Surgical Management of Diabetic Retinopathy

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ABSTRACT

Surgery for late complications of proliferative diabetic retinopathy remains the cornerstone of management even in patients who have received optimal laser photocoagulation and medical therapy. With improvisation in the surgical techniques and development of micro-incision surgical techniques for vitrectomy, the indications for surgical intervention are expanding to include diabetic macular edema with a greater number of patients undergoing early intervention. This review describes the current indications, surgical techniques, adjunctive anti-vascular endothelial growth factor therapy, surgical outcomes, and postoperative complications of pars plana vitrectomy for proliferative diabetic retinopathy and macular edema.

Key words: Diabetic Macular Edema, Diabetic Retinopathy, Pars Plana Vitrectomy, Proliferative Diabetic Retinopathy

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INTRODUCTION

Diabetic retinopathy is one of the leading causes of blindness in the working population. The prevalence of diabetic retinopathy increases with duration of diabetes and nearly all patients with Type 1 and more than 60% with Type 2 diabetes develop some signs of retinopathy after 20 years duration.[1] Diabetic retinopathy is primarily a microvascular complication and is characterized by progressive retinal ischemia resulting in the development of non-proliferative diabetic retinopathy (NPDR) or proliferation of new blood vessels in the late phase leading to development of proliferative diabetic retinopathy (PDR) that progresses to develop contractile epiretinal fibrocellular membranes.[2,3] The new vessels grow along the posterior hyaloid using it as a scaffold and contraction of the fibrocellular membranes causes progressive traction on new vessels resulting in vitreous or pre-retinal hemorrhage, tractional, or combined retinal detachment (CRD).[4,5]

The patients may first present in the advanced stage of disease with retinal detachment that is not amenable to medical management. In addition, despite medical management including laser photocoagulation, tight systemic control of blood glucose, lipids, cholesterol, blood pressure, and intravitreal injections of steroids and anti-vascular endothelial growth factor (VEGF) drugs,[6-11] nearly 5% of patients show continued progression of retinopathy and require surgical intervention. Additionally, patients with tractional diabetic macular edema require pars plana vitrectomy (PPV).[8] Vitrectomy for complications of diabetic retinopathy was first performed in 1970 in an eye with diabetic vitreous hemorrhage.[1]

This article reviews the current indication, outcomes, techniques, and complications of PPV in diabetic retinopathy.

INDICATIONS AND OUTCOMES FOR PARS PLANA VITRECTOMY IN DIABETIC RETINOPATHY

Vitreous hemorrhage

Vitreous hemorrhage is the most common complication of PDR that causes decreased visual acuity and also interferes with panretinal photocoagulation. Earlier studies suggested PPV and endolaser photocoagulation for vitreous hemorrhage that was persistent and non-clearing for more than 3 months.[12-14]

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However, the Diabetic Retinopathy Vitrectomy Study (DRVS) has shown a clear benefit from earlier surgery in patients with Type 1 diabetes, as delay in the surgery may lead to development of aggressive fibrovascular proliferation with increased risk of tractional/CRD.[15-17] The DRVS results indicate that 25% of patients undergoing early PPV regained visual acuity of 20/40 or better compared to 15% of patients who underwent conventional treatment.[17] Since the publication of the DRVS report, this is a trend toward earlier and lower threshold for vitrectomy for diabetic vitreous hemorrhage. With improved surgical techniques the results of PPV for non-resolving vitreous hemorrhage have improved compared to DRVS with a recent study indicating 87% of patients showing improvement by at least 3 ETDRS lines at 12 months.[18] Currently, the general paradigm is to manage patients conservatively for about 1 month from the date of presentation for severe vitreous hemorrhage with no signs of spontaneous clearing in type 1 diabetes while patients with type 2 diabetes are usually given a longer time for spontaneous clearing of vitreous hemorrhage.[5] Other factors influencing the decision to perform PPV include degree of improvement or progression of anterior segment neovascularization, previous panretinal photocoagulation, the visual acuity, and the preference or needs of the patient.[19,20] Simple vitreous hemorrhage clears spontaneously through the zonules via aqueous outflow. The presence of red blood cells in the anterior chamber indicates the patency of this outflow channel. The presence of anterior chamber neovascularization or longstanding vitreous hemorrhage with vitreous base fibrosis blocks this pathway for spontaneous drainage and thus are indications for early vitrectomy.[21]

Tractional retinal detachment

The fibrovascular proliferation of tissue contracts and pulls the underlying retina due to vitreoretinal adhesions resulting in the development of tractional retinal detachment (TRD). The TRD generally begins over the arcades and progresses slowly to involve the fovea and requires PPV. Sometimes TRD is peripheral and spares the fovea. Such cases without vitreous hemorrhage may be left untreated if there is no immediate threat to fovea. However, it is important to monitor these patients for any foveal involvement as this progressive disease may involve the fovea over time, warranting PPV. Surgical outcomes are better in patients with recently reduced vision and poorer in patients with longstanding macular heterotopia.[22,23]

The results of PPV for TRD have improved following the advent of better surgical techniques. For example, up to 75% of patients had improved vision with or without silicone oil tamponade.[23] However, visual prognosis is influenced by a number of factors including the patient age, location and extent of the TRD, and the duration of macular heterotopia. Older age, anterior segment neovascularization, longstanding macular heterotopia have been associated with poorer visual outcomes.[23,24]

Combined tractional and rhegmatogenous retinal detachment

TRD has a fibrovascular component that might contract causing retinal breaks. The development of retinal breaks converts a TRD into a CRD. The retinal break exposes the retinal pigment epithelial cells that cause proliferative vitreoretinopathy with development of tightly adherent membranes on the retinal surface. These pre-retinal membranes contract, adding a component of tangential traction. The visual acuity following PPV for CRD may improve in up to 70% of eyes.[25] These membranes are difficult to dissect from the underlying retina that is mobile and may require bimanual dissection, viscodissection, and silicone oil tamponade.[26-28] The outcome of surgery will depend upon the location and extent of the retinal detachment with eyes having good preoperative visual acuity having good prognosis whereas eyes with macular heterotopia have worse outcomes.[25-28]

Pre-macular hemorrhage

Dense pre-macular hemorrhage is a complication of PDR. O'Henley and Canny[29] reviewed 9 patients with dense pre-macular hemorrhage; of the 5 patients who received early PPV within 4 weeks of the onset of hemorrhage, all achieved a visual acuity of 6/12 and better, while those who did not receive PPV within 4 weeks, all developed late macular traction with visual acuity no better than 6/30.

Diabetic macular edema

Diabetic macular edema that is caused by vitreomacular traction or taut posterior hyaloid membrane is an indication for PPV to remove the tractional component contributing towards macular edema.[30] The role of PPV for macular edema without macular traction is controversial. Few studies suggested the improvement of recalcitrant diabetic macular edema refractory to repeated laser photocoagulation treatments with no evidence of macular traction following PPV.[30,31] However, other studies provide little evidence in terms of improvement in macular thickness and visual acuity in patients who had an attached posterior hyaloid with no clinical evidence of macular traction or taut posterior hyaloid.[32,33] These studies indicate that visual acuity improvement may be compromised by the potential consequences of PPV including progression of cataract, glaucoma, and postoperative vitreous hemorrhage. Persistent DME after PPV with removal of posterior hyaloid may be caused by a taut internal limiting membrane (ILM) and has been reported to respond to PPV and ILM removal.[34] The indications for PPV in diabetic macular edema are summarized in Table 1.

More recently, ILM peeling is being performed along with PPV and again the reports have conflicting results. Though some studies indicated a better visual outcome for diffuse diabetic macular edema following PPV with ILM peeling,[33-36] others reported little benefit in terms of visual gain during short-term follow up.[37-39] For example, quite a few studies have

Table 1: Indications for PPV in diabetic macular edema

Taut posterior hyaloid membrane: Is identified as a glistening reflex over the macula seen on biomicroscopic examination and OCT shows a hyper-reflective membrane with partial posterior vitreous detachment and thickened retina
Vitreomacular traction: Is identified as partial posterior vitreous detachment with focal areas of firm adhesions between the vitreo-retinal interface and retina. These are best identified on OCT
Recalcitrant DME with no TPHM or VMT seen clinically or on OCT
Taut ILM with unresponsive DME post PPV with previously removed posterior hyaloid

PPV: Par plana vitrectomy, OCT: Optical coherence tomography, ILM: Internal limiting membrane, DME: Diabetic macular edema, TPHM: Taut posterior hyaloid membrane, VMT: Vitreomacular traction

reported good long-term outcomes of PPV with ILM peeling in reducing diffuse diabetic macular edema and improving the visual acuity.[40-42] The mechanism of resolution of macular edema in the non-tractional variety is believed to be due to changes in blood flow to the macula following PPV and ILM peeling.[43]

However, a recent study published the results of PPV with or without ILM peeling and reported that PPV and posterior vitreous detachment with or without ILM peeling does not improve vision in patients with diabetic cystoid macular edema and no traction.[44]

TECHNIQUES OF PPV IN DIABETIC RETINOPATHY

PPV for vitreous hemorrhage includes three port core vitrectomy first followed by identification of the posterior hyaloid face (PHF). If there is significant retrohyloidal bleed, an opening is created in the PHF and retrohyloidal blood is aspirated to gain a good view of the underlying retina.[45] Though straightforward, PPV for vitreous hemorrhage may be complicated with intraocular fibrin formation that provides a scaffold for fibrovascular proliferation, and also interferes with clearance of recurrent bleeds through the anterior chamber. Adequate pre-surgery panretinal photocoagulation and good metabolic control are useful in reducing intraoperative fibrin formation.[5] Often, fibrovascular membranes are present on the retinal surface. These membranes are vascularized and bleed intraoperatively and thus cannot be simply peeled from the retinal surface as it results in bleeding and retinal tears.[45-48] The following techniques are useful in dissecting the surface membranes.

Segmentation

It is used to release circumferential traction with the help of vertical cutting scissors or vitreous cutter. These membranes are segmented into small segments that can be left as remnants center on neovascular pegs.[45-48]

Delamination

This technique involves removal of fibrovascular membranes from the surface of retina. Horizontal scissors are used to find the correct plane between the posterior hyaloid and the retina where en bloc delamination can be performed to remove the fibrovascular tissue from the retinal surface.[45-48] It is helpful to keep the posterior hyaloid partially intact that facilitates dissection of epiretinal membranes by elevating the epiretinal membranes due to antero-posterior traction. The dissection maybe performed with a vitreous cutter in cases where there are multiple isolated adhesions with adequate space between retina and vitreous.[45] In cases where these membranes are firmly attached to the underlying retina, the dissection maybe performed using long curved scissors, MPC scissors, picks, and/or forceps.[45-48] Bimanual dissection or illuminated forceps may be used to facilitate dissection. Using perfluorocarbon may aid in dissection of firmly adherent membranes.[49] Many of these eyes require long-term silicone oil tamponade for anatomical and functional stability.[50,51] Due to improved instrumentation, currently, smaller gauge transconjuctival PPV is being favored compared to 20 gauge PPV with faster recovery in patients with PDR [Figures 1-4].[51-54] Issa *et al*.[55] compared the results of 20 and 23 gauge transconjunctival vitrectomy for PDR. In their[55] retrospective review of two series of patients who had undergone primary PPV for PDR and a control group that had undergone 20 gauge vitrectomy, they reported a significant reduction in the incidence of peripheral sclerotomy-related retinal breaks with 23-gauge (5%) versus 20-gauge (16%) vitrectomy.

Endolaser

Endolaser photocoagulation during PPV is performed routinely in all patients undergoing PPV for PDR to minimize postoperative hemorrhage. It is important to examine the retinal periphery for any retinal breaks that warrant laser photocoagulation/ cryotherapy and internal tamponade.

Sima and Zoran[56] prospectively evaluated 174 patients undergoing vitrectomy for diabetic retinopathy and reported retinal breaks in 39% of cases. Though the majority of these breaks were posterior and seen during membrane dissection, 17% were seen at the entry site.[56] In another study,[57] the overall incidence of iatrogenic breaks was reported to be 29% in patients undergoing 20-gauge vitrectomies for diabetic retinopathy. The most common cause of iatrogenic breaks was dissection of fibrovascular membranes with posterior vitreous detachment creation, and shaving of peripheral vitreous associated with retinal breaks formation in only in 8% of cases and retinal dialysis in 2% of cases.[57] Oral retinal dialysis was also associated with increased incidence of postoperative hemorrhage.

ROLE OF PREOPERATIVE INTRAVITREAL BEVACIZUMAB

Intraoperative bleeding from the fibrovascular membranes is the major intraoperative complication in PPV for TRD and CRD. Pretreatment with intravitreal anti- VEGF, 3-4 days

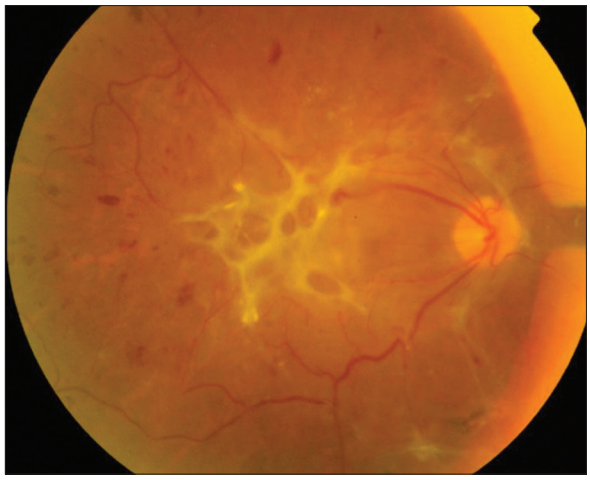

Figure 1: Color fundus photograph of the right eye showing fibrovascular proliferation extending from nasal half of the optic disc to the fovea causing macular pucker. The patient underwent 23-gauge transconjuctival pars plana vitrectomy

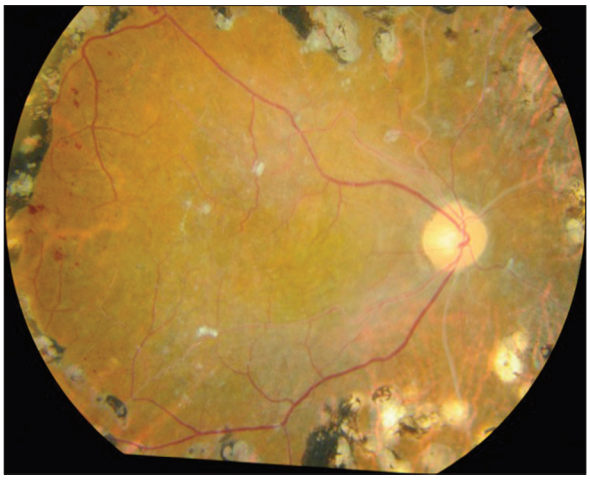

Figure 2: Same eye as in Figure 1, 3 months later showing release of traction over the fovea with normal foveal contour

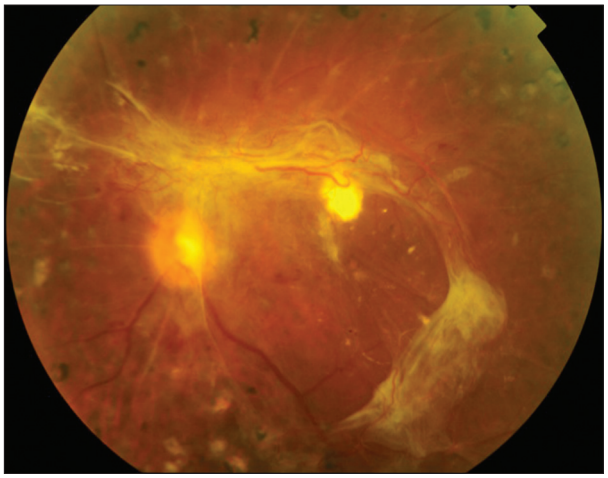

Figure 3: Color photograph of the left eye showing tractional retinal detachment. The patient underwent 23-gauge transconjunctival pars plana vitrectomy

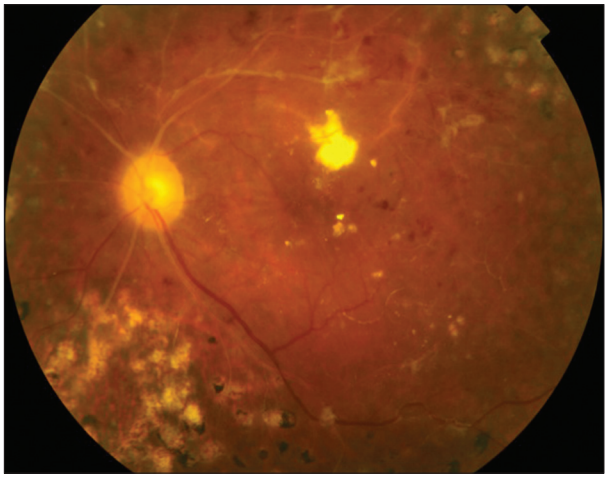

Figure 4: Same eye as in Figure 3, 2 months postoperatively, showing a flat retina. The best corrected visual acuity improved from 20/200 to 20/40 postoperatively

prior to surgery helps in reducing intraoperative bleeding, thus facilitating fibrovascular membrane peeling. It is also reported to reduce postoperative vitreous hemorrhage.[57-62] Preoperative bevacizumab led to improved visual outcome that was maintained at 6-months with reduced occurrence of postoperative vitreous hemorrhage.[62,63] Ushida *et al*.[64] reported safety of intravitreal bevacizumab in 23 patients, and evaluated its effect on the visual function in PDR eyes, and reported that average visual acuity improved postoperatively from 20/250 to 20/70 with no change in visual fields and ERGs. A recent study however reported a higher incidence of early postoperative vitreous hemorrhage (27%) than in a control group (7%).[65] However, the rate of vitreous hemorrhage after 4 weeks was not different between groups.[65] Jirawison and Ittipunkul[66] reported that intravitreal injection of 1.25 mg of bevacizumab at the end of diabetic vitrectomy was associated with lowest incidence of early postoperative vitreous hemorrhage with significant visual recovery at the end of 6 months.

Success with preoperative intravitreal bevacizumab has also reported in eyes that require silicone oil tamponade although it may carry a higher incidence of subretinal bleeding.[67] Intravitreal bevacizumab primarily affects the blood vessels and also regulates the vascular microenvironment by causing the contraction of blood vessels, increasing pericyte ratio, and transforming growth factor-beta expression in fibrovascular membranes; thus making them easier to peel.[68]

Intra- and Post-operative complications

1. *Corneal edema*: Patients with diabetes are reported to have an abnormal basement membrane that causes reduced epithelial adherence resulting in intraoperative corneal edema.[69-71] Use of viscoelastic and corneal lubrication reduces the need for corneal debridement.[71]
2. *Iatrogenic retinal breaks*: Posterior retinal breaks usually occur adjacent to vitreoretinal adhesions during dissection and are commonly seen in eyes where membranes are fibrous while the retina is thin and atrophic.[72,73] Kamura *et al*.[57] evaluated

iatrogenic retinal breaks in 760 eyes of 609 patients who underwent PPV for PDR and found an overall incidence of 29%. They reported a poorer outcome with iatrogenic retinal breaks during fibrovascular membrane dissection than peripheral retinal breaks or oral dialysis.[57] In the absence of retinal break, the tractional retinal detachment can be successfully managed without any tamponade.[74]

3. *Intraoperative bleeding and intraocular fibrin formation*: Intraoperative hemorrhage and fibrin formation are potentially serious complications of vitrectomy in diabetic eyes. However, preoperative bevacizumab has reduced this complication (see above). Significant fibrin in the postoperative period may require injection of recombinant tissue plasminogen activator (tPA).[75,76]
4. *Elevated Intraocular pressure*: The incidence of postoperative intraocular pressure (IOP) of 30mm Hg or more has been reported in up to 35% of eyes following PPV.[77] Eyes with diabetic retinopathy are quite susceptible to visual loss from elevated IOP due to underlying retinal ischemia and require close monitoring.
5. *Cataract*: Intraoperative lenticular opacities can be reduced by supplementation of glucose in the infusion fluid.[70,78] Visually significant cataract occurs in 17-37% of eyes undergoing vitrectomy for diabetic retinopathy.[79,80]
6. *Rubeosis and neovascular glaucoma*: The reported incidence of iris neovascularization following diabetic vitrectomy in the earlier studies is 8-26% in phakic eyes and 31-55% in aphakic eyes and neovascular glaucoma in 4-13% of phakic eyes and 11-35% of aphakic eyes.[81-83] However, these studies were published prior to the development of endolaser and the current rate of rubeosis and neovascular glaucoma is lower.[84,85] Treatment includes topical steroids, cycloplegics and intravitreal bevacizumab.[86] A recent study has reported benefit of intrasilicone injection of bevacizumab in the treatment of patients with iris neovascularization after vitrectomy for advanced PDR with silicone oil tamponade.[87]
7. *Postoperative vitreous hemorrhage*: Postoperative vitreous hemorrhage following PPV for PDR has been reported in 12%-63% of cases and may occur within the first few weeks or even months later.[88-90] Park *et al*.[91] reported comparable rates of postoperative bleed following 23 gauge (17%) versus 20-gauge (26%) vitrectomy.[91] Khuthaila *et al*.[92] reported that 32% of eyes develop vitreous hemorrhage following 23-gauge PPV for diabetic retinopathy and was associated with inadequate laser photocoagulation, phakia, and younger age.[92] Yang *et al*.[93] have reported the use of C3F8 gas tamponade was effective in preventing recurrent vitreous hemorrhage. One must consider that postoperative bleeding may be due to fibrovascular proliferation at the sclerotomy site.[94,95] Yeh *et al*.[94] have reported prophylactic cryotherapy treatment of the sclerotomy sites to prevent postoperative hemorrhage. However, Entezari *et al*.[95] did not find this useful in reducing the postoperative hemorrhage. The current evidence regarding the role of perioperative intravitreal bevacizumab preventing early postoperative hemorrhage is contradictory.[96-99] Jirawion and Ittipunkul[66] reported the lowest incidence of early postoperative vitreous hemorrhage in eyes that received intravitreal bevacizumab injection at the end of diabetic vitrectomy.
8. *Anterior hyaloidal fibrovascular proliferation (AHFVP)*: This complication has been reported to occur in nearly 13% of cases, especially in young patients with long standing diabetes and extensive retinal ischemia.[100,101] Fibrovascular proliferation at the sclerotomy site can produce a similar picture.[102-104] This usually causes vitreous hemorrhage 3-12 weeks after vitrectomy and is reported to be due to increased VEGF levels in the postoperative period.[105] Additional panretinal photocoagulation, cryotherapy of sclerotomy sites, and surgical intervention are usually necessary.

PARS PLANA VITRECTOMY FOR DIABETIC MACULAR EDEMA

In 1988, Nasrallah *et al*.[106] reported the possible role of vitreous traction in causing macular edema. A few years later, Lewis *et al*.[107] reported a group of patients with recalcitrant diabetic macular edema who had a taut, thickened posterior hyaloid and hypothesized the tangential tractional forces were responsible for macular edema. Diabetic macular edema caused by the traction from a taut posterior hyaloid, vitreomacular traction, or epiretinal membranes has been reported to improve following PPV resulting in visual improvement and resolution of macular edema.[107-110] The Diabetic Retinopathy Clinical Research Network reported improvement of visual acuity in 28% to 49% of eyes undergoing vitrectomy for vitreomacular traction, whereas 13% to 31% of eyes experienced a decrease in visual acuity.[111] Furthermore, removal of epiretinal membranes was associated with better visual outcome.[112] There are reports of improvement in macular edema in eyes with no evidence of vitreomacular traction. One study reported a significant improvement in visual acuity in patients with diabetic macular edema non-responsive to grid laser photocoagulation.[113] However, other studies reported a reduction of macular volume without much improvement in visual acuity.[114,115] The mechanism of action of vitrectomy remains unclear in these eyes. It is postulated that diabetic eyes have cytokines that may promote vascular permeability and vitrectomy with or without ILM peeling that removes the vitreous reservoir by facilitating the diffusion of these agents. Furthermore, PPV improves oxygenation, which further improves the integrity of inner blood retinal barrier.

Ocular factors including preoperative visual acuity and foveal average retinal thickness were reported to influence the final visual outcome, and no history of diabetes treatment until diabetic

retinopathy and high glycosylated hemoglobin were associated with poorer outcome.[116] Preoperative integrity of the external limiting membrane was found to be associated with good postoperative visual outcome.[117] Murakami *et al*.[118] performed segmentation analysis of retinal thickness after vitrectomy in diabetic macular edema and found that outer retinal thickness of the temporal subfield was associated with disruption of the junction between the inner and outer segments (ellipsoid zone) at the fovea and was associated with poor visual outcome. In addition, Yoshikawa *et al*.[119] have recently reported that the papillofoveal distance was shortened and the temporal retina thinner in eyes that underwent ILM peeling to treat diabetic macular edema.

PHARMACOLOGICAL VITREOLYSIS

The anatomical and functional success of PPV depends on the complete separation of posterior hyaloid from the retinal surface. Studies have shown that residual cortical vitreous tends to be left behind despite meticulous peeling of posterior hyaloid[120] and the process of surgical separation itself may cause structural damage to the underlying retina.[121] An attempt to peel the ILM for better cortical cleanup also increases the risk of complications including nerve fiber layer damage associated with paracentral scotomas.[122] The term pharmacologic vitreolysis indicates the role of pharmacologic agents to modify the molecular structure of the vitreous that induces vitreoretinal separation. Plasmin, a serine protease is known to degrade laminin, fibronectin[123-125] and generate increased levels of matrix metalloproteinases, elastase resulting in weakening of vitreoretinal insertion and liquefaction of the vitreous.[126,127] Autologous plasmin enzyme (APE) has been reported to cause a nonsignificant increase in spontaneous posterior vitreous detachment in eyes with tractional diabetic macular edema[128-130] and advanced PDR.[131] Azzolini *et al*.[129] reported higher visual acuities at the end of one year in patients with DME who had received intravitreal APE compared with those who had not received.

Microplasmin is a commercially available recombinant molecule that is currently preferred over plasmin for PVD induction. Microplasmin intravitreal injection (MIVI) was a clinical trial designed to assess efficacy at various doses and exposures of microplasmin in enzyme-assisted vitrectomy for the treatment of vitreomacular adhesion related pathologies including tractional DME. Only less than 50% of eyes in any cohort developed spontaneous PVD.[132] The results were dose and exposure dependent. The results of MIVI-II (TG-MV-002) which is a phase II sham-controlled non-vitrectomy study in patients with tractional DME are still being gathered.

CONCLUSION

The role of pars plana vitrectomy is unquestionable for managing complications of proliferative diabetic retinopathy including those that were previously considered blinding. With newer improved techniques and pharmacologic interventions and including minimally invasive vitreoretinal surgery, and intravitreal bevacizumab, early vitrectomy is favored due to better visual outcomes. There is also growing evidence favoring vitrectomy for diabetic macular edema refractory to laser and medical therapy. Pharmacological vitreolysis seems promising and results of more clinical trials in diabetic retinopathy are awaited.

REFERENCES

1. Klein R, Klein BE, Moss SE, Cruickshanks KJ. The Wisconsin Epidemiologic Study of Diabetic Retinopathy, XII: The 14-year incidence and progression of diabetic retinopathy and associated risk factors in type 1 diabetes. Ophthalmology 1998;105:1801-15.
2. Arnos AF, McCarty DJ, Zimmett P. The rising global burden of diabetes and its complications: Estimates and projections to the year 2010. Diabet Med 1997;14:S1-85.
3. Klein R, Klein BE, Moss SE, Davis MD, DeMets DL. The Wisconsin Epidemiologic Study of Diabetic Retinopathy, IV: Diabetic macular edema. Ophthalmology 1984;91:1464-74.
4. Gotzaridis EV, Lit ES, D'Amico DJ. Progress in vitreoretinal surgery for proliferative diabetic retinopathy. Semin Ophthalmol 2001;16:31-40.
5. Gupta V, Gupta A, Dogra MR, Singh R. Diabetic Retinopathy Atlas and text. New Delhi: Jaypee Brothers Medical Publishers (P) Ltd; 2007. p. 75-88.
6. DCCT Research Group. The effect of intensive treatment of diabetes in the development and progression of long-term complication in insulin-dependent diabetes. N Engl J Med 1993;329:977-86.
7. UK Prospective Diabetes Study (UKPDS) Group. Intensive-blood glucose control with sulphonylureas or insulin compared with conventional treatment and risk complications in patients with type 2 diabetes (UKPDS 33). Lancet 1998;317:703-13.
8. Preliminary report on effects of photocoagulation therapy. The Diabetic Retinopathy Study Research Group. Am J Ophthalmol 1976;81:383-96.
9. Gupta A, Gupta V, Thapar S, Bhansali A. Lipid-lowering drug atorvastatin as an adjunct in the management of Diabetic macular edema. Am J Ophthalmol 2004;137:675-82.
10. Evoy KE, Abel SR. Ranibizumab: The first endothelial growth factor inhibitor approved for the treatment of diabetic macular edema. Ann Pharmacother 2013;47:811-8.
11. Abu-El-Asrar AM, Al-Mezaine HS. Advances in the treatment of diabetic retinopathy. Discov Med 2010;9:363-73.
12. Machemer R, Buettner H, Norton RWD, Parel JM. Vitrectomy in the management of severe diabetic retinopathies. Trans Am Acad Ophthalmol Otolayngol 1971;75:813-20.
13. Flynn HW Jr, Chew EY, Simons BD, Barton FB, Remaley NA, Ferris FL 3rd. Pars plana vitrectomy in the Early Treatment Diabetic Retinopathy Study. ETDRS report number 17. The Early Treatment Diabetic Retinopathy Study Research Group. Ophthalmology 1992;99:1351-7.
14. Smiddy WE, Flynn HW Jr. Vitrectomy in the management of diabetic retinopathy. Surv Ophthalmol 1999;43:491-507.
15. Two-year course of visual acuity in severe proliferative diabetic retinopathy with conventional management. Diabetic Retinopathy Vitrectomy Study (DRVS) report #1. Ophthalmology 1985;92:492-502.
16. Early vitrectomy for severe vitreous hemorrhage in diabetic

retinopathy. Four-year results of a randomized trial: Diabetic Retinopathy Vitrectomy Study Report 5. Arch Ophthalmol 1990;108:958-64.
17. Early vitrectomy for severe vitreous hemorrhage in diabetic retinopathy. Two-year results of a randomized trial. Diabetic Retinopathy Vitrectomy Study report 2. The Diabetic Retinopathy Vitrectomy Study Research Group. Arch Ophthalmol 1985;103:1644-52.
18. Gupta B, Sivaprasad S, Wong R, Laidlaw A, Jackson TL, McHugh D, *et al*. visual and anatomical outcomes following vitrectomy for complications of diabetic retinopathy: The Drive UK study. Eye (Lond) 2012;26:510-6.
19. Goldenberg DT, Hassan TS. Small gauge, sutureless surgery techniques for diabetic vitrectomy. Int Ophthalmol Clin 2009;49:141-51.
20. Scalon PH. Why do patients still require surgery for the late complications of proliferative diabetic retinopathy? Eye (Lond) 2010;24:435-40.
21. Landers MB, Perraki AD. Management of post-vitrectomy persistent vitreous hemorrhage in pseodophakia eyes. Am J Ophthalmol 2003;136:989-93.
22. Packer AJ. Vitrectomy for progressive macular traction associated with proliferative diabetic retinopathy. Arch Ophthalmol 1987;105:1679-82.
23. Canan H, Sizmaz S, Altan-Yaycioglu R. Surgical results of combined pars plana vitrectomy and phacoemulsification for vitreous hemorrhage in PDR. Clin Ophthalmol 2013; 7: 1597-601.
24. Thompson JT, Bustrop S, Michels RG, Rice TA. Results and prognostic factors in vitrectomy for diabetic traction retinal detachment of macula. Arch Ophthalmol 1987;105:497-502.
25. Yang CM, Su PY, Yeh PT, Chen MS. Combined rhegmatogenous and traction retinal detachment in proliferative diabetic retinopathy: Clinical manifestations and surgical outcome. Can J Ophthalmol 2008;43:192-8.
26. Grigorian RA, Castellarin A, Bhagat N, Del Priore L, Von Hagen S, Zarbin MA. Use of viscodissection and silicone oil in vitrectomy for severe diabetic retinopathy. Semin Ophthalmol 2003;18:121-6.
27. Grigorian RA, Castellarin A, Fegan R, Seery C, Del Priore LV, Von Hagen S, *et al*. Epiretinal membrane removal in diabetic eyes: Comparison of viscodissection with conventional methods of membrane peeling. Br J Ophthalmolgy 2003;87:737-41.
28. Castellarin A, Grigorian RA, Bhagat N, Del Priore L, Zarbin MA. Vitrectomy with silicone oil infusion in severe diabetic retinopathy. Br J Ophthalmol 2003;87:318-21.
29. O'Hanley GP, Canny CL. Diabetic dense premacular hemorrhage: A possible indication for prompt vitrectomy. Ophthalmology 1985;92:507-11.
30. Lewis H, Abrams GW, Blumenkranz MS, Campo RV. Vitrectomy for diabetic macular traction. Ophthalmology 1982;99:753-9.
31. Harbour JW, Smiddy WE, Flynn HW Jr, Rubsamen PE. Vitrectomy for diabetic macular edema associated with taut posterior hyaloids membrane. Am J Ophthalmol 1996;121:405-13.
32. Thomas D, Bunce C, Moorman C, Laidlaw DA. A randomized controlled feasibility trial of vitrectomy versus laser for diabetic macular edema. Br J Ophthalmol 2005;89:81-6.
33. Patel JI, Hykin PG, Schadt M, Luong V, Bunce C, Fitzke F, *et al*. Diabetic macular edema: Pilot randomized trial of pars plana vitrectomy vs macular argon photocoagulation. Eye (Lond) 2006;20:873-81.
34. Gentile RC, Milman T, Eliott D, Romero JM, McCormick SA. Taut internal limiting membrane causing diffuse diabetic macular edema after vitrectomy: Clinicopathological correlation. Ophthalmologica 2011;226:64-70.
35. Yanali A, Horozoglu F, Celik E, Ercalik Y, Nohutcu AF. Pars plana vitrectomy and removal of internal limiting membrane in diabetic macular edema unresponsive to grid laser photocoagulation. Eur J Ophthalmol 2006;16:573-81.
36. Mason JO 3rd, Colagross CT, Vail R. Diabetic vitrectomy: Risks, prognosis, future trends. Curr Opin Ophthalmol 2006;17:281-5.
37. Patel JI, Hykin PG, Schadt M, Luong V, Fitzke F, Gregor ZJ. Pars plana vitrectomy with and without peeling of the inner limiting membrane for diabetic macular edema. Retina 2006;26:5-13.
38. Hartlet KL, Smiddy WE, Flynn HW Jr, Murray TG. Pars plana vitrectomy with internal membrane peeling for diabetic macular edema. Retina 2008;28:410-9.
39. Dehghan MH, Salehipour M, Naghib J, Babaeian M, Karimi S, Yaseri M. Pars plana vitrectomy with internal limiting membrane peeling for refractory diffuse macular edema. J Ophthalmic Vis Res 2010;5:162-7.
40. Yanyali A, Horozoglu F, Celik E, Nohutcu AF. Long-term outcome of pars plana vitrectomy with internal limiting membrane removal in diabetic macular edema. Retina 2007;27:557-66.
41. Yamamoto T, Takeuchi S, sato Y, Yamashita H. Long-term follow-up results of pars plana vitrectomy for diabetic macular edema. Jpn J Ophthalmol 2007;51:285-91.
42. Kumagai K, Furukawa M, Ogino N, Larson E, Iwaki M, Tachi N. Long-term follow up of vitrectomy for diffuse nontractional diabetic macular edema. Retina 2009;29:464-72.
43. Park JH, Woo SJ, Ha YJ, Yu HG. Effect of vitrectomy on macular microcirculation in patients with diffuse diabetic macular edema. Grafes Arch Clin Exp Ophthalmol 2009;247:1009-17.
44. Hoerauf H, Brüggemann A, Muecke M, Lüke J, Müller M, Stefánsson E, *et al*. Pars plana vitrectomy for diabetic macular edema. Internal limiting membrane delamination vs posterior hyaloids removal. A prospective randomized trial. Graefes Arch Clin Exp Ophthalmol 2011;249:997-1008.
45. Kanski JJ, Gregor ZJ. Retinal detachment: A color Manual of Diagnosis and treatment. Butterworth Heinemann 1994, 160-162.
46. Canny CL, O'Hanley GP, Wells GA. Pars plana vitrectomy for complications of diabetic retinopathy: Report of 131 cases. Can J Ophthalmol 1985;20:11-5.
47. Miller SA, Butler JB, Myers FL, Bresnick GH. Pars plana vitrectomy. Teartment for tractional macula detachment secondary to proliferative diabetic retinopathy. Arch Ophthalmol 1980;98:659-64.
48. Gafencu O. Surgical principles and techniques in severe proliferative diabetic retinopathy. Oftalmologia 2001;52:54-7.
49. Arevalo JF. En bloc perfluorodissection for tractional retinal detachment in proliferative diabetic retinopathy. Ophthalmology 2008;115:21-5.
50. Gupta B, Wong R, Sivaprasad S, Williamson TH. Surgical and visual outcome following 20-gauge vitrectomy in proliferative diabetic retinopathy over a 10-year period, evidence for change in practice. Eye (Lond) 2012;26:576-82.
51. Altan T, Acar N, Kapran Z, Unver YB, Ozdogan S. Transconjunctival 25-gauge sutureless vitrectomy and silicone oil injection in diabetic reinal detachment. Retina 2008;28:1201-6.
52. Sato T, Emi K, Bando H, Ikeda T. Faster recovery after 25-gauge microincision vitrectomy surgery than after 20-gauge vitrectomy in patients with proliferative diabetic retinopathy. Clin Ophthalmol 2012;6:1925-30.
53. Lee JY, Jeong HS, Lee DY, Sohn HJ, Nam DH. Early

postoperative intraocular pressure stability after combined 23-gauge sutureless vitrectomy and cataract surgery in patients with proliferative diabetic retinopathy. Retina 2012;32:1767-74.
54. Ozone D, Hirano Y, Ueda J, Yasukawa T, Yoshida M, Ogura Y. Outcome and complications of 25-gauge transconjunctival sutureless vitrectomy for proliferative diabetic retinopathy. Ophthalmologica 2011;226:76-80.
55. Issa SA, Conor A, Habib M, Steel DH. Comparison of retinal breaks observed during 23 gauge transconjunctival vitrectomy versus conventional 20 gauge surgery for proliferative diabetic retinopathy. Clin Ophthalmol 2011;5:109-14.
56. Sima P, Zoran T. Long-term results of vitreous surgery for proliferative diabetic retinopathy. Doc Ophthalmol 1994;87:223-32.
57. Kamura Y, Sato Y, Deguchi Y, Yagi F. Iatrogenic retinal breaks during 20-gauge vitrectomy for proliferative diabetic retinopathy. Clin Ophthalmol 2013;7:29-33.
58. Rizzo S, Genovesi-Ebert F, Di Bartolo E, Vento A, Miniaci S, Williams G. Injection of intravitreal bevacizumab (Avastin) as a preoperative adjunct before vitrectomy surgery in the treatment of severe proliferative retinopathy (PDR). Grafes Arch Clin Exp Ophthalmol 2008;246:837-42.
59. Yang CM, Yeh PT, Yang CH, Chen MS. Bevacizumab pretreatment and long-acting gas infusion on vitreous clear-up after diabetic vitrectomy. Am J Ophthalmol 2008;146:211-7.
60. da R Lucena D, Ribeiro JA, Costa RA, Barbosa JC, Scott IU, de Figueiredo-Pontes LL, *et al*. Intraoperative bleeding during vitrectomy for diabetic tractional detachment with versus without preoperative intravitreal bevacizumab. Br J Ophthalmol 2009;93:688-91.
61. Oshima Y, Shima C, Wakabayashi T, Kusaka S, Shiraga F, Ohji M, *et al*. Microincision vitrectomy surgery and intravitreal bevacizumab as a surgical adjunct to treat diabetic traction retinal detachment. Ophthalmology 2009;116:927-38.
62. Modarres M, Nazari H, Falavarjani KG, Naseripour M, Hashemi M, Parvaresh MM. Intravitreal injection of bevacizumab before vitrectomy for proliferative diabetic retinopathy. Eur J Ophthalmol 2009;19:848-52.
63. Gupta A, Bansal R, Gupta V, Dogra MR. Six-month visual outcome after pars plana vitrectomy in proliferative diabetic retinopathy with or without a single postoperative injection of intravitreal bevacizumab. Int Ophthalmol 2012;32:135-44.
64. Ushida H, Kachi S, Asami T, Ishikawa K, Kondo M, Terasaki H. Influence of preoperative intravitreal bevacizumab on visual function in eyes with proliferative diabetic retinopathy. Ophthalmic Res 2013;49:30-6.
65. Sato T, Morita S, Bando H, Sato S, Ikeda T, Emi K. Early vitreous hemorrhage after vitrectomy with preoperative intravitreal bevacizumab for proliferative diabetic retinopathy. Middle East Afr J Ophthalmol 2013;20:51-5.
66. Jirawison C, Ittipunkul N. Intravitreal bevacizumab at the end of diabetic vitrectomy for prevention of postoperative vitreous hemorrhage: A comparative study. J Med Assoc Thai 2012;95:136-42.
67. Yeh PT, Yang CM, Lin YC, Chen MS, Yang CH. Bevacizumab pretreatment in vitrectomy with silicone oil for severe diabetic retinopathy. Retina 2009;29:768-74.
68. Nakao S, Ishikawa K, Yoshida S, Kohno R, Miyazaki M, Enaida H, *et al*. Altered vascular microenviornment by bevacizumab in diabetic fibrovascular membrane. Retina 2013;33:975-63.
69. Foulks GN, Thoft RA, Perry HD, Tolentino FI. Factors related to corneal epithelial complications after closed vitrectomy in diabetics. Arch Ophthalmol 1979;97:1076-8.
70. Oyakawa RT, Schachat AP, Michels RG, Rice TA. Complications of vitreous surgery for diabetic retinopathy. Intraoperative complications. Ophthalmology 1983;90:517-21.
71. Garcia-Valenzuela E, Abdelsalam A, Eliott D, Pons M, Iezzi R, Puklin JE, *et al*. Reduced need for corneal epithelial debridement during vitreo-retinal surgery using two different viscous surface lubricants. Am J Ophthalmol 2003;136:1062-6.
72. Abrams GW, William GA. En bloc excision of diabetic membranes. Am J Ophthalmol 1987;103:302-8.
73. Carter JB, Michels RG, Glaser BM, De Bustros S. Iatrogenic retinal breaks complicating pars plana vitrectomy. Ophthalmology 1980;97:848-54.
74. Qamar RM, Saleem MI, Saleem MF. The outcomes of pars plana vitrectomy without tamponade for tractional retinal detachment secondary to diabetic retinopathy. Malays J Med Sci 2013; 20: 55-60.
75. Jaffe GJ, Lewis H, Han DP, Williams GA, Abrams GW. Treatment of postvitrectomy fibrin pupillary block with tissue plasminogen activator. Am J Ophthalmol 1989;108:170-5.
76. Williams DF, Bennett SR, Abrams GW, Han DP, Mieler WF, Jaffe GJ, *et al*. Low-dose intraocular tissue plasminogen activator for treatment of postvitrectomy fibrin formation. Am J Ophthalmol 1990;109:606-7.
77. Han DP, Lewis H, Lambrou FH Jr, Mieler WF, Hartz A. Mechanism of elevated intraocular pressure elevation after pars plana vitrectomy. Ophthalmology 1989;96:1357-62.
78. Haimann MH, Abrams GW. Prevention of lens opacification during diabetic vitrectomy. Ophthalmology 1984;91:116-21.
79. Hutton WL, Pesicka GA, Fuller DG. Cataract extraction in the diabetic eye after vitrectomy. Am J Ophthalmol 1987;104:1-4.
80. Smiddy WE, Stark WJ, Michels RG, Maumenee AE, Terry AC, Glaser BM. Cataract extraction after vitrectomy. Ophthalmology 1987;94:483-7.
81. Aaberg TM. Clinical results in vitrectomy for diabetic traction retinal detachment. Am J Ophthalmology 1979;88:246-53.
82. Rice TA, Michels RG, Maguire MG, Rice EF. The effect of lensectomy on the incidence of iris neovascularization and neovascular glaucoma after vitrectomy for diabetic retinopathy. Am J Ophthalmol 1983;95:1-11.
83. Blankenship GW. The lens influence on diabetic vitrectomy results: Report of a prospective randomized study. Arch Ophthalmol 1980;98:2196-8.
84. Lee MS, Elliott D, Rastogi S, *et al*. Incidence of rubeosis after vitrectomy for proliferative diabetic retinopathy. Invest Ophthalmol Vis Sci 1998;39:674.
85. Helbig H, Kellner U, Bornfeld N, Foerster MH. Rubeosis iridis after vitrectomy for diabetic retinopathy. Graefes Arch Clin Exp Ophthalmol 1998;236:730-3.
86. Andriievic-Derk B, Vatavuk Z, Bencic G, Novak-Laus K, Mandic Z. Intravitreal bevacizumab for neovascular glaucoma. Acta Clin Croat 2008;47:175-9.
87. Salman AG. Intrasilicone bevacizumab injection for iris neovascularization after vitrectomy for proliferative diabetic retinopathy. Ophthalmic Res 2013;49:20-4.
88. Yang CM. Surgical treatment for diabetic retinopathy: 5 year experience. J Formos Med Assoc 1998;97:477-84.
89. Novak MA, Rice TA, Michels RG, Auer C. Vitreous hemorrhage after vitrectomy for diabetic retinopathy. Ophthalmology 1984;91:1485-9.
90. Schachat AP, Oyakawa RT, Michels RG, Rice TA. Complications of vitreous surgery for diabetic retinopathy II Postoperative complications. Ophthalmology 1983;90:522-30.
91. Park DH, Shin JP, Kim SY. Comparison of clinical outcomes between 23-gauge and 20-gauge vitrectomy in patients with proliferative diabetic retinopathy. Retina 2010;30:1662-70.

92. Khuthaila MK, Hsu J, Chiang A, DeCroos FC, Milder EA, Setlur V, *et al*. Postoperative vitreous hemorrhage after diabetic 23-gauge pars plana vitrectomy. Am J Ophthalmol 2013;155:757-63, 763.e1-2.
93. Yang CM, Yeh PT, Yang CH. Intravitreal long-acting gas in the prevention of early postoperative vitreous hemorrhage in diabetic vitrectomy. Ophthalmology 2007;114:710-5.
94. Yeh PT, Yang CM, Yang CH, Huang JS. Cryotherapy of the anterior retina and sclerotomy sites in diabetic vitrectomy to prevent recurrent vitreous hemorrhage: An ultrasound biomicroscopy study. Ophthalmology 2005;112:2095-102.
95. Entezari M, Ramezani A, Ahmadieh H. Cryotherapy of sclerotomy sites for prevention of late post-vitrectomy diabetic hemorrhage: A randomized clinical trial. Grafes Arch Clin Exp Ophthalmol 2010;248:13-9.
96. Romano MR, Gibran SK, Marticorena J, Wong D, Heimann H. Can a preoperative bevacizumab injection prevent recurrent post vitrectomy vitreous hemorrhage? Eye (Lond) 2009;23:1698-701.
97. Ahmadieh H, Shoeibi N, Entrezari M, Monshizadeh R. Intravitreal bevacizumab for prevention of early post vitrectomy hemorrhage in diabetic patients: A randomized clinical trial. Ophthalmology 2009;116:1943-8
98. Romano MR, Gibran SK, Marticorena J, Wong D, Heimann H. Can a preoperative bevacizumab injection prevent recurrent post vitrectomy vitreous hemorrhage? Eur J Ophthalmol 2009;19:618-21.
99. Guthrie G, Hall AB, Dhalla K, Davis RM, Steel DH Bevacizumab as an adjunct to vitreoretinal surgery for diabetic retinopathy in East Africa. Eye 2013; Aug 16 doi: 10.1038/eye2013.182
100. Lewis H, Aaberg TM, Abrams GW, *et al*. Causes of failure after diabetic vitrectomy. Invest Ophthalmol Vis Sci 1998 20:220.
101. Lewis H, Aaberg TM, Williams GA. Anterior hyaloidal fibrovascular proliferation after diabetic vitrectomy. Am J Ophthalmol 1987; 104:607-10.
102. Kreiger AE. Wound complications in pars plana vitrectomy. Retina 1993;13:335-44.
103. Kreiger AE, Straatsma BR, Foos RY. Incisional complications in pars plana vitrectomy. Mod Probl Ophthalmol 1977;18:210-23.
104. Koch FH, Kreiger AE, Spitznas M, Glasgow B, Foos RY, Yoshizumi MO. Pars plana incisions of four patients: Histopathology and electron microscopy. Br J Ophthalmol 1995;79:486-93.
105. Kobayashi T, Machida S, Fujiwara T, Ishibe T, Kurosaka D. Vitreous levels of vascular endothelial growth factor in eyes with anterior hyaloidal fibrovascular proliferation. Clin Ophthalmol 2010;20:1043-6.
106. Nasrallah FP, Jalkh AE, Van Coppenolle F, Kado M, Trempe CL, McMeel JW, *et al*. The role of the vitreous in diabetic macular edema. Ophthalmology 1988;95:1335-9.
107. Lewis H, Abrams GW, Blumenkranz MS, Campo RV. Vitrectomy for diabetic macular traction and edema associated with posterior hyloidal traction. Ophthalmology 1992;99:753-9.
108. Harbour JW, Smiddy WE, Flynn HW Jr, Rubsamen PE. Vitrectomy for diabetic macular edema associated with thickened and taut posterior hyaloids membrane. Am J Ophthalmol 1996;121:405-13.
109. Gandorfer A, Messmer EM, Ulbig MW, Kampik A. Resolution of diabetic macular edema after surgical removal of the posterior hyaloid and the inner limiting membrane. Retina 2000;20:126-33.
110. Kalvoda J, Duskova J, Kovarik Z, Kubena A, Kalvodova B. Efficiency of vitrectomy in diabetic macular edema and morphometry of surgically removed of the internal limiting membrane. Cesk Slow Oftalmol 2010; 66: 76-82.
111. Diabetic Retinopathy Clinical Research Network Writing Committee. Haller JA, Qin H, Apte RS, Beck RR, Bressler NM, Browning DJ, *et al*. Vitrectomy outcomes in eyes with diabetic macular edema and vitreomacular traction. Ophthalmology 2010;117:1087-93.
112. Flaxel CJ, Edwards AR, Aiello LP, Arrigg PG, Beck RW, Bressler NM, *et al*. Factors associated with visual acuity outcomes after vitrectomy for diabetic macular edema: Diabetic retinopathy clinical research network. Retina 2010;30:1488-95.
113. Bahadir M, Ertan A, Mertoglu O. Visual acuity comparison of vitrectomy with and without internal liiting membrane removal in the treatment of diabetic macular edema. Int Ophthalmol 2005;26:3-8.
114. Yamamoto S, Yamamoto T, Ogata K, Hoshino A, Sato E, Mizunoya S. Morphological and functional changes of the macula after vitrectomy and creation of posterior vitreous detachment in eyes with diabetic macular edema. Doc Ophthalmol 2004;109:249-53.
115. Patel JI, Hykin PG, Schadt M, Luong V, Fitzke F, Gregor ZJ. Pars plana vitrectomy for diabetic macular edema: OCT and functional correlations. Eye (Lond) 2006;20:674-80.
116. Yamada Y, Suzuma K, Kumagami T, Fujikawa A, Kitaoka T. Systemic factors influence the prognosis of diabetic macular edema after pars plana vitrectomy with internal limiting membrane peeling. Ophthalmologica 2013;229:142-6.
117. Chhablani JK, Kim JS, Cheng L, Kozak I, Freeman W. External limiting membrane as a predictor of visual improvement in diabetic macular edema after pars plana vitrectomy. Grafes Arch Clin Exp Ophthalmol 2012;250:1415-20.
118. Murakami T, Nishijima K, Akagi T, Uji A, Horii T, Ueda-Arakawa N, *et al*. Segmentation analysis of retinal thickness after vitrectomy in diabetic macular edema. Invest Ophthalmol Vis Sci 2012;53:6668-74.
119. Yoshikawa M, Murakami T, Nishijima K, *et al*. Macular migration towards the optic disc after inner limiting membrane peeling for diabetic macular edema. Invest Ophthalmol Vis Sci 2013;54:629-35.
120. Sonoda KH, Sakamoto T, Enaida H, Miyazaki M, Noda Y, Nakamura T, *et al*. Residual vitreous cortex after surgical posterior vitreous separation visualized by intravitreal triamcilone acetonide. Ophthalmology 2004;111:226-30.
121. Russell SR, Hageman GS. Optic disc, foveal and extrafoveal damage due to surgical separation of the vitreous. Arch Ophthalmol 2001;119:1653-8.
122. Haritoglou c, Ehrt O, gass CA, Kristin N, Kampik A. paracentral scotomas: A new finding after vitrectomy for idiopathic macular hole. Br J Ophthalmol 2001;85:231-3.
123. Sebag J. Pharacological vitreolysis. Retina 1998;18:1-3
124. Uemura A, Nakamura M, Kachi S, Nishizawa Y, Asami T, Miyake Y, *et al*. effect of plasmin on laminin and fibronectin during plasmin-assisted vitrectomy. Arch Ophthalmol 2005;123:209-13.
125. Li X, Shi X, Fan J. Posterior vitreous detachment with plasmin in the isolated human eye. Graefes Arch Clin Exp Ophthalmol 2002;240:56-62.
126. Takano A, Hirata A, Inomata Y, Kawaji T, Nakagawa K, Nagata S, *et al.* Intravitreal plasmin injection activates endogenous matrix metalloproteinase-2 in rabbit and human vitreous. Am J Ophthalmol 2005;140:654-60.
127. Baramova EN, Bajou K, Remacle A, L'Hoir C, Krell HW, Weidle UH, *et al*. Involvement of PA/plasmin system in the processing of pro-MMP-9 and in the second step of pro-MMP-2 activation. FEBS Lett 1997;405:157-62.
128. Sakuma T, Tanaka M, Inoue J, Mizota A, Souri M, Ichinose A.

Use of autologous plasmin during vitrectomy for diabetic maculopathy. Eur J Ophthalmol 2006; 6:138-40.
129. Azzolini C, D'Angelo A, Maestranzi G, Codenotti M, Della Valle P, Prati M, *et al*. Intrasurgical plasmin enzyme in diabetic macular edema. Am J Ophthalmol 2004;138:560-6.
130. Asami T, Terasaki H, Kachi S, Nakamura M, Yamamura K, Nabeshima T, *et al*. Ultrastructure of internal limiting membrane removed during plasmin-assisted vitrectomy from eyes with diabetic macular edema. Ophthalmology 2004;111:231-7.
131. Hirata A, Takano A, Yonemura N, Sagara N, Tanihara H. Plasmin-associated vitrectomy for management of proliferative membrane in proliferative diabetic retinopathy: A pilot study. Retina 2007;27:1074-8.
132. de Smet MD, Gandorfer A, Stalmans P, Veckeneer M, Feron E, Pakola S, *et al*. Microplasmin intravitreal administration in patients with vitreomacular traction scheduled for vitrectomy: The MIVI I trial. Ophthalmology 2009;116:1349-55, 1355.e1-2.

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