ISSN 2706-6819 Vol.8, Issue 2: 1-10, DOI: 10.25236/IJFM.2026.080201

# Research Progress on Individualized Treatment of Diabetic Macular Edema

**Ying He[1,a], Zuhai Zhang[1,b,*], Jingwang Chen[1,c,#]**

*[1]Department of ophthalmology, The First Affiliated Hospital of Yangtze University, Yangtze University, Jingzhou, Hubei, China*
*[a]1720446405@qq.com, [b]zuhai_zhang@outlook.com, [c]chenjingwang@yangtzeu.edu.cn*
**Corresponding author*
*[#]Co-corresponding author*

***Abstract:*** *Diabetic macular edema (DME) is the leading cause of vision impairment in diabetic patients. Although anti-VEGF agents are the first-line treatment, challenges such as drug resistance, frequent injections, and refractory cases persist. This article systematically reviews optimization strategies for DME treatment: regarding first-line anti-VEGF therapy, it discusses drug alternative regimens, precision treatment based on OCT classification, and the application of novel bispecific antibody drugs and sustained-release delivery systems; for refractory DME, it analyzes glucocorticoid alternative therapy, methotrexate application, and surgical interventions such as cystotomy and precise laser photocoagulation; in view of the high incidence of DME after cataract surgery in diabetic populations, it elaborates on perioperative prevention and control strategies from the aspects of systemic metabolic management, OCT and OCTA imaging evaluation, artificial intelligence prediction models, and aqueous humor inflammatory factor monitoring; finally, it prospects future research directions such as nanotechnology, biomarker-targeted therapy, and nutritional metabolic intervention, aiming to provide references for clinical individualized precision treatment.*

***Keywords:*** *Diabetic macular edema; Anti-VEGF therapy; Refractory DME; Cataract surgery; Optical coherence tomography; Artificial intelligence; Inflammatory factors; Precision medicine; Nanotechnology; Biomarkers*

## 1. Introduction

Diabetic macular edema (DME) is the most common cause of vision threat in diabetic patients. According to statistics, approximately 5.47% of the global population suffers from DME [1]. In China, with the increasing prevalence of diabetes year by year, the prevalence rate reached 11.9% by 2019, and with the change of lifestyle, more and more young people are diagnosed with diabetes. These early-onset diabetic patients are more prone to diabetic retinopathy, and DME can occur at various stages of diabetic retinopathy, especially in the proliferative phase, leading to vision decline in patients. The disease burden of DME is becoming increasingly heavy [2-4].

The pathogenesis of DME is complex, including blood-retinal barrier (BRB) destruction, oxidative stress, inflammation, and other factors. The normal function of the retina depends on the "dry" state of its anatomical structure. In DME patients, intra- and extracellular edema occurs, leading to neurotoxicity and subsequent vision damage [1,5,6]. Vascular endothelial growth factor (VEGF) is upregulated in diabetic patients and is one of the key factors currently identified. It is a vascular permeability factor and pro-inflammatory mediator. On the one hand, it not only causes vascular leakage and promotes pathological neovascularization; on the other hand, it can also stimulate the secretion of other cytokines and chemokines, amplifying the inflammatory response in the retina. The inflammatory pathway and vascular endothelial growth factor jointly drive and exacerbate fluid accumulation in the macular area, thereby destroying the "dry" state of the retina and causing retinal structural damage[7].

Anti-VEGF is currently the cornerstone of DME treatment. The advent of intravitreal anti-VEGF agents has created a new paradigm for DME treatment. However, anti-VEGF drugs have certain limitations and still face many challenges in clinical practice: some patients have poor initial response to anti-VEGF drugs or become "resistant" during subsequent treatment; according to traditional protocols, monthly intravitreal injections are required. Although frequent injections can achieve optimal visual gains, they bring heavy economic burden and psychological pressure to patients, reducing treatment compliance [8]; in addition, some patients may progress to refractory DME even after receiving standard treatment.

Compared with non-diabetic patients, the prevalence of cataract in diabetic populations is higher, approximately 2-3 times [9]. Glucose levels in the aqueous humor of diabetic patients are usually high, and the high osmotic pressure caused by high glucose metabolite sorbitol can lead to lens swelling and accelerated progression of lens opacity [10]. Therefore, compared with ordinary patients, diabetic patients have an increased risk of cataract and the disease usually progresses faster. Diabetic patients often require cataract surgery to improve blurred vision symptoms. However, in addition to diabetes itself directly destroying the blood-retinal barrier, the ultrasound energy during surgery and postoperative inflammatory stimulation can also synergistically exacerbate this effect, thereby increasing the risk of DME occurrence and development. Postoperative macular edema is also prone to progress to chronic DME [11-13]. DME is one of the complications after cataract surgery in diabetic populations and is difficult to resolve spontaneously, seriously affecting patients' postoperative vision recovery 14. Therefore, the prevention of postoperative DME has become a clinical focus.

This article aims to summarize the current optimization strategies for anti-VEGF drug therapy in DME and the management approaches for refractory DME. Based on imaging characteristics and molecular mechanisms, it explores the prevention and control of DME following cataract surgery in diabetic populations, and provides a multi-dimensional outlook on potential novel therapeutic modalities for DME.

## 2. First-line Anti-VEGF Therapy

### *2.1 Drug Alternative Strategies*

In diabetic retinopathy, Müller cells, pigment epithelial cells, and pericytes can all secrete vascular endothelial growth factor (VEGF), thereby mediating neovascularization [7]. VEGF plays a significant role in neovascular eye diseases such as diabetic macular edema [15]. Currently, the main anti-VEGF drugs developed in clinical practice include conbercept, aflibercept, ranibizumab, brolucizumab, and bevacizumab [16]. Different anti-VEGF drugs exert their anti-VEGF effects through their respective different structures [17]. Although existing studies have shown that various anti-VEGF drugs have achieved good efficacy in treating diabetic macular edema [18], it cannot be ignored that some patients may develop resistance to a certain drug during treatment or be ineffective from the beginning, thus alternative regimens are often needed in clinical practice to continue treatment to achieve vision improvement [19]. For example, Xing et al. found that for diabetic macular edema patients with poor previous response to intravitreal ranibizumab, switching to conbercept treatment improved vision and reduced central macular thickness (CMT) [20]. A similar prospective trial showed that switching to aflibercept could also achieve good efficacy, and CMT at 3 months after treatment could predict long-term anatomical outcomes—patients with lower macular thickness at 3 months were more likely to maintain good anatomical status after 6 months [21]. Among the comparisons of the above three drugs, a meta-analysis including 8,234 patients showed that although all three drugs could improve patient vision, aflibercept had the best effect and the lowest incidence of ocular adverse events [22]. Other studies have reached different conclusions that ranibizumab has the optimal effect [23]. These controversies may stem from differences in study backgrounds, such as baseline edema severity, follow-up time, and efficacy evaluation indicators of diabetic patients in different trials. In addition, the above studies did not clarify the optimal timing for substitution. A clinical data analysis on switching from bevacizumab to aflibercept showed that patients with thicker CMT at 3 months of bevacizumab treatment may need timely drug replacement [24].

### *2.2 Precision Treatment Based on OCT Classification*

By refining the classification criteria of diabetic macular edema and matching appropriate medication regimens for patients in different situations, better visual prognosis may be brought to patients. A retrospective multicenter study explored the therapeutic effects of anti-VEGF drugs at different stages of diabetic macular edema according to the European Society of Advanced Research in Ophthalmology (ESASO) classification, dividing DME into four stages: early DME (Stage 1), advanced DME (Stage 2), severe DME (Stage 3), and atrophic maculopathy (Stage 4). The results showed that anti-VEGF drugs significantly improved vision in Stages 1 and 2, while vision improvement was poor when the disease progressed to the latter two stages, especially in Stage 4, where anti-VEGF drugs had little effect on

ISSN 2706-6819 Vol.8, Issue 2: 1-10, DOI: 10.25236/IJFM.2026.080201

reducing subretinal thickness in the central retina [25]. Therefore, DME patients should receive anti-VEGF treatment early to obtain better prognosis. This study pointed out that DME staging has better prognostic predictive value than baseline vision and ellipsoid zone/external limiting membrane (EZ/ELM) damage degree [25]. Another retrospective analysis used a different classification, utilizing optical coherence tomography (OCT) to divide patients into three groups: cystoid macular edema (CME) group, serous retinal detachment (SRD) group, and diffuse retinal thickening (DRT) group. The results showed that the SRD group had more severe damage to the external limiting membrane and ellipsoid structure, which was negatively correlated with best corrected visual acuity (BCVA), consistent with the conclusion of the aforementioned study [26]. Previous studies also considered diffuse retinal thickening to be defined as early edema, usually not involving the external limiting membrane and ellipsoid zone; once edema affects these structures, even after treatment and resolution of edema, vision damage is difficult to reverse [27]. However, these studies only emphasized the importance of early intervention. What drugs should be matched for different stages, or whether other treatment methods need to be changed, remains unclear.

### *2.3 Novel Anti-VEGF Drugs and Technologies*

In addition to being related to the staging of macular edema, the therapeutic effect of anti-VEGF drugs is also affected by injection frequency. Thomas et al. treated 40,832, 7,728, and 1,192 DME eyes with anti-VEGF drugs and conducted 1-year, 3-year, and 5-year follow-ups respectively. The results showed that the average vision of all eyes improved, and the more injections, the more obvious the vision improvement: the group receiving ≤9 injections within 5 years improved vision by 1.3 letters, while those receiving ≥38 injections improved by 4.79 letters [28]. However, increased injection frequency increases the economic burden on patients and reduces treatment compliance. Therefore, there is an urgent need to develop more efficient drugs and safe and effective sustained-release strategies. Faricimab is a novel bispecific antibody drug. Angiopoietin-2 (Ang-2), as an inflammatory mediator, can together with VEGF cause vascular leakage and neovascularization. Among many anti-VEGF drugs, faricimab can simultaneously inhibit both factors to treat DME. A randomized controlled study injected faricimab and aflibercept into enrolled subjects respectively and followed up for 100 weeks. The results showed that faricimab could reduce central subfield thickness (CST) faster and more significantly than aflibercept [29]. KSI-301 is a novel anti-VEGF drug under development with good intraocular persistence. Compared with existing anti-VEGF drugs, it has stronger competitive inhibitory effect on VEGF receptors. Preclinical studies (Phase 1a and 1b) of KSI-301 showed that after the first intravitreal injection of KSI-301, 82% of patients in the DME group maintained efficacy for more than 3 months; after the last injection, 72% of patients remained stable for 4 months or more [30]. The Port Delivery System (PDS) is a drug delivery system that can replenish drug implants without removal. This implant is expected to be formally applied to DME treatment. Its convenience can not only ensure the clinical benefits of anti-VEGF but also reduce the burden on patients [31]. A comparative trial compared the efficacy of supplementing or replacing PDS every 24 weeks with intravitreal anti-VEGF injections every 4 weeks. The results showed that the BCVA measured in the two groups at weeks 60 and 64 was comparable [32].

## 3. Salvage Treatment for Refractory DME

Even after receiving standard maximum anti-VEGF treatment, potential untreated low-grade chronic inflammation may still lead to chronic macular edema: conventional treatment is difficult to control, macular structure continues to be damaged, and it develops into refractory macular edema. Refractory DME is usually characterized by CMT persistently greater than 300μm, or CMT reduction less than 10% after receiving 3-6 anti-VEGF treatments. At this time, macular function is difficult to recover, and frequent intravitreal drug injections reduce patient compliance, thus new treatment methods are needed to continue treatment.

### *3.1 Drug Therapy*

A Phase I clinical study explored the effect of anti-VEGF drugs combined with dexamethasone in treating refractory macular edema and conducted follow-up for up to 24 weeks. The results showed that although BCVA did not improve, CMT in all patients was significantly reduced [33]. The lack of BCVA improvement may be due to irreversible damage to photoreceptors caused by long-term macular edema, but anatomical improvement indicates that anti-VEGF drugs successfully prevented further deterioration of visual function. Numerous studies have reported that intravitreal glucocorticoid injection replacing anti-VEGF drugs can also treat refractory macular edema. A 12-month retrospective study showed that

ISSN 2706-6819 Vol.8, Issue 2: 1-10, DOI: 10.25236/IJFM.2026.080201

after switching to glucocorticoid implants for refractory DME that did not respond well to VEGF injections, some patients' vision and CMT improved. Compared with groups that received 1-3 or more than six anti-VEGF treatments, the group that received 4-6 anti-VEGF treatments before switching to steroid therapy had the best effect[34]. In addition, studies have found that intravitreal fluocinolone acetonide sustained-release implants can effectively reduce CMT with efficacy lasting up to 36 months [35]. However, some scholars have pointed out that compared with intravitreal implantation, suprachoroidal implantation can provide patients with better best corrected visual acuity, and because of its delivery characteristics away from the anterior segment, the risks of cataract and glaucoma complications are lower [36]. Other studies have also reported that dexamethasone implants have a positive impact on BCVA [37]. In summary, for diabetic patients who have already received intraocular lens implantation, after excluding diseases such as open-angle glaucoma where steroid treatment is contraindicated, glucocorticoid sustained-release implantation may become the preferred treatment option for chronic macular edema. However, although glucocorticoids can also be used alone to treat DME, monotherapy with glucocorticoids may have a higher risk than monotherapy with anti-VEGF drugs in causing DME patients to progress to proliferative diabetic retinopathy [38]. In addition, methotrexate (MTX) has definite efficacy in the treatment of various eye diseases. When treating DME, it can exert anti-inflammatory effects to improve anatomical structure [39]. A short-term (6-month) study observed that after a single intravitreal injection of methotrexate (MTX), CMT in diabetic macular edema patients was significantly reduced, and no adverse reactions occurred, but the study did not find prognostic vision improvement [40].

### *3.2 Surgical and Laser Treatment*

In addition to drug therapy, some more direct methods are also effective for the resolution of some chronic macular edema. For example, cystotomy. A retrospective study evaluated the long-term efficacy of cystotomy for refractory diabetic macular edema. The results showed that during the 3-year follow-up, patients' average best corrected visual acuity was significantly improved, and average CMT continued to improve [41]. Mizuho et al. conducted a more detailed correlation study, dividing patients into vitrectomy combined with cystectomy group and vitrectomy combined with internal limiting membrane peeling group. Using the "Hokkaido University MF segmentation model," they divided the OCT-measured macula into two regions: inner MF (IMF) within the inner nuclear layer and outer MF (OMF) between the inner nuclear layer and ellipsoid zone. The results showed that vitrectomy combined with cystotomy could more effectively reduce CMT, with significant effects in reducing retinal thickness in the OMF region, and photoreceptor damage in the ellipsoid zone might be smaller, thus bringing better visual prognosis [42]. In addition, the increase in the number of fundus microaneurysms can indirectly reflect the severity of retinopathy. A study used the Navilas® laser system with a pulse time of 30 milliseconds to precisely target microaneurysm locations for photocoagulation closure to reduce vascular leakage. The results showed that this method achieved a closure rate higher than 90% at three months postoperatively, and the rate of CMT decrease was positively correlated with the closure rate [43]. Precise targeted intervention with laser on lesion areas is also particularly suitable for treatment near the foveal center. Tian et al. used a 27+ Flex-Tip laser probe to lift the dilated capillaries at the fovea toward the vitreous cavity and performed local photocoagulation with a curved laser probe from the side, avoiding damage to adjacent tissues and successfully resolving macular edema that was ineffective with anti-VEGF drug treatment [44]. These studies directly eliminate macular edema from the anatomical structure, opening new ideas for the treatment of refractory macular edema.

## 4. Special Population: Prevention and Control of Post-Cataract Surgery DME

### *4.1 Systemic Metabolic Management*

For diabetic patients, controlling blood sugar is the primary key measure to prevent macular edema and obtain good prognostic vision [45]. Existing studies have shown that in the short term, patients with higher glycated hemoglobin (HbA1c) have increased risk of recurrence or progression of macular edema after cataract surgery (risk ratio=1.407, P=0.039) [46], while long-term cumulative high HbA1c exposure increases the risk of DME occurrence more than 20 years after cataract surgery [47].

### *4.2 Application of Imaging and Artificial Intelligence*

Optical coherence tomography (OCT) is a non-invasive "optical microscope" in ophthalmology that

ISSN 2706-6819 Vol.8, Issue 2: 1-10, DOI: 10.25236/IJFM.2026.080201

can detect microscopic structures of the retina invisible to the naked eye. A prospective study used OCT to simultaneously evaluate postoperative CMT and subfoveal choroidal thickness (SFCT) in diabetic and non-diabetic eyes and compared the effects of different surgical methods on CMT and SFCT. The results showed that CMT thickened after cataract surgery in diabetic patients, and even without postoperative retinopathy, SFCT became thinner, suggesting subclinical vascular autoregulatory dysfunction, increased vascular fragility, and reduced perfusion after cataract surgery. In addition, even without postoperative retinopathy, small incision cataract surgery (SICS) was superior to phacoemulsification in terms of postoperative structural stability [48].

Based on OCT's ability to display retinal microstructure, artificial intelligence can be used as an auxiliary means to screen out patients with poor response to anti-VEGF drugs for those already suffering from DME. For example, a generative adversarial network (GAN) composed of a generator (G) and a discriminator (D) can transform non-invasive, ordinary ophthalmic examinations into more advanced and high-resolution images through adversarial learning between G and D, and can predict prognosis. Yang et al. used preoperative images and postoperative OCT contours extracted through LabelMe and OpenCV annotation to train GAN. The results showed that the accuracy of synthetic contours in predicting the degree of DME anti-angiogenic treatment resolution reached 85% [49]. Compared with GAN, Song et al. innovatively established a more reliable model combining grouped convolution, multi-convolution kernels, and spatial pyramid pooling techniques, and fused the model with ResNet50. Test results showed that this model has good performance in accurately predicting the efficacy of anti-VEGF drugs for macular edema [50].

Optical coherence tomography angiography (OCTA), as a technical extension of OCT, can reflect the vascular status of the retina and choroid, and its detection of vascular density changes may predict prognosis. Existing reports show that vascular density of both superficial capillary plexus (SCP) and deep capillary plexus (DCP) increased in diabetic patients after cataract surgery, and the foveal avascular zone (FAZ) area of SCP significantly decreased at 6 months postoperatively. This microvascular change may precede macular structural changes [12,51], thus becoming a potential indicator for monitoring postoperative retinal changes in diabetic patients. Another study pointed out that for patients already suffering from diabetic macular edema, relatively high SCP and DCP vascular density and relatively low foveal avascular zone (FAZ-A) area before anti-VEGF drug injection could predict good postoperative efficacy, and the optimal critical values of these three densities were ≥39.65%, ≥44.05%, and ≤0.3625 mm² respectively [52]. This finding may help clinicians early identify populations insensitive to specific anti-VEGF drugs, thereby adjusting treatment plans in a timely manner.

### *4.3 Aqueous Humor Inflammatory Factors*

Due to hyperglycemia in diabetic patients, advanced glycation end products (AGEs) increase in the body. AGEs binding to various receptors on cell surfaces can enhance oxidative stress and inflammatory responses. AGEs can also induce VEGF gene expression, where inflammatory factors such as TNF-α, IL-1β, and IL-6 and cell adhesion factor expression can cause retinal hypoxia and increased vascular permeability [53]. Compared with observing cytokines reflecting systemic status, assessing substances in aqueous humor may better represent intraocular disease activity and even be used to judge treatment efficacy and assess prognosis. A single prospective study used multiplex microbead immunoassay to measure baseline VEGF, interleukin-6 (IL-6), IL-8, TNF-α, and bFGF levels in aqueous humor, followed by on-demand intravitreal conbercept injection. The results showed that VEGF could independently predict anatomical absolute changes in DME patients and was negatively correlated with BCVA, while elevated IL-6 levels were related to disease severity. The study also observed that patients with higher baseline retinal thickness may require more anti-VEGF drug injections [54]. Another study used laser flare photometry to reflect intraocular inflammation, measuring changes in aqueous flare at preoperative, 28 days postoperative, and 3 months postoperative. The results showed that aqueous flare increased after cataract surgery, especially in patients with increases greater than 100%, where central foveal retinal thickness increased more significantly. Therefore, the authors suggested using a 100% increase in aqueous flare as a critical value to evaluate the therapeutic effects of different medication regimens and consider extending anti-inflammatory treatment based on this [55].

### *4.4 Other Measures*

Non-steroidal anti-inflammatory drugs are commonly used clinically after cataract surgery to resist inflammation and prevent macular edema occurrence. Studies have found that among various NSAIDs, nepafenac can significantly improve prognostic vision, and 0.1% and 0.3% concentrations have

ISSN 2706-6819 Vol.8, Issue 2: 1-10, DOI: 10.25236/IJFM.2026.080201

equivalent efficacy in reducing macular thickness [56,57]. As is well known, cataract surgery itself is also an important factor in increased postoperative macular thickness, even in patients without preoperative complications. Studies have found that intraoperative fluid consumption may increase the probability of macular edema occurrence [58], while a prospective study showed that using cold balanced salt solution perfusion during surgery can reduce postoperative inflammation and have a protective effect on the macula [59]. If macular edema has already occurred, the timing of surgery affects postoperative retinal thickening. Studies have found that compared with intraoperative anti-VEGF treatment, patients who received preoperative anti-VEGF treatment showed no significant change in postoperative CMT, thus suggesting that preoperative anti-VEGF treatment in high-risk populations may play a preventive role in macular edema [60].

## 5. Future Directions

### *5.1 Nanotechnology*

In the future, we hope to apply nanotechnology to the treatment of diabetic macular edema. Nanoparticles have advantages such as small diameter, high biocompatibility, and good stability. While ensuring efficacy durability and safety, nanoparticles can cross the retinal barrier that other drugs may not penetrate, successfully delivering drugs to posterior pole retinal lesion areas to achieve targeted therapeutic effects [61,62]. For example, Bai et al. developed a nanozyme eye drop. Mouse model test results showed that the nanomaterials and liposomes in the eye drops successfully delivered antioxidant enzymes to retinal tissue and effectively cleared reactive oxygen species, thereby reducing pathological neovascularization [63].

### *5.2 Biomarkers and Targeted Therapy*

In recent years, research on DME-related biomarkers has received increasing attention. Biomarkers can reflect current disease status, development trends, and treatment responses, promoting individualized precision treatment. Chan et al. found that different types of miRNA in tears have different relationships with postoperative macular changes [64]. Blood cell-derived inflammatory indicators, such as neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), and systemic immune-inflammation index (SII), the elevation of these biomarkers is expected to be used to predict the risk of increased DME severity and assess treatment response [65]. Due to hypoxia and hyperglycemia in diabetic patients, insulin-like growth factor (IGF-1) and its receptor expression increase. In animal experiments, it was found that IGF-1 can promote VEGF production, angiogenesis, increase vascular permeability, recruit inflammatory cells, and enhance oxidative stress. Any of these mechanisms may affect the occurrence and development of DME. Therefore, targeting upstream or downstream related signaling pathways of IGF-1 may provide new methods for DME treatment [66]. Müller cells in the blood-retinal barrier maintain the stability of BRB structure. Kir2.1 and Kir4.1 channels on their cell membranes maintain ion and water balance inside and outside cells. However, hyperglycemia can cause Müller cells to express substances related to inflammatory response activation or directly express inflammatory factors, thereby participating in DME formation. Therefore, intervening in various pathways in blood-retinal barrier-related cells or performing gene editing on cells is expected to treat or prevent macular edema in diabetic patients [67]. Regarding the non-negligible role of inflammation in the occurrence and development of DME, a mouse experiment found that chemokine ligand 2 (CCL2) can recruit monocyte/macrophage infiltration and induce microglial activation. This study proposed that CCL2 may become a new target for DME treatment [68]. DME-related metabolite research has also created new possibilities for potential new pathogenesis and treatment directions. Wang et al. found that among 190 different metabolites, 5-phospho-β-D-ribosylamine, succinic acid, ascorbyl glucoside, and glutathione disulfide have certain correlations with DME, and their mechanisms are related to elevated uric acid levels and microvascular damage caused by inflammation regulation [69].

### *5.3 Nutritional and Metabolic Intervention*

In addition, we may also explore new ideas for DME treatment from a nutritional perspective. Chen et al. found that after diabetic patients develop retinopathy, antioxidant substances such as vitamin C levels in aqueous humor decrease, and retinal antioxidant capacity decreases accordingly [70]. Through oral intervention of substances related to DME pathogenic pathways. For example, patients receiving anti-VEGF treatment while orally taking antioxidants such as bromelain may stabilize the blood-retinal barrier by intervening in oxidative stress and inflammatory pathways, thereby reducing the risk of DME occurrence[71].

## 6. Summary

Although anti-VEGF is currently the first-line standard therapy for diabetic macular edema, this therapy has potential ocular and systemic side effects, such as endophthalmitis [72]. Therefore, clinicians should carefully evaluate the safety of anti-VEGF application and closely monitor during application. Given the limitations of anti-VEGF and individual differences among patients, we need to formulate more individualized plans for patients, while developing more efficient new drugs, exploring new therapeutic targets and treatment methods [73]. In addition, diabetic patients are more prone to cataract than ordinary populations, and the risk of new-onset DME after cataract surgery increases. Therefore, doing well in perioperative management, predicting and preventing DME occurrence, is crucial for reducing the incidence of postoperative DME complications or preventing existing DME from worsening [74]. In the future, we hope to intervene at any link in the DME mechanism axis to prevent the occurrence and development of DME. However, although various potential treatment methods have been proposed and researched by scholars, large-scale clinical trials are still needed to verify their safety and reliability.

## References

*[1] Zhang, J. et al. Diabetic Macular Edema: Current Understanding, Molecular Mechanisms and Therapeutic Implications. Cells 11 (2022). https://doi.org/10.3390/cells11213362*

*[2] Society, C. D. Guidelines for the Prevention and Treatment of Diabetes in China (2024 Edition) (Excerpt 1). Chinese Journal of Practical Internal Medicine 45, 864-874+892 (2025). https://doi.org/10.3760/cma.j.cn115791-20241203-00705*

*[3] Tsui, C. K. et al. Prevalence, incidence, and risk factors of diabetic retinopathy and macular edema in patients with early and late-onset type 2 diabetes mellitus. J Diabetes Investig 16, 1254-1262 (2025). https://doi.org/10.1111/jdi.70027*

*[4] Fung, T. H., Patel, B., Wilmot, E. G. & Amoaku, W. M. Diabetic retinopathy for the non-ophthalmologist. Clin Med (Lond) 22, 112-116 (2022). https://doi.org/10.7861/clinmed.2021-0792*

*[5] Petkova-Parlapanska, K. et al. Systematic Inflammation and Oxidative Stress Elevation in Diabetic Retinopathy and Diabetic Patients with Macular Edema. Int J Mol Sci 26 (2025). https://doi.org/10.3390/ijms26083810*

*[6] O'Leary, F. & Campbell, M. The blood-retina barrier in health and disease. FEBS J 290, 878-891 (2023). https://doi.org/10.1111/febs.16330*

*[7] Uemura, A. et al. VEGFR1 signaling in retinal angiogenesis and microinflammation. Prog Retin Eye Res 84, 100954 (2021). https://doi.org/10.1016/j.preteyeres.2021.100954*

*[8] Tabano, D. et al. The Economic Burden of Anti-Vascular Endothelial Growth Factor on Patients and Caregivers in the UK, Europe, and North America. Ophthalmol Ther 14, 1869-1892 (2025). https://doi.org/10.1007/s40123-025-01180-5*

*[9] Becker, C. et al. Cataract in patients with diabetes mellitus-incidence rates in the UK and risk factors. Eye (Lond) 32, 1028-1035 (2018). https://doi.org/10.1038/s41433-017-0003-1*

*[10] Albert-Garay, J. S., Icazbalceta de la Pena, J. A., Medina-Arellano, A. E., Gonzalez-Salinas, R. & Ochoa-de la Paz, L. D. Downregulation of TRPV4 and LRRC8A in Crystalline Lenses of Diabetic Patients May Contribute to Cataractogenesis. Clin Ophthalmol 19, 4787-4799 (2025). https://doi.org/10.2147/OPTH.S557358*

*[11] Sukkee, J., Jirarattanasopa, P., Ratanasukon, M., Bhurayanontachai, P. & Dangboon Tsutsumi, W. Association between the progression of diabetic retinopathy and cataract surgery in patients with diabetes: A retrospective study in Thailand. Medicine (Baltimore) 104, e45349 (2025). https://doi.org/10.1097/MD.0000000000045349*

*[12] Yao, H., Yang, Z., Cheng, Y. & Shen, X. Macular changes following cataract surgery in eyes with early diabetic retinopathy: an OCT and OCT angiography study. Front Med (Lausanne) 10, 1290599 (2023). https://doi.org/10.3389/fmed.2023.1290599*

*[13] Fresta, C. G. et al. A New Human Blood-Retinal Barrier Model Based on Endothelial Cells, Pericytes, and Astrocytes. Int J Mol Sci 21 (2020). https://doi.org/10.3390/ijms21051636*

*[14] Zarei-Ghanavati, S., Hadi, Y., Habibi, A., Ashraf Khorasani, M. & Yoo, S. H. Cataract and diabetes: review of the literature. J Cataract Refract Surg 50, 1275-1283 (2024). https://doi.org/10.1097/j.jcrs.0000000000001547*

*[15] Koksaldi, S., Karti, O. & Saatci, A. O. Anti-vascular endothelial growth factor therapies in*

*ophthalmology. Med Hypothesis Discov Innov Ophthalmol 14, 107-135 (2025). https://doi.org/10.51329/mehdiophthal1526*

*[16] Perez-Gutierrez, L. & Ferrara, N. Biology and therapeutic targeting of vascular endothelial growth factor A. Nat Rev Mol Cell Biol 24, 816-834 (2023). https://doi.org/10.1038/s41580-023-00631-w*

*[17] Tatsumi, T. Current Treatments for Diabetic Macular Edema. Int J Mol Sci 24 (2023). https://doi.org/10.3390/ijms24119591*

*[18] Yuen, Y. S. et al. Real-World Evidence in the Management of Diabetic Macular Edema with Intravitreal Anti-VEGFs in Asia: A Systematic Literature Review. Clin Ophthalmol 16, 3503-3526 (2022). https://doi.org/10.2147/OPTH.S378392*

*[19] Hostovsky, A., Moroz, I. & Katz, G. Aflibercept monotherapy or bevacizumab first for diabetic macular edema. Indian J Ophthalmol 72, S260-S264 (2024). https://doi.org/10.4103/IJO.IJO_2107_23*

*[20] Xing, P., Meng, B., Hu, X., Qu, W. & Wang, S. Switching to Conbercept in Diabetic Macular Edema After Unsatisfactory Response to Previous Intravitreal Injection of Ranibizumab. Clin Ophthalmol 17, 3491-3497 (2023). https://doi.org/10.2147/OPTH.S431145*

*[21] Nawar, A. E., Wasfy, T. & Shafik, H. M. Switching to ziv-aflibercept in resistant diabetic macular edema non responsive to ranibizumab injection. BMC Ophthalmol 22, 287 (2022). https://doi.org/10.1186/s12886-022-02503-x*

*[22] Wang, X., He, X., Qi, F., Liu, J. & Wu, J. Different Anti-Vascular Endothelial Growth Factor for Patients With Diabetic Macular Edema: A Network Meta-Analysis. Front Pharmacol 13, 876386 (2022). https://doi.org/10.3389/fphar.2022.876386*

*[23] Zhang, X. et al. Efficacy of Antiangiogenic Drugs in the Treatment of Diabetic Macular Edema: A Bayesian Network Analysis. Front Pharmacol 12, 637667 (2021). https://doi.org/10.3389/fphar.2021.637667*

*[24] Jhaveri, C. D. et al. Risk Factors for Meeting Criteria for Switching from Bevacizumab to Aflibercept When Treating Eyes with Diabetic Macular Edema and Visual Acuity of < 20/40. Ophthalmology 131, 967-974 (2024). https://doi.org/10.1016/j.ophtha.2024.01.037*

*[25] Panozzo, G. et al. Enhancing Diabetic Macular Edema Treatment Outcomes: Exploring the ESASO Classification and Structural OCT Biomarkers. Ophthalmol Ther 13, 1383-1398 (2024). https://doi.org/10.1007/s40123-024-00925-y*

*[26] Zhang, Y. et al. Treatment response to Conbercept of different types of diabetic macular edema classified based on optical coherence tomography. J South Med Univ 41, 1501-1508 (2021). https://doi.org/10.12122/j.issn.1673-4254.2021.10.08*

*[27] Zheng, H., Gong, Y., Cao, X., Li, W., & Zhang, P. Efficacy of conbercept in the treatment of different types of macular edema after cataract surgery in diabetic patients. International Eye Science, 20, 1967-1970 (2020). http: / / ies. ijo. cn*

*[28] Ciulla, T. A., Hussain, R. M., Taraborelli, D., Pollack, J. S. & Williams, D. F. Longer-Term Anti-VEGF Therapy Outcomes in Neovascular Age-Related Macular Degeneration, Diabetic Macular Edema, and Vein Occlusion-Related Macular Edema: Clinical Outcomes in 130 247 Eyes. Ophthalmol Retina 6, 796-806 (2022). https://doi.org/10.1016/j.oret.2022.03.021*

*[29] Lim, J. I. et al. Anatomic Control with Faricimab versus Aflibercept in the YOSEMITE/RHINE Trials in Diabetic Macular Edema. Ophthalmol Retina 9, 655-666 (2025). https://doi.org/10.1016/j.oret.2025.01.017*

*[30] Chandrasekaran, P. R. & Madanagopalan, V. G. KSI-301: antibody biopolymer conjugate in retinal disorders. Ther Adv Ophthalmol 13, 25158414211027708 (2021). https://doi.org/10.1177/25158414211027708*

*[31] Iglicki, M., Gonzalez, D. P., Loewenstein, A. & Zur, D. Next-generation anti-VEGF agents for diabetic macular oedema. Eye (Lond) 36, 273-277 (2022). https://doi.org/10.1038/s41433-021-01722-8*

*[32] Khanani, A. M. et al. Continuous Ranibizumab via Port Delivery System vs Monthly Ranibizumab for Treatment of Diabetic Macular Edema: The Pagoda Randomized Clinical Trial. JAMA Ophthalmol 143, 326-335 (2025). https://doi.org/10.1001/jamaophthalmol.2025.0006*

*[33] Veiga Reis, F. et al. Combined intravitreal dexamethasone and bevacizumab injection for the treatment of persistent diabetic macular edema (DexaBe study): a phase I clinical study. Int J Retina Vitreous 9, 13 (2023). https://doi.org/10.1186/s40942-023-00449-w*

*[34] Raizada, S. et al. Timing of Switching to Steroid Implants in Cases of Recalcitrant Diabetic Macular Edema Not Responding to Anti-vascular Endothelial Growth Factor (VEGF) Therapy: A Real-World Study. Cureus 16, e62385 (2024). https://doi.org/10.7759/cureus.62385*

*[35] Darwisch, W. et al. Real-Life Results after the Administration of a Single 0.19 mg Fluocinolone Acetonide (ILUVIEN(R)) Implant in Patients with Refractory Diabetic Macular Edema. Ophthalmic Res 67, 600-610 (2024). https://doi.org/10.1159/000540459*

*[36] El Rayes, E. N. & Leila, M. Visual function and retinal morphological changes after single*

ISSN 2706-6819 Vol.8, Issue 2: 1-10, DOI: 10.25236/IJFM.2026.080201

*suprachoroidal delivery of fluocinolone acetonide (Iluvien(R)) implant in eyes with chronic diabetic macular edema. Int J Retina Vitreous 9, 20 (2023). https://doi.org/10.1186/s40942-023-00458-9*

*[37] Sadhukhan, K. & Naskar, S. Role of Combined Therapy of Intravitreal Ranibizumab and Dexamethasone in Refractory Diabetic Macular Edema: a Retrospective Study. Maedica (Bucur) 16, 615-619 (2021). https://doi.org/10.26574/maedica.2021.16.4.615*

*[38] Cornish, E. E. et al. Five-year outcomes of eyes initially enrolled in the 2-year BEVORDEX trial of bevacizumab or dexamethasone implants for diabetic macular oedema. Br J Ophthalmol 107, 79-83 (2023). https://doi.org/10.1136/bjophthalmol-2021-319839*

*[39] Abdi, F., Mohammadi, S. S. & Falavarjani, K. G. Intravitreal Methotrexate. J Ophthalmic Vis Res 16, 657-669 (2021). https://doi.org/10.18502/jovr.v16i4.9756*

*[40] Razzaghpour, N., Najafi, A., Sabouri, M. R., Ashoori, N. & Shahraki, K. Intravitreal injection of methotrexate in persistent diabetic macular edema: a 6-month study. Med Hypothesis Discov Innov Ophthalmol 12, 150-156 (2023). https://doi.org/10.51329/mehdiophthal1480*

*[41] Yamada, H. et al. Three-year outcomes of cystotomy and fibrinogen clot removal for diabetic macular edema with subfoveal cystoid macular edema. Sci Rep 15, 16019 (2025). https://doi.org/10.1038/s41598-025-01197-7*

*[42] Mitamura, M. et al. AI-based analysis of surgical outcomes in vitrectomy with and without cystotomy for refractory cystoid diabetic macular edema. Sci Rep 15, 14629 (2025). https://doi.org/10.1038/s41598-025-93847-z*

*[43] Ikegami, Y. et al. Navigated direct photocoagulation with a 30-ms short-pulse laser for treating microaneurysms in diabetic macular edema exhibits a high closure rate. Sci Rep 13, 6092 (2023). https://doi.org/10.1038/s41598-023-33260-6*

*[44] Tanaka, H., Numa, K., Yoshioka, H., Aoki, T. & Sotozono, C. Surgical Management of Foveal Telangiectatic Capillaries in Diabetic Macular Edema. Cureus 17, e91026 (2025). https://doi.org/10.7759/cureus.91026*

*[45] C, R. H., T, S. & N, I. Is glycaemic control essential for cataract surgery among patients with diabetes mellitus? Bioinformation 21, 1011-1015 (2025). https://doi.org/10.6026/973206300211011*

*[46] Kim, M., Park, Y. G. & Park, Y. H. Cataract surgery and the risk of developing recurrence or progression of diabetic macular edema. PLoS One 20, e0328874 (2025). https://doi.org/10.1371/journal.pone.0328874*

*[47] Bek, T., Tilma, K. & la Cour, M. The risk for developing vision-threatening retinopathy after cataract surgery in diabetic patients depends on the postoperative follow-up time. Acta Ophthalmol 100, e719-e725 (2022). https://doi.org/10.1111/aos.14992*

*[48] Choudhary, M., Mohanty, G., Mohanty, S., N, S. & Bhadani, S. Macular and Choroidal Thickness Changes After Cataract Surgery in Diabetic and Non-diabetic Patients: A Prospective Optical Coherence Tomography (OCT) Study. Cureus 17, e95333 (2025). https://doi.org/10.7759/cureus.95333*

*[49] Yang, X. et al. Prediction of OCT contours of short-term response to anti-VEGF treatment for diabetic macular edema using generative adversarial networks. Photodiagnosis Photodyn Ther 52, 104482 (2025). https://doi.org/10.1016/j.pdpdt.2025.104482*

*[50] Song, T. et al. Construction of a predictive model for the efficacy of anti-VEGF therapy in macular edema patients based on OCT imaging: a retrospective study. Front Med (Lausanne) 12, 1505530 (2025). https://doi.org/10.3389/fmed.2025.1505530*

*[51] Kim, J. et al. Alterations in optical coherence tomography angiography parameters after cataract surgery in patients with diabetes. Sci Rep 14, 23814 (2024). https://doi.org/10.1038/s41598-024-73830-w*

*[52] Basiony, A. I., Mohamed Gad Marey, H., Ezzat Abdel Fattah, A. M. & Aly Zaky, M. Predictive value of optical coherence tomography angiography in management of diabetic macular edema. BMC Ophthalmol 24, 429 (2024). https://doi.org/10.1186/s12886-024-03540-4*

*[53] Vujosevic, S. et al. Role of inflammation in diabetic macular edema and neovascular age-related macular degeneration. Surv Ophthalmol 69, 870-881 (2024). https://doi.org/10.1016/j.survophthal.2024.07.006*

*[54] Xie, M. Aqueous-humor biomarkers and real-world efficacy of conbercept for diabetic macular edema: a prospective study in elderly patients. Front Endocrinol (Lausanne) 16, 1632878 (2025). https://doi.org/10.3389/fendo.2025.1632878*

*[55] Aaronson, A. et al. Relationship Between Prolonged Intraocular Inflammation and Macular Edema After Cataract Surgery. Transl Vis Sci Technol 10, 15 (2021). https://doi.org/10.1167/tvst.10.7.15*

*[56] Sultan, M. et al. Efficacy of preoperative 0.1% topical nepafenac in the prevention of cystoid macular edema after cataract surgery in diabetic patients. Pak J Pharm Sci 38, 1321-1327 (2025). https://doi.org/10.36721/PJPS.2025.38.4.REG.13237.1*

*[57] Akbas, Y. B. et al. Comparison of topical nepafenac 0.1% and 0.3% on aqueous flare and macular*

ISSN 2706-6819 Vol.8, Issue 2: 1-10, DOI: 10.25236/IJFM.2026.080201

*thickness in patients with pseudoexfoliation following cataract surgery. Indian J Ophthalmol 73, S424-S427 (2025). https://doi.org/10.4103/IJO.IJO_2916_24*

*[58] Pivic-Kovacevic, I. et al. Effect of Uncomplicated Ultrasound Phacoemulsification Cataract Surgery on Central Macular Thickness Changes in the Early Postoperative Period in Diabetic Patients. Acta Clin Croat 63, 619-625 (2024). https://doi.org/10.20471/acc.2024.63.03-04.21*

*[59] Meduri, A. et al. Role of Cold Balanced Salt Solution (BSS) in the Prophylaxis of Cystoid Macular Edema After Cataract Surgery: A Prospective Randomized Study. Clin Ophthalmol 15, 2519-2526 (2021). https://doi.org/10.2147/OPTH.S304146*

*[60] Guven, Y. Z., Isik, M. U., Ilguy, S. & Yozgat, Z. Phacoemulsification surgery in patients with diabetic macular edema: should intravitreal anti-VEGF therapy be performed before or simultaneously with surgery? Int J Ophthalmol 18, 637-641 (2025). https://doi.org/10.18240/ijo.2025.04.09*

*[61] Liu, Y. & Wu, N. Progress of Nanotechnology in Diabetic Retinopathy Treatment. Int J Nanomedicine 16, 1391-1403 (2021). https://doi.org/10.2147/IJN.S294807*

*[62] Wu, Y. et al. Innovative Nanotechnology in Drug Delivery Systems for Advanced Treatment of Posterior Segment Ocular Diseases. Adv Sci (Weinh) 11, e2403399 (2024). https://doi.org/10.1002/advs.202403399*

*[63] Xue, B. et al. Nanozyme eye drops for retinal barrier penetration and vasculopathy repair. Science advances 11, eadu5571 (2025). https://doi.org/10.1126/sciadv.Adu5571*

*[64] Chan, H. W. et al. A Pilot Study on MicroRNA Profile in Tear Fluid to Predict Response to Anti-VEGF Treatments for Diabetic Macular Edema. J Clin Med 9 (2020). https://doi.org/10.3390/jcm9092920*

*[65] Lin, C., Ye, W., Wu, S. & Huang, Z. Blood Cell-Derived Inflammatory Indices in Diabetic Macular Edema: Clinical Significance and Prognostic Relevance. Biomedicines 13 (2025). https://doi.org/10.3390/biomedicines13122979*

*[66] Malepati, A. & Grant, M. B. The Role and Diagnostic Potential of Insulin-like Growth Factor 1 in Diabetic Retinopathy and Diabetic Macular Edema. Int J Mol Sci 26 (2025). https://doi.org/10.3390/ijms26093961*

*[67] Lai, D., Wu, Y., Shao, C. & Qiu, Q. The Role of Muller Cells in Diabetic Macular Edema. Invest Ophthalmol Vis Sci 64, 8 (2023). https://doi.org/10.1167/iovs.64.10.8*

*[68] Rangasamy, S. et al. Chemokine mediated monocyte trafficking into the retina: role of inflammation in alteration of the blood-retinal barrier in diabetic retinopathy. PLoS One 9, e108508 (2014). https://doi.org/10.1371/journal.pone.0108508*

*[69] Wang, Z. Y. et al. Plasma metabolomic profiling of diabetic macular edema. Sci Rep 15, 10012 (2025). https://doi.org/10.1038/s41598-025-94759-8*

*[70] Chen, Y. N. et al. Analysis of Total Antioxidant Capacity and Ascorbic Acid Levels in the Aqueous Humor of Patients With Diabetic Retinopathy. Transl Vis Sci Technol 14, 31 (2025). https://doi.org/10.1167/tvst.14.8.31*

*[71] Vingolo, E. M. et al. Diabetic Macular Edema in Maintenance Intravitreal Scheduling. Pharmaceutics 17 (2025). https://doi.org/10.3390/pharmaceutics17050605*

*[72] Ferreira, A. M. et al. Intraocular inflammation following intravitreal injections of anti-vascular endothelial growth factor drugs. Graefes Arch Clin Exp Ophthalmol 263, 2885-2892 (2025). https://doi.org/10.1007/s00417-025-06875-w*

*[73] Cheema, A. A. & Cheema, H. R. Diabetic Macular Edema Management: A Review of Anti-Vascular Endothelial Growth Factor (VEGF) Therapies. Cureus 16, e52676 (2024). https://doi.org/10.7759/cureus.52676*

*[74] Chan, L. K. Y., Lin, S. S., Chan, F. & Ng, D. S. Optimizing treatment for diabetic macular edema during cataract surgery. Front Endocrinol (Lausanne) 14, 1106706 (2023). https://doi.org/10.3389/fendo.2023.1106706*