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Surgical Management of Diabetic Macular Edema

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Abstract

Purpose of Review Diabetic macular edema (DME) is the accumulation of fluid in the extracellular space within the macula and is a major cause of visual impairment among patients with diabetes. First-line treatment for DME includes pharmacotherapy with intravitreal anti-vascular endothelial growth factor medications and intravitreal corticosteroids. Alternative therapeutic strategies include laser photocoagulation for non-center involving DME, and surgical options such as pars plana vitrectomy (PPV) with or without internal limiting membrane (ILM) peel in cases with vitreoretinal interface anomalies or DME refractory to pharmacotherapy, and the Port Delivery System (PDS) for sustained release of anti-vascular endothelial growth factor (VEGF) medication. Our aim is to review the existing literature on surgical management of DME including imaging changes in chronic DME and the clinical relevance of surgical intervention.

Recent Findings Imaging changes associated with DME and a worse prognosis include disorganization of the retinal layer, disruption of both the external limiting membrane (ELM) and ellipsoid zone, and vitreomacular interface abnormalities. Studies involving pars plana vitrectomy with and without ILM peel show anatomic improvement but may not always be associated with significant change in visual outcomes. Early studies lacked detailed imaging of the retinal layers and PPV was likely performed as a last resort. In addition, the novel PDS is surgically implanted into the pars plana and works as a drug reservoir with controlled release of drug. However, it has been recalled in patients with wet age-related macular degeneration due to issues with dislodgement.

Summary Surgical interventions for DME include pars plana vitrectomy with and without ILM peel and new surgical therapies for DME such as the PDS and subretinal gene therapy have the potential to reduce the risk of DME progression.

Keywords Diabetic Macular Edema · Pars Plana Vitrectomy · ILM Peel · ERM Peel · Portal Delivery System

Introduction

Diabetic macular edema (DME) is a serious retinal disorder that is the leading cause of progressive visual impairment in patients with diabetes [1]. DME is typically diagnosed by optical coherence tomography (OCT), a non-invasive imaging modality that uses low-coherence light to obtain cross-section photos of the retina. The pathophysiology is not fully understood in DME, and management remains challenging for many of these patients. The mainstay of systemically treating diabetic retinopathy is controlling blood sugar, cholesterol, and blood pressure. Additionally, ophthalmic intervention may be necessary for diabetic retinopathy and/or diabetic macular edema. First-line treatment includes pharmacotherapy with intravitreal anti-vascular endothelial growth factor (VEGF) medications [2–4]. In cases of patients that are unresponsive to anti-VEGF therapy, corticosteroids can be used

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[5]. Surgical intervention by way of pars plana vitrectomy (PPV) with or without internal limiting membrane (ILM) peeling has been used to address anatomic variations seen in DME, such as epiretinal membrane (ERM) formation, ILM thickening, and vitreomacular traction. PPV is currently recommended to treat DME complicated by tractional changes at the vitreomacular interface [6]. However, the role of PPV in cases of DME without such complications remains unclear. New surgical interventions such as the port delivery system (PDS) with a drug reservoir have been developed to facilitate prolonged delivery of anti-VEGF medications with studies currently underway to determine its usefulness in DME.

The purpose of this review is to evaluate imaging of DME, currently available surgical treatments, and novel treatments under development.

Imaging Changes from Chronic DME

OCT can be used to identify specific morphologic characteristics of DME. These include retinal thickening, cystoid macular edema, and subretinal fluid. Additionally, certain OCT findings associated with DME may yield poor prognostic outcomes. Disorganization of the retinal layer (DRIL) includes disruption of the demarcating interface lines between the inner retinal layers. DRIL is thought to represent damaged or disorganized cells within the retina. Eyes with OCT findings of DRIL have been found to have a worse baseline visual acuity and poor visual recovery after anti-VEGF treatment [7–9]. Furthermore, disruption of both the external limiting membrane (ELM) and ellipsoid zone correlates with reduced baseline and final visual acuity [10–12]. Finally, DME associated with vitreomacular interface abnormalities has poor visual outcomes [13, 14]. This includes ERMs and vitreomacular traction (VMT).

Role of Vitrectomy and ILM Peel

Vitreomacular adherence has been postulated to contribute to diabetic macular edema by increasing vascular permeability through both mechanical and physiologic changes. Suggested mechanisms include physical traction on the macula and accumulation of vascular permeability factors within the pre-macular vitreous gel [15, 16]. Nasralla et al. found a lower incidence of DME in eyes with posterior vitreous detachment (55%) as compared to those with an intact hyaloid (20%) [17]. Given the increasing role of the posterior hyaloid, vitrectomy and ILM peel have thus been used as a treatment for DME.

Several prospective studies demonstrated improvement in visual acuity after vitrectomy and ILM peel. In patients with persistent diffuse DME, vitrectomy with ILM peeling was found to be superior to observation for 6 to 18 months when evaluating visual acuity and edema morphology [18]. Similarly, Kumagai et al. found that PPV with or without ILM peeling does improve and stabilize the long-term visual acuity for patients with non-tractional DME [19]. In both the ILM-off and ILM-on group, the mean best corrected visual acuity (BCVA) improved from 20/72 to 20/45 and 20/54, respectively ($p < 0.05$). There was however no statistically significant difference between patients who underwent ILM peel and those who did not. As compared to modified grid laser photocoagulation, PPV with ILM peel was shown to be more effective with a significant decrease in foveal thickness and improved visual acuity in patients with bilateral DME who were laser and PPV naïve and had no evidence of ERMs or VMT [20]. Figure 1 demonstrates a patient with proliferative diabetic retinopathy (PDR) and thickened ILM who underwent ILM peel. BCVA improved from 20/60 preoperatively to 20/30 1 month post-operatively.

Numerous retrospective studies have also showed similar improvement in visual acuity after PPV and ILM peel.

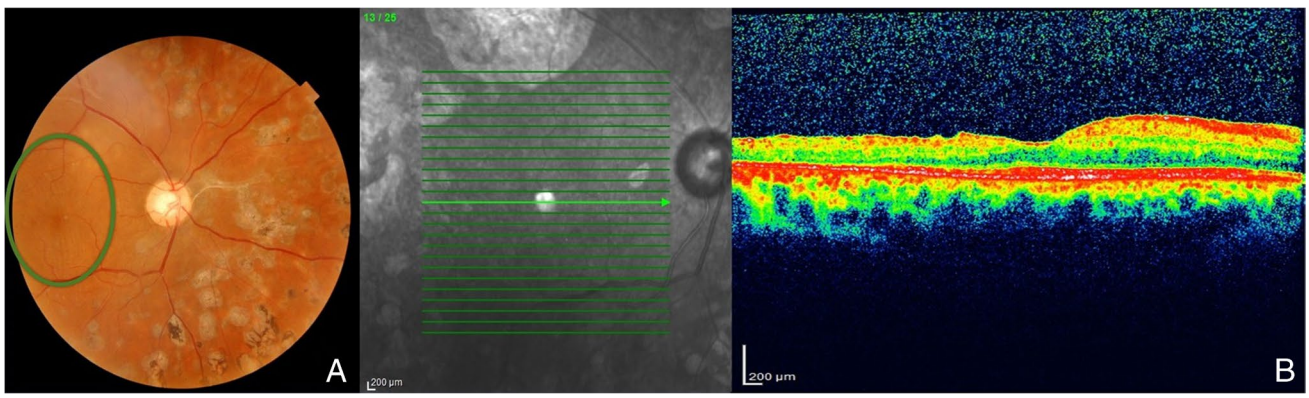

Fig. 1 Fundus photo of the right eye in a patient with DME and PDR with thick ILM prior to ILM peel (**A**). Post-operative infrared reflectance imaging and OCT 1 month after PPV and ILM peel with subsequent improvement in vision (**B**). Photo credit to Mauricio Maia, MD PhD

Browning et al. studied 45 patients with center-involving DME, and found that vitrectomy led to a clinically significant improvement in visual acuity when compared to serial intravitreal anti-VEGF injections over a 12-month follow-up period [21]. Similarly, several studies showed a significant improvement in functional outcomes after early surgical intervention for non-tractional DME [22–24]. In patients with tractional DME, PPV demonstrated a significant improvement in BCVA in more than 50% of patients up to 12 months postoperatively [25]. Cataract progression after PPV was observed in several of these studies; however, only a few patients had BCVA reduction from the advancement of their cataracts.

While much evidence supports the efficacy of vitrectomy to treat DME, not all studies show positive outcomes. As compared to macular argon photocoagulation or modified grid laser photocoagulation, PPV for macular edema did not result in a significant change in visual acuity [26–28]. A systematic review found that PPV may have functional benefits in some eyes with DME, but no statistically significant benefit over laser or observation [29]. Additionally, there was no significant difference in best-correct visual acuity between vitrectomy and intravitreal triamcinolone treatments [30]. Given these findings, it is important to note that direct comparison between medical therapy and surgical intervention is difficult for several reasons. One of which, is that vitrectomy is often reserved for patients who have failed other treatments and may thus have poor vision at baseline. In contrast, nonsurgical treatments, such as intravitreal injections and photocoagulation, are often used as early interventions on patients with likely better pre-treatment vision and more potential for improvement in final visual acuity.

In several studies, the addition of ILM peel to PPV did not result in improved visual acuity [31–33]. Yamamoto et al. found no statistical difference in visual acuity or retinal thickness between the group that underwent ILM peel and the group that did not [34]. Additionally, Bardak et al. compared indocyanine green (ICG)-assisted ILM peeling and triamcinolone acetonide-assisted posterior vitreous removal in patients with diffuse DME, and found no difference in visual acuity [33]. A study looking at vitrectomy with intravitreal triamcinolone acetonide (IVTA) and/or ILM peel to treat diffuse non-tractional DME found no difference in short-term or long-term visual outcomes between treatment groups [15].

Anatomic Benefit of Vitrectomy and ILM Peel

Chhablani et al. used spectral domain OCT to evaluate anatomic predictors of visual improvement in patients with DME after undergoing PPV. The strongest predictor was found to be pre-operative damage to the ELM [35]. Hagenau et al. looked to correlate OCT findings with pathology of the vitreomacular interface in eyes with DME that underwent vitrectomy [36]. A study of 10 patients with DME unresponsive to grid laser photocoagulation showed that PPV and removal of ILM was effective in reducing macular edema with significantly lower mean foveal thickness as determined by OCT [37]. Figueroa et al. found that among a group of 38 patients with DME without retinal traction, vitrectomy with ILM removal or IVTA injection resulted in a significant improvement in macular thickness up to 6 months postoperatively. The improvement was no longer significant at 12 months [15]. Similar studies evaluating patients with non-tractional DME showed anatomic improvement as appreciated by a significant decrease in foveal thickness [22, 23, 32, 38]. These positive results were also found in treatment-naïve patients with DME [24].

Patients with tractional DME also showed a significant decrease in central foveal thickness after undergoing a PPV with low rates of recurrence [25]. When comparing vitrectomy versus IVTA injections alone, there was significant improvement in central macular thickness among both groups. Edema did not recur 6 months after vitrectomy and PPV resolved DME more effectively than IVTA [30]. Additionally as compared to grid laser, PPV with dye-enhanced ILM peel does appear to reduce foveal thickness and macular volume [28]. A study of 65 patients with diffuse diabetic macular edema was evaluated based on their preoperative OCT morphological characteristics, and it was determined that vitrectomy can be a useful intervention, particularly for those eyes with subretinal fluid [39]. The VITAL study, which looked at the change BCVA of 120 eyes with naïve DME that were treated with PPV and ILM peeling, also demonstrated that the presence of subretinal fluid was a predictor of good visual outcomes [23]. Figure 2 demonstrates OCT findings in a patient with ERM and DME who underwent PPV with ERM and ILM peel. The patient was found to have a post-operative visual acuity of 20/100, which was unchanged compared to her preoperative visual acuity, despite decrease in central macular thickness.

When comparing PPV to macular argon photocoagulation, Patel et al. found no significant difference in OCT findings regarding foveal thickness and macular volume between the two groups during a 48-week follow-up period [27]. Furthermore, a meta-analysis from 2014 did not find that vitrectomy was superior to laser when evaluating retinal structure at 12 months [40].

While the studies discussed showed anatomical benefit of patients undergoing PPV with ILM, the effects on visual outcome are inconsistent. Half of the studies showed a significant increase in BCVA postoperatively [22–25, 36, 39]. The other half showed no significant improvement [15, 27, 28, 30, 32, 37, 38].

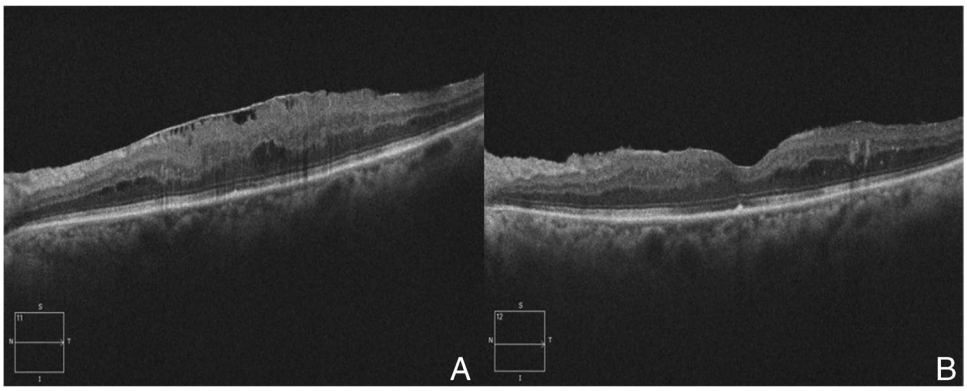

Fig. 2 Preoperative OCT of the left eye with an ERM and DME (**A**). Postoperative OCT of the same patient 3 months after a PPV with ERM and ILM peel (**B**). Visual acuity did not improve despite alleviation of traction caused by the ERM and subsequent decrease in foveal thickness

Port Delivery System

Anti-VEGF intraocular injections are typically delivered monthly with some patients able to have longer intervals depending on their response to the medication. The frequency of injections as well as the cost to patients can create barriers to diabetic care. Non-compliance has been estimated to be up to 39% and can lead to negative outcomes such as retinal detachment, neovascular glaucoma, vitreous hemorrhage, and vision loss [41, 42]. Additionally, multiple injections carry an increased risk of endophthalmitis, intraocular inflammation, retinal tear or detachment, ocular hypertension, and hemorrhage [43–47].

As such, a new procedure to address these concerns uses a port delivery system (PDS) with a drug reservoir. The PDS is surgically implanted into the pars plana and then covered with the Tenon's capsule and conjunctiva. The PDS is made up of four components: a rim on the outside of the sclera, a self-sealing pocket for refilling the drug, the drug reservoir, and a porous metal release control element for the drug to elute into the vitreous cavity [48]. The system was FDA-approved in October 2021 for wet age–related macular degeneration (AMD) with the drug ranibizumab (Susivmo; Genentech, South San Francisco, CA, USA) [49]. However, in October 2022, Susivmo was recalled due to issues of septum dislodgement during testing of the device after repeated punctures [50]. It should be noted that the formulation for the PDS system is different from the one approved for intravitreal injections [51]. The Archway study showed that the PDS system with 100 mg/ml was equivalent to 0.5 mg monthly injections for changes in BCVA [50]. Most patients did not need supplemental ranibizumab treatment and almost 98% of patients successfully went 6 months without a refill. However, there was a threefold increase in the adverse ocular event rates in the PDS group with most occurring within the first month, with specific concerns for endophthalmitis and conjunctival erosion [52]. PAGODA, an ongoing Phase III clinical trial, is studying the use of the PDS system for treatment of DME. Comparisons will include 100 mg/ml ranibizumab against 0.5 mg monthly injections. The primary outcome is BCVA from baseline at weeks 60 and 64 as measured using the ETDRS chart. It is estimated to complete data collection by February 2024 [53].

However, some factors to consider for PDS in patients with DME compared to AMD include impaired wound healing in patients with diabetes. This could result in increased complications with closure of the conjunctiva and Tenon's capsule. Conjunctival retraction was associated with 3 of the 4 endophthalmitis cases in the AMD PDS clinical trials, so this number could increase in the PAGODA study [54]. Additionally, studies show that patients with diabetes have an increased tendency to develop endophthalmitis after surgery and approximately 14–21% of patients who do develop endophthalmitis after surgery have diabetes [55]. Finally, it should be noted that patients with DME need fewer injections over time, so sustained VEGF suppression may be unnecessary in these cases [56]. However, in cases of severe non-proliferative diabetic retinopathy patients with and without DME, the PDS system may have advantages in controlling their disease long-term [57].

Overall, the PDS system could be an option for patients with DME in order to improve adherence with treatment. Patients with diabetes are burdened with multiple visits to various specialists and monthly injections for DME only increase their burden. Additionally, this could potentially lead to decreased health care systems costs, less severe disease, and fewer required procedures.

Conclusion

DME can be a destructive retinal disorder for patients with diabetes. The pathogenesis of this disease has been well studied and imaging changes on OCT are well characterized. We have reported strong correlations between OCT imaging findings and prognostic outcomes. However, despite our understanding of the disease and ability to recognize and diagnose the condition, management options are limited.

Intravitreal anti-VEGF injections continue to be the first line treatment for DME but even with monthly injections, only about 1/3 of the eyes improve in visual acuity while about 1/10 continue to get worse (increase in ≥ 10 or 15 letters and decrease in ≥ 10 or 15 letters lines respectively) [58]. PPV is currently the only surgical treatment for tractional DME. A randomized clinical trial studying PPV for the treatment of DME is needed to better define its role. Finally, clinical trials are underway to evaluate new surgical treatments such as the PDS in DME. The PDS may serve to improve anti-VEGF compliance and relieve the burden of intravitreal injections.

Declarations

Conflict of Interest Jamie Prince, Dipen Kumar, Arko Ghosh, Alice Yang Zhang, declare that they have no conflict of interest.
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Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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