• Review Article •

Therapeutic approaches to diabetic macular edema assessed using optical coherence tomography and optical coherence tomography angiography

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Abstract

● Overt and harmful diabetes mellitus (DM) has detrimental effects on individuals and, by extension, the community. Among the microvascular DM complications is diabetic retinopathy (DR). DR may cause irreversible vision deterioration in cases of poor blood glucose regulation. Changes in vascular permeability are key trigger points for diabetic macular edema (DME), a condition characterized by the accumulation of fluid in the macula. The development of vascular endothelial growth factor (VEGF) pathway inhibitors has provided a pathogenesis-based treatment approach for DME. Optical coherence tomography (OCT) provides high-resolution imaging of the anatomy, including the aging of DME and its structural damage, in distinct morphologic subtypes of macular edema, thereby supporting the assessment of macular edema treatment. The availability of repeated OCT monitoring provides clinical reassurance through the treatment. OCT angiography (OCTA) provides retinal blood flow maps with high spatial resolution. The ability promotes an understanding of disease pathogenesis and facilitates the implementation of new therapeutic methods. This review compares the potential of OCT and OCTA in the diagnosis and treatment of DME, as well as their respective therapeutic applications.

● **KEYWORDS:** diabetic macular edema; optical coherence tomography; optical coherence tomography angiography; vascular endothelial growth factor

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INTRODUCTION

It is predicted that the global burden of diabetes mellitus (DM) is going to hit 642 million in 2040. Diabetic retinopathy (DR) was the sole significant cause of blindness, and the increase in age-standardized prevalence that cured worldwide between 1990 and such a global impact underlines the need for research in this field, particularly one that concerns the identification and treatment of issues such as diabetic macular edema (DME)[1-2].

Complex and multi-factorial reasons cause DME. The rupture of the retinal vasculature results in the leakage of fluid into the intraretinal layers and the activation of pro-inflammatory mediators, such as vascular endothelial growth factor (VEGF) and interleukin (IL)-6, which initiates inflammation in the retina[3].

In severe cases, DME harms central vision, differs sensitivity to color discrimination, and diplopia. It is typically diagnosed through a comprehensive eye examination, which includes visual acuity (VA) testing, a dilated fundus examination, and optical coherence tomography (OCT). Additional exams, such as fluorescein angiography (FA) or indocyanine green angiography, will also help confirm the diagnosis and evaluate the problem[4].

The first DME treatment plan was based on the Early Treatment Diabetic Retinopathy Study (ETDRS). In this research study, clinically significant macular edema (CSME) was defined as retinal thickening adjacent to the foveal center, a density of hard exudates accompanied by immediate thickening, or an area that is thicker than one disc area at one disc diameter[5]. The incidence of CSME is decreasing with the advent of OCT. This non-invasive, fast, in-office modality captures cross-sectional images of the retina. Today, OCT-based treatment recommendations discuss the distinction between the denotation of the presence of DME in centers, such as center-involving DME (CI-DME) and non-CI-DME, to specify the thickness of the central retinal subfield.

The OCT will have the capability to investigate the morphology of the edema and also assess the changes caused by the therapy. A crucial morphological consideration is the central retinal thickness (CRT) in planning therapy[6].

OCT angiography (OCTA) may provide a more comprehensive visualization of the retinal vascular structure without the need for surgery. OCTA images can quantify blood flow imaging. Poor VA is related to the resolution of DME as the foveal avascular zone (FAZ) becomes larger, and the arrangement of the inner retinal layers becomes chaotic[7].

METHODS

Extracted essays were manually searched in online databases, including Scopus, Medline, PubMed, Google Scholar, and Web of Science, to gather sufficient information. These databases also contained all the associated articles, including systemic review articles, narrative review articles, and original articles, up to June 2025.

Online database keywords that we used were: DME, OCT, corticosteroid, DR, retinal vein occlusion, anti-VEGF, proliferative DR, laser photocoagulation, DM, retinal capillary plexus, retina, edema.

To obtain the results of the studies, all the data and articles were organized and analyzed based on their time, subject, and resources.

Inclusion Criteria Studies were considered eligible if they met the following criteria: 1) population: human clinical studies involving adult patients (≥18y) diagnosed with DME, irrespective of disease duration or baseline VA; 2) intervention/assessment: utilization of OCT and/or OCTA for the diagnosis, monitoring, or prediction of treatment response in DME; 3) therapeutic context: assessment of at least one therapeutic modality for DME, including anti-VEGF agents, intravitreal corticosteroid implants, or laser photocoagulation, either as monotherapy or in combination. 4) outcomes: reporting of at least one structural biomarker [*e.g.*, CRT, subretinal fluid (SRF), intraretinal fluid (IRF), hyperreflective foci (HRF), disorganization of the retinal inner layers (DRIL), external limiting membrane (ELM) integrity, ellipsoid zone (EZ) status, FAZ area, vessel density (VD), 300-fovea avascular zone (FD-300)] and/or functional outcome [*e.g.*, best-corrected visual acuity (BCVA), recurrence rate, injection frequency]; 5) study design: randomized controlled trials, prospective or retrospective cohort studies, and case–control studies published in peer-reviewed journals.

Exclusion Criteria Studies were excluded if they met any of the following criteria: 1) population: animal studies, in vitro experiments, or pediatric populations; 2) intervention/assessment: articles not involving OCT or OCTA as part of the diagnostic or evaluative process for DME; 3) study design: case reports, narrative reviews, letters to the editor, conference abstracts without full-text availability, and expert opinions without original data; 4) data reporting: studies lacking quantitative OCT or OCTA parameters or not reporting clinical or functional treatment outcomes; 5) language: articles published in languages other than English.

ANTI-VEGF MONOTHERAPY IN DIABETIC MACULAR EDEMA

Anti-VEGF therapies attack the VEGF and include pegaptanib, bevacizumab, ranibizumab, and fusion proteins in the fight against angiogenesis and neurovascular leakage. These pharmaceuticals are currently thought of as line therapy in DME, and this avoids the systemic toxicities that have been seen in oncologic settings. Treatment is initiated through a continuous regimen using monthly schedules with the

Table 1 Summary of OCT and OCTA biomarkers associated with DME treatment response

Treatment modality	OCT biomarkers	OCTA biomarkers
Anti-VEGF agents (pegaptanib, bevacizumab, ranibizumab, aflibercept, brolucizumab)	CRT reduction Presence/absence of SRF and IRF HRF DRIL ELM and EZ integrity Regional variation in CRT change	FAZ area VD in superficial and deep capillary plexuses FD-300 metric HRF and SRF height reduction
Corticosteroid implants (dexamethasone, fluocinolone acetonide)	CRT and CFT reduction-presence of SRF HRF and DRIL status Restoration of EZ continuity	FAZ area reduction Increased macular perfusion Stable or improved VD
Laser photocoagulation (focal/grid, navigated, subthreshold micropulse)	CRT reduction ONL thickness changes Edema extent mapping for focal laser targeting	FAZ size stability or reduction VD changes post-treatment (notably with subthreshold micropulse laser)

OCT: Optical coherence tomography; OCTA: Optical coherence tomography angiography; DME: Diabetic macular edema; VEGF: Vascular endothelial growth factor; CRT: Central retinal thickness; SRF: Subretinal fluid; IRF: Intraretinal fluid; HRF: Hyperreflective foci; DRIL: Disorganization of retinal inner layers; ELM: External limiting membrane; EZ: Ellipsoid zone; CFT: Central foveal thickness; ONL: Outer nuclear layer; FAZ: Foveal avascular zone; VD: Vessel density.

possibility of a maintenance regimen lasting more than three months in responders. However, changes in anti-VEGF treatment or the addition of steroid therapy can be considered only after the diagnostics of patients, especially with poor response.

In the work of Chronopoulos *et al*[8], the information they had about the action of brolucizumab and its effect on DME and diabetic macular ischemia indicates that it causes a significant improvement in both functional and anatomical aspects of the retinal vascular microstructure. Brolucizumab partially improves macular capillary and perfusion density, as well as the structure of the foveal capillaries. Future research with a large sample size and a one-year follow-up over three years post-analysis will provide more insight into whether the aforementioned effect of brolucizumab on changing macular vascular and perfusion density is definitive or not.

According to their findings, the study by Pastore *et al*[9] suggested that brolucizumab may be an effective treatment option for DME. An assessment of the cyst width-to-height ratio (WHR) at baseline may provide a helpful prognostic benefit in terms of fluid reabsorption: further studies with a longer term should be able to assess the preservation of the effect with an increased time interval after the loading period.

In the study by Magrath *et al*[10], the authors demonstrated superior predictive capability using a deep learning convolutional neural network (CNN) with layer segmentation-based preprocessing for treatment-naive DME response to a single anti-VEGF therapy injection treatment. Combined with clinical evaluations, this prediction can be used in the informed treatment decision-making processes of patients who are expected to have a suboptimal response to anti-VEGF therapy (greater than 30%).

The finding in Kar *et al*[11] study implied that, given features with the most stabilization and discrimination across the multi-institutional/site setting, the radionics model with lesser susceptibility to inter-scanner and inter-site variation could be developed to distinguish between the desirable optimal responders and rebounders of the anti-VEGF treatment in DME. Additionally, the stability of features was found to be linked to geographical and spatial positioning in the eye. The features of retinal tissues were identified as the most stable ones but less discriminatory (Table 1).

OCT Biomarkers for Monitoring Anti-VEGF Response

The two important clinical methods of establishing prescriptions for anti-VEGF medicine are *pro re nata* (PRN) and treat-and-extend (TER). There is regular PRN visitation monthly for a reoccurring macular edema. The frequency, duration, and elimination of over- and under-treatment are tailored to the individual patient in the TER environment[12-21]. Khalil *et al*[22] investigated the effects of TER with Aflibercept on reducing the disease burden in Australian patients with DME and improving functions in 33 patients with DME. Practitioners used OCT scans to determine the timing of the next visit after a patient receives a loading dose of Aflibercept. In cases where no sign of IRF shift greater than 10% was noticed in two follow-ups within the central 6 mm, the follow-up period was extended to 16wk instead of 4wk. When a center of 6 mm exhibited DME, then the interval was reduced by 4wk. Patients made an average of 12.8 visits in three years with an interval of 6.2±2.2wk. There was an improvement in BCVA by 5.8 letters, with a baseline value of 70.4. These findings suggest that the TER plus aflibercept regimen may have the potential to reduce DME and improve functionality. Kulikov *et al*[23] applied OCT, as well as other forms of multimodal imaging, in assessing brolucizumab in DME. The injections for the patients occurred once every six weeks. After

four injections, patients had an overall reduction of 5.7±17.0 μm in CRT and -131.3±91.2 μm and -1.2±0.75 mm³ in CRT and macular volume (MV), respectively. Chatziralli *et al*[24] evaluated the laboratory and imaging biomarkers in patients to assess their effectiveness in predicting response to anti-VEGF medication for DME. This was a one-year follow-up of 36 DME patients who were treated with intravitreal anti-VEGF therapy. All participants underwent baseline testing, including BCVA, FA, OCT, dilated fundoscopy, and color fundus photography (CFP). The central subfield thickness (CST) is indeed a significant predictor of treatment response. The ELM, epiretinal membrane (ERM), and EZ are the best predictors and are excluded from the model. DME patients with a CST of 405 μm or fewer, intact ELM, EZ, and absence of ERM may respond favorably to medication. This is evidence of the potential of OCT imaging to indicate treatment response, which is enhanced by its use. Yamada *et al*[25] evaluated the less responsive OCT 3D map in 46 patients with DME who were initially treated with an anti-VEGF agent. The thickness of the central retina decreased significantly one month after the injection, but the rate of decrease varied across different regions. The thickest area of the retina contracted at a slower rate than the rest after an injection, and the part of the retina remaining edematous had a significantly higher density of microaneurysm than the absorbed area. Certain sectors of DME are poorly responsive to retinal thickness loss following anti-VEGF treatment. This pathophysiology could result from a high-density microaneurysm. The study established that 90% of fluid retention associated with high-density microaneurysm recovered as a result of anti-VEGF injections. These findings suggest that a more individualized and effective process of treating DME could be enhanced by recognizing regional differences in the efficacy of anti-VEGF medications. Kalur *et al*[26] interested in studying how SRF and IRF impact the visual outcomes of patients with clinically treated DME who are treated with anti-VEGF. Total retinal fluid (TRF), SRF, and IRF in OCT images were measured at baseline, month 12, and month 6 using deep-learning artificial intelligence (AI) as at month 3. Linear mixed-effects regression models were used to analyze BCVA predictors. The project is a nonrandomized, retrospective cohort study involving 220 participants and 220 eyes from the Cole Eye Institute at Cleveland Clinic DME. Patients with DME characterized by the greatest volumes of SRF, IRF, and TRF had poorer visual outcomes one-year following anti-VEGF medication. The visual output prediction of AI provids a warm perspective of DME treatment in the future. Mylonas *et al*[27] investigate the role of starting vitreomacular interface conditions on the therapy of DME with three anti-VEGF in DRCR.net Protocol T patients post-hoc. The end and baseline OCT images were analyzed on vitreomacular traction syndrome, partial adhesion, total adhesion, and complete posterior vitreous detachment. This research includes 629 eyes with DME. One year later, total adhesion eyes had increased ETDRS letters of +3.7 relative to posterior vitreous detachment (P<0.001). A year ago, vitreomacular interface status before baseline did not determine CST (P=0.144). The baseline vitreomacular connection state of all treatment groups demonstrated a similar adverse effect in the BCVA improvement. The findings of the study demonstrate that the vitreomacular interface (VMI) and functionality of DME patients are influenced by anti-VEGF therapy. Early vitreomacular adhesion can be helpful with the treatment rather than posterior vitreous detachment. In bovine retinal pigment epithelial (RPE) cells that were tested by Saxena *et al*[28], the cells grow linearly as the production of VEGF deteriorates. The topographic RPE change scores with the topographic evaluation made with spectral-domain OCT were considered afterward in DME after intravitreal treatment of the anti-VEGF factor. This was in a prospective study of a tertiary care center where 44 patients with type 2 diabetes between ages 40 and 65y with DME took the three sequential monthly equivalents of anti-VEGF monomers. The thickness of the average cube and CST of the RPE, spectral-domain OCT, and the changes of the modifications and topography with a 1-empire (retinal pigment epithelium) map were assessed before and after the intervention. A change exceeding two quadrants is Grade 2, two quadrants Grade 1, and no changes Grade 0. After the intervention, Cube's mean thickness went down to 274.1±5.1 μm, and CST was 233.2±7.9 μm, which was lower than the baseline of 354.2±16.0 μm. The scores of a change in RPE were amazing after the intervention. Grade 2 (27 *vs* 2), Grade 1 (17 *vs* 3) and Grade 0 (0 *vs* 39; P<0.001). The treatment with anti-VEGF therapy leads to an improvement in DME RPE alteration scores. Indian Clinical Trial Registry enrolled this study (CTRI/2019/03/018135). You *et al*[29] utilized generative adversarial networks (GAN) to predict the response to anti-VEGF treatment in DME patients based on their baseline OCT images. Retinal specialists were not able to differentiate most of the post-therapeutic OCT images (95/103). The shape of central macular thickness (CMT) between synthetic and natural OCT images stood at 26.74 and 21.28 μm. GAN could assist clinicians in designing effective DME interventions and follow-ups. DME is a vast cause of diabetic loss of vision. The first line of therapy in the treatment of DME entails the use of anti-VEGF therapy based on the fact that VEGF is essential in its growth[29]. The resistance to the anti-VEGF therapy is between 30% and 40% of DME patients. This piece of work contains structural characteristics *via* OCT and cytokines in aqueous humor. There were 28 DME patients whose 40 eyeballs were obtained by the Hangzhou Affiliated Eye

Hospital of Wenzhou Medical University. The anti-VEGF therapy utilized the analysis of the patient's aqueous humor in terms of IL-6, IL-8, IL-10, VEGF, vascular cell adhesion molecule-1 (VCAM)-1, intercellular adhesion molecule-1 (ICAM)-1, transforming growth factor (TGF)-β1, fibroblast growth factor (FGF), and monocyte chemoattractant protein-1 (MCP)-1 levels. OCTs were performed pre and one-month post-anti-VEGF therapy. CMT, MV, choroidal thickness (CT), and HRF were evaluated in the analysis. Each eye was assessed for serous retinal detachment (SRD), CME, and diffuse retinal thickening (DRT). The level of VEGF was significantly increased in DME patients with CME and IL-6, TGF-β1, and MCP-1 in DRT. The thickness and volume of the retina were not related to the aqueous humor cytokines. A thinner CT increases IL-6 (r=0.313) and FGF (r=0.361) in the aqueous humor. The close relations between IL-6, FGF, TGF-β1, triglycerides, and HRF were demonstrated in multivariate linear regression research. In such a way, OCT morphology can suggest treatment of the intraocular inflammatory markers and VEGF levels[29]. Turski *et al*[30] examined changes over a short-term period of a single dose of intravitreal bevacizumab at 4–6wk in DME patients. The retrospective analysis was done on 52 eyes of 46 individuals. The average age of patients was 64.22±8.12y, with 58.7% being male. The average length of DM was 18.47±9.92y. They tried BCVA, CST, and total macular volume (TMV). OCT was able to record positive structural response, and the treatment did not increase VA or mean BCVA. Twenty-two eyes responded; thirty failed to. CST decreased by 10%. Hsieh *et al*[31] compared injectable Iranibizumab and Aflibercept with two-year observations among Taiwanese patients with DME and proliferative diabetic retinopathy (PDR). Spectral-domain (SD)-OCT was used to examine eighty-four eyes and CFP in conjunction with FA. The aflibercept group managed to decrease the number of microaneurysms sooner but did not make variations in log MAR BCVA, CRT decrease, and injection count. Also, the treatment of aflibercept patients used fewer pan-retinal photocoagulation (PRP) and subthreshold micropulse lasers (SMPL). There is a predictor of final VA, starting VA, but these predictors do not include age and starting CRT, with a decrease in 24mo. Alryalat *et al*[32] designed a deep learning model based on the well-known picture segmentation structure, U-Net, to forecast anti-VEGF medication response in DME patients. DME is described as retinal thickness at the center, which is above 320 μm in males and 305 μm in women on OCT. This model comprised the pre-and post-treatment data of 101 patients, including central OCT fovea thickness, number of injections, BCVA of the patient, history of anti-VEGF treatment, phakic status (pseudo-phakic or phakic), glycosylated hemoglobin A1c, and other intraocular diseases. By three months, patients who had a significant decrease in central foveal thickness (CFT) on OCT of more than 25% or 50 microns were ranked as excellent or poor responders to anti-VEGF drugs[33]. They state that the deep learning model was able to predict the response of a patient with 98.9% specifically and 87.9% sensitivity, which was 75% of the classification of patients[34]. Beran *et al*[35] tested ranibizumab in DME. A retrospective study examined 29 eyes of 29 patients with diffuse DME that was nonresponsive to laser therapy. There were 13 women and 16 men patients having an average of 13y of diabetes. Three intravitreal ranibizumab injections of 0.5 mg each were performed after a one-month interval. They reported the BCVA and the CRT of ETRDS optotypes. Prior to treatment, they were assessed at 3, 6, 9, 12, 18, and 24mo. According to the Optical coherence image, ranibizumab reduced CRT and improved BCVA of laser-resistant DME patients. Most considerable improvement is noticed with three Ranibizumab injections and observations. Maggio *et al*[36] followed the OCT outcomes between DME eyes that had been receiving anti-VEGF intravitreal injections over a period. In this study, subfoveal neuroretinal detachment (SND) [presence (SND+) or absence (SND-)] of HRF number [absence/few (HRF-) or moderate/many (HRF+)], CMT, and CRT were compared during DME recurrences at every follow-up. HRF, CMT, CRT, and SND prevalence decreased significantly post-loading. These eyes contained larger SND+ HRF+ than minds that had baseline SND- and HRF-. At baseline, visual or anatomic outcomes were equally not predicted by SND and HRF. However, the worse visual outcome was significantly correlated with high rates of relapsing SND+ and HRF+ during follow-up. DME recurrences always had SND and HRF at baseline level and could, therefore, be sensitive to repeat DME patterns as measures of OCT biomarkers. It has also shown that the recurrence of SND and HRF could further impair visual functioning as compared to the baseline. Borrelli *et al*[37] compare morphology and vision after long-term follow-up of anti-VEGF-treated eyes with DME. The study embraced the follow-up of the patients and the cured DME upon the administration of an anti-VEGF drug over five years. The discomfort of neuroretina or RPE was measured qualitatively during the study visit using structural OCT images. The patients could be classified as poor/intermediate vision (VA less than 20/40) and good vision (VA greater than 20/40) categories during the research visit according to VA, and the poor/intermediate vision patients interrupted ELM and RPE bands more. The thicknesses of the outer retina were affected because of poor/intermediate vision.

OCTA Biomarkers for Monitoring Anti-VEGF Response

Tang *et al*[38] investigated the HRF on OCTA in DME with SRF, the integrity of the photoreceptor, and visual outcomes

following outer retina anti-VEGF treatment. Outer retina HRF, Elm coherency, EZ, and BCVA were attained. The BCVA of DME patients showed significant improvements following the administration of anti-VEGF treatment. However, the BCVA of the SRF patients did not show any significant improvement during the treatment process. Anti-VEGF injection decreased the levels of HRF and SRF height while preserving the integrity of ELM and EZ. EZ and final ELM concerned outer retina HRF. The BCVA of eyes intact ELM and EZ had been better. It was found that Korobelnik *et al*[39] investigated the macular vascular change in aflibercept-treated patients with DME. OCTA looked at such adjustments. They looked at the eyes of 26 patients with DME. On average, each eye received 7.2±2.2 injections. After follow-up, there was a decrease in mean CRT, the volume of the macula, and acuity. In comparison to DME patients, intravitreal injections of aflibercept did not enhance retinal perfusion in DME patients even after 48wk. Hunt *et al*[40] investigated a year of DME with bevacizumab on a fixed regimen. A prospective study was carried out on 27 untreated DME eyes. The images of OCTA were acquired with a scanning area of 6×6 mm^2. DME patients having CMT greater than or equal to 300 μm received nine bevacizumab injections in 12mo. Patients who were used as research subjects experienced a decrease in CMT (401.84±84.54 μm) and an increase in BCVA (65.18±8.21 to 72.63±7.43 letters) after bevacizumab. Recurrent intravitreal injections of bevacizumab caused recovering of the DME. Diabetes-related retinal vascular permeability is improved with anti-VEGF agents. In various research studies, bevacizumab is a human monoclonal antibody against VEGF (anti-VEGF). In DME patients, bevacizumab injections into the eyes enhance eyesight and reduce the centralized thickness of the macula[41]. In the study by Fursova *et al*[42], OCTA was used to assess the effects of aflibercept treatment over 2y in 59 subjects, including 31 participants with DRIL. Two years later, in 11, it involved an increased FAZ and a worse VA. The density of the foveal artery and retinal perfusion augmented on the fifth injective injection and month five. On these measures, the baseline level of DRIL was lower. The indication of circulatory and FAZ was the same in the course of the study. They said that at 03:51 *p.m.*, DRIL could predict the effectiveness of anti-VEGF drugs. Karasu *et al*[43] examined the changes in the vascularity of the eyes with OCTA and continuous wave yellow laser after controlled management of the endpoint damage. In eyeballs, PASCAL yellow lasers were at work. At baseline, 3, and 6mo after treatment, BCVA and OCT/fundus autofluorescence (FAF) imaging were measured. Deep capillary plexus (DCP) FAZ levels were reduced at 6mo compared to baseline. At baseline, foveal superficial capillary plexus (SCP), DCP, and choroidal capillaries VDs changed significantly to the three- and six-month time points. At month 6, the SCP and DCP went down drastically in the superior quadrant. DCP nasal quadrant and choriocapillaris became considerably smaller after walk[6]. The endpoint management (EpM) therapy of non-damaging laser (blending wave yellow laser) alters the SCP, chorio capillary, and DCP to the largest extent, the most normal-DCP-most likely, in the cases of anti-VEGF-resistant DME, in eyes VD is lessened in six months. Evaluate the foveal microcirculation and anti-VEGF treatment that is the cause of DME. This was a retrospective analysis in which DME was identified in 58 eyes of 45 consumers. Treatment comprised a series of 3–5 anti-VEGF injections performed every month. The OCTA evaluated the density of the vessel (%) in FD-300, and FA determined perifoveal leakage (%) in order to obtain microvascular integrity. Of the prognosticating clinical phase, the area under the curve (AUC) for FD-300 was 0.820 and 0.723 for perifoveal leakage. Blood density within 300 μm (BD-300) negative correlation with perifoveal leakage (-0.325, P=0.014). Well-rounded FD-300 and high perifoveal fluorescein leakage implied that the patient had a more serious DME anti-VEGF clinical phase. The tempestuous relation of FD-300 with perifoveal leakage[44]. This study established that continuous intermittent DME lowered the juxta foveal VDs. Chronic macular edema is whitish-gray, Low-FD-300. In this way, additional anti-VEGF injections are required. Superficial vascular plexus/deep vascular plexus (SVP/DVP) is unwanted; FD-300 is an OCTA biomarker, eliminating the error of bias in the division of DME[45]. In a stepwise manner, examine baselines with OCTA. Patients included in DME pre-therapy had poor VA and fixation, resulting in suboptimal OCTA image quality. The macular edema inherent in OCTA can be remitted or reduced in acceptable OCTA images. Second, quantitative analysis should have a superior macular edema remission (or decreased) OCTA image. Third, pre- and post-treatment DME OCTA revealed no changes in FAZ and no changes in macular vascular density[46-48]. They indicate that severe macular edema quantitative analysis is inaccurate. It is possible to diagnose mild macular edema through FAZ vessels. Blood-retinal barriers cause changes in FA. Leaks of fluorescein could upsurge the intravitreal VEGF[48].

OCT and OCTA Biomarkers for Monitoring Anti-VEGF Response Unilateral obstructive retinal arteritis was induced due to several DME intravitreal brolucizumab (IVBr) treatments. After treatment with three sessions of IVBr, a 68-year-old patient treated with DME developed a one-sided retinal artery blockage. The change in IRF improved significantly even though there was no improvement in BCVA following three sessions of IVBr. Unfortunately, intraocular inflammation (IOI) progressed within one month following the 3rd IVBr, with the BCVA improving from 20/32 oculus dexter

(OD) to 20/28 and the CMT in OCT reducing to 368 μm. The betamethasone eye drops reduced the anterior chamber inflammation and IVBr but increased the vascular plexus. Occlusive retinal vasculitis is detected with the help of FA/OCTA. One should monitor for side effects such as increased blood glucose levels. Another possibility was the usage of PRP. Brolucizumab-related IOI and retinal artery occlusive vasculitis in DME patients must been identified quite early. In larger doses, a low-potency anti-VEGF agent called brolucizumab can be used as a treatment for AMD. IVBr increases the risk of IOI compared to other agents. DME is inflammatory; therefore, the IOI should be more frequent than in neovascular age-related macular degeneration (nAMD)[49-57] and OCTA-measured vascular occlusion. Vasculitis requires FA since OCTA is incapable of quantifying the leakage of capillary channels. This advocates for the cautious application of IVBr in DME due to IOI. In mild IOI of nAMD, betamethasone eye drops or sub-tenon triamcinolone acetonide (TA) injection is the treatment option. In AMD-like patients with DME, systemic corticosteroids could curtail disastrous vision deficits due to IOI induced by brolucizumab[55,58-59].

CORTICOSTEROID IMPLANTS IN DIABETIC MACULAR EDEMA

Dexamethasone (DEX) implants are indicated in cases when anti-VEGF drugs cannot be used or fail to provide their effects. Steroid implants should be applied to vasectomized, pseudophakic, and chronic DME patients. The patients are supposed to undergo 3–4 implant procedures each year, lasting approximately four months. Since the rise in intraocular pressure (IOP) in 10% of patients exceeded 25 mm Hg, IOP should be considered during treatment. DEX implants are to be continued in case of a good response, and DME does not take place with a frequency of once every six months. The biomarkers include OCT/OCTA, which can be used to predict the treatment response to DEX implants in DME. Patients with sub-macular, HRF, intra-retinal cysts, and DRIL may be more responsive to treatment. The FAZ and VD can help predict response[59-60](Table 1).

OCT Biomarkers for Corticosteroid Response Prediction

Horozoglu *et al*[61], as one of the most valuable ophthalmology research groups, investing gatebiomarkersmarkers and macular thickness in patients undergoing intravitreal implantation of DEX for DME and retinal vascular occlusions. They studied 89 patients having anti-VEGF-resistant macular edema. OCT biomarkers and CFT had been analyzed before the DEX implant. The CFT was reduced by a large margin after one month of treatment and increased by a significant margin after three months. In HRF and submacular detachment (SMD) there was a large recurrence of macular edema three months later. Scientists found out that DEX implants lowered CFT in the DME and retinal vein occlusion (RVO) victims. HRF and SMD could not predict short-term CFT recurrence, but DEX implant therapy had a positive effect on SMD. İlgüy and Işık[62] used intravitreal DEX (IVD) to be injected in the front of the eye in the treatment of anti-VEGF-resistant DME. The patients had reduced pre-treatment luminal choroidal area (LCA), stromal choroidal area (SCA), and choroidal vascularity index (CVI) than healthy people. IVD implant injection produced a significant decrease in CMT and LCA; however, CVI was not affected. They were also able to demonstrate that CVI can have a negative predictive value for the response to IVD implant. In turn, these results suggest that CVI monitoring may be used to help DME patients estimate their reaction to IVD implantation. Carreira *et al*[63] discussed IOP and OCT investigated parameters of the optic nerve after the staining of DME patients with 4 mg/0.1 mL TA intravitreal injection (IVT). There were two groups. The control group consists of 26 eyeballs, and the group treated with IVT consists of 29. The strengths of the initial IOP and optic nerve measurements were similar to both groups. One month following implantation, there was a further increase in mean IOP in the IVT Group compared to the controls. Ocular hypertension (OHT) was reversed by 17.24% under topical treatment. IVT raises the vertical cup/disc ratio and retinal nerve fiber in the ayer compared to the control. IOP and morphological destruction of the optic nerve were observed in intravitreal TA; OHT, and hypotensives were not used. Huang *et al*[64] investigated the outcomes of IVD implant implantation in the treatment of DME using OCT biomarkers. The combined total of 50 people's DME eyeballs reached[64]. The CRT, SRF, hard exudates, VMI, HRF, EZ disruption (EZD), DRIL, and intraretinal cyst (IRC) were determined prior to and at 3, 6, and 12mo post-treatment. The retinal thickness went up by 100 μm after treatment. There was an enhancement of CRT (>100 μm) in DRIL, SRF, IRC, and EZD, with reductions in EZD. Vision is enhanced as a result of the recovery of EZD and SRF. Therefore, OCT predictors define the success of DEX treatment. The article recommends the use of DEX implants with DME patients having SRF. To assess the predictive role of OCT, Uzel *et al*[65] used the eyes of 34 DEX-implanted patients and studied the 54 eyes after three intravitreal ranibizumab injections. DME therapy should be based on the initial parameters of OCT in the patients. This means that most hyperreflective spots (HRS) and subretinal fluid volume (SRFV) patients have poor prognosis despite early treatment. This paper evidenced that SRF influenced the performance of the anatomical outcomes but not the visual prognosis. It may be caused by the chronicity of SRF and volume imbalance, as large outer nuclear layer (ONL) cysts contribute to the initial damage, affecting both visual and anatomical prognosis.

Previous photocoagulation and ERM did not have any effect on anatomic or visual prognosis. In a prospective, case-control study by Altun and Hacimustafaoglu[66], the transition of subfoveal choroidal thickness (SFCT) in vitrectomized eyes to follow IVD in DME was tested. It consisted of 2 groupings. Group 1 formed DME eyes after diabetic vitrectomy, whereas Group 2 did nothing. Group 1 was administered with one IVD implant. Between groups, there were 96 and 48 eyes. IVD injection resulted in significant improvement of BCVA in Group 1 and OCT-measured layers of the choroid during the first, second, and fourth months. The mean SFCT of DME eyes was thinner and increased in four months. In the study by Cavalleri *et al*[67], OCT was examined with DEX in DME after the change of ranibizumab. Twenty-eight eyes received DEX implants three months following ranibizumab injections. OCT was used to study the inner retinal layers, hyper-reflective patches, EZ, and ELM integrity. The visual outcomes of EZ and ELM interferences were lower but with an elevated DEX VA. This finding confirms those previously reported for EZ and ELM preservation as enhancing visual outcomes after anti-VEGF or DEX drug treatment. In addition, the baseline inner retinal protecting status was connected with significant improvements in vision in cases of DEX treatment. The 12-month follow-up indicated maintenance of eye vision improvement without permanent damage to inner retina layers. Better visual outcome in less than a month of switching to DEX medication was linked to intact EZ, ELM, and reduced HRS. However, eyes involving perturbation of EZ or ELM and with DRIL and greater HRS had significantly greater visual enhancement as high as four months after changing to steroids, and it was found that corticosteroids might have benefit to DME inflammation[67]. Arrigo *et al*[68] analyzed quantitative measures of inflammation, recovery from DME, and the necessity of anti-VEGF intraocular therapy in eyes receiving fluocinolone acetonide (FAc) implants. They recorded CVI and hyporeflective foci (HF) of the choroid with OCT. Fifty eyes treated using FAc implant were assessed in terms of VA and CMT after one year. Its good responders possessed inferior VA, and the CMT was more significant at the baseline but then improved considerably, unlike the poor responders who not only maintained vision but improved their eyesight. Good responders were found with a larger thickness of HF in the choroid with reduced CVI, and poor responders required a greater intake of anti-VEGF. Chorioretinal inflammatory profiles and structural OCT signs of inflammation as objectively measured may indicate that DME eyes can be described as either excellent or poor responder FAc implants. Sacconi *et al*[69] assessed IVD implants in DME patients with and without anti-VEGF contraindications who had severe baseline BCVA. Fourteen consecutive DME patients underwent an interventional, nonrandomized clinical study involving 14 eyes due to a severe baseline BCVA of 0.3 logMAR or worse. Patients were given a sustained-release 700-micron DEX implant at baseline, reassessed after six weeks, and retreated PRN. In DME patients, the intravitreal implant machine presented an opportunity to study the use of DEX in patients with IVD implants who had severe BCVA and contraindications to the use of anti-VEGF therapy, which was administered on PRN basis. Over 12mo, the use of the IVD implants in DME. According to this research, PRN DEX implants with an optional interval of retreatment show a possibility of assisting DME patients with good VA for 12mo. It provided good functional and anatomical outcomes based on small volumes of injection and optimal security. Veritti *et al*[70] also analyzed the immediate influences of DEX implants in DME patients. The 23 study eyes were followed up for up to 90d. This was a study of the rapid macular morphologic and visual functional effects of Ozurdex. Therapy that consists of implantable DEX quickly and progressively lowers the CRT, with half of the maximum decline being detected 72h following therapy. The paper has investigated the qualitative aspects of SD-OCT data (*i.e.*, HRF and external retinal health). They spent much time monitoring them, and during the monitoring that was carried out early in the process, they recorded fewer HRF seven days after the treatment was carried out. The efficacy and tolerability of Ozurdex were demonstrated by the absence of DME relapses and severe adverse events during follow-up. The use of IVD implants in DME patients resulted in a rapid decrease in CRT and improvement in BCVA. Nawar[71] evaluated an altered microneedle by injecting suprachoroidal TA in the field of DME that was resistant. A proposed nonrandomized interventional research consisted of the study of 55 eyes among 39 patients with centrally managed DME who were resistant to anti-VEGF drugs. The patients were SD-OCT. There was a reduction in CMT and an improvement in BCVA after 12mo. One month after injection, IOP increased and was back to baseline in the third. The enhanced morphology and improved functionality of our modified microneedle suprachoroidal TA injection could resist previous anti-VEGF drugs and had no consequences on the eyes or the body.

In the study by Stavrakas *et al*[72], the implantation of IVD may offer functional and anatomical benefits in patients with variable DME who are either untreated or have had prior therapy. Specifically, the CME subtype showed a more positive functional gain, whereas the SRD subtype exhibited a minimal reduction in macular thickness relative to CME and DRT. In patients who had also received treatment, the DEX injection provided outcomes equal to or better than those achieved in patients who had not received treatment. To further establish

our results, additional prospective longitudinal research research research should be conducted to validate the DME subtype as a predictive variable for response to DEX implants in clinical practice.

The study conducted by Oliverio *et al*[73] confirmed the safety and effectiveness of IVD implants in treating patients with DME over a 12-month follow-up period. It has also been confirmed that patients with the presence of DRIL and disturbed EZ have poorer functional reactions to the treatment. Further studies are required, however, to clarify the use of OCT structural biomarkers as indicators of functional responses in DME patients. Additionally, our results underscore the importance of accurately assessing structural biomarkers to inform decisions about the treatment that best suits an individual.

The use of dexamethasone intravitreal implant (DEX-I) in their study by Fasolino *et al*[74] pointed to the drug as effective and safe with persistent diabetic macular edema patients receiving cataract surgeries. The results of our study suggest that cataract surgery yields long-term benefits in terms of functional improvements, regardless of variations in anatomical characteristics. Patients with OCT features suggestive of chronicity and severity (*e.g.*, DRIL, disrupted EZ, and increased CST) at baseline may benefit from the combination of DEX and cataract surgery. The use of OCT biomarkers could provide valuable guidance in the context of treatment responses, underscoring the need for a personalized approach.

OCTA Biomarkers for Corticosteroid Response Prediction

This research was conducted to evaluate post-injection density, thickness, and functionality of the macular vascular in patients treated with an IVD injection to treat DME. The 21 eyes were assessed in terms of OCTA and the structural OCT of the vascular density and thickness of the macula. OCTA was employed in the measurement of capillary network macular vascular density of external networks without fluid to minimize segmentation bias within regions of intra-retinal fluid. Three professionals perceived such sites as dry. Measurements of the visual sensitivity (contrast sensitivity and VA) have been done both before and after the treatment. Intra vitreal implantation with DEX at 30, 60, and 90d led to better retinal perfusion, decreasing the thickness of the macula, and an increase in the VA of the area where the fluid was depleted (P<0.001). Nonetheless, contrast sensitivity has to be enhanced. Cytokines cause the capillary endothelial lesion and microvasculature obstruction, impairing the capillary circulation and ruining ischemia. Thus, due to intraocular DEX implantation, it is possible to regulate leukostasis and stimulate macular perfusion, Particularly in the conditions of anatomical and functional improvement[75]. The study transforms macula blood circulation in patients treated with fluocinolone acetonide intravitreal implant for DME. It will use OCTA in the assessment. It was a retrospective cohort study that involved all adults aged more than 18y with non-proliferative DR and DME at the start of the trial. OCTA of patients was re-examined four months later after the initial measurement. The blood circulation was found to have improved at 24 (40.0%) sites after the therapy. In 14 (23.3%), retinal blood flow was reduced, and in 22 (36.7%), retinal blood circulated as before[76]. The application of primary OCTA illustrations demonstrates that macular ischemia of the eyeballs with DME indicates the success of intravitreal anti-VEGF injections. According to the research, parafoveal and perifoveal macular perfusion is improved after therapy, as indicated by OCTA analysis. Corticosteroids could boost the blood flow to macules by reducing the stagnation of white blood cells. Leukostasis hinders blood flow in the retina and breaks the blood vessels, which accelerates DR. Intravitreal corticosteroids could substantially block the multiplication of leukocytes on the retina. They discovered that fluocinolone acetonide intravitreal implant implants can lessen leukocyte recruitment in the retinal capillaries one year after the therapy. Ceylan *et al*[77] reviewed 34 non-standing DME patients who applied medications with anti-VEGF. The researchers measured FAZ width and VD before and after treatment with an IVD implant. OCTA measurements showed that the superficial plexus FAZ decreased by 1 mm within three months of pre-IVD implant, whereas the deep FAZ decreased by 1 mm within one month. There was no change after three months. The FAZ was significantly decreased, and VD was not reduced in DME patients who cannot be treated with anti-VEGF medicines by using IVD implant dramatically[77].

LASER PHOTOCOAGULATION IN DIABETIC MACULAR EDEMA

The DME treatment guidelines proposed by the European Society of Retina Specialists no longer permit laser photocoagulation. Direct laser photocoagulation on microaneurysms is also a possible alternative treatment of residual focal DME since a large number of the microaneurysms are outside the fovea after anti-VEGF injections. Detection of microaneurysms is carried out with the use of FA pictures, OCT maps, and fundus photos. The newly developed technology of guided laser photocoagulation combines real-time fundus imaging guidance and a tracking laser delivery system to enhance treatment accuracy. Lasers used in traditional therapy can produce night vision, loss of contrast and visual-field sensitivity, abnormal blood vessels in the choroid, and laser scarring. The text by the user is labeled. A newer subthreshold micro-pulse laser (SMPL) causes less damage to retinal tissue than the constant-wavelength lasers. With SMPL, retinal scarring and damage are minimized[75-84](Table 1).

OCT Biomarkers for Laser Treatment Monitoring There is one more step to diagnose and schedule treatment of microaneurysm with laser. The leakage detection of DME and the visualization of DCP using FA are invasive and time-consuming processes[85].

In DME, the comparative study of FA to guided focal laser photocoagulation (FLP) of microaneurysms with en-face-optical OCT was performed by Maltsev *et al*[86]. The study involved 26 eyes with a mean age of 69.5 and the BCVA of 0.52. Both enjoy a similar modification of CRT in one and three months. The en-face OCT group showed a reduction in CRT after three months. This difference could be random since no change in the MV occurred. The BCVA difference between the groups was not significant. In this way, en-face OCT is a non-invasive and valuable tool in FLP planning.

The FLP was used to treat moderate to severe non-proliferative retinopathy with clinically severe retina edema in the ETDRS. Although it is small, it has had a significant influence on the center's vision. When the neuroretina is exposed to laser at 03:51 *p.m.*, laser light might also be absorbed by the neuroretina, although much of the light is absorbed by the retinal pigment epithelium[87-88].

Marques *et al*[89] analyzed the 64 eyes treated with DME (532 nm laser). The research examined the macula structure and function after treatment with FLP. DME remission was carried out with the help of OCT and microperimetry after therapy. Investigation showed the ONL thickness to be reduced by 8 to 3, as well as the sensitivity reducing (-1.0 to -0.4 dB, -2.1% to -0.6%). Laser dot count influenced function and structure. Solutions appeared indefinite as the outcome was not altered by the amount of time taken in the last laser treatment.

In the short-term effects of laser photocoagulation on CT, Adhi *et al*[90] conducted a retrospective SD-OCT study. The FLP was made on 22 eyes with DME, and a high-definition single-line raster was done on 19 naive eyes. SD-OCT scans were made in the patient before and three months after therapy. Lastly, the average CT in the group is the same. The FLP number did not influence the mean CT.

Ikegami *et al*[91] tested retinal sensitivity and morphological changes in DME and microaneurysms patients immediately after photocoagulation of microaneurysms with a 30-ms pulse length. The OCT map characteristics were the CRT, edema-range retinal thickness, and edema-region retinal sensitivity 1 and 3mo following treatment. The study used 17 eyes of 14 individuals. Three months later, the retina thickness improved within the edema range as compared to earlier therapies (P=0.042). Out of 400 sensitive sites, at least 32 were laser-coagulated. One month and three months after treatment, retinal sensitivity changes at these places did not change.

OCTA Biomarkers for Laser Treatment Monitoring A photocoagulation laser is usually used to treat proliferative DR. Such a laser can lead to pre-macular fibrosis, retinal hemorrhage, choroidal neovascularization, and scotoma[92].

Iyer *et al*[93] described the complete PRP in two patients with PDR some years ago and found evidence of laser-induced choroidal neovascularization in the pigmented epithelial layer on the posterior pole using a DLS and SRF present under the pigment epithelial detachment) PED). They recommend swept-source optical coherence tomography angiography (SS)-OCTA versus FA in detecting and following up on patients.

Li *et al*[94] consisted of a comparison of the results of micropulse laser (SML) and conventional laser DME treatment with the help of OCTA pictures after six months. The SML patients healed with no difficulty showed improved BCVA and experienced significantly reduced CMT. OCTA measures of the two groups improved.

SMPL could enhance the macular microvascular network in patients who did not develop maculopathy at an early stage of DME, as well as provide visual and retinal structural benefits, as observed in the Sabal *et al*[95] study. The FAZ size in the SCP was smaller in the SMPL group than in the control group at the 3-month and 3-month follow-up. Enlargement of FAZ is known as the indicator of the development of DME, DR, and macular ischemia. Nevertheless, further comprehensive research, including long-term randomized clinical trials and the use of more advanced imaging methods, is required to elucidate the use of parameters based on OCTA and to provide additional insights into microvasculature alterations in the treatment of mild DME.

Recent studies have examined the connection between nonalcoholic fatty liver disease (NAFLD) and diabetic neuropathy because they have similar metabolic origins. However, recent evidence indicates that the existence of NAFLD does not have much impact when it comes to the prevalence of diabetic neuropathy among individuals with type 2 DM. This serves to emphasize that other playing factors in the pathogenesis of diabetic complications should be taken into consideration and justifies a more selective approach to the assessment and management of microvascular outcomes in diabetes[96].

The study by Noroozi *et al*[97] has shown that elevated visit-to-visit variations in blood pressure, particularly as indicated by standard deviation analysis, increase the risk of DR. This suggests that sustained blood pressure may be crucial in minimizing the likelihood of microvascular complications among diabetic patients. The therapeutic outcomes, recurrence rates, and treatment patterns derived from the included studies are summarized in Table 2, Figure 1.

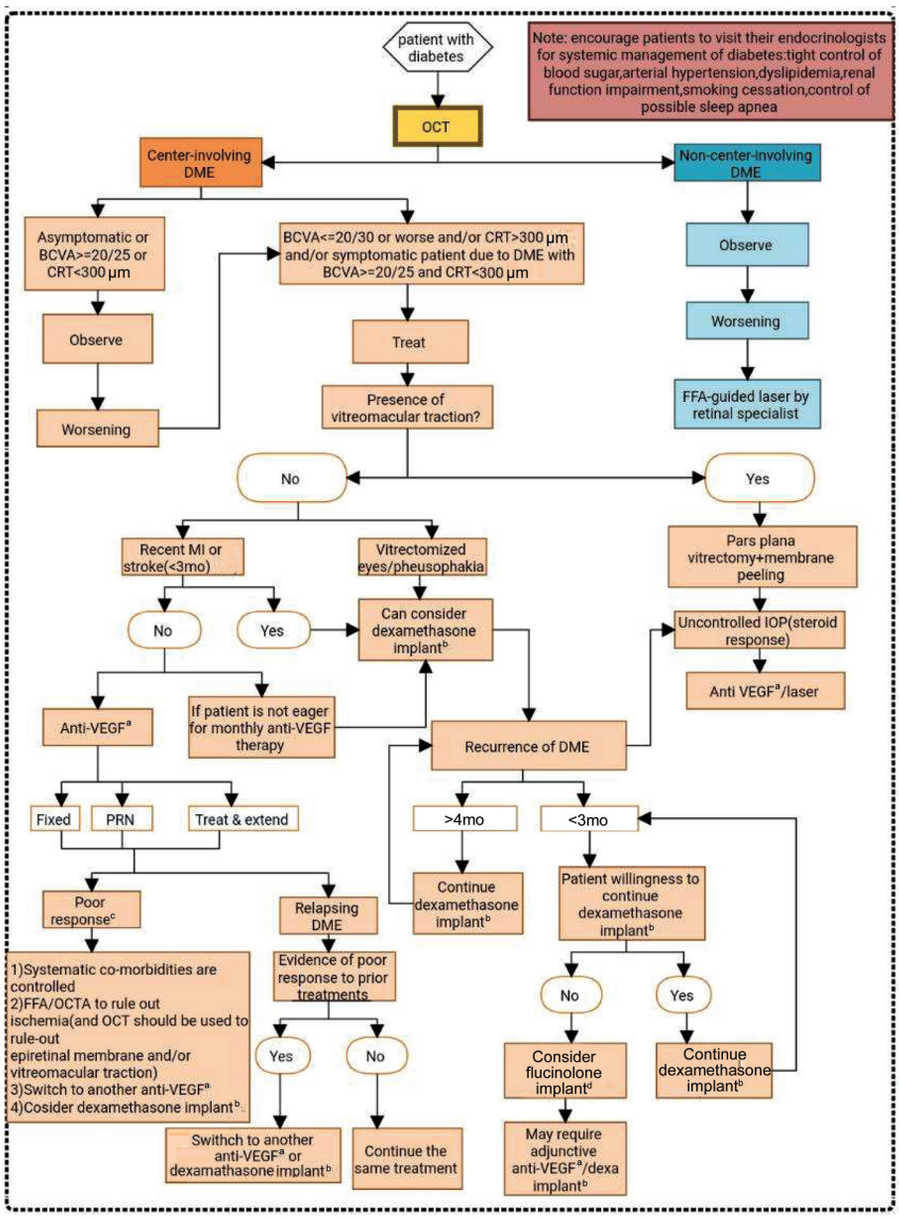

Figure 1 Flowchart for DME management [a]Rule out contraindications for anti-VEGF. [b]Rule out contraindications for dexamethasone implant. [c]Poor response: failure to gain at least 5 letters of vision; failure to reduce CRT by 10%. [d]Rule out contraindications for fluocinolone implant. OCT: Optical coherence tomography; OCTA: Optical coherence tomography angiography; DME: Diabetic macular edema; VEGF: Vascular endothelial growth factor; CRT: Central retinal thickness; BCVA: Best-corrected visual acuity; PRN: *Pro re nata*; MI: Myocardial infarction; FFA: Fundus fluorescein angiography.

Table 2 Therapeutic outcomes and clinical impact of OCT/OCTA-guided DME management

Treatment modality	Visual acuity gains (ETDRS letters)	Recurrence rate	Treatment frequency	Notable findings
Anti-VEGF agents	+5 to +10 letters in responsive eyes	30%–40% non-responders	Monthly or TER regimens	Predictive OCT/OCTA biomarkers enable early identification of suboptimal responders Structural and vascular metrics guide switching/adjunctive therapy
Corticosteroid implants	+5 to +8 letters	Variable (lower in SRF-positive patients)	2–4 implants/year depending on drug and response	Beneficial in pseudophakic or anti-VEGF-resistant eyes OCT predictors (SRF, HRF, DRIL) improve patient selection OCTA confirms improved macular perfusion
Laser photocoagulation	Visual stabilization rather than significant gain	Moderate	1–3 sessions	Best outcomes in focal, non-center-involving DME Subthreshold micropulse laser minimizes retinal damage OCT/OCTA guidance enhances precision

OCT: Optical coherence tomography; OCTA: Optical coherence tomography angiography; ETDRS: Early Treatment Diabetic Retinopathy Study; VEGF: Vascular endothelial growth factor; TER: Treat-and-extend; SRF: Subretinal fluid; IRF: Intraretinal fluid; HRF: Hyperreflective foci; DRIL: Disorganization of retinal inner layers.

CONCLUSION

DME poses one of the greatest threats to sight. However, the introduction of OCT and OCTA has radically altered the approach to treatment. These imaging devices are no longer a type of diagnostic supplement; they become a sort of in-the-moment guide that allows the clinician to individualize treatment to the anatomy and hemodynamics of each eye. OCT provides micrometer-resolution information about the CRT and microstructural biomarkers, including DRIL, HRF, and the condition of the vitreomacular interface. In contrast, OCTA non-invasively maps capillary perfusion and the integrity of the FAZ. Combined, they allow a genuinely precision-medicine strategy, that is, when to initiate, escalate, switch off, or barrage-thread anti-VEGF treatment, steroids, or lasers-not every injection regimen fits all.

Anti-VEGF agents are the mainstay of first-line management, but imaging reveals that up to 40% of eyes will stagnate with monthly dosing. The absence of ELM and the thickness of the central subfield in the baseline OCT criteria, as well as a smaller FD-300 area on OCTA, can be used to predict which patients will obtain solid visual improvements and which ones will require additional measures. Modern subthreshold or image-guided laser and intravitreal corticosteroid implants have experienced a largely unreported resurgence in non-responders, with relief of edema and control of inflammation becoming easily achievable without systemic treatments, provided that determination of candidacy, timing, and monitoring of safety can be accomplished using OCT and OCTA.

The most promising, possibly, of all is data science: already, deep-learning algorithms can predict treatment response based on baseline OCT volumes with astonishing accuracy, and generative models can make predictions of post-injection scans before a single dose of therapy has been administered. The combination of these analytics with precise OCT/OCTA monitoring will effectively reduce unwarranted injections, minimize clinic visits, and, above all, save the vision of hundreds of millions of people with diabetes. The technology is available, and all that is left is the social desire to do something with the images other than marvel over them.

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