

Chapter

Diabetic Macular Edema

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Abstract

Diabetic macular edema (DME) is defined as the buildup of fluid within the retina in the extracellular space, specifically at the level of the macula in the inner nuclear, outer plexiform, Henle's fiber layer, and subretinal space. Diabetes mellitus is one of the leading causes of visual impairment in industrialized countries and DME is the main reason for vision drop in diabetic patients. Several diagnostic methods are available for the characterization and staging of diabetic retinopathy (DR) and DME; the principal one for DME is optical coherence tomography (OCT), a quick and non-invasive technique that helps in decision-making for therapeutic choices based on biomarkers. Various classifications have been suggested over the years to aid in treatment management for DME. Current therapeutic options include laser photocoagulation, anti-VEGF (vascular endothelial growth factor) intravitreal injections or corticosteroids, and surgery. Recently, a surgical approach has been proposed with pars plana vitrectomy (PPV) in case vitreomacular traction is present together with DME. Refractory DME is a challenging scenario, and it may be managed by switching to a different class of intravitreal medications or with surgical intervention or micropulse laser. Future perspectives include artificial intelligence algorithms based on OCT and OCT-angiography images which may improve diagnosis and treatment of DME with better preservation of visual acuity in diabetic patients.

Keywords: macular edema, optical coherence tomography (OCT), fluorescein angiography, anti-VEGF, corticosteroids, laser photocoagulation, biomarkers, vitreoretinal surgery, artificial intelligence

1. Introduction

Diabetes mellitus (DM) is not just a health problem, but a global pandemic, with alarming projections indicating an increase in the number of people affected in the coming years. It is estimated that by 2040, the number of people affected by diabetes will soar to 642 million, an increase of 62% over 2015 [1]. This escalation is mainly attributed to the parallel rise in obesity rates and the lengthening life expectancy of the world's population, underscoring the urgency of addressing this burgeoning health crisis.

Within the broad spectrum of complications arising from this disease, diabetic retinopathy (DR) emerges as one of the leading causes of vision loss in individuals

affected by this disease. Specifically, within the DR landscape, diabetic macular edema (DME) emerges as the main culprit responsible for the decrease in visual acuity (VA) in patients suffering from this complication.

The severity of DR, including proliferative DR (PDR), affects vision and is a critical prognostic indicator for overall life expectancy. It underscores the urgency of effective therapeutic interventions to prevent visual impairment and blindness [2].

Given the serious implications of DR and DME for both individual well-being and public health, it is imperative to explore and develop effective therapeutic strategies to mitigate its impact. This chapter aims to delve into the current landscape of therapeutic interventions for DR and DME, highlighting advances, challenges, and future directions in the field.

1.1 Materials and methods

All images used in this chapter belong to patients followed up in our retinal outpatient clinic at ASST Santi Paolo e Carlo Hospital in Milan, Italy, where the privacy and confidentiality of patients' identities are guaranteed.

Optical coherence tomography (OCT), infrared (IR), autofluorescence, and fluorescein angiography (FA) pictures were taken with Spectralis spectral-domain optical coherence tomography (SD-OCT) (Heidelberg Engineering, Heidelberg, Germany).

2. Pathophysiology

The gold standard for preventing DR and DME is good glycemic control, along with control of other DM parameters such as arterial tension and lipids. The most important factor in the pathogenesis of DR is hyperglycemia, which acts on different molecular pathways and damages the blood-retinal barrier (BRB). The pathological process leading to DME is highly complex, including a sequence of events such as angiogenesis, inflammation, and an overexpression of vascular endothelial growth factor (VEGF). It remains unclear whether angiogenesis following VEGF overexpression is a cause or a consequence of inflammation [3].

Diabetic retinopathy (DR) stems from three main factors: vascular wall lesions, alterations in blood flow, and platelet dysfunction. These factors, along with others, combine to form the underlying lesions of DR: exudation and ischemia.

Exudation and the resulting macular edema appear as a consequence of an imbalance between the liquid passing from retinal vessels to the extracellular space and the reabsorption of the liquid from the extracellular space into the vessels.

There are two types of macular edema: cytotoxic edema, where the liquid is intracellular, and vasogenic edema, where the liquid is extracellular. In DME, we have both forms of edema: cytotoxic edema at the earlier stages and vasogenic edema at the later stages [3].

Ischemia is induced by platelet dysfunction and arteriolar changes leading to vascular occlusion and diminished perfusion. Changes in blood flow, such as erythrocyte hyperaggregability, also contribute to this ischemic state. The obstruction and loss of retinal capillaries eventually lead to retinal hypoxia and ischemia. In an attempt to revascularize the ischemic areas, the retina produces VEGF.

Vascular endothelial growth factor, which is higher in the vitreous of DR patients, is involved in the genesis of PDR and DME by inducing changes in the vascular bed, the rupturing of the blood-retinal barrier, and the induction of angiogenesis [4].

3. Diagnostic methods in DME

Timely diagnosis of DME is crucial for the prevention of irreversible complications in individuals with diabetes. Tools such as OCT and fluorescein angiography (FA) help us to perform thorough assessments and targeted management strategies that aid in preserving visual health.

3.1 Fluorescein angiography

Fluorescein angiography (FA) allows the visualization of leakage from microaneurysms or capillaries and areas of retinal ischemia. Focal leakage from microaneurysms leads to focal DME, in contrast with diffuse DME when scarcely demarcated areas of capillary leakage are present. FA is a more invasive and time-consuming procedure than OCT, yet it is still the only imaging technique to detect vascular leakage (**Figures 1 and 2**). Moreover, it is crucial when planning a retinal laser treatment

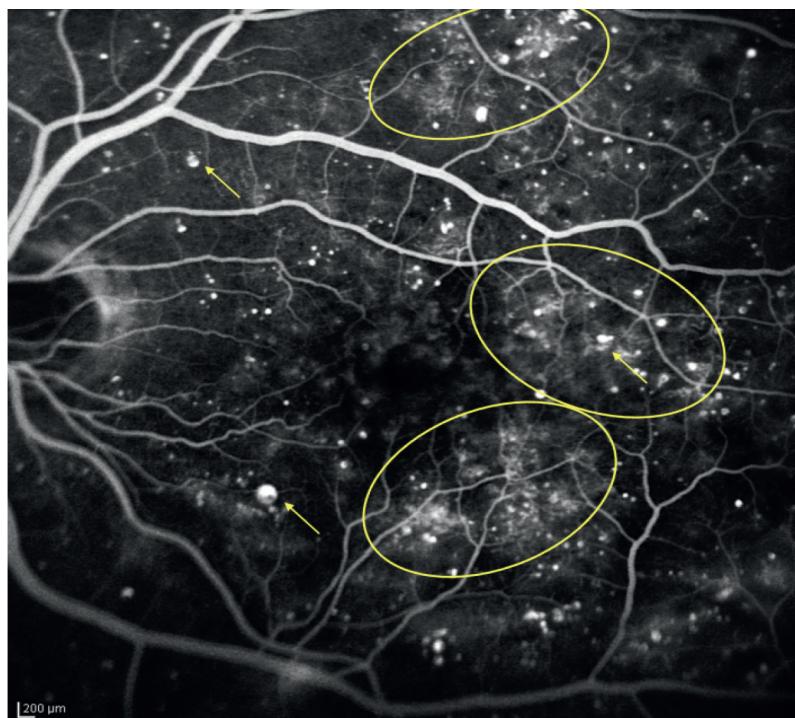


Figure 1.

Fluorescein angiography, SPECTRALIS® scanning laser angiography, intermediate phase, showing multiple microaneurysms in the context of diabetic retinopathy (arrows indicate some of the dozens of microaneurysms). Microaneurysms are visible as variably sized hyperfluorescent dots. Areas of multifocal leakage are visible as poorly demarcated hyperfluorescence (as seen in the circles) from incompetent retinal capillaries, microaneurysms, and microvascular abnormalities.

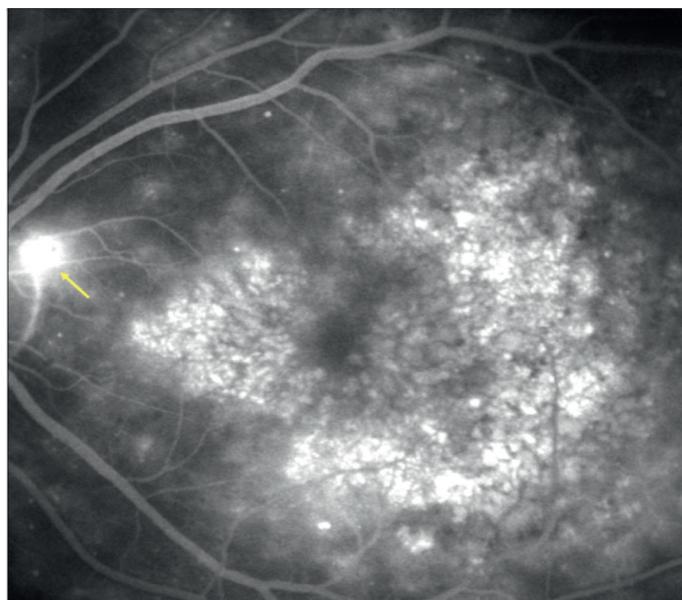


Figure 2.

Fluorescein angiography, SPECTRALIS® scanning laser angiography, late phase. Perifoveal cystoid macular edema is visible as areas of late pooling of the dye, and peripapillary neovessels are seen as bright spots of enhanced leakage (arrow).

since only FA enables the detection of peripheral ischemic areas. It is contraindicated during pregnancy and in case of allergy to fluorescein dye [5].

3.2 Fundus autofluorescence

Fundus autofluorescence (FAF) not only allows anatomical evaluation of the retina but also provides functional information concerning the metabolic activity of the retinal pigment epithelium (RPE). Therefore, it may be useful in assessing the visual potential of patients with long-standing DME. Abnormalities on FAF in patients with center-involving DME may display two different patterns: a “mosaic” pattern with alternating patchy hyper- and hypo-autofluorescence spots at the fovea and a “cystoid” pattern where the cystoid spaces are defined [5].

3.3 Optical coherence tomography (OCT)

Outdated time-domain OCT (TD-OCT) has been replaced by the faster and more detailed spectral-domain (SD-OCT) and swept-source (SS-OCT) machines.

The primary morphological changes of DME can be visualized with OCT (**Figure 3**), namely subretinal fluid (between RPE and neurosensory retina) and cystoid macular edema (within the neurosensory retina). Additional features include disorganization of inner retinal layers (DRIL), alterations of the external limiting membrane, exudates and hyperreflective foci, changes in choroidal thickness, and vitreomacular interface abnormalities (VMIA) including vitreomacular adhesion, vitreomacular traction, and epiretinal membrane (ERM). Identifying VMIA is essential for differentiating between primary DME and secondary causes

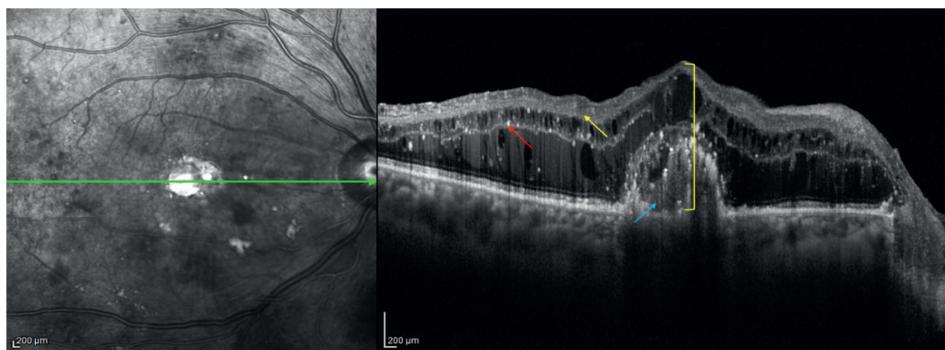


Figure 3.

Spectral-domain optical coherence tomography SD-OCT image (Spectralis, Heidelberg) of diabetic macular edema showing retinal thickening (yellow bracket), intraretinal cysts, disorganization of inner retinal layers (DRIL) (yellow arrow), hyperreflective foci (red arrow), and subfoveal exudates (blue arrow) with disruption of the external retinal layers.

of VMIA, or a combined mechanism. Moreover, OCT is the most useful imaging technique in clinical practice for monitoring intravitreal treatment response in patients. In particular, intraretinal cysts located in the inner nuclear layer tend to be more responsive to either anti-VEGF or corticosteroids than fluid accumulation in the outer nuclear layer [6].

The International Council of Ophthalmology (ICO) guidelines for diabetic eye care have considered center-involved DME versus non-center-involved DME in 2018, depending on retinal thickness involvement or not of the central subfield zone (1 mm in diameter) [7].

In addition to the location of the edema, the Diabetic Retinopathy Clinical Research Network (DCRNet) has given recommendations on central subfield treatment thresholds based on sex-matched standards. These thresholds are different for each OCT device, considering that thickness measurements cannot be compared between different machines, thus each device must have its own normative database and algorithms [8].

Regarding SD-OCT Staging of diabetic maculopathy, four different stages of the disease may be identified based on foveal thickness, intraretinal cysts' size, ellipsoid zone (EZ) and/or external limiting membrane (ELM) status, and DRIL. Namely, early DM, advanced DM, severe DM, and atrophic maculopathy.

The characteristics of intraretinal cysts may also give hints on DME severity, based on the size of cystoid spaces, up to retinal cystoid degeneration where large coalescent macrocysts characterize severe, long-standing disease with Müller cell dysfunction [9].

3.4 Biomarkers of diabetic macular edema

3.4.1 OCT

Optical coherence tomography is a non-invasive and fast tool that provides *in vivo* retinal images. OCT technology is the most used modality for the screening, classification, monitoring, and treatment assessment of DME in our modern day. The management and treatment of DME is based on the evaluation of various biomarkers (Figures 4–6).

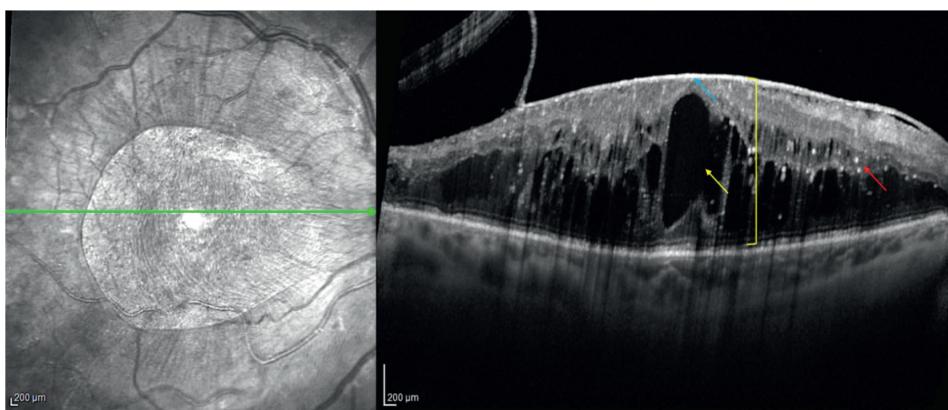


Figure 4.

Spectral-domain optical coherence tomography (SD-OCT) image (Spectralis, Heidelberg) showing diffuse retinal thickening (yellow bracket), macular edema with an elevated foveal contour, and significant intraretinal cystic spaces (yellow arrow), a dense epiretinal membrane overlying the macular surface (blue arrow), hyperreflective foci (red arrow), disorganization of the inner retinal layers and the external limiting membrane and photoreceptor layers.

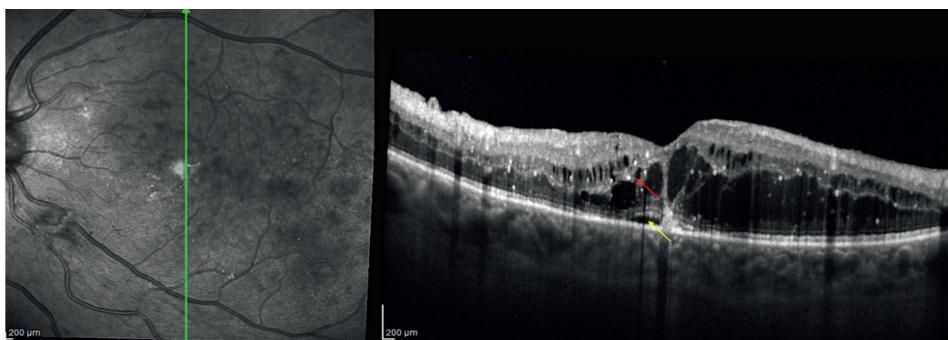


Figure 5.

Spectral-domain optical coherence tomography (SD-OCT) image (Spectralis, Heidelberg) showing intraretinal fluid with a small neuroretinal detachment (yellow arrow), hyperreflective foci (red arrow), large cystic spaces, and exudates.

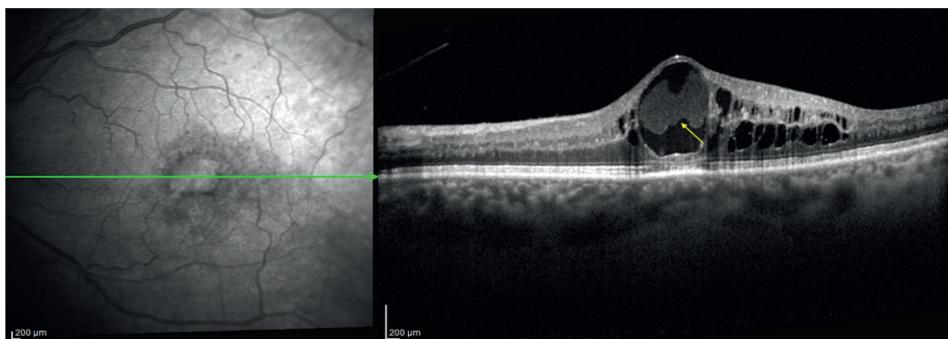


Figure 6.

Spectral-domain optical coherence tomography (SD-OCT) image (Spectralis, Heidelberg) at the fovea showing cystic macular edema, foveal macrocyst with mixed internal reflectivity (yellow arrow).

Biomarkers of DME on OCT include

- intraretinal fluid (IRF) [10]
- disorganization of inner retinal layers (DRIL) [7]
- subretinal fluid (SRF) [10]
- alterations in the inner and outer photoreceptor layers [11]
- alterations in the external limiting membrane (ELM)
- hyperreflective foci
- changes in choroidal thickness

Optical coherence tomography also provides a quantitative measure, the central retinal thickness (CRT), which may be due to diffuse retinal thickening and/or SRF and IRF. The evaluation of CRT and its variation between follow-ups is commonly used in clinical practice to obtain an overview of the DME status. However, it is not enough to determine the decision of treating or retreating a patient with DME.

The SAVE protocol classifies DME based on SRF, the area of the affected retina by IRC, and vitreoretinal interface abnormalities [12]. It uses both OCT and FA to better understand the source of leakage and the prognosis of visual outcomes with different therapeutic approaches [6, 12].

The optimal recommendation is to monitor disease activity every month with OCT, even if no treatment is needed or intended to identify morphological changes as early as possible [13].

3.4.1.1 Angio OCT

Optical coherence tomography angiography (OCT-A) is a non-invasive technology that provides retinal and choroidal microvasculature assessment using motion contrast imaging [14].

While conventional FA permits us to visualize the superficial plexus, OCT-A identifies vascular changes in the deep retinal plexi caused by various retinal diseases, including diabetic retinopathy [15–17]. OCT-A does not require the use of fluorescein, which eliminates fluorescein leakage and allows for better visualization of capillaries (**Figure 7**).

Several studies have shown that OCT-A is less effective at detecting microaneurysms compared to FA. This might be due to the relatively low blood flow in capillaries, which renders the detection of blood flow using motion contrast imaging more challenging [5].

Despite these findings, OCT-A has the advantage of localizing these lesions in their exact intraretinal location [18].

Other DR clinical findings, such as arteriolar wall staining, neovascularization, and intraretinal microvascular abnormalities (IRMA), have different appearances on OCT angiography and fluorescein angiography. On OCT-A, wall staining and arteriolar narrowing are seen as intense attenuation of microcirculation caliber. IRMA are seen as dilated terminal vessels surrounded by capillary loss [15].

Retinal neovessels are detected by observing the flow signal above the internal limiting membrane.

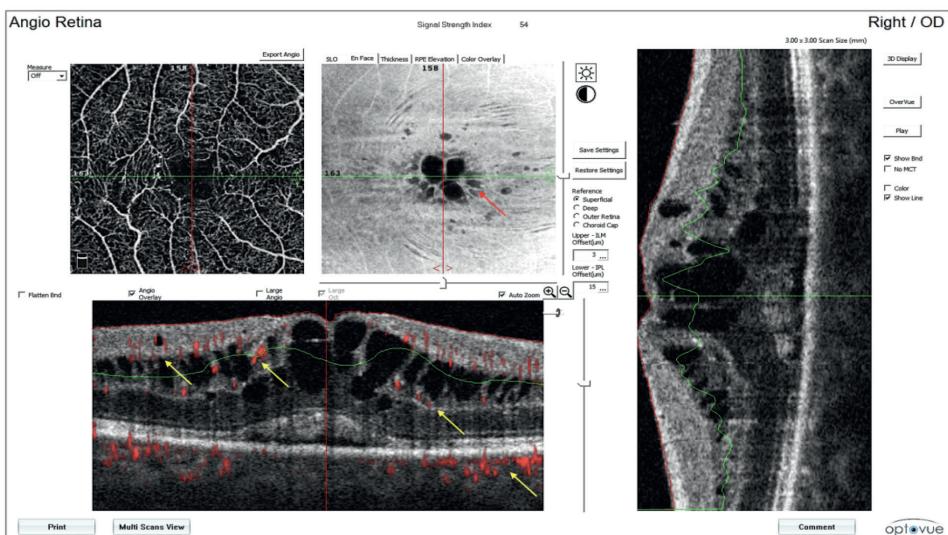


Figure 7.

Optical coherence tomography (OCT) angiography illustrating intraretinal cysts (red arrow) in DME and blood flow (yellow arrows) in the retina and choroid in the macular region that corresponds to 3–3 mm en face flow images from RTVue-100 Optovue OCT.

Hyperfluorescent lesions on fluorescein angiography that appeared indistinguishable from a microaneurysm (MA) were identified as near vision (NV) using OCT-A. This might explain why some patients with vitreous hemorrhage do not have definitive signs of NV on FA [15].

4. DME classification

The Early Treatment Diabetic Retinopathy Study Research Group (ETDRS) defined clinically significant diabetic macular edema (CSDME) as any one of the following:

- retinal edema located at or within 500 µm of the center of the macula
- hard exudates at or within 500 µm of the center associated with thickening of the adjacent retina
- a zone of thickening larger than one disk area located within 1 disk diameter of the center of the macula

The Diabetic Macular Edema Diseases Severity Scales (DMDSS) defined:

- Edema *absent* as any of the following:
 - Retinal thickness apparently regular to the posterior pole
 - Absence of hard exudates to the back pole
- Edema *present* as any of the following:

- Retinal areas with an apparent increase in the thickness to the back pole
- Presence of hard exudates to the back pole
- **Edema Mild**
 - Increase of the retinal thickness or hard exudates not involving the macula
- **Edema Moderate**
 - Increase of the retinal thickness or hard exudates next to the macula
- **Edema Severe**
 - Increase of the retinal thickness or hard exudates involving the macula

Various attempts have been made to classify DME based on its location (center-and non-center-involved), extent (focal and diffuse), and nature (vasogenic and non-vasogenic). Nevertheless, a classification involving all these features obtained with SD-OCT is still missing [2, 19–21].

Optical coherence tomography has also been shown to be effective for both the qualitative and quantitative description of DME. The widely accepted classification is proposed by Kim et al.

They described and classified five patterns of DME according to OCT [22]:

- Diffuse retinal Thickening (DRT)
- Cystoid macular edema (CME) (**Figure 8**)
- Serous retinal detachment (SRD) without Posterior hyaloid traction (PHT) (**Figure 9**)
- PHT without Traction retinal detachment (TRD) (**Figures 10 and 11**)
- PHT with TRD (**Figure 12**)

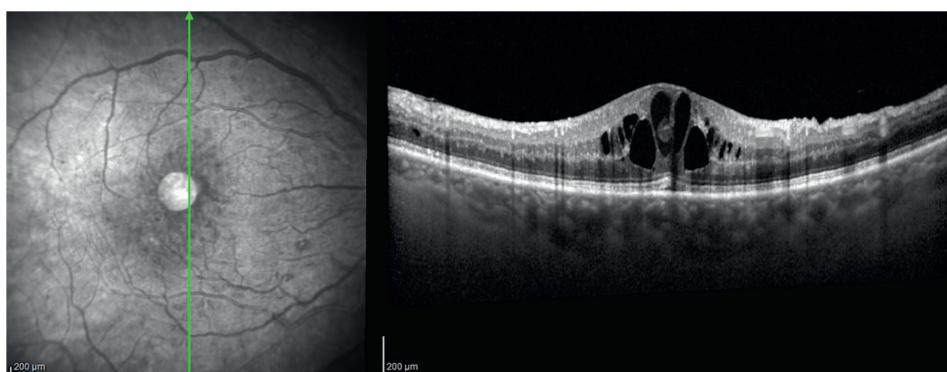


Figure 8.

Spectral-domain optical coherence tomography (OCT-SD) image (Spectralis, Heidelberg) shows irregularities in the outer retinal layers due to cystoid macular edema with intraretinal cysts disrupting the retinal layers.

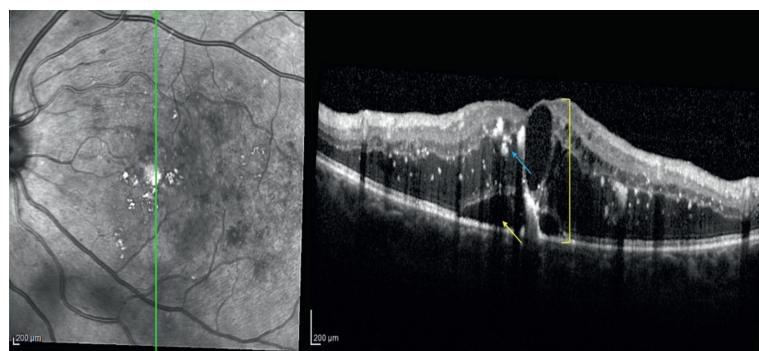


Figure 9.

Spectral-domain optical coherence tomography (OCT-SD) image (Spectralis, Heidelberg) shows serous retinal detachment (SRD) (yellow arrow) without Posterior hyaloid traction (PHT), diffuse retinal thickening (yellow bracket), and dense foveal exudates (blue arrow).

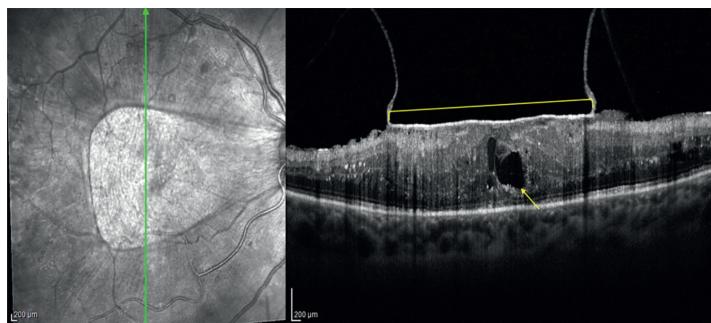


Figure 10.

Spectral-domain optical coherence tomography (OCT-SD) image (Spectralis, Heidelberg) shows Posterior hyaloid traction (bracket) without Traction retinal detachment, intraretinal cysts (arrow), and disturbance of the normal organization of retinal layers.

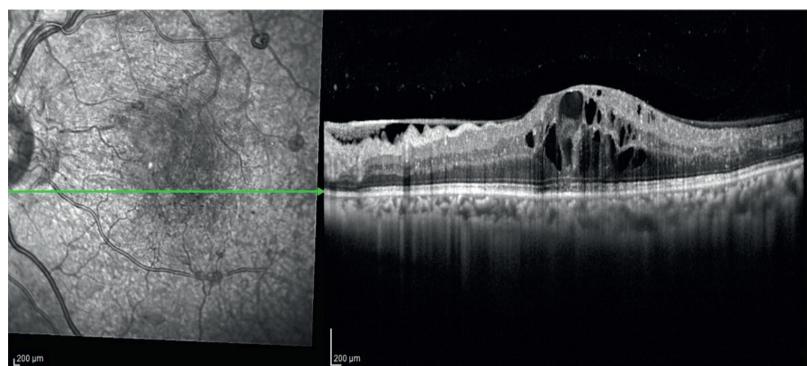


Figure 11.

Posterior hyaloid traction without Traction retinal detachment. Conservation of the outer layers is evident, along with the presence of cystoid macular edema and traction of the posterior hyaloid (Spectralis, Heidelberg).

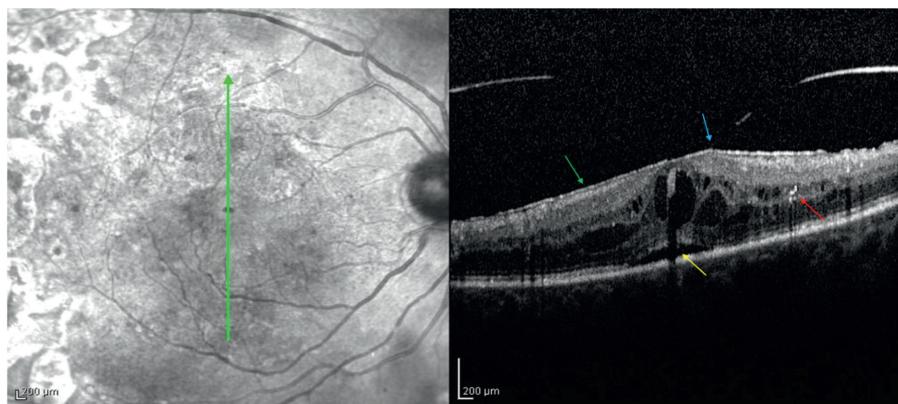


Figure 12.

Posterior hyaloid traction with Traction retinal detachment. A small retinal detachment can be observed with overlying intraretinal fluid (yellow arrow), hyperreflective foci and exudates (red arrow), epiretinal membrane (green arrow), and traction of the hyaloid (blue arrow) (Spectralis, Heidelberg).

5. Therapeutic options

Tighter control of systemic factors, such as hypertension, hyperglycemia, and hyperlipidemia, is generally beneficial in reducing retinopathy in patients with both type 1 and type 2 diabetes mellitus [23].

5.1 Laser photocoagulation

Laser photocoagulation has been a cornerstone in the management of diabetic macular edema. It reduces edema and prevents further vision loss by destroying the ischemic retina to increase oxygen perfusion to the viable retina and reduce the release of cytokines, angiogenic factors, and VEGF [24].

Subtypes of laser photocoagulation include Focal/grid, which is used for well-defined areas of edema, and Panretinal, which is more extensive. The type of approach used depends on the type of macular edema.

Despite its importance in the treatment of DME, laser photocoagulation has limited use in the case of macular DME due to the expansion of retinal atrophy over time and the consequent risk of vision loss from central scars.

Focal laser energy should be applied to leaking MA in combination with grid laser treatment of areas of diffuse macular leakage and non-perfusion in thickened retinas. Complications associated with laser treatment include color vision, night vision, and contrast sensitivity impairment, along with enlargement of laser scars, secondary choroidal neovascularization, subretinal fibrosis, and visual-field sensitivity deterioration. Vision loss, along with other listed complications, has led to the investigation of pharmacological therapies for DME. The two main categories are anti-VEGF agents and corticosteroids.

The ETDRS demonstrated that patients with clinically significant macular edema who were treated with focal photocoagulation experienced a 50% decrease in the risk of moderate visual loss compared to the control group [25]. However, only 3% experienced an improvement in visual acuity of 3 or more lines.

The DRCR.net Protocol I evaluated the role of prompt or deferred laser treatment in addition to ranibizumab therapy in improving best corrected visual acuity (BCVA)

after five years of treatment. This study showed that the number of patients achieving a > 15-letter BCVA gain was higher in patients with deferred laser therapy.

In the presence of DME and high-risk non-PDR or PDR, DRCR.net Protocol S data revealed the superiority of anti-VEGF (ranibizumab) therapy as the sole intervention that improves BCVA and additionally induces regression of PDR (**Figures 13 and 14**) [26].

5.2 Anti-VEGF

Before the introduction of anti-VEGF agents in the twenty-first century, the treatment of DME was limited to laser photocoagulation. It was not until 1994 that a

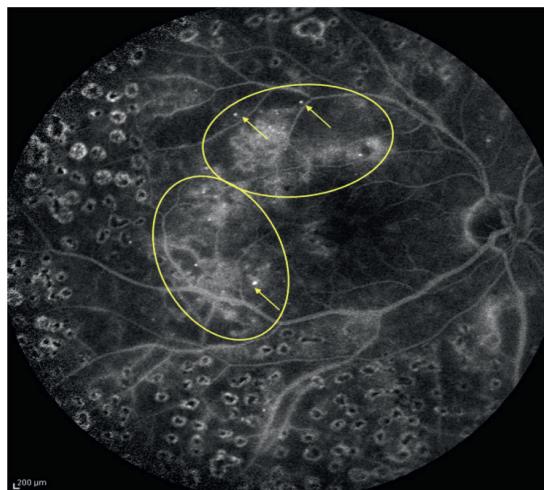


Figure 13.
Fluorescein angiography, SPECTRALIS® scanning laser angiography, intermediate phase, showing signs of previous retinal laser treatment for ischemic areas. Multiple microaneurysms (arrows) and areas of leakage (circles) from microaneurysms and microvascular abnormalities are also evident.

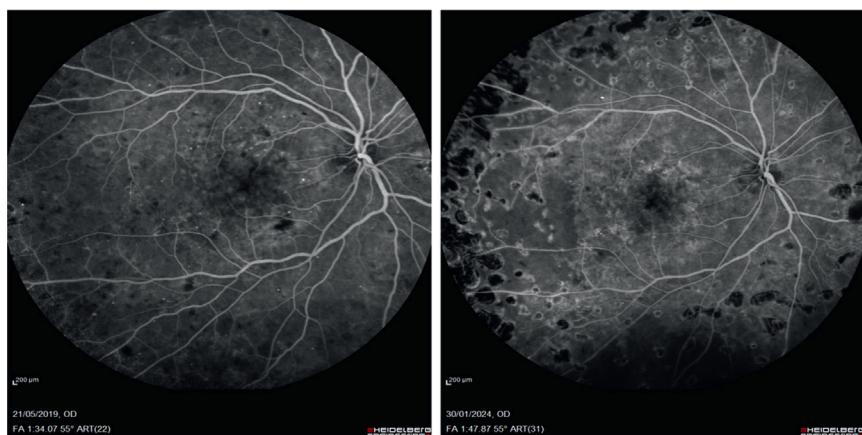


Figure 14.
Fluorescein angiography, SPECTRALIS® scanning laser angiography demonstrating pre- and postphotocoagulation laser treatment for ischemic areas in diabetic retinopathy with residual ischemic areas temporal to the fovea.

study published in the American Journal of Pathology demonstrated that the hypoxic retina produces vascular endothelial growth factor (VEGF), changing definitively the understanding of this pathology [27]. In this study, primate retinas were subjected to laser photocoagulation to induce ischemia and the result was iris neovascularization along with elevated levels of messenger VEGF-mRNA and VEGF protein, demonstrating a role for VEGF in angiogenesis. Along with this significant finding, in 1997 Bevacizumab began to be used for the adjuvant treatment of metastatic colon cancer, prompting the development of the first ocular antiangiogenic, pegylated anti-VEGF aptamer pegaptanib, whose trade name was Macugen. In 2004, pegaptanib was the world's first antiangiogenic approved for ocular neovascularization in humans, thus beginning the era of anti-VEGF.

Vascular endothelial growth factor levels in the vitreous and retina are increased in patients with diabetic retinopathy and have been shown to increase vascular permeability through activation of the protein kinase C pathway, a protein located at the tight junctions between endothelial cells [28, 29]. Treatment with vascular endothelial growth factor inhibitors (anti-VEGF) reduces this process and the abnormal angiogenesis that leads to edema formation in diabetic retinopathy and improves visual acuity in patients with DME [28].

Four intravitreal anti-VEGF agents dominate the global DME market at the time of writing this chapter: Bevacizumab, Ranibizumab, Aflibercept, and Faricimab. Numerous studies have been performed comparing the safety and efficacy of various anti-VEGFs and between the use of corticosteroids and laser treatment. **Table 1** describes some of the main studies and their results [30–33].

Virgili G. et al. in a meta-analysis considered 6007 patients with DME. The result showed that approximately 10% of people improved their vision by 3 or more ETDRS lines with laser after one year, while the ranibizumab group as well as the bevacizumab group improved vision after one year in 30% of patients. Aflibercept achieved this gain in 40% of patients [34]. Also, the RISE and RIDE trials comparing ranibizumab with laser and the VISTA and VIVID trials comparing aflibercept with laser were unable to demonstrate any benefit in the treatment of this pathology with laser.

Considering a single study, we can assume that e.g. in Protocol T it was demonstrated that the use of antiangiogenics under study (bevacizumab, ranibizumab, and aflibercept) improves VA with less need for injections in the second year. Furthermore, it was observed that there is no difference in visual outcomes if the patient has a visual acuity >20/50, but if it is less than 20/50 the visual outcomes were better with the use of aflibercept and ranibizumab. This was also demonstrated in a meta-analysis conducted in 2021, where 45,032 eyes with DME were analyzed and the authors noted that the visual outcome was significantly higher by +3.01 ETDRS letters for aflibercept compared to bevacizumab [35].

In 2022, Faricimab was approved by the US Food and Drug Administration (FDA) and it is the first bispecific antibody approved for the eye, as it is designed to block the angiopoietin-2 (Ang-2) and vascular endothelial growth factor A (VEGF-A) pathways.

The YOSEMITE and RHINE studies showed that administering Faricimab at intervals of up to four months resulted in visual gains that were not inferior to those of aflibercept administered every two months. In the RHINE study, the mean increase in vision at one year was +10.8 and +11.8 letters in the Faricimab and 2-month extension treatment arms, respectively, and +10.3 letters in the aflibercept group. This increase in application interval brought great advantages to the use of anti-VEGF, as many patients did not adhere to monthly anti-VEGF treatment. Greater reductions in central subfield thickness (CST) and intraretinal fluid were also demonstrated with Faricimab [30].

Study	Study design	Primary endpoint	Results
Rise & ride	randomized, parallel, multi-centre clinical trials	To compare the effectiveness of different doses of Ranibizumab versus SHAM with laser rescue in DME. Patients received monthly injections of <ul style="list-style-type: none"> • 0.3 mg ranibizumab • 0.5 mg ranibizumab • sham 	Ranibizumab is effective in treating DME. The average number of injections was 24. More patients in the sham group received macular laser or panphotocoagulation.
Restore	Phase IIIb, multicenter, 12-month, randomized core study and 24-month open-label extension study.	To demonstrate the superiority of ranibizumab 0.5 mg with or without laser vs. laser treatment alone in improving VA over 1 year in patient with DME. <ul style="list-style-type: none"> • 0.5 mg ranibizumab • 0.5 mg ranibizumab + Laser • sham & Laser 	Ranibizumab alone or combined with laser resulted in a higher number of patients with a gain of >15 ETDRS letters.
Resolve	A 12-month, randomized, controlled, double-masked, multicenter phase II study	Efficacy and safety of ranibizumab in diabetic macular oedema: <ul style="list-style-type: none"> • 0.3 mg ranibizumab • 0.5 mg ranibizumab • sham 	At one year, there was a statistically superior increase in VA in the ranibizumab group, with an increase of 10.3 letters. Foveolar thickness decreased by 194.2 versus 48.4 µm in the ranibizumab and sham groups, respectively.
DRCR protocolo I	multicenter randomized clinical trial	To assess the efficacy and safety of: <ul style="list-style-type: none"> • Sham + focal laser • Ranibizumab with focal laser • Ranibizumab • triamcinolone + focal laser 	<ul style="list-style-type: none"> • The ranibizumab group with laser and delayed laser had better visual acuity and macular thickness on macular OCT, however in pseudophakic patients final VA was achieved. • Lower VA is obtained if focal laser is performed at baseline with ranibizumab instead of delayed laser. <p>Results at 5 years: The visual acuity gained in the first year has been maintained up to 5 years with progressive decrease in the number of applications, the delayed laser was associated with better visual acuity.</p>
DRCR protocolo T	multicentre randomized clinical trial	Comparison of the three antiangiogenic agents in 660 patients with central DME using monthly use: <ul style="list-style-type: none"> • ranibizumab 0.3 mg • aflibercept 2.0 mg • bevacizumab 1.25 mg 	All 3 anti-VEGFs demonstrated improvement in VA with less need for injections in the second year. In patients with good baseline visual acuity there is no difference between antiangiogenics, however, in patients with visual acuity <20/50 aflibercept and ranibizumab was better than bevacizumab. More thromboembolic events with ranibizumab.

Study	Study design	Primary endpoint	Results
DRCR protocolo TX	Single-visit 5-year follow-up study of patients who were enrolled in Protocol T	A Comparative Effectiveness Study of Intravitreal Aflibercept, Bevacizumab, and Ranibizumab for Diabetic Macular Edema, 5-year extension of Protocol T.	The mean change in VA at 5 years was +8 letters aflibercept, +76 letters ranibizumab, +6.6 letters bevacizumab. In terms of OCT CRT changes was -154 µm in all 3 groups.
Bolt	Prospective, randomized, masked, single-center, 2-year, 2-arm clinical trial.	Report 2-year outcome comparing bevacizumab versus macular laser therapy.	At two years the average best-corrected VA was 20/50 with Bevacizumab and 20/80 with laser.
VIVID/ VISTA	Two similarly designed phase 3 trials: VISTADME and VIVIDDM	To compare the safety and efficacy of aflibercept with macular laser photocoagulation for diabetic macular edema (DME) over 3 years. <ul style="list-style-type: none">• 2 mg every 4 weeks• 2 mg every 8 weeks after 5 monthly doses• laser control	Both studies demonstrate superiority of aflibercept. The proportion of patients who gained more than 15 letters was 38.3%, 33.1% and 13% in VISTA and 38.2%, 31.1% and 12.1% in VIVID respectively. The most frequent adverse event was cataract 2.4%, 1% and 0.3%.
Kestrel and kite	Double-masked, 100-week, multicenter, active-controlled, randomized trials.	To compare the efficacy and safety of brolucizumab with aflibercept in patients with diabetic macular edema. Kestrel <ul style="list-style-type: none">• 3 mg/ 6 mg brolucizumab• Aflibercept 2 mg Kite <ul style="list-style-type: none">• 6 mg brolucizumab• Aflibercept 2 mg	Brolucizumab 6 mg showed robust visual gains and anatomical improvements. The incidence of ocular serious adverse events was 3.7% (brolucizumab 3 mg), 1.1% (brolucizumab 6 mg), and 2.1% (aflibercept) in KESTREL; and 2.2% (brolucizumab 6 mg) and 1.7% (aflibercept) in KITE.
Yosemite and rhine	Randomized, double-masked, non-inferiority trials across 353 sites worldwide up to the week 100	To reduce treatment burden and optimize patient outcomes in diabetic macular oedema, <ul style="list-style-type: none">• 6.0 mg faricimab every 8 weeks• 6.0 mg faricimab per personalized treatment interval (PTI)• aflibercept 2.0 mg every 8 weeks (PTI dosing intervals were extended, maintained, or reduced (every 4 weeks up to every 16 weeks) based on disease activity at active dosing visits.)	Robust vision gains and anatomical improvements with faricimab were achieved with adjustable dosing up to every 16 weeks, demonstrating the potential for faricimab to extend the durability of treatment for patients with diabetic macular oedema.

Table 1.

A summary of various studies conducted over the years, with emphasis on their design, main objective, and salient results. Table columns: Study: Name of the clinical study. Study Design: Description of the methodological design of the study and the duration of the study. Primary endpoint: The main objective or research question the study sought to answer. Results: Main findings or results of the study that summarize its most important conclusions.

Comparing the different agents on the market and analyzing the studies mentioned in **Table 1**, it can be concluded that neither these nor the following studies and meta-analyses demonstrated any additional benefit of macular laser when administered together with anti-VEGF treatment, so that laser is no longer routinely recommended in diffuse DME (**Figures 15 and 16**).

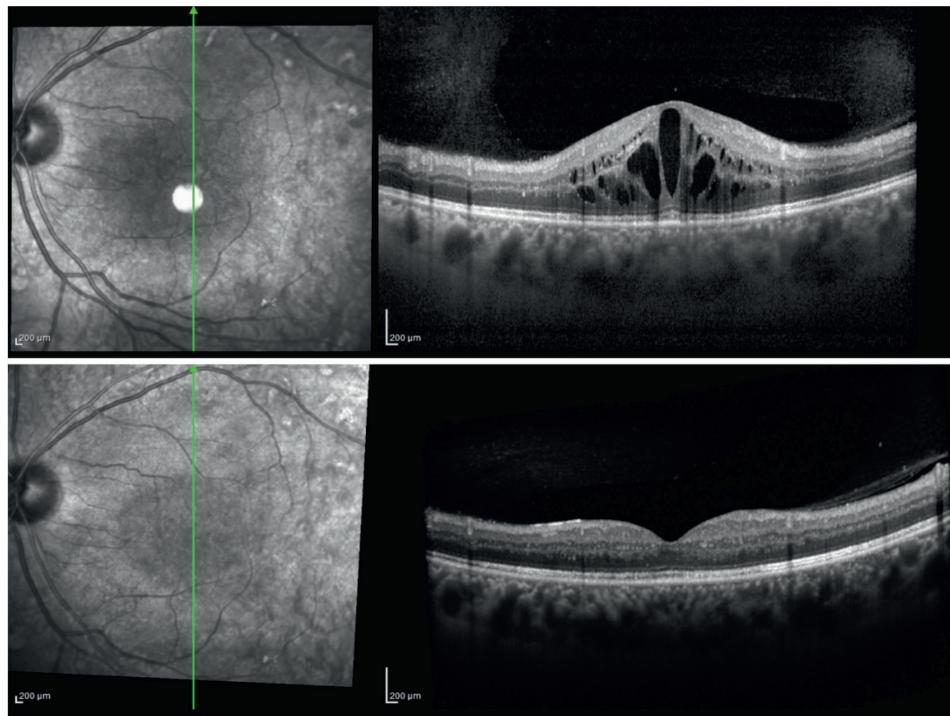


Figure 15.
Spectral-domain optical coherence tomography (SD-OCT) images demonstrating cystoid macular edema in diabetic retinopathy (picture above) and its resolution (picture below) at one month after intravitreal anti-VEGF injection.

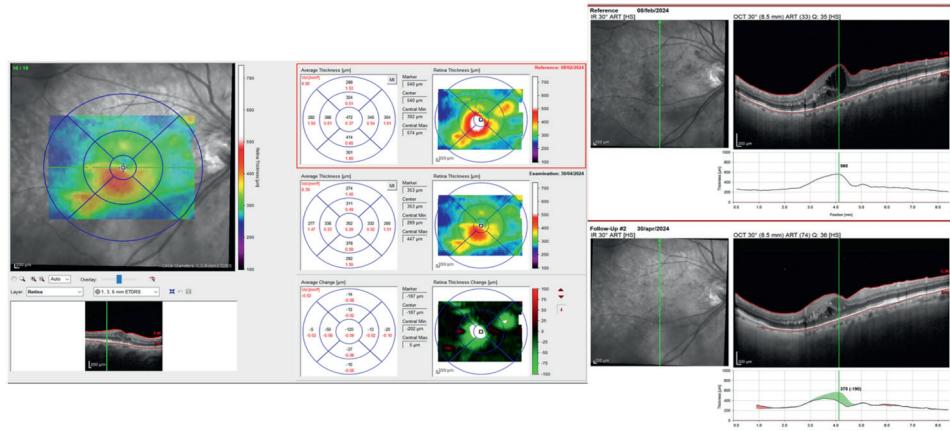
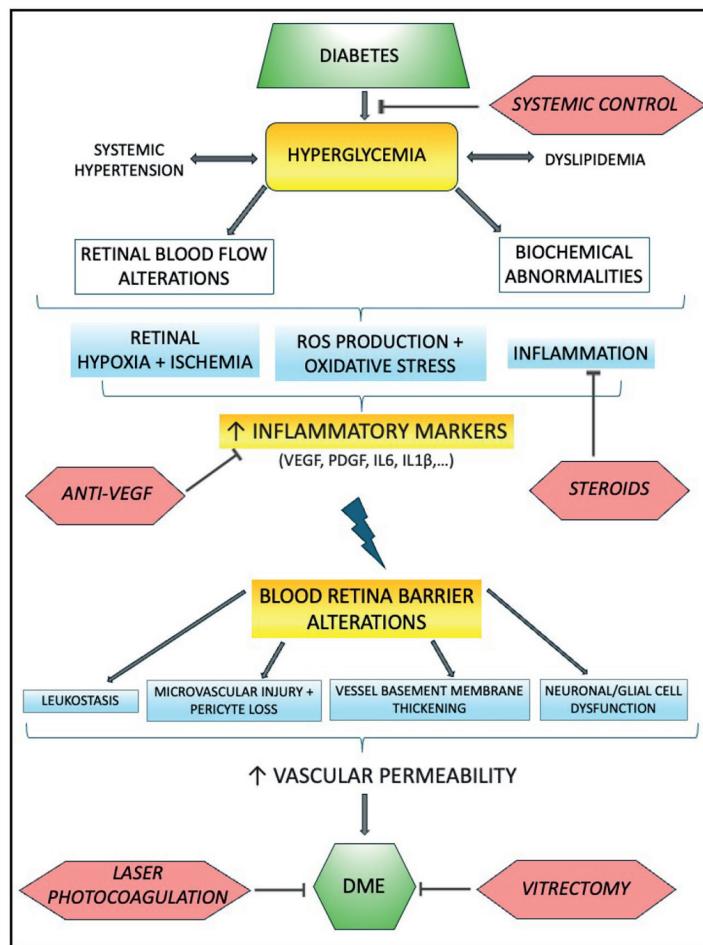


Figure 16.
Spectral-domain optical coherence tomography (SD-OCT) macular map and single-line images demonstrating changes in macular thickness due to reduction of intraretinal cystic spaces in DME after intravitreal anti-VEGF injection.

5.3 Corticosteroids

Recent evidence highlights the role of inflammation in the development of DME; therefore, one of the options for the treatment of this pathology is corticosteroids. Corticosteroids have an anti-inflammatory effect that decreases the

**Figure 17.**

The figure describes the main pathological pathways involved in diabetic macular edema and the principal therapeutic interventions (highlighted in red) aimed at ameliorating these changes or at interrupting the pathological mechanisms.

synthesis of VEGF and inflammatory mediators, which has been shown to improve the BRB function. It was also seen to downregulate intracellular adhesion molecule (ICAM)-1, which is implicated in increased retinal leukostasis, vascular permeability, and BRB breakdown in diabetes. However, its common adverse effects are the development of ocular hypertension and cataracts in phakic patients, which limits its therapeutic indication (Figure 17) [36].

Currently, the corticosteroids for intravitreal use on the market are triamcinolone acetonide, fluocinolone (Iluvien), and the posterior segment dexamethasone delivery system (Ozurdex). The use of corticosteroids has been studied in large protocols such as B and I which are published by the DRCR for the management of diabetic macular edema. The latter is an independent, multicenter, randomized, controlled clinical trial of 5-year duration, in which the use of sham injection + immediate laser, 0.5 mg ranibizumab + immediate laser, 0.5 mg ranibizumab + delayed laser (≥ 24 weeks), or 4 mg triamcinolone acetonide + immediate laser was compared in patients with DME. After one year, triamcinolone and laser treatment resulted in a 4-letter gain from baseline, compared with a

9-letter gain obtained by the ranibizumab group. In addition to having a lower visual gain, he had 50% intraocular pressure (IOP) elevation ≥ 10 mm Hg compared to the ranibizumab group (9%) or the laser group (11%), during two years of follow-up [37, 38].

Fluocinolone acetonide-Iluvien was approved by the FDA in 2014. The approved dose for fluocinolone acetonide (FLA) is 0.19 mg, with sustained release for at least one year [39]. In a randomized controlled study conducted over one year, the efficacy of FLA was compared with that of photocoagulation in diabetic macular edema. After this period, it was observed that 57% of patients treated with FLA had resolved DME, compared to 20% treated with photocoagulation alone [40]. However, after a 3-year follow-up, it was found that 95% of patients developed cataracts [41].

The dexamethasone drug delivery system (DDS) (*Ozurdex, Allergan Inc., Irvine, California*) is a biodegradable, sustained-release device approved by the FDA for the treatment of DME in patients who have not shown any response to anti-VEGF treatment, or patients with significant cardiovascular disease.

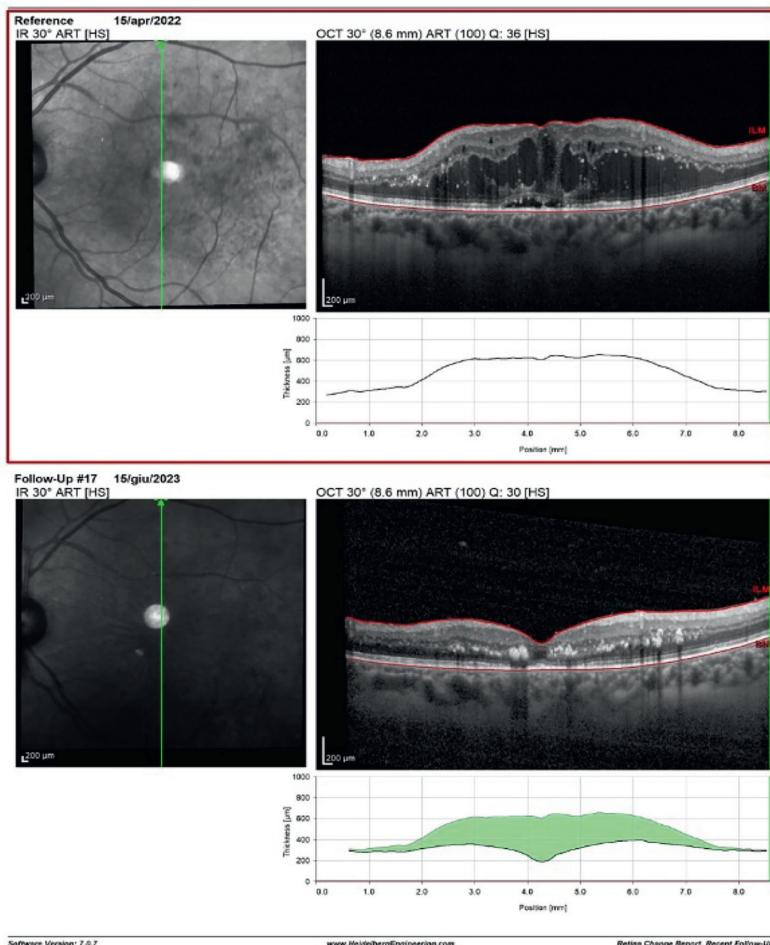


Figure 18.

The spectral-domain optical coherence tomography (SD-OCT) images demonstrating cystoid macular edema with subfoveal neuroretinal detachment, intraretinal hyper-reflective dots, intraretinal exudates in diabetic retinopathy (picture above), and the resolution of intraretinal edema and neuroretinal detachment with persistence of exudates (picture below) at two months after intravitreal corticosteroid implant.

Time	Antiangiogenic Limitations	Corticosteroid Limitations
Immediately	<ul style="list-style-type: none"> Requires frequent injections Second option in patients with a severe cardiovascular history Subconjunctival hemorrhage 	<ul style="list-style-type: none"> Risk of increased intraocular pressure Slightly more difficult application technique Subconjunctival hemorrhage Caution in patients with a history of viral infections such as herpes simplex. Should not be used in case of active ocular herpes simplex
0–3 months	<ul style="list-style-type: none"> Variable response in different patients Risk of ocular complications due to more frequent applications such as endophthalmitis 	<ul style="list-style-type: none"> Possible development of cataracts
3–12 months	<ul style="list-style-type: none"> Need for continuous monitoring Some patients may develop resistance Costly ongoing treatment 	<ul style="list-style-type: none"> Need for repeated dosing Potential for increased intraocular pressure
>12 months	<ul style="list-style-type: none"> Risk of recurrence of macular oedema Risks of scloromalacia at injection sites No adequate data on use in pregnant women 	<ul style="list-style-type: none"> Risk of eye infection May not be effective in all patients No adequate data on use in pregnant women

Table 2.

Limitations of antiangiogenic and corticosteroid treatments in patients with diabetic macular edema over time. It is important to note that these limitations may vary depending on the specific type of antiangiogenic or corticosteroid used, as well as individual patient characteristics. In addition, advances in research and the development of new treatments may change these limitations over time.

The implant releases the corticosteroid into the vitreous for a period of ≤6 months [42]. Therefore, retreatment is recommended after this period has elapsed and simultaneous administration in both eyes is not recommended. A phase 2 randomized controlled trial (RCT) in patients with persistent macular edema secondary to DME showed that over six months of dexamethasone DDS produced improvements in visual acuity, macular thickness, and fluorescein leakage (**Figure 18**) [43].

Similar results have been reached in the study by Boyer DS et al., where dexamethasone DDS was reported to improve final visual acuity and macular thickness in previously vitrectomized patients with diffuse DME [44].

Up to now, corticosteroids have proven to be a valuable tool in treating patients with DME, albeit often as a secondary option. This is particularly the case for patients who have not responded well to anti-VEGF treatment. Conversely, they might be preferred as a first-line option for patients with a significant cardiovascular history. Studies suggest that after continuous monthly anti-VEGF treatment over a 2-year period, these patients may face heightened risks of mortality and potential stroke [45]. Further limitations of both anti-VEGF agents and corticosteroids are outlined in **Table 2**.

5.4 Surgical management of diabetic macular edema

5.4.1 The role of the vitreous and vitrectomy in DME

The vitreous has been implicated as a cause of macular edema in people with diabetes via several mechanical and physiological mechanisms, all of which are postulated to lead to an increase in vascular permeability [46]. Suggested mechanisms include the following [47]:

1. destabilization of the vitreous by abnormal glycation and crosslinking of vitreous collagen, leading to traction on the macula
2. accumulation and concentration of factors causing vascular permeability in the premacular vitreous gel
3. accumulation of chemoattractant factors in the vitreous, leading to cellular migration to the posterior hyaloid, contraction, and macular traction

The reduction in DME followed by improved oxygenation and the release of mechanical traction on the macula, either by spontaneous posterior vitreous detachment or by vitrectomy, supports the suggested mechanisms and highlights the potential advantage of vitrectomy in these cases [48].

Vitrectomy improves oxygenation at the inner retinal surface by increasing the flow of oxygen-rich aqueous from the highly vascularized iris and ciliary body to the posterior pole. Increased oxygen tension counteracts the diabetes-induced retinal hypoxia responsible for VEGF upregulation and blood-retinal barrier breakdown, decreasing exudation from the retinal capillaries and resolving DME.

Kim et al. [22] noticed a significant association between decreased visual acuity and the presence of Posterior hyaloid traction (PHT) without tractional retinal detachment (TRD). The traction produced by the vitreomacular interface alone has been postulated to play a role in the development of DME. This vitreomacular interface has been thought to cause tangential traction, which could lead to macular edema. Hence, identifying the structural changes in patients with DME using OCT may allow more effective management of these patients.

5.4.2 Vitrectomy: when?

Vitrectomy should be taken into consideration as the primary therapeutic option if vitreo-macular traction is present and identified with biomicroscopy or OCT, to mechanically remove the traction itself (**Figures 10–12**) [49–53].

In the Diabetic Retinopathy Clinical Research Network (DRCR.net) trial, 241 eyes were enrolled [54], and a decrease in the mean subfield thickness from 412 microns to 278 microns was demonstrated six months after vitrectomy. Visual acuity significantly improved in eyes with worse VA at baseline ($P < 0.001$) and in eyes requiring ERM peeling ($P = 0.006$), even though the entire cohort's average VA (20/80) remained the same.

Moreover, eyes with a worse baseline VA were more likely to have a greater improvement in VA and a larger reduction in macular thickness. Although the most relevant decrease in macular thickness was shown in eyes with the greatest preoperative thickness, the trial could not clearly demonstrate that the final visual acuity is independently associated with baseline macular thickness. This is probably explained by the slight possible improvement when either or both macular thickness and visual acuity are relatively small.

A better outcome in VA was present when ERM was removed during vitrectomy, while the amount of macular thickness reduction was not affected, possibly indicating a resolution in metamorphopsias rather than an improvement in DME. Instead, a relevant decrease in retinal thickness was observed with internal limiting membrane (ILM) peeling, with no improvement in VA.

Factors associated with changes in anatomic outcomes or VA after pars plana vitrectomy (PPV) for DME were evaluated only in a few studies in the literature. Kumagai et al. [55] conducted a retrospective study demonstrating that VA at 1-year examination

was better after ILM removal as compared to ILM preservation, after evaluating 486 eyes that underwent lensectomy and PPV for diffuse non-tractional DME.

Tamura et al. [56] carried out a histopathologic analysis of the ILM after vitrectomy and peeling from eyes with diffuse diabetic macular edema. ILM examined by light microscopy revealed the presence of five cell types on the vitreous side of the specimens, namely glial cells, fibroblast-like cells, macrophages, neutrophils, and lymphocytes, while immunohistochemistry corroborated the presence of glial cells and macrophages.

The advantages of ILM removal in eyes with DME are underlined in several papers; nevertheless, the major issue is the difficulty in preoperative DME characteristics standardization, given that previous laser treatments or intravitreal steroid/anti-VEGF are likely to interfere.

Randomized clinical trials (RCTs) with an appropriate follow-up have not been conducted yet concerning vitrectomy compared with other methods in DME management; therefore, its application and role remain unclear, with regard to its potential risks and benefits.

Diffuse DME without evident traction may not benefit from vitrectomy; moreover, low visual acuity after complete resolution of DME may be explained by macular ischemia [57, 58], photoreceptor dysfunction [51, 59], or accumulated subfoveal hard exudates [60]. The poor visual outcome may be predicted with a better photoreceptor layer visualization, as assessed by SD-OCT, especially for what concerns the integrity of the external limiting membrane (ELM) and inner and outer segments (IS/OS) of the photoreceptor junction.

In conclusion, a surgical approach in patients with DME should aim at rapidly drying the retina as much as possible. It is clear that the posterior hyaloid should be completely removed, whereas ILM peeling remains controversial. Postoperative VA may be predicted with detailed SD-OCT evaluation of the ELM and IS/OS layer done before and after surgery; furthermore, a quick and long-lasting improvement in VA may be achieved with early vitrectomy to significantly reduce macular thickness. However, a randomized trial comparing vitrectomy with the current standard of care should be carried on.

As medical budgets become tighter, and alternative therapies, including anti-VEGF injections, become more expensive, vitrectomy may emerge as the preferred low-cost, longer-duration therapy.

6. Refractory or persistent DME

Medications used for vascular endothelial growth factor inhibition (anti-VEGF) have significantly changed visual and anatomical outcomes in people with diabetic macular edema (DME). However, success is not always assured, and some patients continue to experience persistent diabetic macular edema (PDME), despite intensive treatment. Approximately 30–65% of patients are thought to be refractory [61]. “Refractory or persistent macular edema” is defined as a < 10% or 20% decrease in central retinal thickness (CRT) compared to baseline data or when visual gain is suboptimal, i.e. patients achieve <5-letter increase in best corrected visual acuity (BCVA) on the ETDRS or less than one line of sight on the Snellen poster [62].

In daily practice, there is no standardized treatment for this pathology that supports the superiority of one strategy over another. Consequently, it is the treating professional who decides on the therapy, taking into account various clinical factors, complementary examinations, and the particular characteristics of each patient.

Several treatment options are currently being proposed. One is to switch to a drug with a different affinity for VEGF and which can block cytokines via other pathways, maximizing the therapeutic potential. This is generally used after an inadequate response after three to six injections, at the discretion of the treating ophthalmologist. Another option is to change the therapeutic agent to corticosteroids. Intravitreal corticosteroids such as dexamethasone or fluocinolone have been shown to achieve remarkable improvements in visual and anatomical outcomes in people who do not respond to anti-VEGF treatment, due to their anti-inflammatory and antiangiogenic effects. Finally, in cases where the origin of the lack of therapeutic response is an epiretinal membrane, vitreous traction, or macular ischemia, pars plana vitrectomy can be the option.

6.1 Analysis of the evidence

One of the hypotheses for the treatment of this type of pathology is “replacement of one antiangiogenic molecule by another,” but the timing of switching anti-VEGF agents remains a matter of debate, as there are so far insufficient well-designed, prospective, randomized clinical trials assessing the efficacy of switching. Some advocate switching early, before permanent structural damage is observed due to persistent chronic macular edema, arguing for a more favorable long-term visual outcome. This idea is supported by findings obtained in Protocol I, where it is stated that if visual gain is poor after the first three applications of anti-VEGF, continuing with the same therapeutic agent will likely result in suboptimal visual gain.

A marked difference in efficacy in favor of aflibercept compared to bevacizumab was also observed in Protocol T. Therefore if the decision is made to switch from anti-VEGF after only three monthly applications, the most effective switch would be from bevacizumab to aflibercept or ranibizumab. Several investigations have supported this hypothesis, demonstrating similar results of a gain of 3–5 lines of sight in favor of switching [63, 64].

On the other hand, also in Protocol T, it is suggested that caution should be exercised when considering changing treatment for DME if there is a limited response in the first few months of treatment. This is because it was observed that in some cases, there is continued resolution of edema on OCT, especially with monthly and continuous use of aflibercept and ranibizumab, from week 12 to week 24. Similar results were observed in the Protocol I study, in which 30% of the treated patients, who did not achieve a BCVA of >5 letters in the first three anti-VEGF applications, achieved a BCVA > or equal to 10 letters at the end of the 3-year follow-up.

With the recent emergence of Faricimab, some studies have found benefits in its use in patients who are non-responders to aflibercept, especially in terms of treatment interval in patients with PDME. Visual and anatomical improvements were also demonstrated, but further long-term studies are required for confirmation [65, 66]. Rush et al. found that patients who switched from aflibercept to Faricimab showed significant improvements in both visual acuity and central macular thickness (CMT) compared to those who continued aflibercept treatment for persistent DME [65]. In their study, 37.5% of patients achieved a CMT < 300 µm, and 41.7% of patients showed an improvement of >0.2 logMAR (Logarithm of the Minimum Angle of Resolution) four months after switching to Faricimab. This could reduce the financial burden, the need for multiple visits and injections, the likelihood of infection, and systemic complications associated with treatment.

Another alternative frequently used in daily practice is the use of corticosteroids, either as an adjunct or as a single therapeutic agent. Considering that there is evidence

suggesting that the late phase of DME may be due to inflammatory activities rather than angiogenic factors. Another reason is that not all patients respond to anti-VEGF. Up to 40% of participants in pivotal clinical trials did not reach a VA threshold of 20/40 [67]. In addition, dexamethasone intravitreal implants (DEX DDS) may extend the therapeutic interval in those who cannot cope with the intensive regimen required for anti-VEGF therapy.

6.2 Future developments

Given the high incidence of this disease and the challenge of treating it, new studies with innovative therapeutic approaches are underway, some of which include:

- RGX-314 (Regenxbio): is a virus-mediated gene therapy that enables the production of a Fab Anti-VEGF fragment. The study, called ALTITUDE (Aliskiren Trial in Type 2 Diabetes Using Cardio-Renal Endpoints), is in phase 2 and evaluates the efficacy, safety, and tolerability of RGX-314E gene therapy for diabetic retinopathy.
- OPT-302 (Opthea): is an anti-VEGF combination therapy against vascular endothelial growth factor-C and -D (VEGF-C and -D) and with available anti-VEGF agents. Phase 2 data from patients with refractory DME treated with combination therapy showed a 52% improvement in VA \geq 5 letters at 12 weeks compared to baseline
- APX3330 (Ocuphire Pharma): is a Phase 2 oral therapy for the treatment of diabetic retinopathy. So far, it was demonstrated that up to 24 weeks, no treated patient showed a binocular worsening \geq 3 steps of the Diabetic Retinopathy Severity Rating System (DRSS) from baseline, compared to 16% of placebo-treated patients.

In conclusion, the treatment of persistent diabetic macular edema is a major challenge for the treating ophthalmologist. The lack of consensus and the diversity of available therapeutic options reflect its complexity. Therefore, the choice of treatment requires a careful assessment of the patient's medical history, socioeconomic situation, and individual response to treatment.

Continued research and interdisciplinary collaboration are essential to advance the understanding and management of persistent diabetic macular edema.

7. Artificial intelligence and future perspectives

The complementary use of artificial intelligence (AI) in medicine, particularly in ophthalmology, has increased in recent years and this trend is expected to continue. This tool has proven useful in different pathologies, particularly in diabetic macular edema (DME), thanks to AI's great capacity to analyze a large amount of data quickly and accurately. This has allowed it to be used as a means of screening, diagnosis, and treatment, marking a significant milestone in ophthalmology and changing the approach to the disease [68].

For diagnosis, AI algorithms allow the identification of subtle patterns in retinal images, facilitating early detection of DME, before symptoms are evident. This anticipation facilitates a timely and effective approach that leads to the preservation of vision in diabetic patients.

In 2018, for the first time, the US Food and Drug Administration (FDA) approved an AI algorithm, called “IDx-DR,” based on a non-mydriatic fundus photograph using a Topcon Fundus camera (Topcon Medical) for the identification and screening of diabetic retinopathy (DR) without interpretation by an ophthalmologist.

These algorithms were based on the initial studies by Abramoff et al., which showed that Deep Learning (DL), specifically the Convolutional Neural Network (CNN), achieved a high sensitivity rate of 96.8% in identifying DR from sets of images [69]. Since then, algorithms have been developed to identify DR from fundus photographs, with high sensitivity and specificity [70].

Optical coherence tomography (OCT) is the most widely used complementary study for the diagnosis and monitoring of this disease. It has been successfully coupled to AI, creating a large database and thanks to its machine learning capabilities, algorithms for the diagnosis and prognosis of the course of DME have been obtained.

De Fauw et al. conducted a study demonstrating the effectiveness of DL in identifying DME and other causes of macular edema using OCT as a diagnostic tool [71]. By analyzing 14,884 scans, they were able to develop an algorithm that showed an error rate lower than that performed by a group of trained retina specialists and optometrists. Tang et al. demonstrated similar findings using 73,746 OCT images to create a multitasking CNN to classify different types of DME. The results revealed an area under the receiver operating curve (ROC) greater than 0.93 [72], reinforcing the idea of the efficacy of the DL approach in this specific clinical application.

Optical coherence tomography angiography (OCT-A) is also a study widely used in recent years in the detection and monitoring of DME, because it can show changes in vascular density, decreased capillary permeability in superficial and deep capillary plexuses, and an increase in the foveal avascular area. Therefore, OCT-A DL algorithms are currently being designed for the diagnosis and monitoring of DME.

Le et al. demonstrated that a neural network trained with OCT-A diagnosed diabetic retinopathy with a sensitivity of 83.76% and a specificity of 90.82% [73]. Similarly, Ryu et al. designed a diagnostic algorithm that arrived at results with similar levels of predictability [74].

Concerning DME management, AI facilitates follow-up analysis to assess disease progression and adjust treatment plans in a continuous and personalized manner. This optimizes therapeutics, thus reducing the occurrence of large morphological variations, which are directly reflected in a poor final visual outcome [75].

In terms of treatment, AI has also influenced the development of more targeted and individual therapies. By better understanding the characteristics of each patient's DME, AI contributes to the optimization of drugs and procedures, maximizing benefits and minimizing side effects [76].

In summary, the integration of artificial intelligence in ophthalmology has revolutionized the way DME is approached, significantly improving early diagnosis, efficient management, and personalization of treatments, resulting in more effective care and more successful preservation of vision in diabetic patients.

8. Conclusion

Effective treatment of diabetic macular edema (DME) is a fundamental pillar in preserving visual acuity and improving the quality of life of affected patients. Advances in diagnostic methods now make it possible to provide patients with early diagnosis and targeted treatment.

Pharmacological advances have been extraordinary, as evidenced by the introduction of new agents such as Faricimab, which has significant potential in improving visual function and prolonging application intervals. Further advances in the pharmacological field are expected to offer even more effective treatments for patients. Ongoing research and development of drugs targeting different pathophysiological pathways in diabetic macular edema could expand the available therapeutic options, thereby improving anatomical and visual outcomes.

Retinal surgery has also undergone substantial progress, characterized by less invasive, more precise, and safer techniques. This progress is due to the development of specialized instrumentation and the constant improvement of surgical techniques, allowing surgeons to achieve better outcomes in patients with DME.

Finally, the incursion of artificial intelligence into the field of DME diagnosis, treatment, and monitoring promises to open new doors toward more efficient and accurate medical care.

In summary, the progress achieved in these various fields augurs new prospects for patients affected by this disease.

Author contributions

Author contributions according to CREDIT (Contributor Roles Taxonomy):

F.P.: Conceptualization, Supervision, Writing—Original Draft, Writing—Review and Editing;

L.M.R.: Conceptualization, Supervision, Writing—Original Draft, Writing—Review and Editing;

A.C.: Writing—Original Draft, Writing—Review and Editing, Formal analysis;

R.R.: Writing—Original Draft, Writing—Review and Editing, Formal analysis;

L.C.: Writing—Original Draft, Writing—Review and Editing, Formal analysis;

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All authors have read and agreed to the published version of the manuscript.

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