Chapter

# High-Risk Diabetic Maculopathy: Features and Management

*Maya G. Pandova*

## Abstract

A substantial group of patients with diabetic macular edema in our clinical practice is at high risk for profound and irreversible vision deterioration. Early identification of modifiable factors with long-term negative impact and their management, close monitoring and timely adjustments in the treatment can significantly reduce the probability of visual disability in the individual patient. This approach can also provide important guidelines for proactive decision making in order to avoid the risk of suboptimal response and unsatisfactory outcome.

**Keywords:** Retinal symptoms and signs, systemic risk factors, treatment options, management stages

## 1. Introduction

The introduction of intravitreal pharmacotherapy dramatically improved the visual prognosis of the patients with diabetic macular edema (DME). However, the pivotal randomized clinical trials demonstrated that a sizable proportion of the eyes remained with disabling visual acuity despite intensive treatment and vigorous monitoring for 2 years [1]. Moreover, after transition to standard clinical care for the next 3 years, the visual acuity worsened even in patients with significant vision gain [2]. Real-world studies on DME management from Europe, USA, Japan and Australia reveal significant differences in the registration, national policies and restrictions for the use of the medications. A common issue is a tremendous pressure on the ophthalmic care providers to reduce the cost of visits and treatment. This invariably has resulted in visual outcomes that were meaningfully inferior to those achieved in randomized controlled trials [3–8].

These data suggest that a substantial group of patients with diabetic macular edema in our clinical practice is at high risk for profound and irreversible vision deterioration. Early identification of modifiable factors with long-term negative impact and their management, close monitoring and timely adjustments in the treatment can significantly reduce the probability of visual disability in the individual patient. Such a systematic approach can also provide important guidelines for proactive decision making in avoiding the risk of suboptimal response and unsatisfactory outcome.

## 2. Low visual acuity at baseline

Post hoc analysis of the best-corrected visual acuity (BCVA) achieved in DRCR.net Protocol T randomized clinical trial after anti-VEGF treatment [1] demonstrated that 96–100% of eyes enrolled in the trial with BCVA 20/32 to 20/40 retained high vision after 6 months even in the presence of persistent edema. A small

proportion - 8% of these eyes - deteriorated below 20/40 at the end of the first year and further 5–8% worsened after 2 years, and only if the edema was persistent. The outcome in eyes with baseline BCVA 20/50 to 20/320 was far less – through the 24th week 21–41% of them failed to improve over 20/50, and the results were worse if the edema was persistent – 31–51% of them had BCVA less than 20/40. By the end of the first year 11–30% of these eyes were still seeing below 20/40 and the outcome was worse if the edema was persistent – 33–46% remained in the low vision group. After 2 years of anti-VEGF treatment 17–25% of these eyes did not improve over 20/50 and their proportion reached 46% in eyes with persistent edema. Standard clinical care in the next three years resulted in vision deterioration by at least one Snellen line (4.8 letters) in the whole cohort and the proportion of eyes with BCVA less than 20/40 increased from 16% at the end of the second year to 27% [2]. The overall impression from the clinical trials and real-life practice is that significant vision gain is achievable even in eyes with low baseline vision at relatively low risk of severe vision loss, however it requires intensive treatment and the long-term outcome is often unstable. In contrast, eyes with higher visual acuity at baseline have much better chance to retain it in the next 2 and 5- year interval with appropriate management.

## 3. Imaging and biomarkers

**Stereoscopic examination** of the retina readily reveals signs predicting slow, limited visual response to treatment and tendency for recurrence:

Diffuse edema, ischaemic areas in the posterior pole, hard exudates close to the fovea and atrophic changes in the deep layers are often associated with **long-standing disease**. These changes persist if pharmacotherapy was provided occasionally and in long intervals.

**Previous laser treatment close to the macula** leaves chorioretinal scars that slowly progress towards the fovea, particularly if the photocoagulation spots were confluent and with high intensity.

**PDR** - active proliferative disease, signs of hypo- or nonperfusion and particularly the presence of retinal ischaemic areas in the equatorial zone and periphery indicate advanced microvascular damage and carry poor visual prognosis if left untreated. As noted in the secondary analysis of Protocol T patients, eyes with less than severe nonproliferative diabetic retinopathy (EDTRS severity levels 10 to 47) had 3.1 letters more visual acuity improvement after treatment for 2 years compared to patients with inactive advanced PDR and no prior panretinal photocoagulation [9].

**Panretinal photocoagulation (PRP)** for advanced PDR (EDTRS severity levels 61 to 75) at baseline in the same clinical trial was associated with approximately 3 letters less vision gain after 2 years [9]. This finding needs careful interpretation. Often, advanced PDR is associated with various stages of macular edema, and laser treatment that prevented the total blindness is such patients, was done years prior to the introduction of pharmacotherapy for the macular complication. On the other hand, confluent, high-intensity laser treatment applied over large areas in one or two sessions is associated with significant thermal trauma and can lead to inflammation, worsening of the macular edema, followed by atrophic changes and vision deterioration that may not respond to treatment.

Glistening, taut **epiretinal membranes** in the posterior pole with characteristic folds and retinal distortion require close monitoring - they may limit the vision gain in response to treatment, particularly in the presence of atrophic macular changes (**Figure 1**).

Anterior–posterior **vitreo-macular traction** can cause edema per se and will not respond to intravitreal treatment [10].

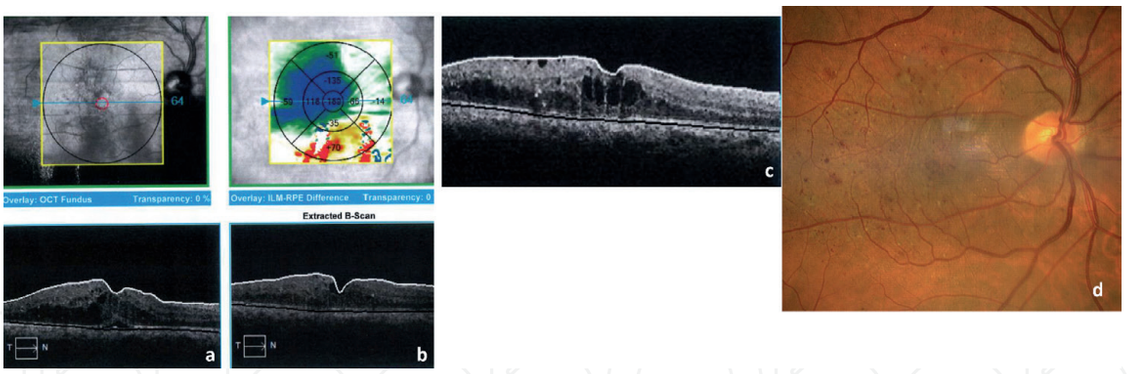


**Figure 1.**
*63 years old male, DM for 23 years, DME, PDR. a –VA decreased from 20/40 to 20/80 in two month during decompensation of CAD and CABG -epiretinal membrane, lamellar macular hole, severe recurrence of intraretinal edema with macrocysts, subsensory fluid collection; b -after 5 anti-VEGF injection –persistent intraretinaledema, resolved subsensoryfluid, VA 20/40, c – 27 months and 9 anti-VEGF injections later – persistent intraretinal edema, hyperreflective foci, epiretinal membrane, lamellar macular hole, VA 20/40; d –persistent macrocysts, ischemic areas, hard exudates and microaneurisms.*

## 4. Optical coherent tomography

Systematic analysis of OCT at the initial visit provides insight into the severity and duration of the disease and guides the appropriate choice of treatment and regimen.

**The location, size and content of intra- and subretinal fluid collections**: **Cystic spaces exceeding 200 μm** involving the outer nuclear layer (ONL) are seen in late stage of DME and have a worse impact on macular function than smaller cysts or cystoid formations occurring in inner retinal layers (**Figure 2b**). **Large cysts located in the perimacular area** tend to extend centrally with time (**Figure 3b** and **d**). Even though in the early phases the visual acuity is not severely deteriorated, in the presence of other risk factors treatment has to be initiated – these patients have excellent chances to retain good function without major fluctuations. Lack of retinal bridges between the cystic spaces in the inner and outer retina is a sign of long-standing severe disease and is associated with poor visual prognosis despite resolution of the fluid post treatment (**Figure 2d**). **Subfoveolar neurosensory detachment** is seen in cases with more severe edema and has been associated with more active inflammatory components of the disease (**Figure 1a**). These patients responded favorably in the pivotal clinical trials on anti-VEGF and dexamethasone treatment with significant functional gains. This type of edema has a tendency to recur in chronic cases with interrupted intravitreal treatment, deterioration of the systemic disease or after cataract surgery (**Figure 4**).

**Hyperreflective retinal foci** appear as small lesions with size less than 30 μm with reflectivity similar to retinal nerve fiber layer and without back-shadowing over the underlying layers. They appear to represent subclinical lipoproteins that extravasate after breakdown of inner blood–retinal barrier, although there are suggestions that they might be activated microglial cell, and indicate chronicity and predominant inflammation in the eye. Increased number of the spots indicate tendency for recurrence of the edema and require close monitoring (**Figures 1c** and **7d**).

**Hard exudates** present in the OCT as hyperreflective intraretinal accumulations larger than 30 μm with back-shadowing. The deposits are thought to consist of lipoproteins and indicate advanced microvascular damage and chronicity. In severe cases they can form fibrotic lesions that are associated with visual decline, especially if located in or close to the macula (**Figure 5**) [11].

**Disorganization of retinal inner (DRIL) and outer layers within the central 1 mm retinal zone** may not be readily distinguishable if the edema is severe and

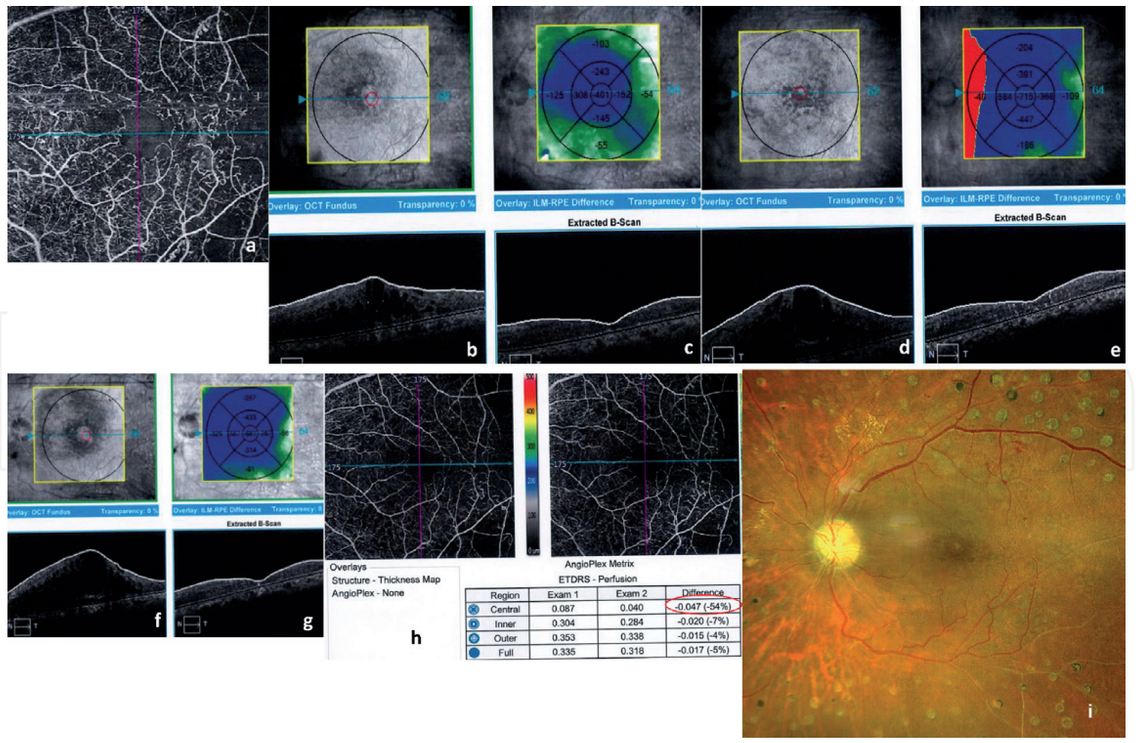


**Figure 2.**
*58 years old male, nephropathy, diabetic foot, CAD, PDR, recurrent macular edema, neovasculargla ucoma after glaucoma drainage implant (Ahmed valve). a –OCTA total retina –broad areas of hypoperfusion, microaneurisms, enlarged distorted foveolar avascular zone; b -severe recurrence during Leukemoid reaction, HbA1c 11%, VA 20/200; c -one week after anti-VEGF injection, VA 20/70; d – 3 months later -recurrence after treatment on Imatinib for 3 months, VA 20/100; e -one month after anti-VEGF injection, VA 20/50; f –recurrence during deteriorated foot ulcer, HbA1c 9% VA 20/150; g –one month after anti-VEGF intravitreal injection, VA 20/50; h –OCTA superficial plexus-decreased central perfusion by 54% in 6 months after 4 major recurrences; i –advanced OND pallor, macrocystsand atrophic areas in the macula, severe ischemia and NVE.*

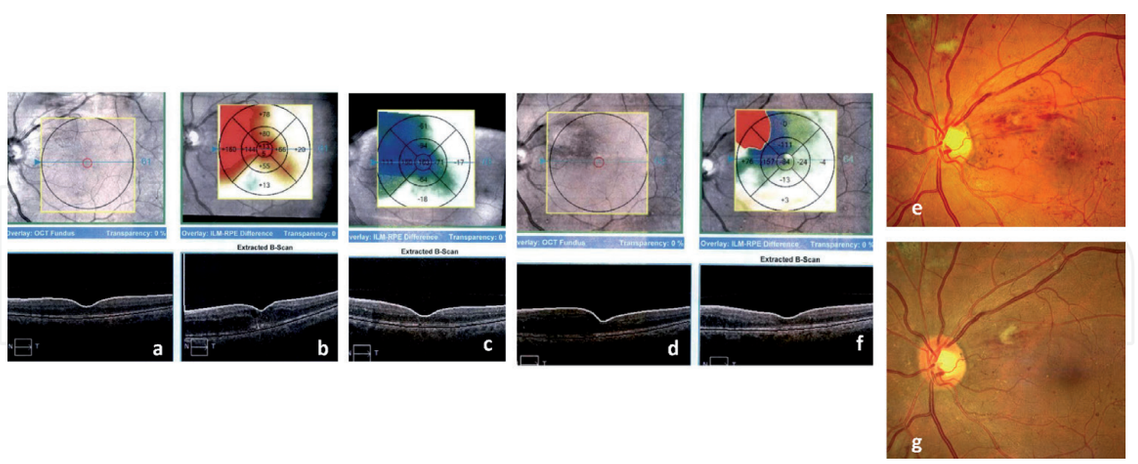


**Figure 3.**
*60 years old female, 20 years of poorly controlled DM, arterial hypertension; multiple recurrences of perimacularedema, NPDR. a –One month after anti-VEGF injection, VA 20/20; b –treatment interrupted for 8 months, VA 20/30, 5 months after hysterectomy; c –one month later after anti-VEGF, VA 20/20; d, e–3 months later-new recurrent intraretinal edema progressing towards the macula, new ischemic areas, VA 20/30, f, g–one month after anti-VEGF injection and focal laser, persistent perimacular ischemia, VA 20/20.*

associated epiretinal membranes and hyperreflective lesions, especially if there are media opacities (**Figure 2**). It is becoming evident in the course of the treatment after regression of the edema and explains the low visual acuity and minimal vision gain. DRIL has been attributed to macular capillary non-perfusion, the size and erosion

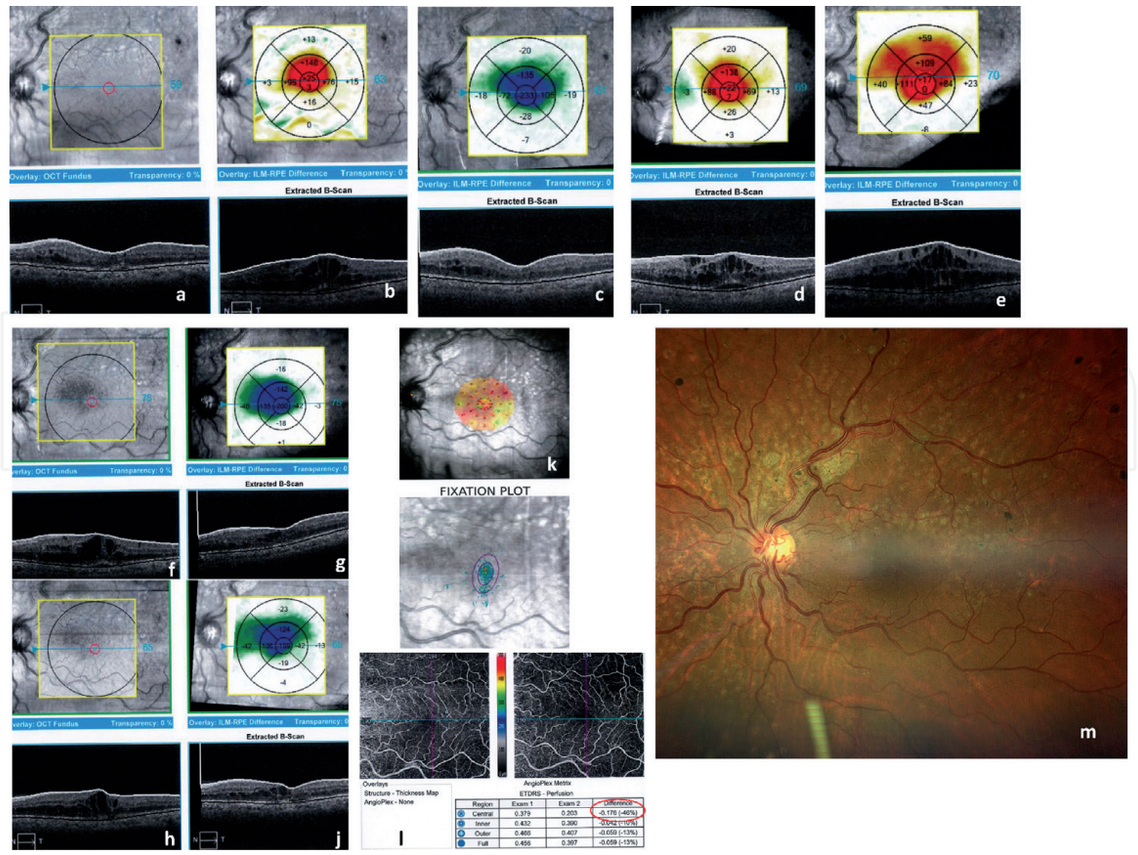


**Figure 4.**
*57 years old female, DM for 25 years, sleeve gastrectomy, chronic cholecystitis, CAD, DME, PDR, secondary glaucoma. a –after 3 anti-VEGF injections and 1 OzurdexVA 20/60, cataract; b –deteriorated edema with subsensory fluid 14 days after phacemulsificationVA 20/60; c – 14 days after anti-VEGF injection, VA 20/30; d – recurrent edema during CABG, subsensory fluid, hyperreflective foci VA 20/40; e –severe edema after pyocele and sepsis, VA 20/40; f –recurrence after stroke, VA 20/30; g – 7 days after Ozurdex, VA 20/25; h –severe recurrence 3 months after the second Ozurdex, VA 20/40; j –rapid response to Iluvien, VA 20/25; k –microperimetry-decreased central retinal sensitivity, unstable central fixation; l -decreased central perfusion in the superficial plexus by 46% in 18 months; m –microcystic edema and hard exudates in the macula, stable PDR, visible Iluvien implant.*

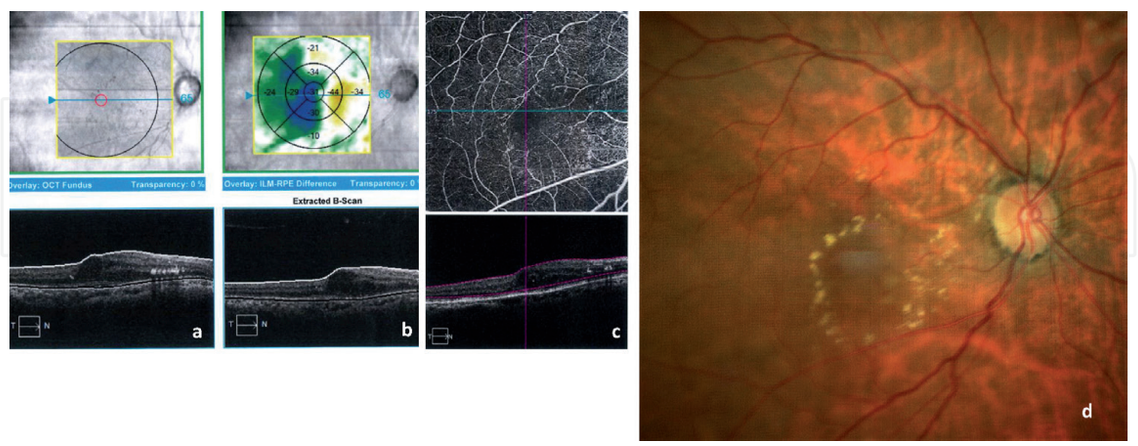


**Figure 5.**
*70 years old female. Chronic macular edema, NPDR, chronic uveitis, secondary glaucoma for 12 years, poorly controlled diabetes, arterial hypertension, lost for follow up for 4 years. a –Three weeks after intensive topical steroids and antiglaucoma medications VA 20/250; b -after 4 anti-VEGF and focal laser –persistent macrocystic edema, regressing hard exudates, VA 20/50, c –OCTA –total retina-significant capillary dropout, enlarged irregular foveolar avascular zone; d –chronic edema, circinate hard exudates.*

of the foveolar avascular zone and has been correlated with increasing severity of the retinopathy, especially in patients with proliferative disease (**Figure 6**). The presence of DRIL can be associated with disorganized outer retinal layer disruption,

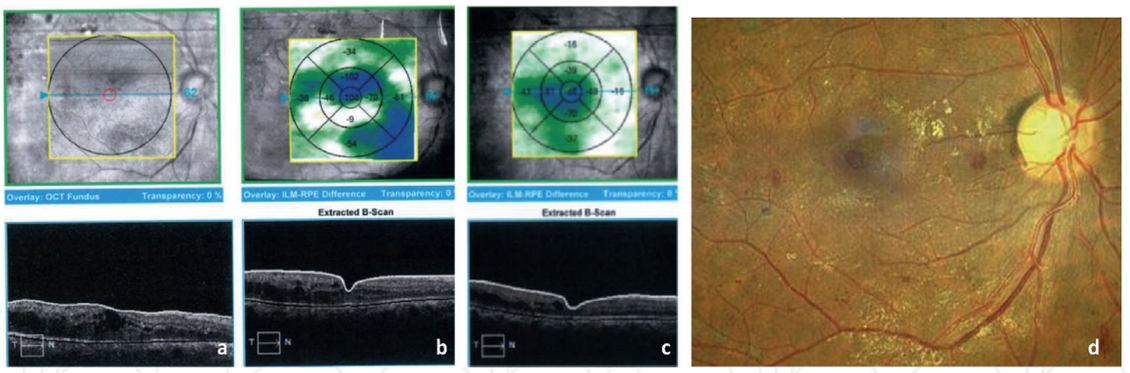


**Figure 6.**
*60-years old female, 20 years of poorly controlled diabetes. Phacoemulsification and vitrectomy, choroidal effusions. a -Severe DME, epiretinal membrane, DRIL one month after surgery; b – 4 months later after 3 anti-VEGF injections –incomplete, unstable response; c – 6 months later after 2 Ozurdex implants –residual perimacular degenerative fluid spaces; d –persistent macular edema, mild DRIL, epiretinal membrane, hard exudates and microaneurisms.*

specifically ellipsoid zone (EZ) and external limiting membrane (ELM). Moreover, Sun and colleagues have found that an increase in DRIL during 4 months predicted a decline of visual acuity by one line [12].

OCT assessment of the **vitreomacular adhesions and traction** is indispensable in the choice of treatment. The presence of anterior–posterior traction is considered an indication for pars-plana vitrectomy in eyes with DME, however other OCT findings - greater retinal thickness, presence of subretinal fluid, lack of external limiting membrane integrity and disruption of the ellipsoid zone - have been associated with a poorer final absolute BCVA [10]. Macular edema in eyes with lamellar holes associated with tangential traction needs careful consideration – it often responds favorably to intravitreal treatment and may remain stable, however should be monitored closely in the presence of active PDR and may eventually require surgical management (**Figure 1**).

## 5. Optical coherent tomography angiography

The contribution of OCTA in the assessment of high-risk DME is substantial. It will detect capillary dropout, microaneurisms and neovascularization in detailed 3-dimentional segments (**Figure 2a**) and provide quantitative estimates of the perfusion and vascular density by areas [13] (**Figure 4I**). A recent study demonstrated that although there was no significant difference in the superficial capillary plexus between anti-VEGF responders and poor responders, poor responders tended to show greater damage and more microaneurysms in the deep capillary plexus and a larger foveolar avascular zone (FAZ) area. The topographic location of the disrupted synaptic portion of the outer plexiform layer in SD OCT exactly corresponded to the nonflow area of the deep capillary plexus in OCTA [14]. The enlargement and irregularities of the FAZ have to be interpreted carefully in the presence of large central cysts as such findings could be associated with capillary displacement rather than ischemia, especially in eyes with retained inner and outer retinal morphology. OCTA assessment of patients with DME and neurosensory detachment demonstrated improvement in cysts area and perfusion density in the superficial and deep capillary plexus in response to treatment with Dexamethasone and ranibizumab [15]. Persistent microaneurisms and declining perfusion in the deep capillary plexus in another comparative work was associated with less vision gain and incomplete resolution of the edema after treatment with aflibercept [16].

## 6. Fundus autofluorescence

Short-wavelength FAF derives its signal mainly from lipofuscin in the RPE. Long wavelength autofluorescence or near-infrared FAF derives its signal from melanin, which is present in RPE and choroid. Intraretinal cysts in DME unmask the underlying RPE by displacing the luteal pigment in the fovea and this prevents the normal blockage of foveal FAF signal. Granular and patchy hyper- and hypo-autoflurescent lesions in the parafoveolar area have been described and correlated with foveolar cystoid spaces in DME patients. Larger area of hyper-autofluorescence in eyes with higher number of hyperreflective foci and presence of subfoveal neuroretinal detachment may indicate a prevalent inflammatory condition in DME with specific response to steroidal treatment [17, 18].

## 7. Microperimetry

Micoperimetry is able to quantify macular sensitivity and fixation pattern in an exact, fundus-related fashion, thus adding detailed information about the degree and pattern of macular function alteration (**Figure 4k**). It has been successfully used in the diagnosis and follow-up of different macular disorders, including age-related macular degeneration, myopic maculopathy, macular dystrophies, and diabetic macular edema. Vujosevic S et al. have demonstrated in a series of studies that macular sensitivity is significantly affected when diabetic macular edema develops and it deteriorates further in eyes at more severe stages of macular edema even in the absence of ischemia. The stability of the fixation is decreasing late in the disease and indicates advanced photoreceptor damage and chronicity [19].

## 8. Glaucoma in eyes with DME

In a recent meta-analysis of prospective cohort studies the pooled risk ratio of the association between primary open-angle glaucoma (POAG) and diabetes was 1.36 [20]. The prevalence of glaucoma in diabetics ranges from 4.96% to 14.6% with significant variations in geographic regions and racial groups. Moreover, there is a statistically significant association between the duration of diabetes and glaucoma [21]. Hou et al. compared rates of visual field (VF) loss and retinal nerve fiber layer thinning for patients with POAG and found no difference in progression between patients without and with type 2 diabetes and no detectable diabetic retinopathy. They also found that treated diabetes was linked to significantly slower loss of RNFL thickness [22].

The risk of ocular hypertension in a patient presenting with DME needs to be considered in the treatment choice. While anti-VEGF agents are generally safe, a key DRCR.net report on eyes with center-involved DME and no preexisting open-angle glaucoma treated on ranibizumab and monitored for 3 years demonstrated increase in the risk of sustained IOP elevation or the need for ocular hypotensive treatment after anti-VEGF treatment [23]. In patients with POAG and DME treated with ranibizimab and monitored for 24 months, Fursova et al. report a decrease in the functional and structural parameters of the retina and optic nerve, and a higher rate of progression of glaucomatous optic neuropathy compared to patients without DME. Long-term results have not revealed a significant deterioration in the structural parameters of the optic disc and retina as a consequence of anti-VEGF therapy [24].

Intravitreal steroids will induce hypertensive response in up to 50% of the eyes with DME. The MEAD Study reported that over 40% of eye required initiation of a topical ocular hypotensive agent and 0.3% of eyes required incisional glaucoma surgery after Ozurdex [25]. In the FAME Studies, 18.4% of eyes that were injected with the 0.2 μg Iluvien-FA per day implant developed an IOP higher than 30 mmHg and 4.8% underwent incisional glaucoma surgery [26]. After a follow-up of 5 years, 9% of eyes that had multiple injections of triamcinolone acetonide required a trabeculectomy [27]. An eye that does not develop substantial IOP elevation after a challenge course with a topical steroid may still respond with an IOP rise after Ozurdex or Iluvien, however in most cases it is well controlled on antiglaucoma medications [28].

Patients with refractive DME and well compensated glaucoma on one or two antiglaucoma drops responded favorably to both Ozurdex and Iluvien in our practice (**Figure 4**). An eye with advanced glaucoma on more than 2 medications is at a high risk of uncontrollable IOP and severe vision loss after intravitreal steroid, and glaucoma surgery has to be performed prior to the switch from anti-VEGF.

Neovascularization of the iris or neovascularization of the angle that ultimately lead to neovascular glaucoma is a consequence of long-standing ischemia in patients with PDR. The incidence of neovascular glaucoma is further increased in patients who have undergone vitrectomy and lensectomy. Breach of the posterior capsule from a complicated cataract extraction or even from Nd: YAG laser capsulotomy may allow angiogenic factors to gain access to the anterior segment more readily, accelerating formation of neovascularization. The management of DME in these eyes with intravitreal anti-VEGF provides temporary regression of the iris neovascularization, decrease in the PDR severity and facilitates the panretinal photocoagulation [29]. Early glaucoma surgery significantly improves the visual prognosis of DME in eyes with neovascular glaucoma, however they remain at high risk of IOP decompensation, reactivation of the PDR and recurrences of the macular edema and need prompt, often urgent treatment (**Figure 2**).

## 9. Uveitis

History of a previous uveitis episode or evidence of a chronic intraocular inflammation in a patient with DME heralds high rate of complications and difficult management (**Figure 5**). A large database from the UK was analyzed for the prevalence of acute uveitis over a six-year period among populations without (n = 889,856) and with diabetes (n = 48,584) and evaluated the impact of glycaemic control on disease risk. Poor glycaemic control increases the risk of acute uveitis, with patients that have an HbA1c over >11.3% almost 5 times more likely to have an event. Acute uveitis was also more common in those with proliferative retinopathy. The odds ratio (OR) for acute uveitis was significantly higher in patients with type 1 DM (OR 2.01), Black (OR 20.17) or Asian (OR 2.09) ethnicity, proliferative disease (OR 2.42) and escalated with increasing HbA1c, however the association with maculopathy was less - OR 1.15 [30]. In a cohort of middle-aged diabetic patients with uveitis, who were followed up for 4 years, 42% had final visual acuity worse than 6/18. In 53% of the eyes, the poor visual acuity was thought to be uveitis related, and a half of these eyes had clinically significant macular edema. Progression of diabetic retinopathy to proliferative stage occurred in 10% of the eyes. In patients with available HbA1c data, the levels were over 7.0% on almost all cases in the quiescent period and rose by 1.5–4% in the acute episodes. The authors conclude that uveitis occurring in patients with pre-existing diabetes can be associated with numerous ocular complications and recurrences. Macular involvement related to both the uveitis and the diabetes appears to be the main cause of reduced vision [31].

In clinical practice, diabetic patients with macular edema and uveitis have higher tendency to develop fibrinous exudates in the anterior chamber and posterior synechiae, particularly after intraocular surgery. They respond favorably to topical, periocular and intravitreal steroids and require close monitoring for intraocular pressure spikes. Interestingly, the IOP in many patients with uveitic glaucoma decreases in response to appropriate anti-inflammatory management; in the meantime the macular edema deteriorates, particularly if the patient is on systemic steroids or a biological agent and with significant fluctuations in the glucose levels. The recurrence of the edema may remain unnoticed in eyes with media opacities and active inflammation and is "discovered" once the uveitis subsides in the search for explanation of the poor vision - severe macrocysts in the macula are usually accompanied by exudative subsensory fluid collections. Early detection of the DME while the visual acuity is still reasonable and prompt intensive intravitreal treatment improve greatly the visual prognosis (**Figure 5**). These patients are very unstable - they present frequently with recurrent uveitis and macular edema in the course of each attack of their systemic inflammation or in periods of deteriorated metabolic control.

## 10. Cataract surgery and DME

Cataract surgery in diabetic patients has been associated with higher risk of complications, including postoperative macular edema (Irvine-Gass syndrome) and worsening of pre-existing DME (**Figure 4b**). The risk is high in patients with inconsistent previous treatment or chronic edema with incomplete response to intravitreal management. The prevalence is increased by intraoperative vitreous loss, vitreous traction at incision sites, vitrectomy for retained lens fragments, iris trauma, posterior capsule rupture, intraocular lens dislocation, early postoperative capsulotomy, iris-fixated intraocular lenses and placement of an anterior chamber intraocular lens and is further exaggerated by persistent postoperative inflammation [32, 33]. In clinical practice the edema is usually revealed late in the postoperative period and the differentiation between pseudophakic cystoid (Irvin-Gass) and macrocystic diabetic edema may not be very straightforward on OCT. The presence of hard exudates, atrophic changes and hypoperfusion in the posterior pole and some degree of retinopathy in an eye with low vision is more suggestive of a DME (**Figure 5**) while better vision and characteristic fluorescein angiography findings like retinal telangiectasis, capillary dilatation, and leakage from perifoveal capillaries in the early phase frames, and perifoveal hyperfluorescent spots classically described as a "petalloid" pattern in the late phase frames are suggestive of pseudophakic cystoid macular edema. While in most cases, acute pseudophakic CME spontaneously resolves with relatively good vision, the eyes with deteriorated DME after cataract surgery remain with low vision despite vigorous treatment on intravitreal anti-VEGF and steroids. There is a general consensus that DME and severe diabetic retinopathy should be stabilized before undergoing cataract extraction and proactive management is recommended in preparation for surgery. Recurrence or worsening of DME has been successfully prevented by preoperative or intraoperative ranibizumab [34] and triamcinolone acetonide (TA) [35], however the efficacy was short lasting and a sizable group of the eyes with TA develop elevated IOP. Dexamethasone implants have been used intraoperatively and postoperatively [36, 37], however if inserted 2 to 4 weeks prior to surgery they reach their peak activity at the time of the procedure and help control the postoperative inflammation. The initial improvement in visual acuity and decrease in the edema in the first 1–2 months start deteriorating in the next 2–3 months, yet these eyes respond favorably to repeated dexamethasone treatment [38].

## 11. Diabetic macular edema after vitrectomy

The development and use of smaller gauge instrumentation has been associated with a trend towards earlier surgical intervention for diabetic retinopathy. PPV indications include non-clearing vitreous hemorrhages, traction retinal detachment in PDR, and vitreoretinal interface abnormalities impeding macular edema resolution. The role of pars plana vitrectomy (PPV) for eyes with DME without traction elements is less clear. Debate still exists as to the necessity of ILM removal during vitrectomy for DME [39]. Several studies over the past 3 decades have established the structural improvements following vitrectomy in recalcitrant DME cases. Visual improvements however have not been as consistent and as significant as the reduction in retinal thickness following the procedure. Surgical intervention continues to be reserved for those cases that have had chronic and severe forms of DME when retinal damage is usually irreversible thereby compromising the results [40]. Vitrectomy itself is associated with morphological changes in the posterior pole. Detailed evaluation of the macular microstructure after vitrectomy has demonstrated deteriorated photoreceptor outer segment (PROS) length, ellipsoid zone (EZ) and external limiting membrane (ELM). The postoperative recovery was uneven – while PROS increased significantly after 12 months, ELM recovered but did not improve by 24 months when compared to baseline, and the EZ continued improving up to 24 months [41, 42]. Another factor contributing to lower postoperative visual results is post-vitrectomy cystoid macular edema that ranges between 5–47% and has been associated with combined cataract surgery, silicone oil tamponade and its removal, and removal of retained lens fragments in the diabetic eye. This inflammatory condition needs to be differentiated from a recurrence of pre-existing DME after PPV. The presence of dense hard exudates, disorganized retinal layers in the edematous macula, paramacular laser spots, capillary dropout on OCTA and persistent ischemic changes anywhere in the retina indicate the increased risk of poor postoperative vision, however, early intensive management on intravitreal steroids and anti-VEGF combined with careful laser treatment will significantly improve the prognosis (**Figure 6**). A recent meta-analysis estimated the overall pooled incidence of neovascular glaucoma (NVG) after PPV in PDR patients at 6%. The study showed a positive correlation for NVG after PPV in PDR patients with higher baseline IOP, preoperative iris neovascularization, lack of panretinal photocoagulation, preoperative or intraoperative combined cataract surgery, postoperative vitreous hemorrhage and a negative correlation with age [43]. Persistent macular edema in these eyes is a therapeutic challenge. Early glaucoma valve surgery with perioperative anti-VEGF, followed by appropriate intravitreal treatment can stabilize these eyes despite the grave prognosis, moreover that successful combined management of DME correlated closely with long-term recovery of photoreceptor integrity and visual outcome in patients with resolved DME in the presence of retained vascular density in the deep capillary plexus [44].

## 12. Age

The participants in Protocol T were enrolled at an average age of 61 years [45–58]. Secondary analysis of the baseline factors associated with visual outcome after 2 years of intensive anti-VEGF treatment revealed that even in such a relatively young cohort with every decade of age the scope of mean visual improvement decreased by 2.1 EDTRS letters. When the change in visual acuity over 2 years was estimated longitudinally as area under the curve (AUC), the improvement was reduced by 1.9 letters for each decade of life [9]. This

association supports previous findings from DRCR.net Protocol I on treatment with a single anti-VEGF [59] and the RISE and RIDE trials where the odds of achieving at least a 15-letter gain at 2 years fell for every 5-year increase in the age of the patients.

## 13. Glycemic control

There is controversy on the correlation of HbA1c and visual response to anti-VEGF from large phase 3 trials. An analysis of ranibizumab-treated patients from the RISE and RIDE trials did not find an association between mean change in BCVA at weeks 52 and 100, with the baseline HbA1c [60]. This is in contrast to an analysis of aflibercept-treated patients from the VISTA and VIVID trials, which found that the mean improvement in VA at 2 years was dependent on HbA1c levels [61]. An exploratory analysis of DRCR.net Protocol T, in which participants were randomized to receive bevacizumab, ranibizumab, or aflibercept, found that the magnitude of vision improvement after anti-VEGF treatment decreased by 1 letter for each 1% increase in HbA1c levels at baseline [9]. More recently, lower HbA1c levels at baseline (7% or less) were significantly associated with greater reduction in central macular subfield thickness at one month after injection of bevacizumab or ranibizumab, however the change in BCVA after treatment did not have any correlation with the glycemic control [62]. Chen et al. reported that after one year of treatment on ranibizumab, only in the responder group the baseline level of HbA1c was significantly associated with the changes in BCVA and the final BCVA [63]. The common methodological issue with these trials and cohorts under observation is the estimate of glycemic control – HbA1c at baseline, only. There is a significant variability in the glucose plasma levels in diabetic patients. Its impact on microvascular complications in type 2 diabetes was investigated in a post-hoc analysis of 12 042 participants in both Action to Control Cardiovascular Risk in Diabetes (ACCORD) and the Veteran Affairs Diabetes Trial (VADT) that were observed for 84 to 87 months. Variability measures included coefficient of variation and average real variability for fasting glucose. Both indices were associated with development of future microvascular outcomes - higher risk of developing PDR that requires laser treatment - even after adjusting for other risk factors, including measures of average glycemic control (ie, cumulative average of HbA1c). Meta-analyses of these 2 trials confirmed these findings and indicated fasting plasma glucose variation may be more harmful in those with less intensive glucose control [64]. A patient with DME and significant fluctuations in the plasma glucose, hypoglycaemic episodes and HbA1c over 7.5% needs close monitoring – even though the edema may respond structurally to intravitreal treatment, the visual outcome will be limited and very unstable. In addition to the ubiquitous dietary mistakes and sedentary lifestyle, often there are problems associated with ongoing infections, diabetic foot ulcers, non-ocular surgeries and systemic steroid treatment (**Figures 2** and **4**) Dynamic fasting and random plasma glucose and HbA1c re-assessment at the clinic and prior to intravitreal treatment are easy and useful in identifying these patients, particularly during worsening of the DME and diabetic retinopathy after periods of stabilization.

## 14. Cardiovascular disease

The association between cardiovascular disease and diabetic retinopathy was studied mainly in patients with mild retinal lesions. A recent meta-analysis was

performed on 7604 individuals with type 2 diabetes from 8 prospective population-based surveys that were monitored for 5.9 years (3.2 to 10.1 years) where DME was identified in retinal photographs. DME was observed in 0.5% to 7.6% of the participants and was related to an increased risk of first-ever cardiovascular disease - incidence rate ratio 1.65 and fatal cardiovascular disease - incidence rate ratio 2.85. The incidence rate ratio for first-ever coronary heart disease was 1.57 and for fatal coronary heart disease - 3.55. These associations were consistent after multivariable adjustment for vascular risk factors, including smoking, systolic blood pressure, use of hypertension medication, total cholesterol level, and body mass index. When duration of diabetes, use of treatment for diabetes, and glycosylated hemoglobin level were included in the multivariable model, the relationship remained significant [65]. This analysis resonates with an early report on markers for subclinical cardiovascular disease in diabetic patients: CSME was associated with a high coronary artery calcium score (odds ratio, OR 2.86), low ankle-brachial index (OR 4.08) and high ankle-brachial index (OR 21.4) after adjusting for risk factors including hemoglobin A1c level and duration of diabetes, but there was significant association with carotid intima-media thickness or carotid stenosis, defined as >25% stenosis or presence of carotid plaque [66]. The diagnosis of CSME in these studies was based on fundus photographs; had OCT been used as a more sensitive imaging modality [13, 45, 67], the proportion of DME patients with increased cardiovascular risk could have been even higher. In clinical practice, confirmed or probable decompensated coronary artery disease is usually associated with more severe retinal ischemia, unstable response to treatment and higher risk of cardiovascular complications after intravitreal anti-VEGF if used in the course of an acute episode. The extent of macular edema and rate of its recurrence decrease notably after successful angioplasty or coronary bypass graft, however these patients remain at high risk as they are prone to new coronary heart attacks, severe infections and vision-threatening complications – neovascular glaucoma, ischemic diabetic optic neuropathy, vitreous hemorrhages and chronic macular edema (**Figures 1**, **3** and **4**).

## 15. Diabetic nephropathy and hemodialysis

Chronic kidney disease has been related with progression to PDR and DME in type 2 diabetic patients in advanced stages of their microvascular impairment. Systematic assessment of 2135 type 2 diabetic patients for 8 years revealed in 9.2% of new-onset DME identified in fundus photographs that had meaningful relationship with albumin/creatinine ratio below 31 mg/g at baseline, mean follow- serum creatinine levels and estimated glomerular filtration rate 30 and 45 mL/min/1.73 m2 [46]. This longitudinal study clearly emphasizes the importance of screening the DME patients for abnormal renal profile at baseline and throughout the whole follow up. A marked VEGF expression secondary to glomerular injury and elevated levels of serum VEGF in patients with advanced nephropathy could explain the incomplete and unstable response of their macular edema to intravitreal treatment. Introduction to hemodialysis of patients with end-stage renal disease and coexisting DME was associated with significant reduction in the central retinal thickness lasting over the next 12 months, to a level that eliminated the need for intravitreal treatment in 93.2% of the eyes. The fluid resolution was greater in eyes with subretinal detachment compared to spongelike swelling and macrocystic edema. A significant correlation between changes of BCVA and central retinal thickness at 12 months after hemodialysis initiation was found in the patients with good BCVA (over 20/50) but not in the patients with poor BCVA (less than 20/50) [47]. In clinical practice, a sizable group of patients with advanced renal decompensation

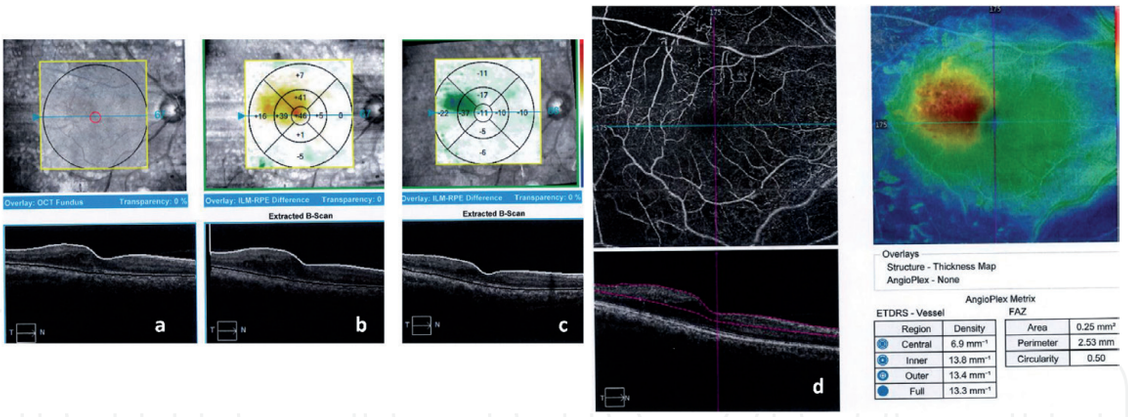


**Figure 7.**
*59 years old male, DM for 25 years, renal failure, chronic hemodialysis, CAD, DME, PDR, recurrent anterior uveitis, recurrent iris neovascularization, secondary glaucoma. a, b -Perimacular edema progressing centrally during deterioration of CAD and CABG, VA 20/20, c – 6 months and 4 intravitreal injections later, VA 20/20, d - OCTA –superficial plexus, capillary dropout, microaneurisms, hyperreflectivefoci and distorted enlarged foveolar avascular zone.*

had notable stabilization of their DME after induction of hemodialysis and needed less intensive management, however they remain at high risk for recurrences of the edema and severe retinal ischemia (**Figure 7**).

## 16. Treatment plan

Patients with DME at high risk for complications and vision loss require close monitoring at short intervals, intensive flexible treatment and arrangements for urgent visits and referrals. Very often, the patients present with multiple ophthalmic and systemic risk factors or develop them while they are under our care. Unrecognized and poorly treated complications and their exacerbations will readily explain the lack of results after "routine" management. Instead of labeling the patient as "non-responder" and giving up treatment altogether, or waiting for the inevitable vision deterioration in order to "start reacting", a "proactive" approach is more effective to achieve high and stable visual acuity, even in difficult patients.

## 17. Early start with high visual acuity

Initiation of treatment in high-risk eyes with BCVA better than 20/40 (Decimal 0.5, LogMAR 0.3) has resulted in better response and higher visual outcome in short- and long term. In our cohort of 152 eyes, 82.89% had BCVA 20/40 at their final visit after 3 to 8 years of management. Out of 126 eyes with BCVA 20/40 and better prior to treatment, 76.96% retained it through the follow up, however only 34.63% of the eyes with BCVA 20/50 and less could improve to 20/40 and better. Final BCVA 20/150 and less (the level of legal blindness in Kuwait) was seen in 4.82% of the eyes with high initial visual acuity and in 23.06% in the eyes with worse baseline vision.

## 18. Early start in eyes with perimacular edema

Recent or chronic edema close to the macula seldom affects the visual acuity, however it tends to progress centrally after major non-ocular surgeries, severe infections

and exacerbations of cardiovascular and renal complications (**Figures 3**, **4** and 7). Early intravitreal treatment is usually effective and results in high visual acuity – in our cohort, 40% of the eyes with final BCVA 20/40 and better had significant perimacular edema at baseline. In eyes with more distant chronic lesions where persistent leakage and hypoperfusion are evident, intravitreal treatment can be followed by delicate focal laser once the edema has regressed. The classical perivascular technique of P. Hamilton performed with the 50 micrometer spot and minimal power settings applied in the temporal half of the posterior pole is suitable in severe chronic cases.

## 19. Severe NPDR and PDR in an eye with DME

Nowadays these patients seldom come without any previous treatment. Incomplete retinal laser and particularly interrupted intravitreal anti-VEGF injections for PDR have resulted in sight-threatening complications. PRP, primary vitrectomy or pharmacotherapy, alone or in combination, have been proposed with excellent outcome. The choice greatly depends on the ability of the patient to visit the clinic for regular follow up or emergency. Serious comorbidities and psychiatric diseases are associated with lengthy admissions and recuperation – and lack of eye treatment. Such patients will benefit from completion of the PRP and a longer-acting intravitreal medication while they are still ambulant. The main concern with PRP is the peripheral visual field (VF) loss associated with photocoagulation burns. A recent ad hoc review of DRCR.net Protocol S data reports decline of the pericentral and peripheral visual field 5 years after treatment with 20 ranibizumab injections to a level close to the pattern in eyes with PRP and 7 ranibizumab injections, suggesting that there are factors besides PRP associated with VF loss in eyes treated for PDR. In the longitudinal model describing total VF point score loss, the amount of loss depended on the type of laser treatment applied. On average, additional PRP sessions were associated with less VF loss than an initial PRP session, and endolaser application during vitrectomy was associated with more loss than an initial PRP session. The losses may be direct and immediate effects of heavier vs. lighter photocoagulation or reflections of delayed deleterious effects of the treatments, conditions associated with the persistence or return of neovascularization necessitating additional treatment, cataract progression, or, in the case of endolaser with vitrectomy, adverse effects of vitreous hemorrhage or the surgical procedure, such as cataract [48]. In practice, early, gradual and sparing laser technique with smaller spot size and less duration, particularly after intravitrel pharmacotherapy, is seldom associated with significant field loss – these defects appear after severe ischemia and correspond to non-perfusion areas.

## 20. Anti-VEGF medications as first choice

Abundant published data emphasize the safety of all off-label and approved drugs. Ranibizumab (Lucentis®, Novartis, Basel, Switzerland) and Aflibercept (EYLEA®; Bayer HealthCare, Berlin, Germany/Regeneron Pharmaceuticals Inc., Tarrytown, NY, USA) are preferable as initial treatment for eyes with DME and primary or secondary glaucoma, however the IOP needs close monitoring for spikes if larger volume has been injected intravitreally. This class of antibodies induces regression of the iris neovascularization and resolution of intraretinal edema and hemorrhages in eyes with PDR and this facilitates greatly the completion of PRP. An important consideration is the partial response and persistence of macular edema - data from Protocol T demonstrated chronic fluid in up to 65.9% of the eyes on bevacizumab, in 44.2% of the eyes on ranibizumab and

39.2% of the eyes on aflibercept after 2 years of treatment [1]. The number of intravitreal injections during the first year is decisive – in Protocol T, after the loading dose, the eyes that ended up with chronic edema had on average 3 injection from the 24th to 52nd week vs. 6 injections in eyes without chronic DME for the same period. Even though the eyes with chronic edema were given 4 to 6 injections during the second year, they remained with persistent fluid, unlike the eyes without fluid after the first year – they maintained relative stability on 2–3 injections during the second year [1]. The ability of a high-risk patient to complete such an intensive treatment, particularly if the edema is bilateral, needs to be discussed beforehand.

## 21. Intravitreal dexamethasone as first choice

The use of Dexamethasone intravitreal implant (0.7 mg) (Ozurdex, Allergan, Inc., Irvine, CA, USA) in eyes with DME, alone or in combination with anti- VEGF drugs, vitrectomy and retinal laser has been studied extensively since 2011. The implant provides rapid resolution of the macular fluid in all compartments that is sustained oved the next 2–4 months. It decreases the existing hard exudates and prevents the formation of new ones [49], and reportedly reduces the rate of progression of retinopathy [50]. Dexamethasone implant is selected as primary treatment in patients with recent and severe cardiovascular complications or pregnancy where the risk of systemic side effects from anti-VEGF injections needs to be avoided. Severe chronic maculopathy is often refractory to anti-VEGF management and a trial loading dose with these drugs may turn out to be an unnecessary delay. A dexamethasone implant as initial treatment might be a better choice for such patients, moreover that treatment–naïve eyes consistently fared better that eyes on long previous non-steroidal management. The main concerns are the formation of cataract in phakic eyes and elevation in the IOP. In the MEAD studies, the incidence of cataract-related side effects was 67.9% in the 0.7 mg dexamethasone implant and the rate of cataract surgery was 59.2%. In the same trial, an increase in IOP was observed in 27.7% of the eyes and 1.4% of them required a glaucoma procedure (trabeculoplasty, iridotomy, iridectomy, or trabeculectomy) [51]. A patient with advanced glaucoma, even well compensated on topical treatment or after glaucoma surgery, is at risk of developing further optic nerve disc damage and vision deterioration after a steroid- induced IOP spike. A short trial use of dexamethasone drops 4–5 times daily readily provokes a meaningful IOP elevation in a steroidal responder and foretells similar issues with the implant. In clinical practice, an increase in the IOP is observable a week after implantation and responds well to topical beta blockers and carbonic anhydrase inhibitors. The IOP needs monitoring for at least three months as in some cases it decreases after resolution of the implant, and in others it remains permanently high and requires consistent glaucoma care. The DME patients with glaucoma on intravitreal dexamethasone in our practice remained controlled on topical medications and none needed glaucoma surgery. The progression of cataract after several dexamethasone implants and the need for surgery as part of the vision rehabilitation has to be discussed with the high-risk patients beforehand - in most cases the possibility of good functional results outweigh the apprehension and fear (**Figures 4** and **6**). In vitrectomized eyes with aphakia, large iridectomies, zonulolysis, large peripheral defects in the posterior lens capsule and dislocated IOLs the implant tends to migrate in the anterior chamber and induce elevated IOP and corneal edema to a point that may require a corneal graft. A peribulbar depo-steroid might be a safer option in such complicated eyes.

## 22. Vitrectomy as first choice

The introduction of small gauge platforms and refined instrumentation have greatly improved the safety and reliability of PPV as primary treatment for eyes with DME and vitreomacular traction. The role of primary PPV for eyes with DME without traction elements is less clear. An earlier publication of Michalewska Z et al. [52] on 20-G vitrectomy and ILM removal, the multicenter trial of Iglicki M et al. [53] using 25-G PPV and ILM peeling and the report of Lin HC et al. [54] on 23-G vitrectomy with ILM peeling as a first line treatment for DME demonstrate substantial increase and stabilization of visual acuity, macular fluid resolution and rapid regression of hard exudates, without additional therapy up to 24 months post surgery. Prognostic factors associated with a greater visual gain include no history of prior macula laser treatment, lower hemoglobin A1c, recent onset of the edema and younger age, however delay of the procedure and damage of the IS/OS and ellipsoid zone at baseline had negative effect on the vision gain 12 and 24 months postoperatively. The complications after PPV can not be ignored – lamellar and full-thickness macular holes, non-resolving preretinal hemorrhages and rhegmatogenous retinal detachments have all been reported, and up to 50% of the phakic eyes develop significant cataract during the next 12 to 24 months that requires surgery compared to 7.14% of the eyes in the pharmacotherapy group [53]. These results suggest that earlier intervention with pars plana vitrectomy may be beneficial for treatment-naïve eyes, but they need to be replicated in larger prospective controlled trials.

## 23. Management of diabetes and its complications

Partnership and regular consultations with the diabetologist or treating physician are essential part of the management in high-risk DME patients. The adjustments or frank replacement of diabetic medications, provision of glycemic monitoring devices, lifelong screening for cardiovascular and renal complications, prompt referral to the necessary subspecialist create the foundation for better glycemic control, improved stability and less severe retinal complications. Regular measurements of HbA1c at the retinal clinic and RBS prior to intravitreal injections easily screen patients with unsatisfactory glycemic control and have become routine in our practice. Sudden worsening of the retinopathy and macular edema are often preceding serious systemic complications and a swift arrangement for medical assessment may prevent a major disability or even save the life of the patient (**Figure 1**). Discussing the medical background with a patient presenting with relapsing DME reveals sometimes bureaucratic and financial barriers to qualified medical care. Direct contacts with a dedicated medical team and suitable procedures for referral are particularly helpful in challenging situations that need consistent management. Holistic approach, continuous interest and candid conversations with the patients improve substantially the compliance and, in the long run, the outcome of DME treatment.

## 24. First outcome – review and adjustments of the treatment

Careful observation of high-risk eyes one week after the first anti-VEGF intravitreal injection reveals a degree of fluid resolution (**Figure 2c**) and its recurrence one month later. Rather than lack of response, this indicates ongoing retinal ischaemia and the need for tight metabolic control and management of systemic comorbidities. An early positive response on OCT may not be associated with immediate improvement of the visual acuity, however the monthly injections with the chosen drug need to be

continued until the loading dose is completed. Meanwhile, if patient and physician have decided to perform further laser treatment for eyes with PDR and severe ischemia, it is split in suitable intervals. Intensive metabolic control - and the much needed changes in the diet – are usually followed by short episodes of hypoglycemia and deterioration of the retinopathy severity and recurrences of the edema. The patients need to be prepared for this difficult initial period in order to comply with the visits and procedures without anxiety and confusion. Monthly monitoring of eyes with advanced maculopathy is highly advisable – edema that is persistent after one or two anti-VEGF injections and is associated with large cysts, hyperreflective spots and particularly progressive disorganization in the outer retinal layers indicate severe disruption of the blood-retinal barrier and active inflammation. Extending the loading dose to 24 weeks will not provide better functional or anatomic outcomes and prompt transition to a dexamethasone implant at this point will be more beneficial (**Figure 4g**). At month 12, the probability of achieving a BCVA improvement of ≥10 letters was reported as 3.71 times greater after intravitreal dexamethasone vs. anti-VEGF treatment [55]. High-risk eyes with good response to anti-VEGF in terms of vision gain and fluid resolution by the end of the 3rd to 4th month, need sufficient number of injections and comprehensive medical care in the next years in order to maintain the outcome. Patients with high vision and completed intravitreal course in the first 2 years may present with recurrences - they are still at high risk – however they continue responding well to treatment and retain the acuity with minor variations.

An eye with a high-risk DME, good response to dexamethasone implant as initial treatment and well controlled IOP is already facing recurrence of the edema and deterioration of vision after 3 to 4 months (**Figure 4h**). Insertion of the implant at this point reduces the fluctuations in the edema and resulting detrimental changes in the outer retina. Improved metabolic control, successful cardio-vascular management and particularly, induction into hemodialysis are associated with more stable maculopathy – this allows increase the intervals between implants or even transition to anti-VEGF on "as needed" regimen.

## 25. Further management

The eyes with high-risk DME remain unstable even after they have responded well to intravitreal treatment. The patients often present with recurrences during and after severe systemic infections, major surgeries, trauma and stress. There are also fluctuations in the edema associated with variations in the metabolic control, ongoing ischemic events in patient with cardiac and renal complication and ocular surgeries. The visual acuity of a well treated diabetic eye is not severely affected by the new fluid in the first few months, however if left untreated, it causes gradual functional deterioration that may not be reversible. The management of these eyes is oriented towards early detection of the recurrences and timely treatment, in parallel with dynamic collaboration with the diabetologist in order to control the systemic complications.

Frequent assessment, sufficient number of intravitreal injections and adequate treatment of the retinopathy in the first 2 years are critical, and they need to continue for lifetime in order to maintain the visual outcome. The initial therapy needs modifications and combinations in response to the challenges of the disease.

A shift to a longer acting medication needs to be considered for eyes that can not remain stable for more than 45–60 days. There are some early results from the KITE and KASTREL studies on brolucizumab where 55.1% of the eyes in KESTREL and 50.3% of the eyes in KITE remained on a three-month dosing interval through year one, based on a treatment approach determined by disease activity assessment. If disease activity was detected, the patients were switched to two-month intervals through the end of the first

year [56]. Faricimab, the first bispecific antibody to target both anti-Angiopoietin-2 and anti-vascular endothelial growth factor (VEGF) was investigated in YOSEMITE and RHINE trials as monotherapy for DME. More than 70% of patients achieved every-12-week or better dosing status at week 52--73.8% in the YOSEMITE study and 71.1% in the RHINE study with every 12-week and every-16-week dosing [57].

Temporary use of dexamethasone implants is convenient for systemically unstable patients or in preparation for major surgeries or ocular procedures - this will reduce the probability of severe inflammation and macular edema, provided the patient is able to use the antiglaucoma drops.

A patient with favorable response to dexamethasone is a good candidate for an intravitreal fluocinolone sustained-release Implant (**Figure 4g** and **m**). Two parallel, prospective, randomized, sham injection-controlled, double-masked, multicenter clinical trials (FAME trials) demonstrated significant reduction of the central macular thickness, mean BCVA improvement and a higher proportion of patients achieving a BCVA improvement of ≥15 letters in eyes with the implant vs. sham. The need of glaucoma surgery was 3.7% and 0.5% in the implant and sham groups, respectively [58]. A comparison of the effectiveness and safety of the fluocinolone acetonide intravitreal implant between the observational Iluvien Clinical Evidence study in the United Kingdom (ICE-UK) and the Fluocinolone Acetonide in Diabetic Macular Edema (FAME) randomized controlled trials (RCTs) in people with diabetic macular edema demonstrated statistically significant improvements in visual acuity 12 months after implantation in both the real-world study and in the RCTs. The improvement in vision and central retinal thickness in the RCTs was marginally greater than in the real-world study; however, recruits in the real-world study had more severe visual morbidity at baseline [68].

Flexible arrangements for walk-in visits or open appointments prevent delays in the evaluation of patients missing their regular review or presenting with a deterioration. Leaving a few empty slots for such unplanned patients in the daily schedule decreases the disorder in the medical retina clinic. A registry of the DME patients is useful in tracking any lapse in treatment of 3 months or longer that increases the probability of poorer outcome.

## Author details

Maya G. Pandova
New Ahmadi KOC Hospital, Ahmadi, Kuwait

*Address all correspondence to: mayapandova@gmail.com

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