatment-naïve eyes that underwent vitrectomy for diabetic macular edema. These eyes tended to have a poorer visual acuity at presentation [50]. Nevertheless, the authors noted a significant improvement in central retinal thickness from a mean of 595 um to 266 um which was sustained for a period of 6 months. Vision also improved in all but 1 of 44 eyes. These patients were not followed for more than 6 months.

Figure 19.1 demonstrates the resolution of macular edema in a patient with no OCT evidence of hyaloid traction who underwent vitrectomy for treatment-resistant DME.

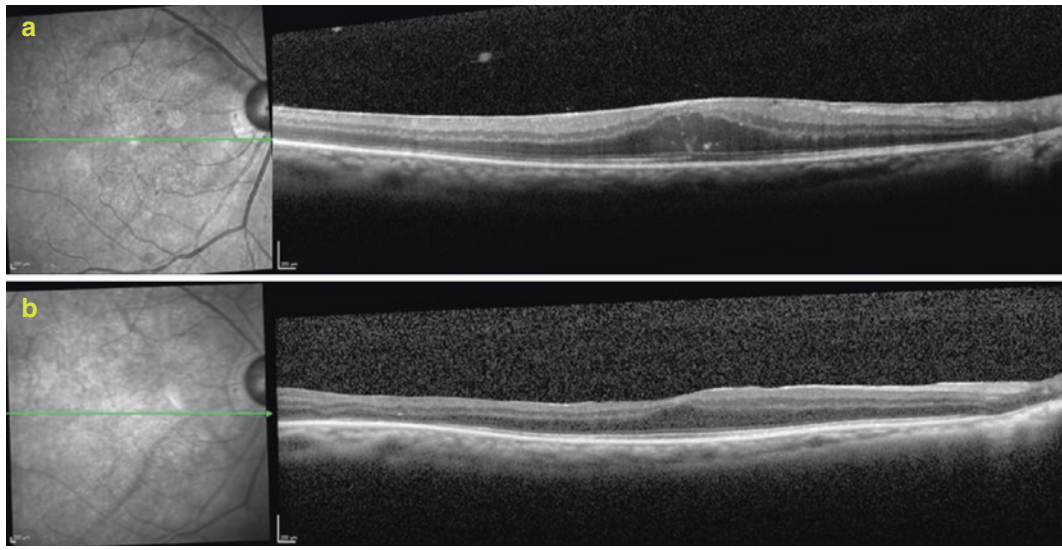

Fig. 19.1 Pre- (**a**) and postoperative (**b**) OCT examination demonstrating resolution of macular edema after vitrectomy, right eye in a 64-year-old male. The patient had no OCT evidence of hyaloid traction and was resistant to anti-VEGF treatment. Six months after surgery, the patient demonstrated anatomic resolution of macular edema. There was also significant improvement in subfoveal ellipsoid zone disruption with the reconstitution of this layer postoperatively. The patient's best-corrected visual acuity improved from 20/80 to 20/60

19.5 Surgical Procedure

The choice of anesthesia remains largely surgeon-, anesthesia-, and institution-dependent. However, special consideration should be given to the general health status of the patient and his or her suitability for general and/or local anesthesia. The patient's systemic health, particularly in the context of possible cardiovascular and renal complications secondary to diabetes, should be considered by the anesthesia team.

The standard surgical technique involves a thorough posterior vitrectomy using a standard three-port pars plana technique, using a separate infusion cannula, a fiberoptic endoilluminator, and an automatic vitrectomy probe. In order to prevent lens opacification in phakic patients, dextrose should be instilled into the Balanced Salt Solution (BSS) Plus infusion solution. This is not necessary in pseudophakic or aphakic patients. Epinephrine can also be added to reduce intraoperative bleeding, although the increased risk of vasoconstriction and decreased vascular perfusion should also be evaluated by the surgeon.

The choice of gauge is surgeon-dependent, and a diabetic vitrectomy can be successfully performed using 23-G, 25-G, or 27-G vitrectomy systems. The authors routinely perform 25-G diabetic vitrectomies due to the ability of the vitrector to effectively engage and cut membranes obviating the need for scissors. The 25-G probe has a sufficiently small sphere of influence to allow efficient and safe dissection and is now complemented with a wide range of instruments that are available in this gauge size [51]. Smaller gauge instrumentation has also been successfully used, although the surgeon should be aware of their increased flexibility and the lack of a full range of instrumentation at the time of writing.

A detachment of the posterior hyaloid is critical for the success of a diabetic vitrectomy, regardless of indication. Intravitreal triamcinolone can be used to stain the hyaloid and provide improved visualization. Posterior vitreous detachment may be difficult to achieve particularly in cases where there is a component of a tractional retinal detachment. The hyaloid can be engaged with active suction. Care must be taken to ensure that excessive aspiration does not result in the worsening of a focal tractional detachment or the creation of a rhegmatogenous component. A sharp edge dissection may be needed with the help of a myringotomy blade or a microvitreoretinal forceps. Once an opening in the hyaloid is achieved, this can be lifted carefully with the aid of suction using a small-gauge vitrector. Alternatively, end-grasping forceps or diamond-dusted forceps can also be used to engage the posterior hyaloid and extend the hyaloidal detachment peripherally. The surgeon should ensure that the posterior hyaloid is elevated off the macula as well. This may require additional attempts to elevate other hyaloidal remnants particularly given that there is a reasonably high chance that vitreoschisis (or splitting of the hyaloid) may be encountered. The posterior hyaloid detachment should be extended as far out to the periphery as can be safely achieved without causing iatrogenic breaks. The internal limiting membrane may be peeled, and the role of ILM peeling will be further explored in this chapter. Peripheral shaving of the vitreous is recommended to ensure that traction is adequately relieved. Scleral depression is important to identify any peripheral breaks, which should be treated with endolaser or cryotherapy, although the former is preferred by the authors, due to a reduced risk of postoperative inflammation. A fluid–air exchange can be performed to ensure adequate closure of sclerotomies. Gas or silicone oil can be used as a long-term tamponade agent, the choice of which depends on the status of the retina and the presence of any concomitant breaks or detachment at the conclusion of the surgery. The surgeon should ensure that the incisions are water-tight and suture the sclerotomies if there is any leak. Sutureless diabetic vitrectomies with small-gauge instrumentation is effective and safe, as demonstrated by Mikhail et al. [30]. This is contingent on creating well-constructed sclerotomies and ensuring no immediate postoperative leak. If there is any doubt, leaking sclerotomies must be sutured.

19.6 Adjunctive Techniques

19.6.1 Internal Limiting Membrane Peeling

The ILM may contribute to DME because of its rigidity, and removing it may allow for the release of tangentially oriented tractional forces. Some have advocated routine ILM peeling in DME cases, although the literature is still unclear as to the benefits of this approach. Similar to a taut posterior hyaloid or vitreomacular traction, tangential traction caused by an ILM is relieved once it is peeled. A thickened ILM also acts as a barrier to the diffusion of oxygen from the vitreous and its removal may improve retinal oxygenation [22, 52]. More importantly, these patients often have an attached cortical vitreous, and peeling ILM ensures complete detachment of the posterior hyaloid, particularly in cases where vitreoschisis is suspected. Removing the ILM scaffold may help prevent the formation of epiretinal membranes postoperatively. Figures 19.2 and 19.3 demonstrate a representative case.

In practice, the results of ILM peeling for diabetic DME remain mixed, as in the DRCR.net Vitrectomy Study which showed that 54% of surgeons elected to routinely peel ILM [40]. As techniques have been refined in recent years, greater numbers of surgeons peel ILM in macular surgery.

The actual contribution of the ILM to tractional DME was explored by Abe et al. [53]. The authors performed 3-D OCT imaging on preoperative DME eyes and only peeled ILM on eyes that demonstrated fine folds or a frank epiretinal membrane. They demonstrated an improvement in retinal thickness in these eyes and suggested that folds on 3-D imaging can help stratify patients who may benefit from ILM peeling [53].

This subject has been explored extensively in the literature and the results have been conflicting. Kamura et al. examined 34 eyes with DME that underwent vitrectomy with or without ILM peeling and reported no significant functional difference between the two groups [54]. This was replicated by Yamamoto et al. who looked at 15 eyes undergoing vitrectomy with or without ILM peeling and determined that no significant difference in vision or anatomy [55]. These results were corroborated by Bahadir et al. who again found no difference between patients who under-

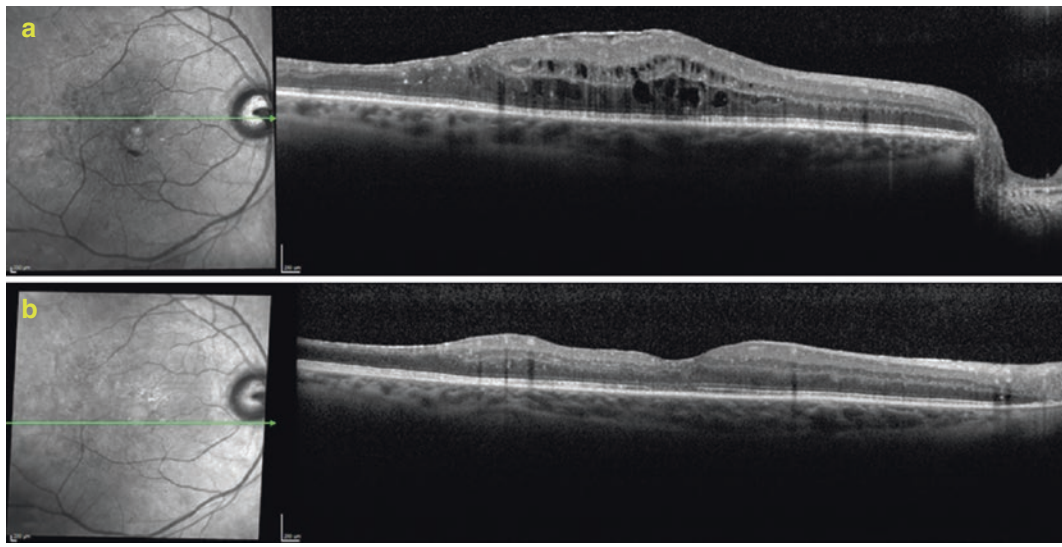

Fig. 19.2 Pre- (**a**) and postoperative (**b**) OCT examination demonstrating resolution of macular edema after vitrectomy, right eye in a 62-year-old male. Epiretinal and internal limiting membrane peeling was performed. There is significant improvement in cystoid macular edema and these results were maintained over a period of 4 years. Vision improved from 20/100 to 20/60

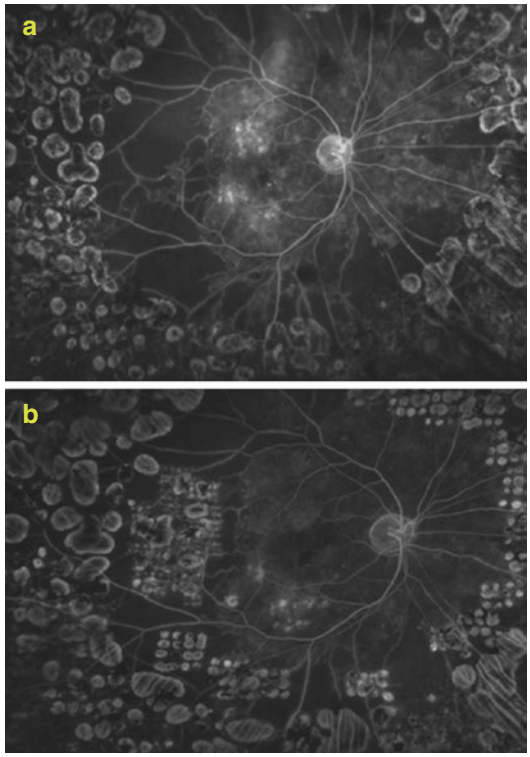

Fig. 19.3 Pre- (**a**) and postoperative (**b**) fluorescein angiography of the patient noted in this figure, demonstrating interval improvement in late leakage consistent with macular edema. There is no significant improvement in vascular perfusion

went vitrectomy alone, compared to those who had their ILMs peeled [56]. Rinaldi et al. examined this topic in detail in a meta-analysis, looking solely at eyes who underwent vitrectomy and ILM peeling vs eyes that underwent vitrectomy alone. The authors included eyes with no clinical evidence of traction [10]. They concluded that ILM peeling as an adjunct to vitrectomy did not significantly improve visual or anatomic outcomes.

Others have suggested a beneficial role for ILM peeling. Patel et al. assessed 10 eyes with refractory DME after vitrectomy and ILM peeling and found significant anatomical improvement, but no gains in visual acuity [45]. Rosenblatt et al. reviewed 26 of their eyes with refractory DME without evidence of clinical traction and reported significant gains in vision and reduction of mean foveal thickness after vitrectomy and ILM peeling [37]. Recchia et al. studied 10 patients who underwent vitrectomy and ILM peeling for refractory DME previously treated with laser and reported improvements in macular edema and vision [57]. Yanyali et al. compared eyes undergoing vitrectomy and ILM peeling vs. focal laser alone, and reported gains in the former group, with no significant improvement in the latter [58]. Similarly, in this cohort, 27 eyes that underwent vitrectomy with ILM peeling reported significant gains in vision and anatomy [59]. Most recently, a meta-analysis by Hu et al. examined 14 studies and concluded that a vitrectomy with ILM peeling demonstrated a higher rate of reduction of central macular thickness and improved vision compared to vitrectomy alone [60].

In summary, the majority of these studies reported some additional benefit to ILM peeling. It is often impossible for the surgeon to determine with certainty whether there is evidence of clinically silent posterior hyaloidal traction, for which an ILM peel may prove beneficial. OCT examination may not adequately address this, and it remains difficult to ascertain whether refractory DME is secondary to subclinical traction by the ILM itself. As the primary goal in such surgeries is to separate the posterior hyaloid from the macula, at a minimum, peeling ILM ensures that all hyaloidal elements are removed. For a number of such reasons, the authors prefer to perform ILM peeling in all cases of vitrectomy for DME.

If a decision is made to peel ILM, the surgeon should use adjunctive staining techniques to identify any residual cortical vitreous, as well as ILM. In the attached retina, ILM peeling is not technically challenging and may provide for a reduction in traction or, at the very least, a reduced risk of epiretinal proliferation in those eyes. In detached retina, the decision is less clear, and it remains up to the surgeon's discretion whether ILM can be safely peeled without causing further damage. At the very least, while several studies have shown that ILM peeling may not provide an additional benefit, none have suggested additional harm. These studies may lack long-term follow-up and the implications of an

ILM peel on the macula's anatomic status remains unclear. An ILM peel is likely to improve a patient's anatomic status but vision may not necessarily improve, which may be a reflection of a diseased retinal microcirculation.

19.6.2 Removal of Hard Exudates

Recently, Imai et al. reported en bloc removal of cystoid lesions during vitrectomy. En block removal resulted in improvement in central retinal thickness, with no significant change in vision. The authors hypothesized that a cystoid lesion is an aggregate of fibrinogen, a provasogenic factor that contributes to further worsening of DME [61]. Subretinal forceps have also been introduced through paramacular retinotomies and used to manually extract hard exudates [62]. There are no large-scale studies to evaluate the efficacy of these techniques, and in the age of widespread intravitreal anti-VEGF injections, they are likely not commonly used.

19.6.3 Iatrogenic Subfoveal Detachment

Subfoveal detachment has been described as a technique to remove subretinal inflammatory mediators and flush out chronic subretinal fluid. For example, Takagi et al. described a procedure by which they detached the fovea and flushed out hard exudates with subretinally injected BSS. Their patients included those with massive foveal exudation with largely end-stage eyes [63]. Nevertheless, they observed some, albeit minimal, improvement in postoperative visual acuity [63]. This technique has been popularized by other authors as a means to rapidly induce resolution of macular thickening. Morizane et al. evaluated a similar technique using 41-G focal subretinal BSS injections in treatment-naïve eyes, as well as those which had been previously treated with anti-VEGF agents [64]. In their series of 20 eyes, mean central retinal thickness decreased significantly, and vision improved in 13 eyes. Subretinal BSS is thought to change the oncotic pressure of subretinal fluid, and may allow for its drainage into the underlying choroid [65]. The authors also hypothesized that BSS flushes out inflammatory mediators, thereby allowing for an improved microenvironment and a potentially more active RPE pump. It is notable that in their eyes, the effect of their surgery lasted for greater than 6 months without further treatment.

This technique has been previously described in the treatment of macular holes, macular translocation in age-related macular degeneration, displacement of submacular hemorrhages, and gene therapy [66]. Extrapolating from our experience in these cases, the authors recommend that if a subfoveal detachment is attempted, the surgeon should use a controlled viscous fluid injection system that is widely available on most vitrectomy machines. The surgeon should test the most optimal injection pressure that would allow a safe, steady, and controlled injection of fluid in the subretinal space prior to entering the eye. This allows for more controlled subretinal injection and reduces the risk of macular hole induction with forceful injection or choroidal injury. If the surgeon experiences difficulty with the initial retinotomy puncture, consideration should also be given to peeling the overlying ILM.

19.7 Prognosis

There are multiple prognostic predictors for the improvement of DME after vitrectomy. These include the duration of macular edema, the extent of previous laser treatment, the degree of macular ischemia, and the amount of exudation. Dysfunction of the photoreceptor layer due to chronic edema, damage induced by laser photocoagulation, and loss of macular perfusion are known to limit visual recovery, despite anatomic improvement.

In a study by Iglicki et al., the timing of surgery was significantly correlated with functional results. For every day vitrectomy was postponed, the patient's chances of gaining greater than five letters at 24 months decreased

by 1.8% [67]. Chronic edema can result in outer retinal damage and more permanent vision loss [50]. The preoperative length of photoreceptor outer segment length was shown to positively predict a positive response in these patients [68]. The presence of submacular fluid was also shown to predict a more positive visual prognosis after 24 months for patients undergoing vitrectomy [69].

It is important to closely follow these patients. While vitrectomy is often thought to be a "permanent" solution to recalcitrant diabetic macular edema, this has not been validated extensively. Yamamoto showed that in treated eyes, a reduction in macular thickness is only seen 4 months after the procedure [70]. Yang showed that resolution occurred 3 months after surgery [39]. Results may be sustained up to 24 months after surgery [70]. Regardless, these patients require lifelong follow-up and adjuvant pharmacotherapy may be required.

19.8 Conclusion

Despite the advent of intravitreal pharmacology for the treatment of DME, pars plana vitrectomy, with or without adjunctive techniques, remains an important tool in the vitreoretinal surgeon's armamentarium, particularly in cases of recalcitrant and treatment-naïve DME, with or without clinically identifiable vitreomacular traction. The current literature is replete with multiple, retrospective, noncontrolled studies with limited evidence, but the general trend seen by most is for anatomic and/or functional improvement in those eyes. While there is clear evidence to suggest the role of vitrectomy in eyes with a clinically visible taut, thickened hyaloid, the absence of OCT or clinical evidence of vitreomacular traction should not be used as an exclusion criterion. The decision to pursue surgery should be based on a mutual discussion between surgeon and patient, with an assessment of other factors, such as visual acuity, response to prior intravitreal anti-VEGF treatment, duration and extent of macular edema, presence and degree of macular ischemia, systemic comorbidities as well as an assessment of the direct and indirect costs of alternative therapy. Regardless, further prospective, controlled clinical, long-term trials are sorely needed to address the usefulness of this powerful tool for the management of DME, particularly in this age of widespread intravitreal injection therapy with anti-VEGF agents and steroids.

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