We are IntechOpen, the world's leading publisher of Open Access books Built by scientists, for scientists

6,900
Open access books available

185,000
International authors and editors

200M
Downloads

Our authors are among the

154
Countries delivered to

TOP 1%
most cited scientists

12.2%
Contributors from top 500 universities

CLARIVATE ANALYTICS
BOOK CITATION INDEX
INDEXED

WEB OF SCIENCE™

Selection of our books indexed in the Book Citation Index
in Web of Science™ Core Collection (BKCI)

Interested in publishing with us?
Contact book.department@intechopen.com

Current Management of Diabetic Macular Edema

Ogugua Ndubuisi Okonkwo, Toyin Akanbi
and Chineze Thelma Agweye

Abstract

Diabetic macular edema is a complication of diabetes mellitus (DM) which contributes significantly to the burden of visual impairment amongst persons living with diabetes. Chronic hyperglycemia triggers a cascade of pathologic changes resulting in breakdown of the retinal blood barrier. Understanding the pathophysiological and biochemical changes occurring in diabetes has led to developing novel therapeutics and effective management strategies for treating DME. The clinical utility of optical coherence tomography (OCT) imaging of the retina provides a detailed assessment of the retina microstructure, valid for individualization of patient treatment and monitoring response to treatment. Similarly, OCT angiography (dye-less angiography), another innovation in imaging of DME, provides an understanding of retinal vasculature in DME. From the earlier years of using retinal laser photocoagulation as the gold standard for treating DME, to the current use of intravitreal injection of drugs, several clinical trials provided evidence on safety and efficacy for the shift to intravitreal steroids and anti-vascular endothelial growth factor use. The short durability of available drugs leading to frequent intravitreal injections and frequent clinic visits for monitoring constitute an enormous burden. Therefore, extended durability drugs are being designed, and remote monitoring of DME may be a solution to the current challenges.

Keywords: Diabetes Mellitus, Hypertension, Diabetic Macular Edema, Diabetic Macular Ischemia, Intravitreal Anti Vascular Endothelial Growth Factor, Intravitreal Steroids, Retinal Laser Photocoagulation, Optical Coherence Tomography, Clinical Trials

1. Introduction

The rising number of persons living with diabetes worldwide has significant implications for global blindness. Diabetes is a condition of public health importance and paramount health concern in our time, with about 463 million adults worldwide living with diabetes as of 2019 [1]. The prevalence of diabetes for all age groups worldwide is 2.8% in 2000 and will increase to 4.4% in 2030 [2]. Projections suggest that the total number of individuals with diabetes will more than double from 171 million in 2000 to 366 million by 2030 [2]. Diabetic retinopathy (DR) is a microangiopathy and a significant finding amongst people living with diabetes. About 140 million patients are estimated to have diabetic retinopathy, and 10% of this number, i.e., about 14 million, have impaired vision. Diabetic macular edema (DME) is the commonest cause of visual impairment amongst persons living with diabetes [3].

The prevalence of DME is influenced by the type of diabetes and the use or non-use of insulin treatment [4]. The ten-year incidence of DME is highest amongst older onset patients on insulin, in which a rate as high as 25% has been reported. In research examining the prevalence and risk factors for DME in the United States, non-Hispanic blacks had a higher odd of developing DME than non-Hispanic whites [5]. There was a more significant burden of DME among non-Hispanic blacks, individuals with high hemoglobin A1c, and those with a longer duration of diabetes. It would appear that race plays a vital role in developing DME.

Development of DR and DME is associated with well-researched risk factors, including long duration of diabetes, suboptimal glycemic control as evidenced by elevated HbA1c, hypertension, obesity, elevated serum lipid levels, anemia, pregnancy, associated kidney disease, and smoking [6–10]. DME patients are at increased risk of cerebrovascular accidents (stroke) and cardiovascular disease (CVD) when compared to other DM patients without DR [11]. Also, DME has been shown to negatively impact the quality of life (QoL) of the patient [12]. The most feared complication of all the complications associated with diabetes is a loss of vision [13].

The management of a patient living with diabetes requires the input of a multidisciplinary team [14, 15]. It includes such psychosocial support as can be provided by the family, peers, and even the workplace. This kind of support will help improve patient compliance to treatment and result in an overall healthier patient. There are physician and patient challenges in the care of DR and DME. Physician challenges include managing wide variations in patient responses to treatment, the complex comorbidity profile of the high-risk population, and the suboptimal outcomes associated with delayed initiation of treatment with intravitreal anti-VEGF therapy. Obvious patient challenges include compliance to treatment and clinic attendance for monitoring, the cost of treatment and medical insurance, the burden associated with long-term follow-up and management, problems with access to health care and treatment (especially amongst the low and medium-income), and the time spent on treatment, visits, and follow-up, particularly for the working-age population. Nonetheless, to prevent visual impairment and blindness from DR and DME amongst patients living with diabetes, timely intervention is required. It is possible through the early detection of treatable retinopathy.

2. Screening for DR and DME

DR and DME occur in DM patients, and risk factors are as outlined previously. Therefore, this disease lends itself to early detection through screening of at-risk persons. DR is a progressive disease. The early stages of DR, which can be asymptomatic, can progress to more advanced sight-threatening forms of the disease. The role of ophthalmic screening for early detection of vision-threatening disease in at-risk patients living with diabetes is an essential and practical strategy for preventing vision loss from DR and DME. Though systematic screening is preferred and has proven to reduce rates of blindness from DR effectively, few nations have this in place. In most countries, only some form of opportunistic screening is available or no screening at all [16].

There are different real-world examples of the benefit gained through DR screening. The English national health service (NHS) diabetic retinopathy screening program is a successful model of a screening program that has evolved from opportunistic to effective systematic screening [16]. The UK's systematic screening has effectively reduced the prevalence of DR-related blindness in the UK. The UK national screening program was established in 2004 to provide standardized, quality-assured DR screening across England. All patients living with diabetes

above the age of 12 years are invited at least annually for an ophthalmic screen. Those patients at higher risk could have more frequent visits, while those at least level of risk could be considered for more extended visits. Screening is done by qualified screeners who carry out two-field retinal photography, using an updated list of persons living with DM. Images are then digitally transferred to a centralized location for retinal grading by qualified individuals (graders). A comprehensive quality-assurance system is set up, including regular auditing of grading carried out by individuals grading within the English screening program. The UK's screening program has a coverage of 83% and screened close to 3 million persons in 2018/2019. The entire program has reported successes, such that after seven years of the program, a review of the causes of blindness in the UK showed that DR was no longer the most common cause of blindness amongst the working-age [17]. This UK experience of DR screening provides compelling evidence that systematic diabetic retinopathy screening, coupled with timely treatment of sight-threatening disease, can reduce vision impairment and blindness.

For a DR screening program to be effective, it should be composed of the following seven component pathways, 1. identifying the population eligible for screening; 2. invitation and information; 3. testing; 4. referral of screen positives and reporting of screen-negative results; 5. appropriate diagnosis; 6. intervention, treatment, and follow-up; 7. reporting of outcomes [16].

The entire framework of the screening program should be based on the following, resources and infrastructure, a pathway for screening, quality of screening, and equity in access to high-quality screening. In addition, standardization of the process, quality assurance, and auditing of the screening program should be implemented to ensure effectiveness and a high level of sensitivity for timely detection of sight-threatening disease and appropriate referral. Although there are well-designed guidelines for DR screening, considerable gaps exist in deciding the best screening methods and how often to screen, infrastructure and resources for screening, and the fact that several patients living with diabetes fail to keep screening appointments. In addition, in several low- and mid-income countries, healthcare coverage is not countrywide. There is a scarcity of updated information on persons living with diabetes who are the targets of such DR screening programs [16].

In consideration of the economic aspect of DR screening, issues relating to the overall cost-effectiveness of ophthalmic care, the cost-effectiveness of systematic versus opportunistic screening, how screening should be organized and delivered, how often screening should be performed, have all been raised. It has been shown that systematic screening for DR is cost-effective in terms of sight years preserved than no screening [18]. In addition, teleophthalmology screening offers remote screening by trained paramedics in out-of-hospital facilities, including rural and hard-to-reach communities [19, 20]. Other remote screening initiatives include healthcare kiosks and smartphone tele screening, which provide teleophthalmology solutions for a broader range of patients, including in underserved locations and rural communities. In countries with inadequate primary care systems, without a routine systematic screening program, a holistic approach to screening for diabetes is recommended to prevent end-organ damage. This holistic approach should include at least retinal screening, foot examinations, blood pressure monitoring, urine albumin testing, HbA1c, and lipid testing [19]. A significant side benefit of DR screening is that it can also identify other ophthalmic conditions, including cataracts, glaucoma, and other retinal and retinovascular diseases.

In recent times, the entry of artificial intelligence (AI) algorithms further provides immediate grading and feedback on fundus photographs acquired by trained personnel in an out-of-hospital location (including primary care clinics and pharmacies) [21–23]. These AI-backed systems feature automated retinal image

analysis (ARIA) [24, 25]. The image to be graded or analyzed can be acquired using digital fundus cameras, and now even handheld mobile devices, including smartphones, can be used. Internet access is required to upload the image for grading to the AI software. The software then compares the uploaded image with cloud-based images. It can provide information on if there is a presence of sight-threatening DR or not with a high level of sensitivity and specificity. This AI software-based screening is the future of DR screening. Utilizing ARIA, detection of DR can be done without the need for human image graders. ARIA, in turn, standardizes the process, is more efficient, and covers a larger area within a shorter period. The EMERALD Study is a recent multicenter study conducted in 13 centers within the UK [26]. This study examined the sensitivity, specificity, and acceptability of an alternative pathway using spectral-domain OCT to detect DME and 7-field Early Treatment Diabetic Retinopathy Study [ETDRS] and ultra-widefield fundus images for PDR. These images were interpreted by trained nonmedical staff (ophthalmic graders) to detect reactivation of previously treated disease. The authors compare this alternative pathway with the current standard of care (face-to-face examination by ophthalmologists). They concluded that this new alternated pathway has acceptable sensitivity and offers a significant release of resources.

At this time, home screening using optical coherence tomography (OCT) device has been explored, "Home OCT device" [27]. Success and experience gained from using the Foresee Home Device in monitoring eyes with AMD have evolved into the idea that patients at risk of DME can be monitored remotely from their homes using the Home OCT device, reducing the number of hospital visits [28]. Home OCT can be combined with home monitoring of visual acuity and other aspects of visual function. This innovative idea also provides information on DME's entire clinical evolution and history, which is missed between clinic visits for several patients. The patient uses the Home OCT device to scan the macula for early disease detection constantly. Therefore, home teleophthalmology and home monitoring combined can detect early disease, lead to intervention early in the disease process, and prevent vision loss from DR and DME. This home screening and monitoring of DME is another current reality in the COVID 19 era and provides a way out for a future lockdown, as happened during the COVID 19 pandemic.

To conclude, DR screening of at-risk patients living with diabetes is essential for the early detection of sight-threatening disease to enable timely, effective treatment. With increasing numbers of patients diagnosed with diabetes, DR-related visual disabilities will likely increase in the coming years. An interdisciplinary organized public health approach will provide the best approach to achieving screening for many patients. Collaboration amongst all different partners is required to reduce the incidence of vision loss resulting from DME and DR. This multidisciplinary approach will ensure that relevant information about diabetes and the eye screened is shared with the screened patient and across the system responsible for diabetes care. This will facilitate integrated care for the patient. Other incidental findings diagnosed during eye screening, such as cataracts or glaucoma, should be referred to the appropriate eye care team.

3. Pathophysiology of DME

3.1 Pathophysiology

The pathophysiology of DME is multifactorial and has not been clearly and completely defined since it involves various complex pathological processes [29–31]. In health, the retinal circulation is unique in that retinal capillaries are

non-fenestrated, and their endothelial cells have tight junctions which do not allow fluid leakage. A lymphatic system does not exist in the retina, but leakage can occur in the presence of retinal pathology, causing edema and swelling [32]. Chronic capillary non-perfusion and retinal ischemia are said to be the primary contributors to DME [33]. Signaling molecules such as insulin-like growth factor-1 (IGF-1), platelet-derived growth factor (PGF), angiopoietin, and most importantly, vascular endothelial growth factor (VEGF) all play a role in the subsequent development of diabetic microangiopathy [33].

The trigger for the vascular damage has been convincingly linked to the chronic hyperglycemia present in DM. Vessel damage occurs via the glucose metabolic pathways, which include the Diacylglycerol (DAG)–protein kinase C (PKC) pathway, Advanced glycation end-products (AGE), Polyol (sorbitol) pathway, Hexosamine pathway, and the plasma kallikrein-kinin system (KKS) [34–36]. The blood-retinal barrier (BRB) is an essential structure that regulates normal visual function [31, 37]. It is a physiologic barrier that tightly regulates the balance of electrolytes, protein, solute, and water movement in and out of the retina. It is composed of both an outer and an inner portion [31, 37]. The inner BRB comprises tight junctions between retinal capillary endothelial cells, basement membrane surrounding it, and pericytes outside [31, 37]. The outer BRB tight junctions exist between retinal pigment epithelial cells located between them the fenestrated choriocapillaris and the outer retina [31, 37].

In DME, disruption of the BRB is common, leading to increased vasopermeability associated with vascular leakage, neovascularization, and inflammation [38]. In chronic hyperglycemia, cellular and structural alteration in the BRB is characterized by the breakdown of cell–cell junctions between endothelial cells, pericyte loss, basement membrane thickening, increased deposition of extracellular matrix components, and Muller cell metabolism disturbance heralding the beginning of the microangiopathy [30, 37, 39]. Over time, continued retinal microvasculature damage results in the release of reactive oxygen species and inflammatory mediators and capillary nonperfusion, giving rise to retinal hypoxia and ischemia that drives upregulation of angiogenic factors, such as vascular endothelial growth factor (VEGF) and breakdown of the BRB [29, 39]. The breakdown of the inner BRB then results in the accumulation of plasma proteins such as albumin, which exerts a high oncotic pressure in the neural interstitium, inducing interstitial edema, neural tissue impairment, and ultimately vision loss if there is a delay in treatment or no treatment at all [29, 31, 40].

Patients with DME have elevated vitreous levels of VEGF, Intracellular Adhesion Molecule-1 (ICAM-1), interleukin-6 (IL-6), and monocyte chemoattractant protein-1 compared to nondiabetic patients [41]. VEGF-A mediates angiogenesis by promoting endothelial cell migration, proliferation, and survival [41]. VEGF-A also possesses inflammatory properties through its capacity to mediate microvascular permeability and increase the adhesion of leukocytes. It has been noted to stimulate expression of ICAM-1 and vascular cell adhesion molecule −1 (VCAM-1), thus incorporating the inflammatory cascade, initiating early diabetic retinal leukocyte adhesion, and aiding the development of diabetic vasculopathy [39, 41]. VEGF-A inhibitors have been shown to reduce vascular permeability [30, 31]. Anti-VEGF agents such as Ranibizumab, Aflibercept, and Bevacizumab administered according to various treatment protocols are currently the gold standard for treating center-involving DME [31, 37, 42]. The introduction of intravitreal anti-VEGF therapy has led to notably improved outcomes for some patients with DR/DME [39]. Nevertheless, there are several practical limitations to the treatment with anti-VEGF. They include; cost, need for frequent intravitreal injections, undertreatment, and incomplete response in some patients [39, 43].

3.2 Alternative pathways

Furthermore, clinical trials have demonstrated that only 33–45% of DME patients on intravitreal anti-VEGF agents showed three lines or more of visual improvement. Other DME patients showed an intermediate response (5–9 letters of improvement) or inadequate response (<5 letters of improvement or worse). Eyes with suboptimal early vision response showed poorer long-term visual outcomes than eyes with pronounced early response [37, 44, 45]. In the clinical setting, available data have shown that anti-VEGF therapy does not live up to the high goals set by clinical trials, leaving patients with suboptimal vision [46]. These limitations have resulted in exploring alternate pathways involved in aberrant angiogenesis, including the Tie-2 pathway and the effect of genetics [39].

The angiopoietin-tyrosine-protein kinase (Ang-Tie) system plays an essential and complementary role alongside VEGF-mediated vessel formation and vascular stability [42]. The angiopoietins, Ang-1 and Ang-2, are a family of growth factors that interact with one another to play a vital role in vessel homeostasis, angiogenesis, and vascular permeability via interacting with the Tie-2 transmembrane receptor tyrosine kinase [37, 39, 42]. Ang-1 plays a protective role in pathological angiogenesis, supports quiescent vessel maturation, and prevents intravesical inflammation [39, 42]. In contrast, Ang-2 promotes vascular instability through its competition with Ang-1 and inhibition of Tie-2, contributing to DME [47]. Ang-2 is upregulated in response to hyperglycemia and plays a vital role in altering the BRB in DME [37]. Increased Ang-2 leads to decreased phosphorylation of Tie-2, which results in increased retinal vascular permeability [37]. Together Ang-2 and VEGF-A have been reported to produce accelerated neovascularization in the developing retina and ischemic retina [39].

3.3 Systemic control

The UKPDS and FIELD studies concluded that good control of modifiable risk factors of diabetic retinopathy delayed its development and progression [48–51]. Howbeit, findings of the ADVANCE trial came to a contrary conclusion [52]. Moreover, it has been observed in clinical practice that despite prolonged periods of poor control of glycemic and systemic blood pressure in some patients, DR was not observed, contrary to expectations. On the other hand, some other patients would develop DR within a relatively shorter period of diabetes, despite better control [53, 54]. These observations suggest that mechanisms other than hyperglycemia, elevated blood pressure, and hyperlipidemia contributes to the development and progression of DME and diabetic retinopathy in some patients [55]. In addition, disparities in the risk of developing diabetic retinopathy have been noted among patients of different ethnic groups even after correcting for environmental factors, alluding to the fact that genetic factors may play a role in the pathogenesis of diabetic retinopathy [56–59]. This ethnic bias and variable predisposition bring to the fore the consideration of a concept of genetic predisposition to DME and DR in individuals of diverse ethnicity and genetic constitution.

3.4 Genetics of DME and DR

Gene mapping has been employed to identify novel genetic variants underlying DME and DR. However, only weak associations have resulted [55, 60]. The Genome-wide association studies (GWAS) had identified loci of interest MRPL19 and NRXN3 as novel loci with suggestive association with DME and PDR, respectively, which are sight-threatening complications of DR [61]. Although DR-associated genes have yet

to be replicated and confirmed, these early findings represent the initial groundwork and maybe a preview of DR genetics' complexity [55, 60, 62].

3.5 Macular ischemia

Retinal ischemia has been recognized as a primary risk factor for developing proliferative diabetic retinopathy (PDR); it sometimes occurs with DME. A paucity of studies describing diabetic macula ischemia (DMI) exists, mainly due to difficulty in its detection using fluorescein angiography and limited treatment options [63]. Clinically, DMI is defined by an enlargement of the foveal avascular zone (FAZ) and paramacular areas of capillary nonperfusion [64]. Two anatomical changes can be characteristically seen in the retina of patients with DMI. First, due to marked cellular and extracellular damage, there is extensive loss of neuro-retinal tissue. Secondly, there is notable occlusion of the vessels supplying the retina [63]. DMI results in the upregulation of growth factors such as VEGF, which contribute to DME development [65], making it difficult to observe and anatomically characterize DMI in isolation. The anatomical and physiological basis of this disease is still very poorly studied [63]. Recently optical coherence tomography angiography (OCTA) offers a better image of macular microvasculature and is superior to conventional FA in assessing DMI. Anatomically the microcirculation supply to the retina is divided mainly into superficial capillary plexus (SCP) and deep capillary plexus (DCP) [66]. Choroidal circulation seems to be the most critical blood supply to the central macula, including the photoreceptor inner segment (IS) band, which appears to be the most critical consumer of oxygen [67]. It is thought that the DCP is responsible for up to 15% of the blood supply to the photoreceptors, especially during dark adaptation [65, 66].

3.6 Classification of DME

3.6.1 The classification of diabetic retinopathy (DR) and DME

The classification of diabetic retinopathy (DR) and DME have evolved over the years. About five decades ago, experts in ophthalmology gathered in Airlie House for a symposium to review the state of knowledge of DR; an outcome from that meeting was developing a standardized classification of DR [68–70]. Afterward, this classification was modified for use by the Diabetic Retinopathy Study (DRS) [69, 70]. The modified Airlie House classification of diabetic retinopathy used in the DRS was further developed for the Early Treatment Diabetic Retinopathy Study (ETDRS). This randomized, prospective study evaluated the efficacy of laser treatment for macular edema [68]. It became the gold standard for many years. The ETDRS introduced the term clinically significant macular edema (CSME). CSME was defined using slit-lamp biomicroscopy, when it met any of the three criteria viz. "(1) thickening of the retina at or within 500 μm of the center of the macula; or (2) hard exudate at or within 500 μm of the center of the macula associated with thickening of the adjacent retina; or (3) a zone of retinal thickening one disc area or larger, any part of which is within one disc diameter of the center of the macula" [71]. After that, fluorescein angiography was used to guide laser treatment [72]. The ETDRS found that macular laser photocoagulation effectively reduced moderate visual loss by at least 50% in laser-treated eyes with CSME compared to untreated eyes [68, 70]. In 2003, an international classification called the Diabetic macular edema disease Severity Scale with greater simplicity was proposed [29, 73]. The DME disease severity scale put forward that DME is 'apparently present' when some apparent retinal thickening or hard exudates exist in the posterior pole; DME is proposed to be 'absent' otherwise [29, 70]. When DME is present, it is classified

into mild, moderate, or severe if the retinal thickening or hard exudate is distant from the center of the macula, approaching the center of the macula but not involving the center and involving the center of the macula, respectively [29, 70]. Ten years after ETDRS, Optical Coherence Tomography (OCT) became the new imaging modality that enabled ophthalmologists to utilize the qualitative and quantitative measurement of central subfield macular thickness (CSMT) and visual acuity to diagnose and determine the response of DME to treatment [29, 72]. OCT is invaluable due to its reliability and reproducibility; its importance in evaluating and monitoring DME cannot be over-emphasized [41, 74].

A classification based only on slit-lamp biomicroscopic evidence of retinal thickening is grossly insufficient to precisely describe DME and determine the appropriate therapeutic modalities for the various morphologies [72, 75].

3.6.2 DME classification based on OCT

DME classification based on OCT is described using various morphology (1) diffuse edema type (sponge-like diffuse retinal thickening), (2) cystoid macular edema (CME) type (thickening of the fovea with intraretinal cystoid change), (3) serous retinal detachment (SRD) type (thickening of the fovea with subretinal fluid) and (4) vitreomacular interface abnormalities as seen in incomplete or complete posterior vitreous detachment and epiretinal membrane (ERM) formation or vitreomacular traction or both [74–76].

Other parameters deployed by the OCT in DME diagnosis include retinal thickness, volume (quantitative data), and inner and outer layers of the retina [72, 74].

3.7 Clinical presentation (symptoms and signs)

Patients with DME may be asymptomatic if the macula center is not involved. However, some eyes having center involving DME (CI-DME) have been seen to have no visual disturbance, presumably because of the recent involvement of the center [32]. Depending on the degree of fovea involvement and the chronicity of the edema, patients may present with an array of visual symptoms [32]. These include gradual progressive diminution and distortion of central vision over some time (usually moderate, unlike the severe loss after vitreous hemorrhage or retinal detachment involving the macula in proliferative diabetic retinopathy), metamorphopsia, and loss of color vision. They may also experience poor night vision and 'washing-out of vision in bright sunlight with poor dark–light adaptation [32, 77, 78].

On dilated biomicroscopic examination, retinal thickening may be observed in commonly identified patterns. Focal edema often occurs in association with a cluster of microaneurysms, sometimes surrounded by an incomplete ring of hard exudates. Diffuse DME may be very difficult to identify clinically if the retina is uniformly thickened due to the lack of reference landmarks. Clues include the height of the retinal blood vessels over the pigment epithelium, cystoids spaces, or even loss of the foveal depression. Other features that are sometimes seen with macular edema include variable loss of retinal transparency, a significant number of microaneurysms, intraretinal hemorrhages, and dispersed areas of hard exudates [32].

3.8 Evaluation of DME

3.8.1 The control of systemic metabolic abnormalities

The control of systemic metabolic abnormalities observed in diabetes mellitus has a significant effect on the development and progression of

diabetic microvascular complications, including DME [79]. The United Kingdom Prospective Diabetes Study (UKPDS) and the Diabetes Control and Complications Trial (DCCT) did demonstrate that optimal metabolic control could reduce the incidence and progression of DR [50, 80]. To achieve good management of a patient with DME, a multidisciplinary approach involving different medical subspecialists such as ophthalmology, endocrinology, nephrology, neurology, cardiology, orthopedics is key [29]. Systemic workup involving blood investigations helps monitor the systemic status of these patients. These investigations including fasting blood glucose (FBG), glycosylated hemoglobin levels (HbA1C), serum electrolyte, urea, creatinine, and fasting lipid profile. Other investigations that may be required would be based on systemic complaints, examination findings, and other suspected comorbidities [29]. The recommended values for HbA1c, blood pressure, and LDL cholesterol are < 6.5–7%, <130/<85 mmHg, and < 100 mg/dl, respectively [81]. However, many patients fail to achieve or maintain these levels of metabolic control. In patients who significantly reduce HbA1c, there is an associated increased risk of severe hypoglycemia [33, 50, 80]. Managing physicians must recognize correctable risk factors of DR and DME, such as hyperglycemia, hypertension, and/or hyperlipidemia, to ensure appropriate monitoring and referral for eye care.

3.8.2 Ophthalmic evaluation

I. Over the last two decades, a wide range of imaging modalities, including fundus photography, fluorescein angiography (FA), optical coherence tomography (OCT), and OCT-Angiography (OCT-A), have been utilized not only for the diagnosis and classification of disease but also to monitor disease progression and treatment [82]. **Figures 1**–**5** illustrate the significance of these imaging technologies in DR and DME. DME is diagnosed clinically with the slit-lamp biomicroscopy or indirect ophthalmoscopy with features such as visible microaneurysms, hard exudates, cysts, and retinal thickening. However, stereoscopic fundus photography and fluorescein angiography have greater sensitivity in detecting DME than ophthalmoscopy because of superior optics of the former, the enhanced contrast of fluorescein angiography, ability to make confirmation of vascular leakage, and the ability of the observer to evaluate magnified images without the interference of patients moving or blinking [83].
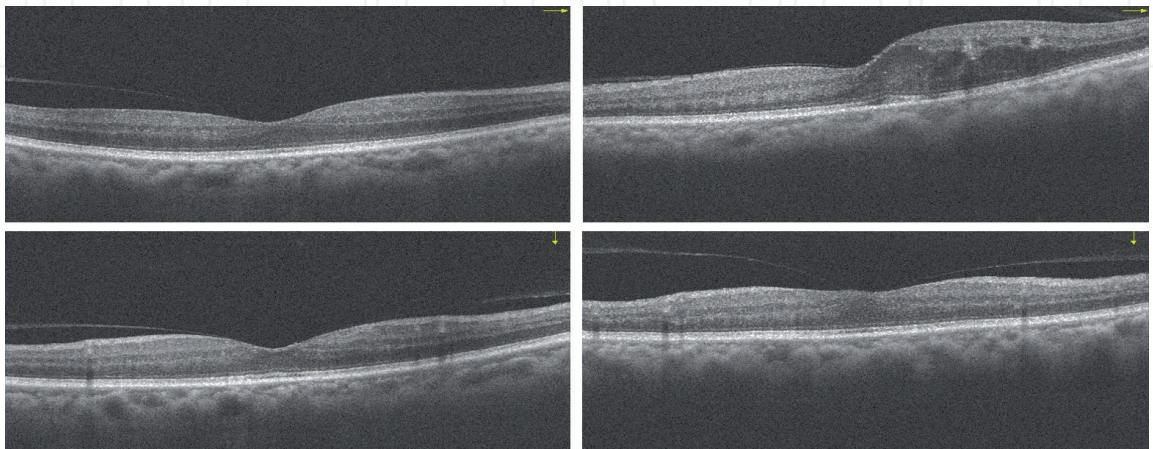

Figure 1.
OCT image of both eyes of a patient who suffers from DME in the left eye. The right eye shows typical retinal microstructure, while the left eye shows thickening in the foveomacula area from intraretinal cystic spaces due to diabetic macular edema. Notice that the posterior vitreous membrane is "partly" attached to the retina in both eyes.
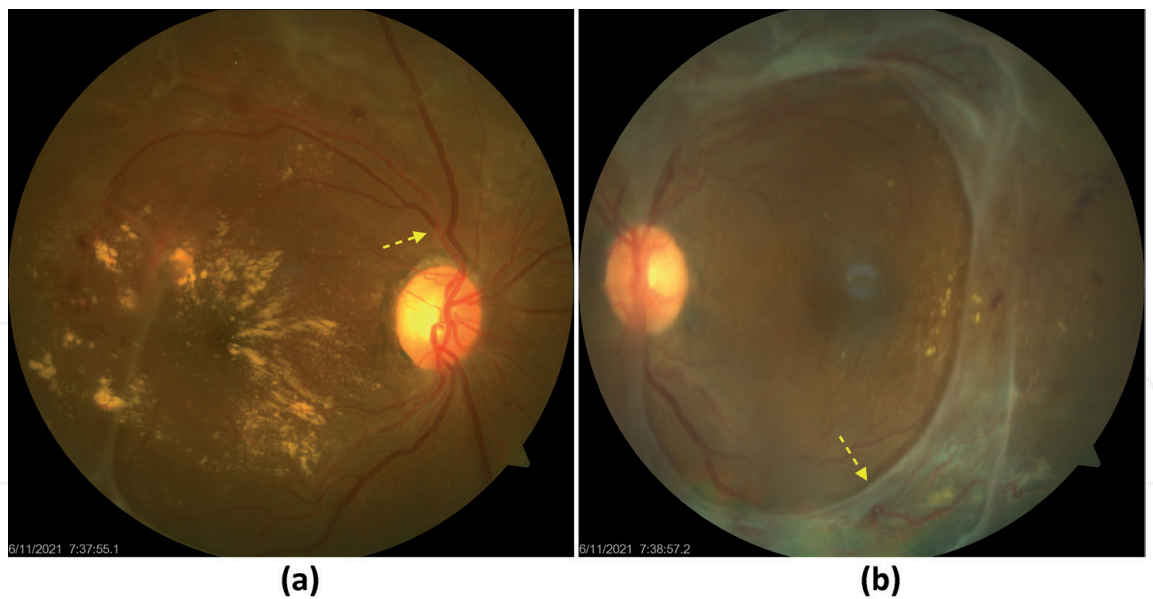
(a) **(b)**

Figure 2.
(a) Right eye fundus photograph, with the star shaped appearance of hard exudation, the nasal portion of which involves the fovea. There are dot hemorrhages and microaneurysms involving the temporal macula and superiorly within the superotemporal arcade. Notice the arteriovenous nipping (broken yellow arrows) suggestive of co-existing hypertensive retinopathy. There are opacities within the vitreous. (b) Left eye fundus photograph, a ring of fibrovascular tissue extends from the retina into the pre retinal space and vitreous cavity. Hard exudates, hemorrhages, and microaneurysms are present within the temporal macula beneath the fibrovascular tissue. Contraction of fibrovascular proliferative tissue creates a tractional effect on the inferotemporal arcade (broken yellow arrows).
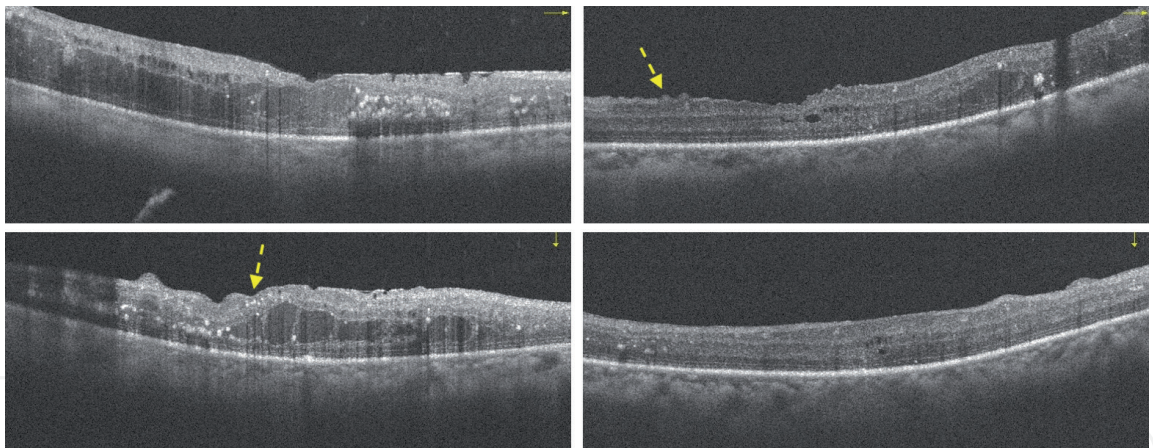

Figure 3.
*OCT images of both eyes as in **Figure 2a** and **b**. There is intraretinal cluster of hard exudates and intraretinal cystoid spaces, worse in the right eye (correlating with the fundus photographs). Epiretinal membrane is present in both eyes (broken yellow arrows).*

Stereoscopic fundus photographs provide an opportunity to evaluate and document long-term changes in the retina [32, 82]. The ETDRS study used the 7 standard fields (7SF) 30° photographs of the retina (three horizontally across the macula and four around the optic nerve). This combination gave nearly 75° of visualization [29]. Mydriatic or nonmydriatic fundus imaging with $\geq 30^0$ mono- or stereo photography is used with or without OCT [84]. Ultra-wide-field imaging is currently used for the screening and detection of DR, as is ultra-wide-field angiography [83].

Fundus fluorescein angiography (FFA) visualizes the retinal vasculature. It identifies lesions of diabetic retinopathy, patchy areas of hypo fluorescence representing ischemia as demonstrated by capillary dropout, areas of impaired BRB function, and microaneurysms manifest as areas of hyper fluorescence demonstrated by leakage of dye and visualize expansion of the foveal avascular zone (FAZ) [59, 82].
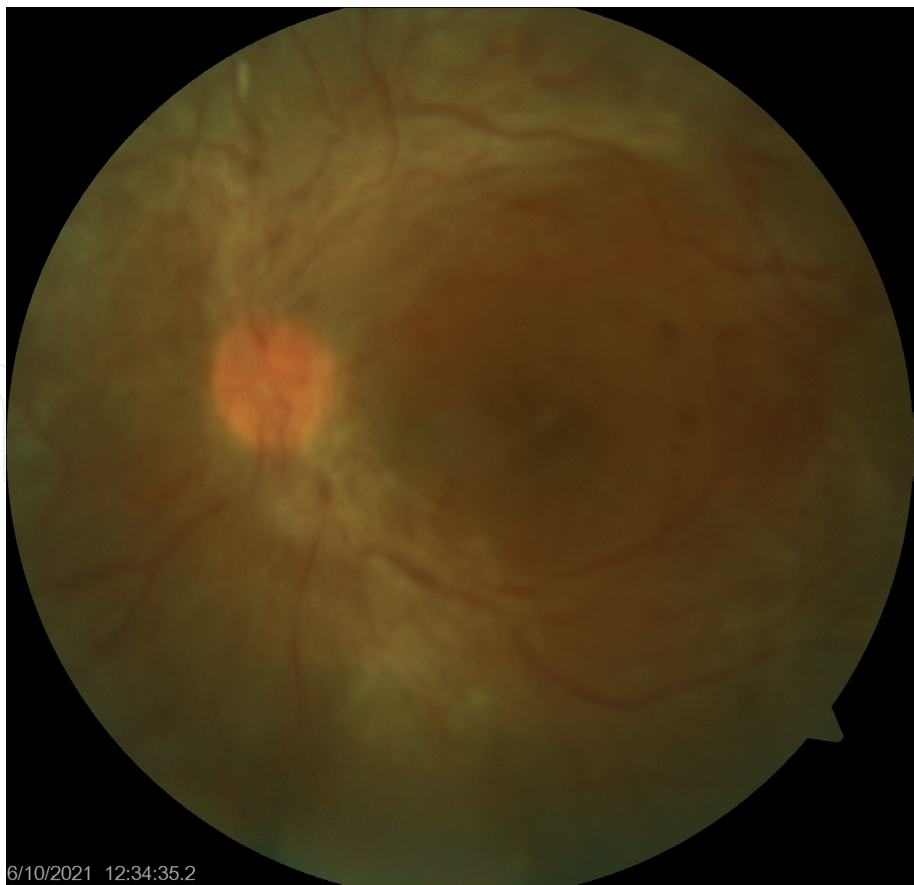
Figure 4.
Left eye fundus photograph showing extensive fibrovascular tissue proliferation across the macula and optic disc. There is a faint view of retinal hemorrhages in the temporal macula.
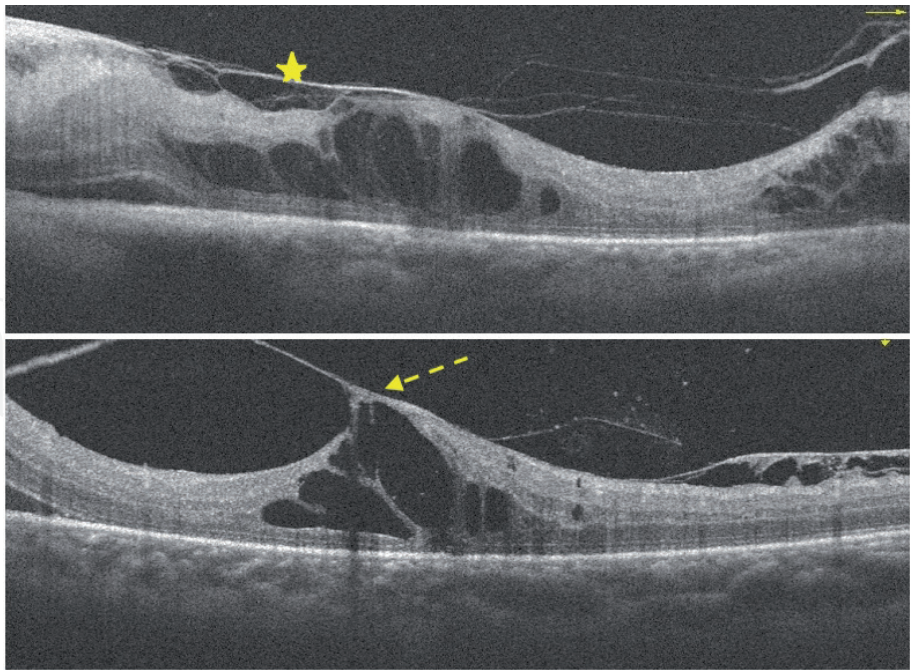

Figure 5.
*The OCT image of the left eye fundus photograph in **Figure 4**. Tangential (yellow star) and vertical (yellow dotted arrow) tractional elements in the preretinal space extend into the vitreous. This thick taut hyaloid creates foveomacular traction-induced macular edema (evident as the large cystoid spaces within the macula).*

Previously FFA helped predict prognosis and response to treatment in DME [59]. A case of diffuse DME was defined by fluorescein leakage involving most of the macula. This form of DME is more challenging to treat than focal DME involving

leakage from identified lesions [85]. FFA also revealed the degree of capillary non-perfusion and macular ischemia, shown by an enlarged foveal avascular zone [59]. With the development of ultra-widefield imaging, FFA can now be performed with visualization of up to 200° of the retina. Extensive ischemia in the retinal periphery has been associated with recalcitrant disease, and the ultra-widefield FFA may help identify DME that is likely to be treatment-resistant [59]. It reveals areas of peripheral ischemia and non-perfusion, which can be promptly treated with pan-retinal laser photocoagulation. The significant advantage of FFA is that it was the only imaging modality commonly used in DR that provides information on vascular flow and vessel permeability over time by visualizing leakage and pooling [82]. The disadvantage of FFA is that it is an invasive procedure that involves the administration of intravenous dye. It should be performed carefully, especially in patients with severe DR and associated systemic vascular complications such as severe renal disease and clinical or subclinical cardiovascular disease [29, 82, 86, 87]. The most common adverse reactions are nausea and vomiting, but more severe side effects include localized reactions, urticaria, seizures, and, very rarely, anaphylaxis [29, 82]. Before performing FFA, the ophthalmologist must carefully consider whether the information provided is necessary to make therapeutic decisions and whether the same or equivalent information can be provided by OCT which is non-invasive [83].

II. Since its first introduction, OCT has become the most frequently used diagnostic tool in ophthalmology for the past two decades and has revolutionized clinical imaging for diagnosis and disease management in most retinal diseases, including DME [78, 82]. The diagnostic utility of the OCT can be seen in the case illustrated by **Figures 6** and 7. The fast, non-invasive, high-resolution imaging available with OCT of the posterior segment allows for close study of the retinal anatomy and assessing retinal thickness profile and morphology in DME [82, 83]. A significant advantage of OCT is that it can be easily repeated several times, within the same day, with a high degree of reproducibility. Therefore, it can be used to monitor the effect of therapy, e.g., intravitreal anti-VEGF given the same day or shortly after, to detect or objectively quantify response to therapy [82, 83]. This value of the OCT to monitor treatment is illustrated with **Figures 8** and **9**.
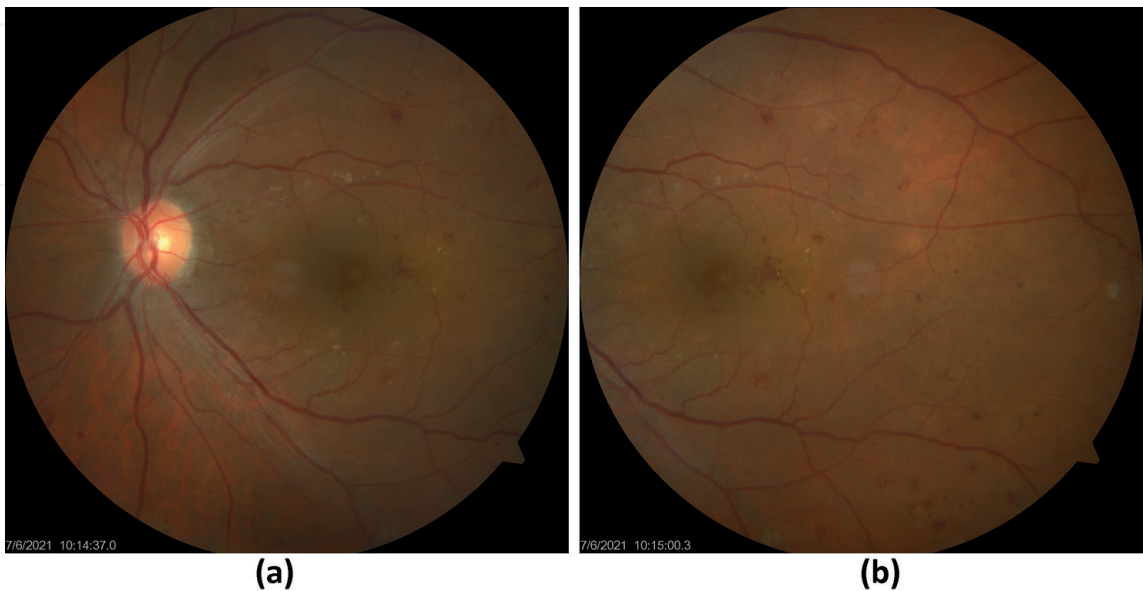

(a)   (b)

Figure 6.
(a and b) The left eye fundus photograph shows dot hemorrhages, microaneurysms, and few hard exudates, over the macula (a) and extending to the temporal retina (b). This is a clinical diagnosis of non-proliferative diabetic retinopathy and DME.
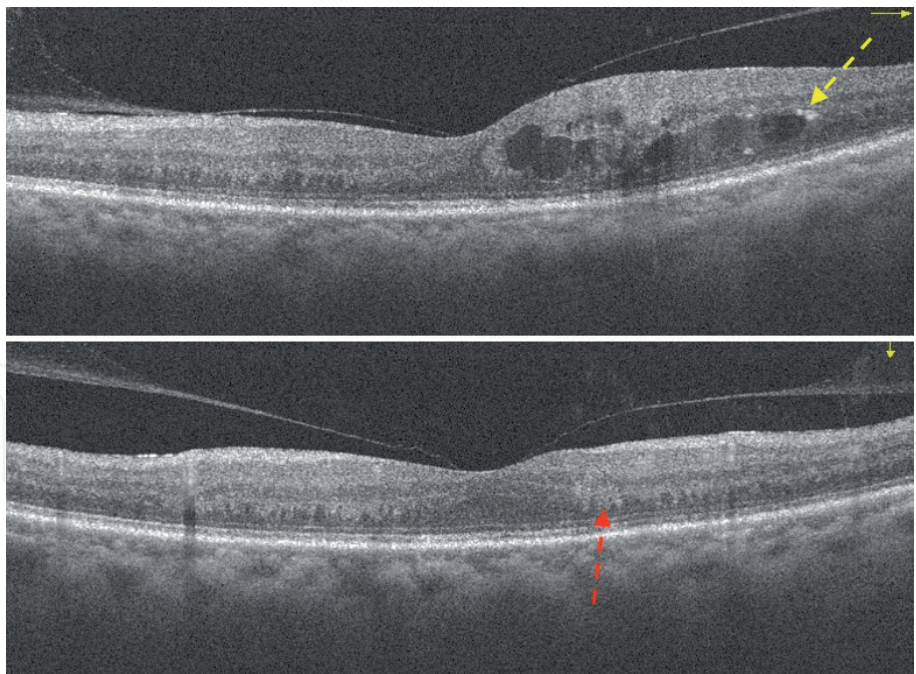
Figure 7.
*OCT of fundus image in **Figure 6** showing intraretinal cystoid spaces and a few hard exudates clustering around the cystoid (broken yellow arrows). Hyper reflective digitations are extending into the outer nuclear layer (broken red line).*
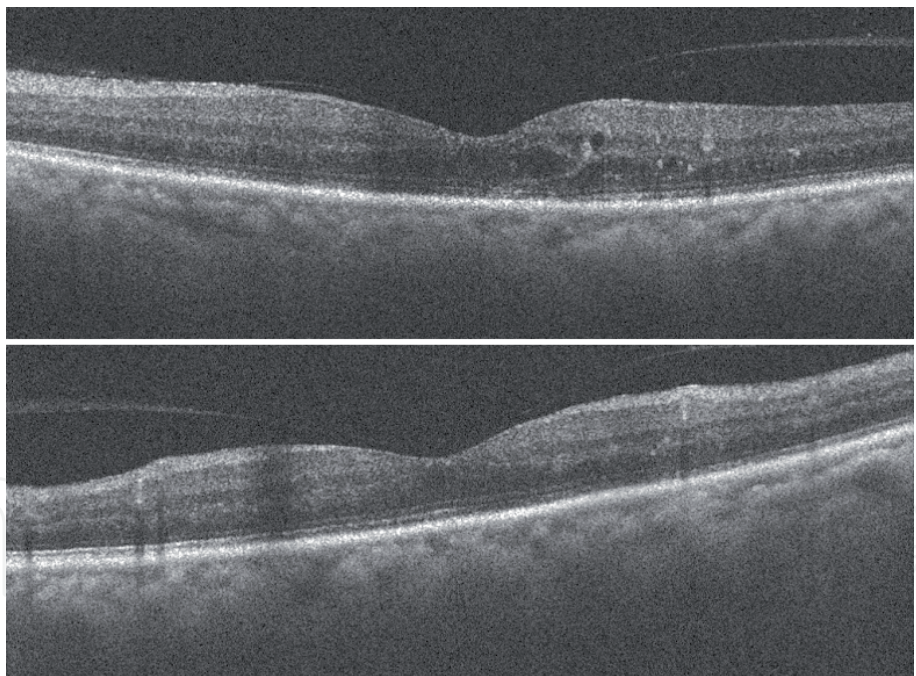

Figure 8.
*This is the OCT image of the same eye as in **Figure 7** after intravitreal injection of Bevacizumab. Notice the reduction in intraretinal cystoid space size. The foveomacular retina is no longer thickened, as in **Figure 7**.*

There are three types of OCT: time-domain (TD), spectral-domain (SD), and swept-source (SS) [82]. Spectral-domain OCT is the most commonly used, allowing three-dimensional raster scans of up to a few hundred B-scans, also creating high-resolution images. It supersedes time-domain (TD)-OCT, the first generation that allowed imaging of 6 radial cuts only [78, 83]. The most recent third-generation OCT technology uses a swept-source (SS) light source that allows high-speed imaging and provides three-dimensional raster images of high microstructural resolution, also referred to as optical histology [78]. OCT is highly sensitive and more accurate in
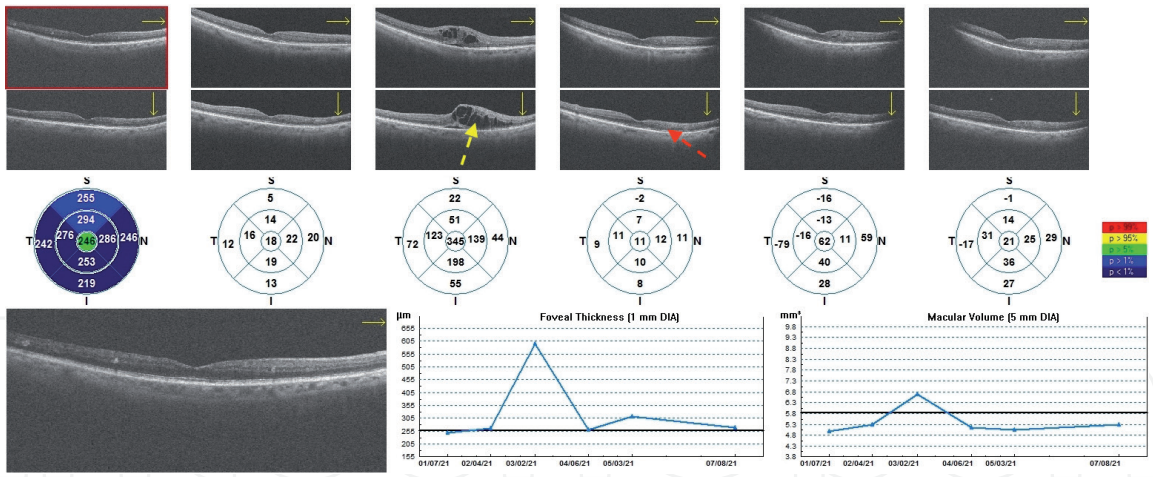
Figure 9.
This serial OCT shows longitudinal follow-up of a case of recurrent macular edema, which resolves after initial treatment with intravitreal Ranibizumab. However, recurrence of edema (broken yellow arrow) occurs after an attempt at extending the injection interval from monthly to two monthly, then three monthly (treat and extend protocol). The resolution of edema (broken red arrow) occurs again after repeating intravitreal injection of Ranibizumab. The macula remains dry at subsequent visits.

diagnosing DME when compared to fundus stereo photography and biomicroscopy [78], see **Figures 1, 3** and **5**. It is currently the gold standard for the diagnosis and monitoring of DME.

It is used to determine whether DME is center-sparing or center -involving, an essential criterion in determining treatment [78]. A limitation noted is that image segmentation could be a problem in eyes with marked DME and dome-shaped macula [88].

OCT not only identifies the presence or absence of disease activity such as the intra-retinal fluid (IRF) and the sub-retinal fluid (SRF) as seen in DME, it localizes them in the retina. It allows for quantification to assess the disease's response to anti-VEGF therapy [89], as demonstrated in **Figure 9**. It has been demonstrated that OCT using microstructural changes seen in IRF and SRF at baseline can prognosticate response to intravitreal treatments [90].

III. Certain features of retinal morphology seen on the SD-OCT, such as central subfoveal thickness (CST), vitreoretinal interface abnormalities, and the epiretinal membrane (ERM), can be used as surrogate markers and act as predictive factors for visual acuity (VA) outcomes in the treatment of DME [91–93]. CST was initially used as a predictor of visual outcome after treatment due to the ease of identifying and obtaining this parameter, but this had limitations [92]. Consequently, other aspects of OCT have been investigated to determine their usefulness as possible bio-markers and correlations for VA and treatment outcomes. These include an external limiting membrane (ELM) and ellipsoid zone (EZ) disruption, and disorganization of retinal inner layers (DRIL) [91, 92]. Sun et al. described an OCT feature termed disorganization of the inner retinal layers (DRIL) [94]. It was observed that an improvement in DRIL following treatment for DME was predictive of better VA outcomes. There was an association with VA after the resolution of centre-involving DME [95, 96]. An association between DRIL, the disruption of the outer retina, and increasing DR severity have been observed [91].

IV. The role of OCT-A is evolving as a tool in the evaluation of DME. OCT-A is an imaging technique that uses motion contrast and faster scan speeds, including spectral-domain (SD) and swept-source (SS), to obtain three-dimensional cubes, which then undergo automated segmentation into layers [82], as seen in **Figure 10**. In DME, as with FFA, OCTA can visualize the increase in the size of the fovea avascular zone (FAZ) and perifoveal intercapillary area [97], seen in **Figure 11**. It can also
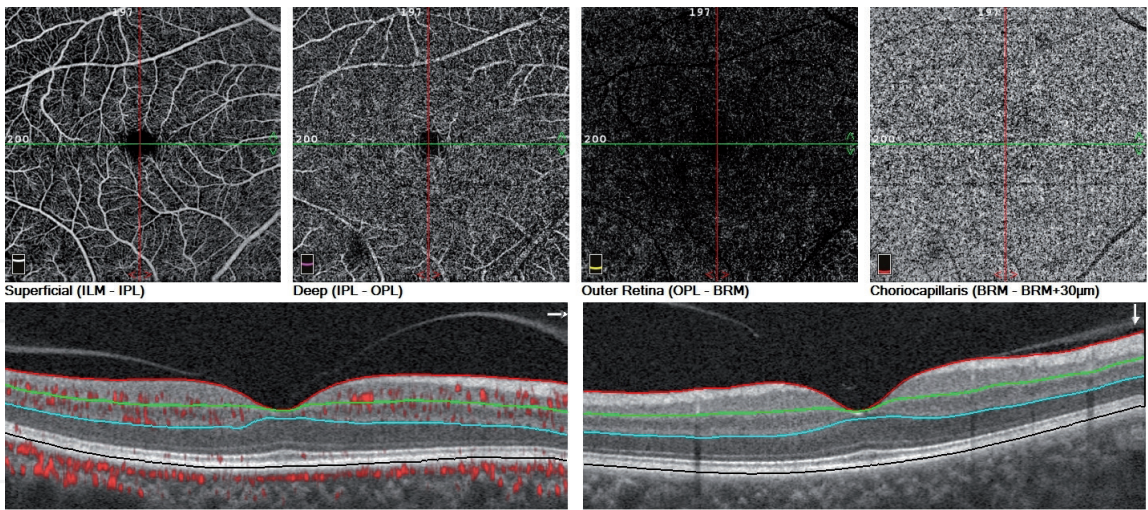
Figure 10.
A normal OCT-Angiography (OCT-A) scan of the right eye, showing the four segmented layers, including superficial and deep plexi, outer retina and the choriocapillaris layers. Also shown are the cross sectional OCT scans, highlighting the borders and planes of tissue segmentation.
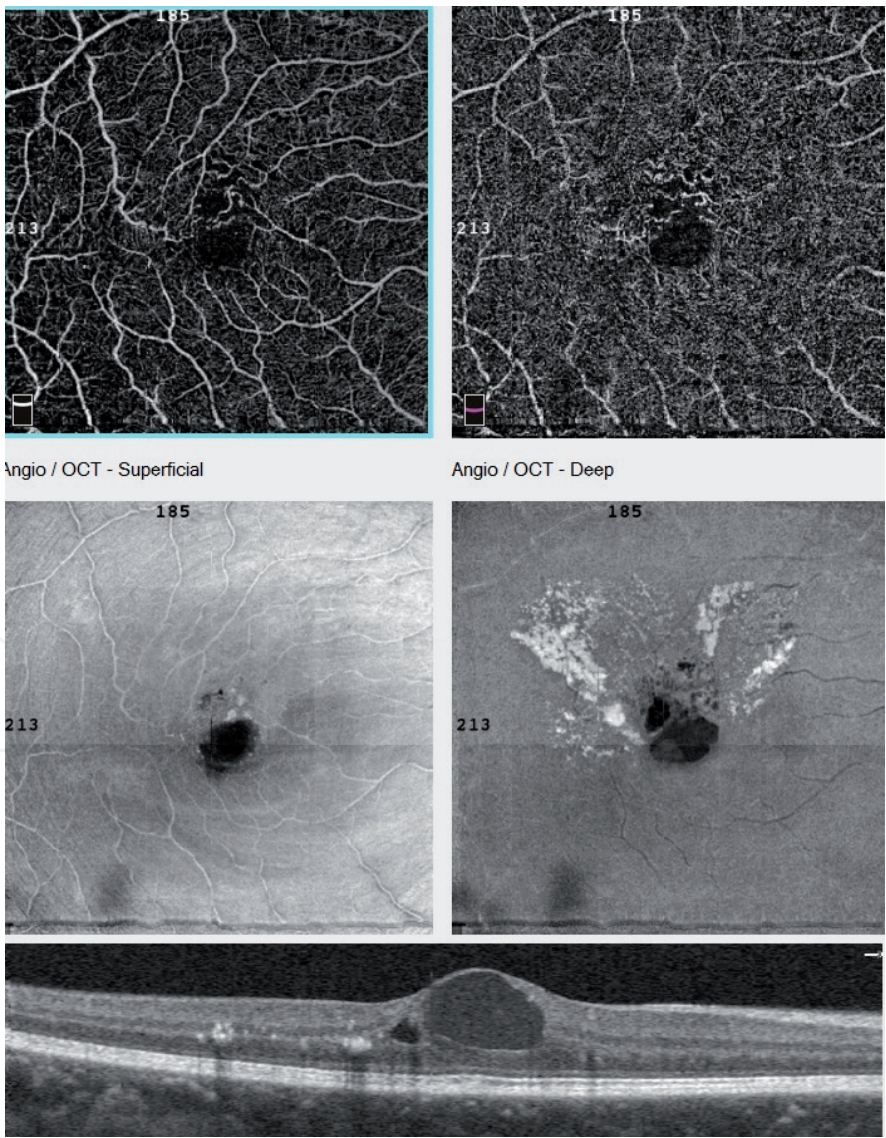

Figure 11.
OCT-A, showing a well perfused macular and what looks like shunt vessels within the foveal avascular zone. The en face OCT images show radiating hard exudates centered on the fovea. The cross sectional OCT shows large intra retinal cystic space in the fovea, and there is aggregation of hard exudates observed within the retina (outer nuclear layer) microstructure.

study the retinal vascular plexuses in layers, determine microvascular parameters, and correlate them with functional and morphological data [98].

The advantages of OCT-A are: It provides "3-D" imaging information of the macula and visualizes peripapillary capillaries [99]. It is dye-free, thereby suitable for patients with adverse reactions to the dyes and poor intravenous access or renal failure [100]. It is reproducible with a faster acquisition time [99, 101]. An advantage of OCT-A over conventional FA is that the absence of dye leakage using OCT-A enables visualization of the distinct margins and sizes of neovascularization since there is no leaking of dye to obscure the neovascularization complex's margins seen in the later frames of the FFA [33]. The disadvantages of OCT-A include its inability to visualize leakage of dye in the retina, a common feature of inflammatory vascular pathology, and a sign of blood-retinal barrier breakdown [100]. Limitation to detecting peripheral retinal ischemia as it can scan mostly the posterior pole [100]. Studies suggest that in the future management of DME, OCT-A could be used to prognosticate the evolution of visual acuity with the help of biomarkers such as low vascular density (VD) and enlargement of the foveal avascular zone (FAZ) [102–104]. OCT-A could also be used to aid in the monitoring of the response of DME to anti-VEGF treatment such as Ranibizumab since poor responders show significant damage to the DCP, but not SCP [105, 106].

Initially, the major limitation of OCTA was the small field of view, with the greatest resolution achieved at smaller scanning sizes such as the commonly used 3 × 3 mm scan [33, 82]. Wider field OCTA scans are already available such as the 9 × 9 mm and 12 × 12 mm. Experimental wide-field OCTA using faster scanning OCTA is being researched and could be available in the future [102, 103, 107].

Other drawbacks noted are that OCTA is subject to projection artifacts. Vasculature from outer layers is projected onto the deep plexuses and choriocapillaris, affecting the accurate interpretation of vascular pathology in the deeper layers. It is also prone to movement artifact; patient movement presents as horizontal white lines, and artifact blinking appears as black lines across the image [83]. Solutions to artifacts include the incorporation of software to correct the motion artifacts [108].

Visual acuity is still viewed as the gold standard in clinical settings for assessing vision using the Snellen or ETDRS charts, but it does not entirely reflect functional vision [109, 110]. Functional vision depicts the impact of sight on the quality of life as expressed by the patient [109]. Various visual function disturbances such as waviness, relative scotoma, and reduction in contrast sensitivity are known to precede loss of visual acuity in patients with DME. However, they are not assessed and quantified during a routine eye examination. For assessing these abnormalities, microperimetry is used to identify vision-threatening retinopathy before visual acuity is affected. Microperimetry is a diagnostic tool used to assess retinal sensitivity while the fundus is directly examined; it enables exact topographic correlation between macular pathology and corresponding functional abnormality [109, 110]. It is rapid, safe, and non-invasive [110]. Microperimetry is of value in prognosticating the functional outcome as foveal thickness returns to normal following the treatment of DME [109]. Microperimetry has been used to demonstrate low retinal sensitivity present in the areas of capillary drop out in eyes with ischemic DME [111].

Multifocal electroretinogram is an electrophysiologic test. It is used to objectively identify functional changes of the retina in the early phases of DR and DME [112] and is also helpful for objectively monitoring eyes on intravitreal antiVEGF treatment such as Ranibizumab for DME [113].

4. Treatment of DME

4.1 Systemic control

The control of all systemic risk factors is vital in the treatment of DME. Optimizing control of diabetes, hypertension, and serum lipids should be emphasized. Optimization of care involves visits to the internist. The intervention aims to reduce glycated hemoglobin, elevated blood pressure, and elevated serum lipids to produce measurable effects in macular thickness in as little as six weeks [114].

The Diabetes Control and Complications Trial (DCCT) reported that tight blood glucose control in patients with type 1 diabetes reduced the cumulative incidence of macular edema at 9-year follow-up by 29% and reduced the application of focal laser treatment for DME by half [115, 116].

The United Kingdom Prospective Diabetes Study (UKPDS), a randomized clinical trial of patients with type 2 diabetes, reported that tighter blood glucose control reduced the requirement for laser treatment at ten years by 29%, compared with looser control; 78% of the laser treatments were for DME [50]. This study also demonstrated that a mean systolic blood pressure reduction of 10 mm Hg and a diastolic blood pressure reduction of 5 mm Hg over a median follow-up of 8.4 years led to a 35% reduction in retinal laser treatments 78% were for DME [51].

The Action to Control Cardiovascular Risk in Diabetes (ACCORD) eye study compared the progression of DR in a Simvastatin plus placebo group, Simvastatin plus fenofibrate group. The rate of progression of DR was lower in the fenofibrate group than in the placebo group [117].

High plasma cholesterol may be associated with more severe hard exudates at the macula [118, 119]. It has been reported that oral Atorvastatin reduced lipid migration to the subfoveal region and decreased the severity of hard exudates in type 2 DM patients with dyslipidemia who had CSME [120]. Nephropathy and anemia can contribute significantly to the risk of DR and DME. Weight loss and cessation of smoking are also crucial in preventing DR and DME.

4.2 Observation

The DRCR Network, Protocol V study, addressed the management of well-controlled DM with center involving DME (CI - DME) and good vision. Randomization of study participants was to observation, focal laser, and intravitreal Aflibercept [121]. The results suggest that patients with CI-DME and good vision (20/25 or better) can be managed initially with observation and close follow-up. These eyes should receive treatment if they suffer a decrease in vision.

For many years, focal and or grid macular laser photocoagulation (MLP) was the gold standard for DME treatment; newer laser techniques are now available. These minimize the side effects of a traditional laser. Intravitreal anti-Vascular endothelial growth factor (anti-VEGF) injections are now the mainstay of CI-DME. Although intravitreal anti-VEGFs have become popular, intravitreal steroids are often indicated in the treatment of DME. Vitrectomy is also used to treat DME. Combination therapy is another strategy employed for treating DME.

4.3 Intravitreal anti-vascular endothelial growth factors (anti VEGF).

Anti VEGFs inhibit upregulated VEGF, which has been implicated in the pathogenesis of DME. The efficacy of anti-VEGF injections in DME has been demonstrated by several studies [122–125]. Anti-VEGF therapy, however, requires frequent intravitreal

injections that are difficult to transpose to clinical practice. Thus, fewer injections are administered in clinical practice than in clinical trials; this contributes to decreased efficacy as the results of clinical trials have been difficult to replicate in real life [126].

4.3.1 Pegaptanib

The first anti-VEGF drug used to treat DME was Pegaptanib (Macugen®, Bausch and Lomb, Rochester, NY, USA), which selectively blocks the 165-isoform of VEGF [127]. A phase II trial by the Macugen Diabetic Retinopathy Study Group reported that at 36 weeks, Pegaptanib led to better BCVA gain, a more significant reduction in central macular thickness (CMT), and less requirement for laser in DME when compared to sham [128]. However, it has been observed that Pegaptanib is less effective at improving visual outcomes than other anti-VEGF agents that target all VEGF-A isoforms [129].

4.3.2 Bevacizumab

Bevacizumab, a humanized monoclonal antibody that inhibits VEGF, was initially developed as a concomitant medication for use in combination with existing metastatic colorectal cancer regimens [130]. The FDA does not approve it for the treatment of DR or DME. However, the intravitreal Bevacizumab or laser therapy in the management of diabetic macular edema (BOLT) study examined the efficacy of Bevacizumab versus focal laser for DME and reported that Bevacizumab is superior to focal laser alone [131].

Patients in the Bevacizumab group showed significant BCVA improvement over patients in the laser group [131]. Bevacizumab costs much less than the FDA-approved intravitreal anti-VEGF drugs [132]. It is, therefore, more cost-effective in treating DME than Ranibizumab or Aflibercept [133, 134]. It is usually given as a 1.25 mg in 0.05 ml dose. The incidence of severe ocular and monocular adverse events was low for intravitreal Bevacizumab [135].

4.3.3 Ranibizumab

Ranibizumab (IVR, Lucentis®, Novartis, Basel, Switzerland) is a fully-humanized monoclonal antibody fragment that binds to VEGF-A's multiple variants [136]. The Ranibizumab for Diabetic Macular Edema (A Study of Ranibizumab Injection in Subjects With Clinically Significant Macular Edema With Center Involvement Secondary to Diabetes Mellitus (RIDE) and A Study of Ranibizumab Injection in Subjects With Clinically Significant Macular Edema With Center Involvement Secondary to Diabetes Mellitus (RISE) trials investigated the use of monthly Ranibizumab given in two doses—0.5 and 0.3 mg—for the treatment of DME [137]. The FDA approves it for the treatment of DME and DR at a dose of 0.3 mg monthly.

Port Delivery System (PDS) with Ranibizumab is a permanent refillable eye implant, approximately the size of a grain of rice, designed to deliver a customized formulation of Ranibizumab continuously over an extended duration, i.e., six months; potentially reducing the treatment burden associated with frequent eye injections [138].

The LADDER trial demonstrated that PDS with the 100 mg/mL formulation is non-inferior to monthly intravitreal injections of Ranibizumab in terms of visual and anatomical outcomes in neovascular age related macular degeneration (AMD) eyes [139]. In the ARCHWAY trial, 98.4% of PDS patients could go six months without needing additional treatment and achieved vision outcomes equivalent to in AMD patients receiving monthly Ranibizumab injections, a

current standard of care [138]. Therefore, PDS could reduce the number of anti-VEGF treatments to two per year.

It is surgically implanted via a specialized tool through an incision in the sclera and pars plana. Reported adverse effects include conjunctival bleb, vitreous hemorrhage, conjunctival erosion, conjunctival retraction, endophthalmitis, rhegmatogenous retinal detachment, and hyphaema [138].

Two trials, PAGODA (will evaluate the efficacy, safety, and pharmacokinetics of the PDS With Ranibizumab in participants with DME compared with intravitreal Ranibizumab) and PAVILION (a multicenter, randomized study in participants with diabetic retinopathy without center-involved DME to evaluate the efficacy, safety, and pharmacokinetics of Ranibizumab delivered via the PDS relative to the comparator arm) are underway to study the safety and efficacy of PDS in subjects with DME and those with DR without CI-DME [140, 141].

4.3.4 Aflibercept

Aflibercept (IVA; VEGF-trap eye, Eylea, Regeneron Pharmaceuticals, NY, USA) is a recombinant chimeric fusion protein containing the second domain of VEGFR-1 and the third domain of the VEGFR-2 attached Fc portion of human IgG1 [142]. It has a dimeric structure, the molecular weight of the protein is 97kD, and the total molecule after glycosylation is 115kD [143]. Aflibercept acts as a decoy receptor binding VEGF-A, VEGF-B, and PlGF, thereby preventing their binding with their original receptors [144]. VEGF-A binds to both VEGFR-1 and VEGFR-2, but PlGF binds to only VEGFR-1. The FDA approves it for the treatment of DME and DR in patients with DME at a dose of 2 mg. It was studied in the Intravitreal Aflibercept for Diabetic Macular Edema (VISTA and VIVID) trials which compared Aflibercept with a focal laser to treat DME [145]. These studies demonstrated the superiority of Aflibercept over laser in terms of visual acuity improvement.

A comparative effectiveness randomized clinical trial compared Bevacizumab with Ranibizumab and Aflibercept for DME and found that all three agents are effective treatments at the two-year follow-up [146]. However, in eyes with visual acuity of 20/50 or worse, Aflibercept was superior to Ranibizumab and Bevacizumab at one year. In contrast, at two years, Aflibercept was no longer superior to Ranibizumab but remained superior to Bevacizumab [132, 147].

A concomitant effect of intravitreal anti-VEGF treatment for DME noticed with Ranibizumab and Aflibercept is improvement in retinopathy severity or slowing of the rate of progression of retinopathy [148]. Another concomitant effect is thinning of the choroid [149, 150].

4.3.5 Brolucizumab

Brolucizumab (IVBr, Beovu; Novartis; Basel, Switzerland), a single-chain antibody fragment, was approved for the treatment of nAMD in October 2019 and in February 2020 in the USA and the European Union [151]. The potential benefits of Brolucizumab are assumed to be related to its low molecular weight with subsequent better tissue penetration as well as higher molar concentration [152, 153]. Its use is mentioned here for completeness. It is no longer in "popular" use due to safety concerns. Brolucizumab was associated with reports of intraocular inflammation (IOI) and retinal vasculitis with or without occlusion [154, 155].

Positive 1-year results of the phase III KESTREL and KITE studies, evaluating the efficacy and safety of Beovu (Brolucizumab) 6 mg in DME were reported. Both studies met their primary endpoints of noninferiority in the change in BCVA from

baseline for Beovu 6 mg versus Aflibercept 2 mg at year one [156]. However, the Beovu trials have been discontinued because Beovu was associated with higher rates of intraocular inflammation, including retinal vasculitis and retinal vascular occlusion versus Aflibercept [157].

4.3.6 Faricimab

Faricimab is a novel anti-Ang-2/anti-VEGF bispecific antibody designed explicitly for intraocular use [158, 159]. It is assembled using Roche's CrossMAb technology (Basel, Switzerland) and binds both VEGF-A and Ang-2 with high affinity and specificity [158, 160]. Faricimab is the first investigational bispecific antibody designed for the eye [161].

It targets two distinct pathways – via angiopoietin-2 (Ang-2) and vascular endothelial growth factor-A (VEGF-A) – that drive several retinal vascular diseases [161]. Ang-2 and VEGF-A contribute to vision loss by destabilizing blood vessels, causing new leaky blood vessels to form and increasing inflammation [162]. By simultaneously blocking both pathways involving Ang-2 and VEGF-A, Faricimab is designed to stabilize blood vessels, potentially improving vision outcomes for a longer duration in patients living with retinal conditions [162].

Faricimab is a promising molecule that is still undergoing investigation primarily for nAMD. The STAIRWAY Phase 2 Randomized Clinical Trial concluded that at week 52, Faricimab dosing every 16 weeks and every 12 weeks resulted in maintenance of initial vision and anatomic improvements comparable with monthly Ranibizumab [163]. TENAYA and LUCERNE phase 3 trials evaluate the efficacy, safety, and extended durability of up to 16 weekly dosing of intravitreal Faricimab in patients with nAMD [164]. YOSEMITE and RHINE are ongoing trials evaluating the efficacy, durability, and safety of Faricimab 8 weekly or a protocol-driven regimen based on treat-and-extend in DME patients [165]. Positive first-year results have been reported for Faricimab, which may emerge as an essential option if equivalent second-year results are reported with no safety flags.

4.4 Regimens

There is no consensus about the ideal treatment regimen with anti-VEGF agents [166]. Different treatment algorithms have been studied in clinical trials for AMD and applied in clinical practice, including monthly injections (ANCHOR, MARINA, CATT, HARBOR, EXCITE, IVAN, VIEW) as needed 'pro re nata' PRN (SUSTAIN, MONT BLANC, SAILOR, CABERNET, PrONTO, IVAN, CATT, HARBOR, OCTAVE), and 'treat and extend' regimen (TREND, LUCAS) [167].

Monthly maintenance dosing is a tremendous burden for both patients and the healthcare system. It has a real risk of overtreatment. The pro re nata (PRN) regimen is a treatment protocol where follow-up intervals remain fixed. At the same time, decisions to carry out an injection are based on the anatomic findings at each respective visit [168]. The PRN regiment has a risk of undertreatment or overtreatment, and patients may fail to attend. A treat-and-extend regimen (TER) is an individualized dosing scheme of titrating the injection interval based on the patient's response [169]. Therefore, if a patient shows no sign of active disease (e.g., the macula remains dry, without any leakage), intervals will be extended; if there is fluid accumulation, the next interval will be shortened. Fixed dosing lacks long-term practicability in real-world settings due to overtreatment and high costs; thus, PRNs or TERs have been suggested as feasible alternatives [169]. TERs have advantages: their cost-effectiveness due to less frequent visits and increased efficacy

based on proactive treatments. However, TER involves more injections than a PRN regimen, leading to overtreatment [170].

4.5 Side effects of intravitreal injection of anti VEGFs

Endophthalmitis, intraocular inflammation (IOI), rhegmatogenous retinal detachment, intraocular pressure elevation, and ocular hemorrhage have been reported as complications of intravitreal anti-VEGF injections [171]. There are reports of ocular inflammatory events with Brolucizumab intravitreal injection [172, 173]. Recently, occlusive retinal vasculitis has been reported with the use of Brolucizumab. For this reason, the use of Brolucizumab has been discontinued. Furthermore, the experience with Brolucizumab has increased the surveillance by an ophthalmologist of drug-related IOI.

Intraocular silicone oil droplets and protein aggregates have also been reported with intravitreal anti-VEGF injections [174]. Several systemic adverse events of anti VEGFs have been reported in different studies, including systemic hypertension, cerebrovascular accidents, heart attacks, and death [175, 176].

About 40–60% of eyes that receive anti-VEGF injections show an insufficient response with recurrent and persistent macular edema, even after repeated injections [177, 178].

4.6 Intravitreal steroids

4.6.1 Corticosteroids

Corticosteroids inhibit leukostasis, adhesion, transmigration of leukocytes and downregulate the expression of prostaglandins, cytokines, and growth factors, especially VEGF [179]. They also alter the composition of the basal endothelial membrane by changing the local ratio of laminin isoforms, suppressing basement membrane dissolution, and strengthening tight junctions to limit permeability and leakage [180]. Long-term steroid use may have a neuroprotective effect on the retina [181].

Corticosteroids are now usually second-line therapy. Some of the indications for intravitreal steroids in DME include non-response to anti-VEGF, non-compliant patients, pregnancy, history of recent arterial thromboembolic events (ATEs), patients with hard exudates (HE) at the center of the fovea, pseudophakic patients (there is no risk of cataract) and vitrectomized eyes [182]. In vitrectomized eyes, corticosteroid intravitreal implants release drugs at a constant rate and provide predictable pharmacokinetics [183, 184].

In clinical trials that studied the use of intravitreal steroids in treating DME, pseudophakic eyes were shown to have better visual acuity (VA) outcomes than phakic eyes [185, 186]. The DRCRnet, protocol U concluded that pseudophakic patients with persistent DME showed better VA outcomes with combination treatment of Ranibizumab and Dexamethasone intravitreal (DEX) implant compared with Ranibizumab alone [187].

4.6.2 Dexamethasone sustained-release implants

Dexamethasone intravitreal (DEX) implant (0.7 mg) (Ozurdex, Allergan, Inc., Irvine, CA, USA) consists of micronized dexamethasone in a biodegradable copolymer of polylactic-co-glycolic acid, which slowly releases steroids into the vitreous for about 6 months [188, 189]. In 2014, based on the results of the MEAD study [190], the FDA and most European countries approved Ozurdex for the treatment

of DME. DEX is a potent anti-inflammatory agent; its potency is twice that of Fluocinolone acetonide (FA) and 5-fold more than Triamcinolone Acetonide (TA) [191]. In contrast to TA, the pharmacokinetics of the DEX implant were not significantly different in vitrectomized and nonvitrectomized animal eyes [192]. There have been reports of the benefits of using DEX implant in naive DME as a first-line option [193, 194] and the advantages of early switching in patients not responding to anti-VEGF [195].

4.6.3 Fluocinolone acetonide (FA) implant

FA has a 25-fold higher anti-inflammatory potency than cortisol [196]. It has selective and potent agonist properties by binding to the cytosolic glucocorticoid receptor with high affinity; it is devoid of mineralocorticoid activity [197–199]. FA is available as an intravitreal implant. It is small (3.5 mm in length, 0.37 mm in diameter), non-biodegradable, and designed for injection using a 25-gauge injector via the pars plana into the vitreous cavity [200]. The approved implant (ILUVIEN®) contains 0.19 mg of FA initially released at 0.25 μg/day (average, 0.2 μg/day); it lasts 36 months [201]. The Fluocinolone Acetonide for Diabetic Macular Edema (FAME) studies evaluated the use of 2 different FA doses (0.2 vs. 0.5 μg/day) compared to sham injections [202, 203]. This study showed the efficacy of FA implants for chronic DME that is resistant to conventional treatment.

4.6.4 Triamcinolone Acetonide (TA)

TA has a 7.5-fold higher anti-inflammatory potency than cortisone [204]. It was the first widely used intravitreal injectable medication for DME [205]. Several clinical trials have shown the efficacy of TA in the treatment of DME [206–208]. TA Half-life in the vitreous of a nonvitrectomized eye has been reported as 18.6 days, in contrast to a much shorter duration in a vitrectomized eye, 3.2 days [209]. A single intravitreal injection of 4 mg of TA lasts approximately three months in the nonvitrectomized human eye [209, 210]. DRCR.net Protocol B investigated the efficacy and safety of 1 mg and 4 mg doses of TA compared with focal or grid laser photocoagulation and concluded that focal laser was superior to intravitreal triamcinolone [211, 212].

4.6.5 Adverse effects

Adverse effects of intravitreal steroids include ocular hypertension, cataract, infectious endophthalmitis, pseudo endophthalmitis, and sterile endophthalmitis [213]. A steroid-induced cataract is the most common adverse event of intravitreal corticosteroids [213]. Up to 50% of eyes injected with intravitreal corticosteroid will develop elevated intraocular pressure [214, 215]. Both the DEX and FA implants have been reported to migrate into the anterior chamber, potentially leading to corneal edema, corneal endothelial decompensation, and ocular hypertension [216, 217]. The DEX implant has been accidentally injected into the crystalline lens rather than into the vitreous cavity [218]. In terms of outcomes, Gillies et al. reported that the Dexamethasone implant (Ozurdex, Allergan) was as efficacious as Bevacizumab in reducing DME [219].

4.7 Macular laser photocoagulation for DME

4.7.1 Macular laser photocoagulation (MLP)

MLP was the first proven treatment for DME [220, 221]. Though its mechanism of action is not entirely understood, it improves DME through several proposed

mechanisms. Photoreceptors and retinal pigment epithelium RPE cells are destroyed via a photothermal mechanism, thus reducing oxygen consumption. The reduced oxygen consumption in the outer retina is postulated to increase oxygen flux from the choroid to the inner retina, causing arteriolar constriction and decreased hydrostatic forces that drive edema [222].

Photocoagulation also induces changes to the RPE cells, causing their proliferation and releasing cytokines such as transforming growth factor-beta TGF-β, which antagonize the effects of VEGF [223].

The Early Treatment Diabetic Retinopathy Study (ETDRS) demonstrated a 50% reduction in moderate vision loss in patients with clinically significant diabetic macular edema (CSME) who underwent immediate focal laser photocoagulation [221]. MLP causes iatrogenic tissue damage, subretinal fibrosis, choroidal neovascularization, and laser scar enlargement [224, 225].

The DRCR.net re-examined this coagulation technique and reported it as a modified (m) ETDRS focal/grid photocoagulation protocol [226], but the risk of macular tissue damage remained.

The DRCR.net Protocol A reported that mETDRS laser is better than modified macular grid laser for DME while DRCR.net Protocol B noted that mETDRS focal laser is superior to intravitreal triamcinolone for DME [227]. DRCR.net Protocol K also reported that 20–60% of eyes that initially respond to focal laser might continue to improve after four months, suggesting durability of effect [228]. The macular laser had been considered the gold standard for many years [229]. According to the European Society of Retina Specialists (EURETINA) guidelines, focal/grid laser is now reserved mostly for non-center-involving DME [78].

4.7.2 Subthreshold micropulse diode (SDM) laser photocoagulation

SDM has been used in the treatment of DME [230–232]. Compared with conventional laser photocoagulation, SDM is a tissue-sparing technique: it avoids protein coagulation and prevents retinal scars, allowing retinal anatomic and functional preservation [233]. It has been hypothesized that SDM, by inducing a controlled thermal elevation of the retinal tissue, can selectively stimulate the retinal pigment epithelium (RPE) [234, 235]. Its advantages include the absence of RPE scarring, no subsequent choroidal neovascularization, and elimination of paracentral visual field scotomas [232, 236]. Its disadvantages include no visible endpoint for treatment, making it difficult to determine where treatment has and has not been applied. Furthermore, there is no standardized, consensus set of treatment parameters or guidelines for treatment within the foveal avascular zone. The reduction in macular edema after subthreshold laser photocoagulation occurs with a slower time course, and more treatments are necessary to eliminate edema [232]. Some randomized clinical trials have demonstrated that subthreshold grid laser treatment is as effective as conventional focal/grid laser photocoagulation, though slower in terms of resolution of DME, in achieving the same functional and anatomical effects [237, 238]. There have been reports of the benefits of combining SDM and intravitreal anti VEGFs in treating DME [239, 240].

4.7.3 Selective retinal therapy (SRT)

SRT is a laser procedure in which the RPE is selectively damaged without affecting the neural retina and choroid [241–243]. A microsecond pulsed laser is used to induce an instantaneous temperature rise just at the melanosomes

within RPE cells, which leads to the formation of microbubbles around these melanosomes. Their temporary expansion results in a cell volume expansion and eventually mechanical cellular disruption without increasing temperature in the surrounding tissue. Studies have shown that SRT is effective in treating DME [243, 244].

4.7.4 Patterned scanned laser (PASCAL)

In PASCAL, the shorter pulse duration is used in an array of multiple burns to provide speed, better spatial localization, and reduced collateral damage by providing more precise control of the depth of the impact [245]. PASCAL is an ideal laser method to place the accurate "subthreshold" (subvisible) focal-grid laser in DME in contrast to conventional laser therapy [246, 247]. The advantages of PASCAL over conventional laser therapy include shorter treatment duration, increased safety, uniform, and precise spot placement, accurate "subthreshold" grid-pattern placement, and reduced pain and visual field defect [248]. However, the efficacy of PASCAL laser appears to be diminished compared to conventional laser therapy when the same number of laser spots were delivered [249].

4.7.5 Navigated laser (NAVILAS)

NAVILAS is a fundus imaging and laser treatment device developed by Neubauer et al. (OD-OS GmbH, Teltow, Germany) [250, 251]. The device utilizes retina navigation via computerized image capture and tracking assistance with high precision and reproducibility of <60–110 um [250]. It appears that the rate of retreatment for DME is reduced with NAVILAS when compared to the conventional mETDRS focal laser technique [251].

A 92% hit rate of microaneurysm via NAVILAS compared to 72% in conventional laser focal coagulation has been reported [252]. Focal laser therapy using NAVILAS will have more impact in the future to improve visual acuity and reduce the burden of anti-VEGF injection numbers in patients [253, 254].

4.8 Vitrectomy for DME

Optical coherence tomography has shown that vitreomacular adhesion is a risk factor for DME [255], as illustrated in **Figure 5**. Complete separation of posterior hyaloid with Posterior Vitreous Detachment (PVD) is associated with a decreased rate of DME [256]. Vitrectomy removes traction, improves macular oxygenation, removes VEGF and pro-inflammatory cytokines, and allows additional endolaser and steroids placement [257]. It was introduced for treating eyes with a taut posterior hyaloid adherent to the macula, often associated with shallow traction macular detachment, which had failed previous focal/grid laser [258, 259], as can be seen in **Figure 5**. It has also been used to treat eyes with an attached but non-thickened, non-taut posterior hyaloid or for eyes with persistent DME despite previous focal laser or intravitreal triamcinolone injection regardless of the status of the posterior hyaloid [260, 261], Illustrated in **Figures 12** and **13**.

Vitrectomy has been used as a potential primary therapy in eyes with more severe edema and greater visual acuity loss at presentation [262, 263]. Reports on the outcome of vitrectomy for DME are conflicting; some reports suggest that vitrectomy reduces macular thickening but does not improve visual acuity [264, 265]. Others have report improved visual acuities simultaneous with decreases in macular thickening or lagging behind the reduction in macular thickness by a
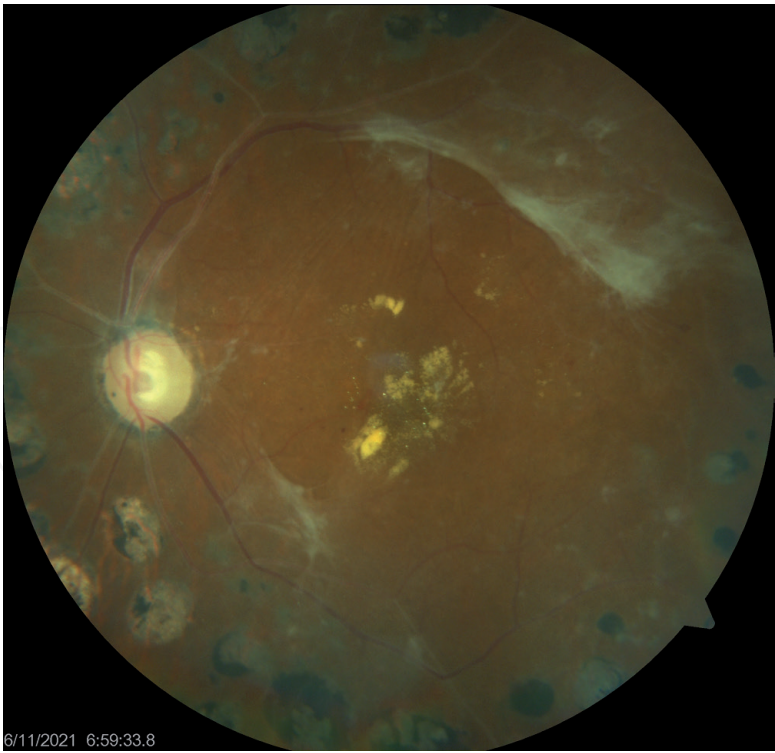
Figure 12.
This is a fundus photograph of the left eye in a patient who suffers a combination of DME and proliferative diabetic retinopathy (PDR). This eye has had vitrectomy with pan-retinal laser photocoagulation for the treatment of PDR. Notice residual fibrovascular proliferation within the superotemporal vascular arcade. Conspicuous hard exudates cluster in the foveomacula region, with few microaneurysms located inferio-nasal to the hard exudates. Retinal laser photocoagulation marks are present. There is also a pale cupped optic disc and sheathing of the retinal arteries and veins.
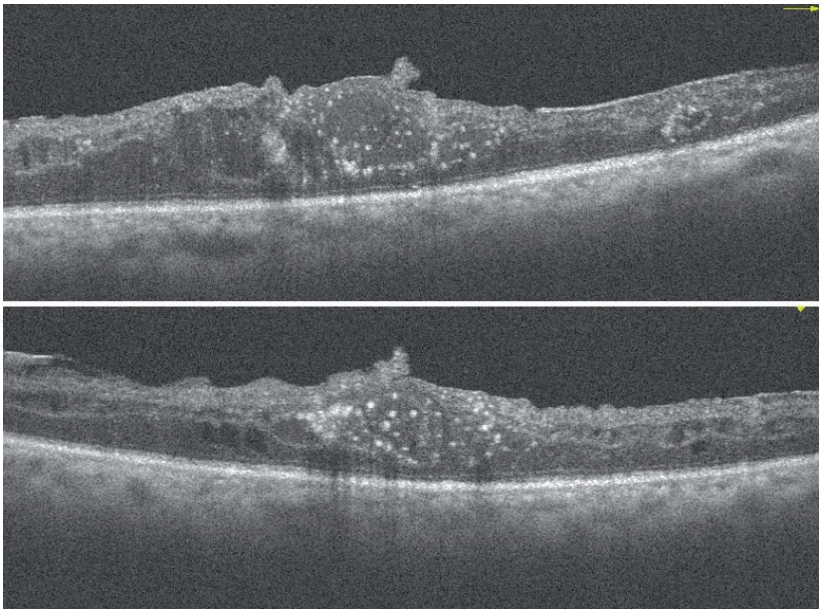

Figure 13.
*OCT of the fundus photography in **Figure 12**. This shows significant thickening of the fovea and loss of the normal foveal depression, disorganization of the intraretinal microstructure, aggregation of hard exudates, intraretinal cystoid spaces, and epiretinal membranes. This patient would have benefited from peeling of the internal limiting membrane during the vitrectomy. Post vitrectomized eyes with persistent DME can benefit from intravitreal steroid injections, e.g., Orzudex implant. Intravitreal steroids are beneficial in pseudophakic and aphakic eyes, in which the risk of cataract formation does not exist.*

few months [266, 267]. There have also been reports of improved visual acuity in cases with macular traction but no visual improvement in cases without traction [268, 269].

4.9 Plasma kallikrein inhibitors

Plasma kallikrein is highly upregulated in vitreous patients with DME [270]. It is a mediator of vascular leakage and inflammation. There is evidence that it is involved in DME pathogenesis in VEGF independent fashion and VEGF interdependent mechanisms [271]. Several small molecules and bicyclic peptides targeting the plasma kallikrein/kinin system are currently under investigation for DME treatment via intravitreal, oral, and topical administrations [271]. These include KVD001 (KalVista Pharmaceuticals) a highly potent and selective plasma kallikrein inhibitor, currently being developed as an intravitreal therapy), THR-149 (Oxurion NV), RZ402 (Rezolute Bio), and VE-3539 (Verseon Corp) [271]. Orally administered plasma kallikrein inhibitors are efficacious in reducing retinal edema and preserving retinal function in preclinical models. Plasma kallikrein inhibition is emerging as a promising new treatment modality for DME [271].

5. Clinical Studies in DME

The evidence for much of the guidelines on DME management has been gathered from clinical trials that have provided information on the safety and efficacy of different therapeutic options, investigated the systemic associations in patients diagnosed with DME, and considered newer and better therapies. This section will provide an overview of DME trials and emphasize the most important findings. Emphasis will be placed on those pharmacotherapies in current use (especially intravitreal injectable drugs).

As mentioned earlier, VEGF plays a central role in the pathogenesis of DME by increasing vascular permeability and blood flow in the setting of microvascular damage secondary to prolonged hyperglycemia. Therefore, intravitreal anti-VEGF has become the standard of care in the treatment of several forms of DME. In many cases, DME can be reversed, and this is associated with sustained improvements in vision. Several RCT have provided data and evidence for the use of intravitreal anti-VEGFs.

Ranibizumab (Lucentis, Genentech, South San Francisco, CA, USA) has been described earlier. It has a molecular weight of approximately 48 kilodaltons as it lacks an Fc region, unlike Bevacizumab. It is prepared in *Escherichia coli* with tetracycline in the nutrient medium. Due to its relatively small size, Ranibizumab penetrates the deeper layers of the retina, including the RPE and choroid.

Ranibizumab was the first anti-VEGF approved by the US Food and Drug Administration (FDA) for the treatment of DME and DR at a dose of 0.3 mg monthly. Also, the 0.5 mg dose has been used for treating DME. The 0.3 mg is as effective as the 0.5 mg. Also, the higher dose was found to confer no additional benefit compared to the 0.3 mg but was associated with more fatalities at three years (i.e., 6.4% compared to 4.4% with 0.3 mg monthly). Furthermore, at three years reported stroke rate was 4.8% and 2%; and adverse thromboembolic events (ATE) were 10.4% and 10.8% with monthly 0.5 mg and 0.3 mg Ranibizumab, respectively. Because of these systemic risks, the FDA approved the 0.3 mg dose of Ranibizumab instead of the 0.5 mg dose. However, a reduced dose is not available for other available anti-VEGF, i.e., Bevacizumab or Aflibercept. It is, however, essential to consider that the occurrence of these systemic adverse events is not uncommon after prolonged diabetes.

RISE and RIDE: These were two landmark trials. RISE was A Study of Ranibizumab Injection in Subjects With Clinically Significant Macular Edema With Center Involvement Secondary to Diabetes Mellitus. RIDE was A Study of Ranibizumab Injection in Subjects Clinically Significant Macular Edema With Center Involvement Secondary to Diabetes Mellitus [137]. These studies compared

two doses of Ranibizumab with sham injections and confirmed the superiority of intravitreal Ranibizumab compared to sham injections. The study investigated using monthly Ranibizumab at two doses (0.5 and 0.3 mg) to treat DME. At month 24, the study results showed that 98% of patients-maintained vision with 0.3 mg monthly intravitreal injections, 34–45% of patients gained at least three lines (15 letters); and mean BCVA gain was 10.9 to 12.5 letters. Significantly higher numbers in the Ranibizumab arm gained >15 letters at month 24 compared to sham ie 44.8% vs. 18.1% in RISE; P < 0.0001, and 33.6% vs. 12.3%; P < 0.0001 in RIDE. Only 45–49% of patients needed macular laser compared with 91–94% in the control group. Also, there was no additional effect with the use of the higher strength 0.5 mg Ranibizumab when compared with the 0.3 mg dose.

In the RISE and RIDE extension phase, patients in the sham control group could cross over and receive monthly Ranibizumab injections in the 3rd year. The 36-month outcomes demonstrated that the rapid and sustained response of Ranibizumab in DME is further maintained for an additional 3rd year of continued monthly treatment. In addition, the group with delayed initiation of Ranibizumab therapy gained fewer letters compared to groups initially randomized to receive Ranibizumab (+4.7 vs. +10.6 letters in the 0.3 mg Ranibizumab arm). This finding suggests that chronic retinal edema (for an average of 4.5 years before Ranibizumab therapy) may result in irreversible loss of vision, and therefore prudent to initiate Ranibizumab therapy earlier. The RISE and RIDE study has become a vital landmark study against which other studies investigating more recent intravitreal pharmacotherapies have been compared.

RESOLVE: Safety and Efficacy of Ranibizumab in Diabetic Macular Edema With Center Involvement. This trial compared Ranibizumab versus sham in DME patients with BCVA of 20/40–20/160. It showed a better mean gain in letters with Ranibizumab than sham (10.3 letters gain versus a loss of 1.4 letters respectively). The patients were given three monthly injections, followed by PRN injections over a 12-month follow-up. A rescue laser could be performed if needed. CMT reduction was also more with Ranibizumab compared to sham. This study also suggested that Ranibizumab treatment was superior to laser (7.8 ETDRS letters gained versus −1.7 ETDRS letters lost).

READ-2: Ranibizumab for Edema of the mAcula in Diabetes-2). This study was A phase II, RCT to compare Ranibizumab alone (group 1), the focal laser alone (group 2), and combination of laser and Ranibizumab (group 3), i.e., randomized patients 1:1:1 to receive 0.5 mg Ranibizumab, laser, or both. Inclusion criteria were BCVA of 20/40–20/320 and CSMT of 250microns. The study demonstrated a BCVA gain of 7.4 letters in the RBZ arm at three months compared to 0.5 letters in the laser arm.

Change in mean BCVA in ETDRS letters at six months for the three groups was +7.24, −0.43, and + 3.8, respectively. However, at 24 months, it was demonstrated that Ranibizumab alone or in combination was superior to laser alone in DME.

READ-3 study (compared regular versus high dose RBZ) was a double-masked, multicenter RCT that evaluated two doses of RBZ (0.5 mg versus 2 mg). The study outcome showed that 2 mg RBZ (high dose) did not show any additional benefits over 0.5 mg dose at the primary endpoint at month 6 (+7.01 in the 2 mg group vs. +9.43 letters in the 0.5 mg group; P = 0.161).

RESTORE: A Twelve-Month Study to Assess the Efficacy and Safety of Ranibizumab (Intravitreal Injections) in Patients with Visual Impairment Due to Diabetic Macular Edema and a 24 month open-label extension study. It was a phase 3 RCT that was designed to compare RBZ with laser therapy. At 12 months, BCVA gain was highest in the RBZ monotherapy arm at the primary endpoint (+6.1 vs. +0.8 letters in the laser arm; P < 0.001).

REVEAL: A phase 3 RCT comparing Ranibizumab with laser. At the 12-month study endpoint, RBZ monotherapy was superior to laser since there was a gain of +5.9 letters in the Ranibizumab monotherapy arm vs. +1.4 letters in the laser arm;

P < 0.001. In addition, RESTORE and REVEAL studies showed that combining Ranibizumab with laser did not improve the BCVA.

LUCIDATE: Lucentis (Ranibizumab) in Diabetic Macular Oedema: Compared macular laser with Ranibizumab or combination in DME. This study further showed that in addition to improvements in BCVA and CMT, treatment of patients with center involving DME with monthly Ranibizumab was associated with an improvement in contrast threshold, retinal sensitivity on microperimetry amplitudes, and implicit times on electrophysiology.

With the use of several studies, the DRCR network answered questions relating to the effectiveness and timing of intravitreal pharmacotherapy use, combination therapy, and retinal laser photocoagulation to treat DR and DME. An example of such a study is Protocol T.

PROTOCOL-T of DRCR.net: Compared Ranibizumab, Bevacizumab and Aflibercept in DME. While the FDA had approved Ranibizumab and Aflibercept, the use of Bevacizumab was off-label. The study results revealed improvement in vision from baseline to one year with all three drugs. Improvement was most significant with Aflibercept (+13 letters) than Ranibizumab (+11 letters) or Bevacizumab (+10 letters), a statistically significant mean difference of 2–3 letters at one year. This difference appeared to be driven by baseline vision. Half of the

Name; Year of Study	Therapeutic Agents	Study Design	Study Outcome
READ -2 (2010)	RBZ / Laser	RCT	Demonstrated that Intraocular injections of Ranibizumab provided benefits for patients with DME for at least two years. When combined with focal or grid laser treatments, the amount of residual edema was reduced, as were the frequency of injections needed to control edema.
RIDE and RISE (2012)	RBZ/Sham	Two parallel Phase III RCT	Demonstrated that Ranibizumab rapidly and sustainably improved vision, reduced the risk of further vision loss, and improved macular edema in patients with DME. RISE: At 24 months, 18.1% of sham patients gained ≥15 letters versus 44.8% of 0.3-mg (P < 0.0001) RIDE: 12.3% of sham patients versus 33.6% of 0.3-mg patients (P < 0.0001).
RESTORE (2011)	RBZ/Laser	RCT	Demonstrated that Ranibizumab alone and combined with laser were superior to laser monotherapy in improving mean average change in BCVA letter score from baseline to month 1 through 12 (+6.1 and + 5.9 versus +0.8; both P < 0.0001).
RETAIN (2016)	RBZ (PRN/T&E)	RCT	Demonstrated the T&E is a feasible treatment option for patients with DME, potentially reducing the treatment burden. Slightly more injections were required versus PRN.
REVEAL (2015)	RBZ/Laser	RCT	Demonstrated that Ranibizumab monotherapy, combined with laser, showed superior BCVA improvements over laser treatment alone in Asian patients with visual impairment resulting from DME.
RESPOND (2015)	RBZ/Laser	RCT	Demonstrated that Ranibizumab as monotherapy or combined with laser resulted in significantly higher improvements in visual acuity and vision-related quality of life at month 12 than laser monotherapy.
RELATION (2018)	RBZ/Laser	RCT	Demonstrated that Ranibizumab plus laser is a valuable treatment option for the management of DME. It also showed that eyes with DME in PDR might also benefit from combined therapy compared to laser alone.

Name; Year of Study	Therapeutic Agents	Study Design	Study Outcome
DA VINCI (2011)	AFL/Laser	Phase II RCT	Demonstrated that significant gains in BCVA from baseline were achieved at week 24 and were maintained or improved at week 52 in all VEGF Trap-Eye groups.
VISTA & VIVID (2015)	AFL/Laser	Two similar Phase III RCT	Demonstrated that in both VISTA and VIVID, the 52-week visual and anatomic superiority of Aflibercept over laser control was sustained through week 100, with similar efficacy in the 2q4 and 2q8 groups.
PROTOCOL I (2011)	RBZ/Triamcinolone/Laser	Phase III RCT	Demonstrated that anti-VEGF given by the protocol-specified prn treatment regimen was very effective for treatment of DME.
PROTOCOL T (2015)	AFL/RBZ/BEVA	RCT (Comparison of 3 Anti-VEGFs for treatment of DME)	Demonstrated that when vision was better than 20/50, the efficacy of all three intravitreal anti-VEGF medications for DME was similar. Bevacizumab thinned the retina less than Ranibizumab or Aflibercept, but the visual acuities were the same up to two years. However, when baseline vision was 20/50 or worse, Aflibercept had a superior benefit over the others with statistically significant better vision results at one year.
PROTOCOL V (2019)	AFL/Laser/Observation	RCT	At two years, the rates of 5 or more letter vision loss were similar in all three groups (16–19%), and the mean vision in each treatment group was 20/20. Given the costs and potential adverse events associated with intravitreal injections and laser, observation is likely a reasonable initial strategy for treatment-naïve eyes with good vision despite center-involved DME as long as these eyes are followed closely and treated with anti-VEGF if vision worsens.
BOLT (2010)	BEVA/Laser	RCT	The study showed that BCVA at 12 months was 61.3+/−10.4 (range 34–79) in the Bevacizumab group and 50.0+/−16.6 (range 8–76) in the laser arm (P = 0.0006). Another finding was central macular thickness decrease from 507+/−145 microns (range 281–900 microns) at baseline to 378+/−134 microns (range 167–699 microns) (P < 0.001) in the Bevacizumab group, whereas it decreased to a lesser extent in the laser group, from 481+/−121 microns (range 279–844 microns) to 413+/−135 microns (range 170–708 microns) (P = 0.02).
BEVORDEX (2014)	BEVA/DEXA	Phase II RCT	Demonstrated that Dexamethasone implant achieves similar rates of visual acuity improvement compared with Bevacizumab for DME, with superior anatomic outcomes and fewer injections. Both treatments were associated with improvement in visual quality-of-life scores. However, more dexamethasone implant–treated eyes lost vision, mainly because of cataracts.
IBERA DME (2015)	BEVA/RBZ	RCT	This study concluded that intravitreal Bevacizumab and intravitreal Ranibizumab are associated with similar effects on central subfield thickness in patients with DME through 1 year of follow-up. Ranibizumab is associated with greater improvement in BCVA at some study visits, and the mean number of injections is higher in the Bevacizumab group.
LUCIDATE (2014)	RBZ/Laser	RCT (Single center)	Demonstrated that Ranibizumab therapy in the treatment of DME appears to improve retinal function and structure and this was demonstrated by this evaluation of different assessment methods including structural imaging and functional measures such as visual acuity, microperimetry, color contrast sensitivity, electroretinography (full field and multifocal).

Name; Year of Study	Therapeutic Agents	Study Design	Study Outcome
MEAD (2015)	DEXA/Sham	Phase III RCT	Demonstrated that DEX implant 0.7 mg and 0.35 mg met the primary efficacy endpoint for improvement in BCVA. Rates of cataract-related adverse events in phakic eyes were 67.9%, 64.1%, and 20.4% in the DEX implant 0.7 mg, DEX implant 0.35 mg, and sham groups, respectively. Only 2 patients (0.6%) in the DEX implant 0.7 mg group and 1 (0.3%) in the DEX implant 0.35 mg group required trabeculectomy.
FAME (2011)	FA/Sham	RCT	The study showed that both low- and high-dose Flucinolone Acetonide inserts significantly improved BCVA in patients with DME over 2 years, and the risk-to-benefit ratio was superior for the low-dose insert.
OZDRY (2015)	DEXA (Fixed/PRN)	RCT	Demonstrated the non-inferiority in terms of the mean change in BCVA of 5-monthly fixed dosing of Ozurdex compared to OCT-guided PRN Ozurdex therapy for refractory DME.
PLACID (2013)	DEXA/Laser	RCT	Demonstrated that though there was no difference between the groups at 12 months, significantly greater improvements in BCVA, occurred in patients with diffuse DME treated with DEX implant plus laser than in patients treated with laser alone.

AFL: Aflibercept, BEVA: Bevacizumab, DEXA: Dexamethasone, FA: Flucinolone Acetonide, RBZ: Ranibizumab, PRN: Pro re nata, T&E: Treat and Extend, RCT: Randomized Controlled Trial.

Table 1.
Summary of Anti-VEGF and Steroid for DME studies.

study participants had BCVA of 20/40 or 20/32. The mean letter score improvement in these patients was +8.3 with Ranibizumab, +8.0 with Aflibercept, and + 7.5 with Bevacizumab (each pairwise comparison p > 0.5).

However, when initial visual acuity was 20/50 or worse, the mean letter improvement was +18.9 with Aflibercept, +14.2 with Ranibizumab and + 11.8 with Bevacizumab (p values: Aflibercept-Bevacizumab <0.001, Aflibercept-Ranibizumab = 0.003, Ranibizumab-Bevacizumab = 0.21) (**Table 1**).

6. Variation between clinical trials and real-world outcome using intravitreal injection of pharmacotherapy

There has been a universal observation of divergence between the outcomes obtained from the use of intravitreal anti-VEGF in the real world and outcomes reported in randomized clinical trials. The visual outcomes and gains in vision observed have been much poorer. This finding has led to investigations into the reason for this difference. Some possible explanations for this observation include that participants are pre-selected using strict selection criteria and are well ahead motivated to complete the treatment schedule in clinical trials. This is not the case in real life, in which the patients have to grapple with significant challenges ranging from financial to demands on time and often have to deal with other comorbidities. These challenges could be of considerable impact on patients from low socio-economic backgrounds. It has also been shown that undertreatment is a common feature in real-world experience and that most patients do not receive the

recommended number of intravitreal anti-VEGF. This real-life experience results in a mismatch between real-world visual outcomes and those of major clinical trials. The frequent clinic visits and treatment burden contributes to this discrepancy. To resolve this challenge, a host of pharmaceuticals with extended durability are at different stages of development. Hopefully, some extended durability options may make it to the bedside soon. Some of the extended durability options in the pipeline include intravitreal injections such as Faricimab, OPT-302, and KSI-301. There are implantable devices such as the Port delivery system (PDS) and Vorolanib. Gene therapy options include RGX-314, and ADVM-022. These therapeutics are currently being investigated for AMD, but could apply to DME if approved. It is expected that any therapy that will join the list of already available anti-VEGFs will be required to have the same or better safety data if compared with already available drugs.

7. Newer and emerging concepts in DME

The burden of DME and its impact on vision begs for more efficient care and better outcomes for treatment. This situation has fueled the drive for new concepts in understanding the disease process and alternative treatment.

Some of the new concepts in the understanding of DR and DME include in genetic studies, which aim to understand the variable risk diabetes poses to each person living with the disease. This risk may be affected by the individual's genetic make-up. Also, the role of epigenetics may be an essential factor in determining the response to treatment. Screening for DR and DME will take on a newer feel by introducing artificial intelligence algorithms and software, combined with the advantages of teleophthalmology. This will open up access to more persons who can benefit from screening, including persons in more remote places with limited health and eye care. Home OCT for monitoring of DME will provide information into the clinical evolution of DR and DME and answers to what happens to the eye when patients cannot attend the regular clinics. Home OCT will be an added benefit in reducing the burden of attendance to regular clinics to monitor anti-VEGF therapy. The desire for a reduction in clinic visits is a critical need.

The quest to explore alternative pathogenetic pathways outside the anti-VEGF pathway has resulted in the current progress investigating the Ang-Tie pathways and the Kallikrein pathways. In addition, pharmacotherapies are being developed based on these newer principles.

More innovation will be seen as the years unfold and will significantly benefit treatment outcomes, individualizing DME treatment, and patient satisfaction.

8. Conclusion

It is expected that the number of people living with diabetes will continue increasing, resulting in more patients diagnosed with DR and DME. There is a need to develop more efficient health systems providing holistic care for patients living with diabetes. These systems should provide for the visual needs and consider the psychological and other health needs. Medicare for such patients should ideally be with reduced treatment burden compared to the current situation and preferably fewer hospital visits.

If we succeed in creating these systems, it will positively affect the patients living with diabetes and the society. This will increase the productivity of our DR and DME patients, who then can live a happier and more fulfilling life.

Acknowledgements

Conflict of interest

None of the authors have any relevant conflict of interest to declare.

Author details

Ogugua Ndubuisi Okonkwo[1*], Toyin Akanbi[2] and Chineze Thelma Agweye[3]

1 Eye Foundation Hospital and Eye Foundation Retina Institute, Lagos, Nigeria

2 Eye Foundation Hospital, Abuja, Nigeria

3 University of Calabar Teaching Hospital, Calabar, Nigeria

*Address all correspondence to: o_okonkwo@yahoo.com

IntechOpen

References

[1] International Diabetes Federation. IDF Diabetes Atlas 9th Edition. 2019. Available at: www.diabetesatlas.org. Accessed: October 2020.

[2] Sarah Wild, Gojka Roglic, Anders Green, Richard Sicree, Hilary King. Global Prevalence of Diabetes. Estimates for the year 2000 and projections for 2030. Diabetes Care. 2004; 27: 1047-1053. DOI: 10.2337/diacare.27.5.1047

[3] Lightman S, Towler HM. Diabetic retinopathy. Clin Cornerstone. 2003;5:12-21. DOI: 10.1016/s1098-3597(03)90015-9. PMID: 12800477.

[4] Ling R, Ramsewak V, Taylor D, Jacob J. Longitudinal study of a cohort of people with diabetes screened by the Exeter Diabetic Retinopathy Screening Programme. Eye (Lond). 2002; 16: 140-5. DOI: 10.1038/sj.eye.6700081.

[5] Varma R, Bressler NM, Doan QV, et al. Prevalence of and risk factors for diabetic macular edema in the United States. JAMA Ophthalmol. 2014; 132(11):1334-1340. doi:10.1001/jamaophthalmol.2014.2854

[6] Ding J, Wong TY. Current epidemiology of diabetic retinopathy and diabetic macular edema. Curr Diab Rep. 2012; 12:346-54. DOI: 10.1007/s11892-012-0283-6. PMID: 22585044.

[7] Jew OM, Peyman M, Chen TC, Visvaraja S. Risk factors for clinically significant macular edema in a multi-ethnics population with type 2 diabetes. Int J Ophthalmol. 2012; 5:499-504. DOI: 10.3980/j.issn.2222-3959.2012.04.18.

[8] Klein R, Knudtson MD, Lee KE, Gangnon R, Klein BE. The Wisconsin Epidemiologic Study of Diabetic Retinopathy XXIII: the twenty-five-year incidence of macular edema in persons with type 1 diabetes. Ophthalmology. 2009; 116(3):497-503. doi:10.1016/j.ophtha.2008.10.016

[9] Do DV, Shah SM, Sung JU, Haller JA, Nguyen QD. Persistent diabetic macular edema is associated with elevated hemoglobin A1c. Am J Ophthalmol. 2005; 139:620-3. DOI: 10.1016/j.ajo.2004.10.063.

[10] Asensio-Sánchez VM, Gómez-Ramírez V, Morales-Gómez I, Rodríguez-Vaca I. Edema macular diabético clínicamente significativo: factores sistémicos de riesgo [Clinically significant diabetic macular edema: systemic risk factors]. Arch Soc Esp Oftalmol. 2008; 83:173-6.

[11] Nguyen-Khoa BA, Goehring EL, Werther W, et al. Hospitalized cardiovascular events in patients with diabetic macular edema. BMC Ophthalmol. 2012;12:11. DOI:10.1186/1471-2415-12-11

[12] Er Chen, Mark Looman, Marianne Laouri, Meghan Gallagher, Karen Van Nuys, Darius Lakdawalla & Joan Fortuny. Burden of illness of diabetic macular edema: literature review, Current Medical Research and Opinion. 2010; 26:7, 1587-1597, DOI: 10.1185/03007995.2010.482503

[13] Strain WD, Cos X, Hirst M, Vencio S, Mohan V, Vokó Z, Yabe D, Blüher M, Paldánius PM. Time to do more: addressing clinical inertia in the management of type 2 diabetes mellitus. Diabetes Res Clin Pract. 2014 Sep; 105(3):302-12. doi: 10.1016/j.diabres.2014.05.005.

[14] Yam JC, Kwok AK. Update on the treatment of diabetic retinopathy. Hong Kong Med J. 2007 Feb; 13(1):46-60.

[15] Moss SE, Klein R, Klein BE. Ten-year incidence of visual loss in a diabetic population. Ophthalmology. 1994 Jun; 101(6):1061-70. doi: 10.1016/s0161-6420(94)31217-6.

[16] WHO Europe: Diabetic Retinopathy screening: a short guide. https://www.

euro.who.int/en/publications/abstracts/ diabetic-retinopathy-screening-a-short-guide-2020

[17] Liew G, Michaelides M, Bunce C. A comparison of the causes of blindness certifications in England and Wales in working age adults (16-64 years), 1999-2000 with 2009-2010. BMJ Open 2014; 4:e004015. doi: 10.1136/ bmjopen-2013- 004015

[18] Jones S, Edwards RT. Diabetic retinopathy screening: a systematic review of the economic evidence. Diabet Med. 2010 Mar; 27(3):249-56. doi: 10.1111/j.1464-5491.2009.02870.x.

[19] Pearce E, Sivaprasad S. A Review of Advancements and Evidence Gaps in Diabetic Retinopathy Screening Models. Clin Ophthalmol. 2020; 14:3285-3296. Published 2020 Oct 14. doi:10.2147/ OPTH.S267521

[20] Vujosevic S, Pucci P, Casciano M, Daniele A, Bini S, Berton M, Cavarzeran F, Avogaro A, Lapolla A, Midena E. A decade-long telemedicine screening program for diabetic retinopathy in the north-east of Italy. J Diabetes Complications. 2017 Aug;31(8):1348-1353. doi: 10.1016/j. jdiacomp.2017.04.010.

[21] Gunasekeran DV, Ting DSW, Tan GSW, Wong TY. Artificial intelligence for diabetic retinopathy screening, prediction and management. Curr Opin Ophthalmol. 2020 Sep; 31(5):357-365. doi: 10.1097/ ICU.0000000000000693

[22] Bellemo V, Lim G, Rim TH, Tan GSW, Cheung CY, Sadda S, He MG, Tufail A, Lee ML, Hsu W, Ting DSW. Artificial Intelligence Screening for Diabetic Retinopathy: the Real-World Emerging Application. Curr Diab Rep. 2019 Jul 31; 19(9):72. doi: 10.1007/s11892-019-1189-3.

[23] Kwan CC, Fawzi AA. Imaging and Biomarkers in Diabetic Macular Edema and Diabetic Retinopathy. Curr Diab Rep. 2019 Aug 31; 19(10):95. doi: 10.1007/s11892-019-1226-2.

[24] Sim, D.A., Keane, P.A., Tufail, A. et al. Automated Retinal Image Analysis for Diabetic Retinopathy in Telemedicine. Curr Diab Rep 15, 14 (2015). https://doi.org/10.1007/ s11892-015-0577-6

[25] Fuller SD, Hu J, Liu JC, Gibson E, Gregory M, Kuo J, Rajagopal R. Five-Year Cost-Effectiveness Modeling of Primary Care-Based, Nonmydriatic Automated Retinal Image Analysis Screening Among Low-Income Patients with Diabetes. J Diabetes Sci Technol. 2020 Oct 30:1932296820967011. doi: 10.1177/1932296820967011.

[26] Lois N, Cook JA, Wang A, Aldington S, Mistry H, Maredza M, McAuley D, Aslam T, Bailey C, Chong V, Ganchi F, Scanlon P, Sivaprasad S, Steel DH, Styles C, Azuara-Blanco A, Prior L, Waugh N; EMERALD Study Group. Evaluation of a New Model of Care for People with Complications of Diabetic Retinopathy: The EMERALD Study. Ophthalmology. 2021 Apr; 128(4):561-573. doi: 10.1016/j. ophtha.2020.10.030.

[27] Tiarnan D.L. Keenan, Michaella Goldstein, Dafna Goldenberg, Dinah Zur, Shiri Shulman, Anat Loewenstein. Prospective, Longitudinal Pilot Study: Daily Self-Imaging with Patient-Operated Home OCT in Neovascular Age-Related Macular Degeneration. Ophthalmology Science.2021, Volume 1, Issue 2. https://doi.org/10.1016/j. xops.2021.100034.

[28] Yu HJ, Kiernan DF, Eichenbaum D, Sheth VS, Wykoff CC. Home Monitoring of Age-Related Macular Degeneration: Utility of the ForeseeHome Device for Detection of Neovascularization. Ophthalmology. Retina. 2021 Apr;5(4):348-356. DOI: 10.1016/j.oret.2020.08.003.

[29] Tripathy K, Sharma YR, Karthikeya R, Chawla R, Gogia V, et al. Recent Advances in Management of Diabetic Macular Oedema. Current Diabetes Reviews, 2015, 11, 79-97.

[30] Romero-Aroca P. Targeting the pathophysiology of diabetic macula oedema. Diabetes care, 2010 33(11): 2484-2485.

[31] Trinh HM, Joseph M, Cholkar K, Pal D, Mitra AK. Novel strategies for the treatment of diabetic macular oedema. World J Pharmacol, 2016 March 9; 5(1): 1-14

[32] Musat O, Cernat C, Labib M, Gheorghe A, Toma O et al. Diabetic macular oedema. Romanian Journal of Ophthalmology, 2015, 59(3):133-136

[33] Powers M, Greven M, Kleinman R, Nguyen QD, Do D et al. Recent advances in the management and understanding of diabetic retinopathy. 2017, 6(2063), 1-9

[34] AbuEl-Asrar AM, Al-Mezaine HS, Ola MS. Pathophysiology and management of diabetic retinopathy. Expert Rev. Ophthalmol. 2009; 4(6): 627-647

[35] Zhang X, Zeng H, Bao S, Wang N,Gillies MC. Diabetic macular edema: new concepts in pathophysiology and treatment. Cell & Bioscience. 2014; 4(27): 1-14

[36] Maetzel A, Feener EP. Plasma Kallikrein Inhibition in Diabetic Macular Edema: Targeting a novel, VEGF-independent pathway of DME could preserve and recover vision. Retinal Physician. 2020; 17: 26-28

[37] Uriasa EA, Uriasa GA, Monickaraja F, McGuireb P, Das A. Novel therapeutic targets in diabetic macular edema: Beyond VEGF. Vision Research. 2017, 139: 221-227

[38] Akwii RG, Sajib MS, Zahra FT, Mikelis CM. Role of angiopoietin-2 in vascular physiology and pathophysiology. Cells. 2019; 8:1-19

[39] Hussain RM, Neiweem AE, Kansara V, Harris A, Ciulla TA. Tie-2/Angiopoietin pathway modulation as a therapeutic strategy for retinal disease. Expert Opinion on Investigational Drugs. 2019:1-11

[40] Mathew C, Yunirakasiwi A, Sanjay S. Updates in the Management of Diabetic Macular oedema. Journal of Diabetes Research. 2015, 1-8

[41] Browning DJ, Stewart MW, Lee C. Diabetic macular oedema: Evidence-based management. Indian J Ophthalmol 2018; 66:1736-1750.

[42] Khan M, Aziz AA, Shafi NA, Abbas T, Khanani AM. Targeting Angiopoietin in Retinal Vascular Diseases: A Literature Review and Summary of Clinical Trials Involving Faricimab. Cells, 2020, 9 (1869): 1-14

[43] Hussain RM, Ciulla TA. Emerging vascular endothelial growth factor antagonists to treat neovascular age-related macular degeneration. Expert Opin Emerg Drugs. 2017 Sep;22(3):235-246.

[44] Elman MJ, Aiello LP, Beck RW, Bressler NM, Bressler SB et al. Randomized trial evaluating ranibizumab plus prompt or deferred laser or triamcinolone plus prompt laser for diabetic macular edema. Ophthalmology 2010, 117, 1064-1077.

[45] Elman MJ, Qin H, Aiello LP, Beck RW, Bressler NM et al. Intravitreal ranibizumab for diabetic macular edema with prompt versus deferred laser treatment: Three-year randomized trial results. Ophthalmology 2012, 119, 2312-2318

[46] Ng DS, Yip YW, Bakthavatsalam M et al. Elevated angiopoietin 2 in aqueous

of patients with neovascular age related macular degeneration correlates with disease severity at presentation. Sci Rep. 2017; 7:45081 (16)

[47] Fiedler U, Reiss Y, Scharpfenecker M et al. Angiopoietin-2 sensitizes endothelial cells to TNF-alpha and has a crucial role in the induction of inflammation. Nat Med. 2006; 12:235-239 (17)

[48] Keech A, Simes RJ, Barter P, Best J, Scott R, et al. Effects of long-term fenofibrate therapy on cardiovascular events in 9795 people with type 2 diabetes mellitus (the FIELD study): randomised controlled trial. Lancet 2005;366(9500):1849-1861.

[49] Matthews DR, Stratton IM, Aldington SJ, Holman RR, Kohner EM. Risks of progression of retinopathy and vision loss related to tight blood pressure control in type 2 diabetes mellitus: UKPDS 69. Arch Ophthalmol 2004; 122(11):1631-1640

[50] UK Prospective Diabetes Study (UKPDS) Group. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). Lancet 1998; 352:837-853

[51] UK Prospective Diabetes Study Group. Tight blood pressure control and risk of macrovascular and microvascular complications in type 2 diabetes: UKPDS 38. BMJ 1998; 317(7160):703-713.

[52] Patel A, MacMahon S, Chalmers J, Neal B, Woodward M et al. Effects of a fixed combination of perindopril and indapamide on macrovascular and microvascular outcomes in patients with type 2 diabetes mellitus (the ADVANCE trial): a randomised controlled trial. Lancet 2007:829-840.

[53] Keenan HA, Costacou T, Sun JK, Doria A, Cavellerano J et al. Clinical factors associated with resistance to

microvascular complications in diabetic patients of extreme disease duration: the 50-year medalist study. Diabetes Care 2007; 30(8):1995-1997.

[54] Wong TY, Liew G, Tapp RJ, Schmidt MI, Wang JJ et al. Relation between fasting glucose and retinopathy for diagnosis of diabetes: three population-based cross-sectional studies. Lancet 2008; 371(9614):736-743

[55] Liew G, Klein R, Wong TY. The Role of Genetics in Susceptibility to Diabetic Retinopathy. Int Ophthalmol Clin. 2009; 49(2): 35-52.

[56] Wong TY, Klein R, Islam FM, Cotch MF, Folsom AR, Klein BE, Sharrett AR, Shea S. Diabetic retinopathy in a multi-ethnic cohort in the United States. Am J Ophthalmol 2006; 141(3):446-455.

[57] Klein R, Sharrett AR, Klein BE, Moss SE, Folsom AR et al. The association of atherosclerosis, vascular risk factors, and retinopathy in adults with diabetes: the atherosclerosis risk in communities' study. Ophthalmology 2002; 109(7):1225-1234.

[58] Harris MI, Klein R, Cowie CC, Rowland M, Byrd Holt DD. Is the risk of diabetic retinopathy greater in non-Hispanic blacks and Mexican Americans than in non-Hispanic whites with type 2 diabetes? A U.S. population study. Diabetes Care 1998; 21(8):1230-1235.

[59] Bahrami B, Zhu M, Hong T, Chang A. Diabetic macular oedema: pathophysiology, management challenges and treatment resistance. Diabetologia (2016) 59:1594-1608

[60] Cabrera AP, Mankad RN, Marek L, Das R, Rangasamy S, et al. Genotypes and Phenotypes: A Search for Influential Genes in Diabetic Retinopathy. Int. J. Mol. Sci. 2020, 21(2712): 1-22

[61] Graham PS, Kaidonis G, Abhary S, Gillies MC, Daniell M et al.

Genome-wide association studies for diabetic macular edema and proliferative diabetic retinopathy. BMC Medical Genetics. 2018; 19(71): 1-8

[62] Omar AF, Silva PS, Sun JK. Genetics of diabetic retinopathy. Semin Ophthalmol 2013; 28:337-46

[63] Usman M. An Overview of Our Current Understanding of Diabetic Macular Ischemia (DMI). Cureus. 2018; 10(7):1-7

[64] Sim DA, Keane PA, Zarranz-Ventura J, et al. Predictive factors for the progression of diabetic macular ischemia. Am J Ophthalmol. 2013; 156:684-692.

[65] Garcia JM, Lima TT, Louzada RN, Rassi AT, Isaac DL, Avila M. Diabetic Macular Ischemia Diagnosis: Comparison between Optical Coherence Tomography Angiography and Fluorescein Angiography. Journal of Ophthalmology. 2016; 1-6

[66] Manousaridis K, Talks J. Macular ischaemia: a contraindication for anti-VEGF treatment in retinal vascular disease? British Journal of Ophthalmology. 2012; 96(2): 179-184.

[67] Hwang TS, Jia Y, Gao SS et al. Optical coherence tomography angiography features of diabetic retinopathy. Retina, 2015; 35 (11): 2371-2376

[68] Solomon SD, Goldberg MF. ETDRS Grading of Diabetic Retinopathy: Still the Gold Standard? Ophthalmic Res 2019; 62:190-195

[69] Jampol LM. Classifications of diabetic macular edema. European Journal of Ophthalmology 2020, Vol. 30(1) 6-7

[70] Wu L, Fernandez-Loaiza P, Sauma J, Hernandez-Bogantes E, Masis M. Classification of diabetic retinopathy and diabetic macular edema. World J Diabetes 2013, 4(6): 290-294.

[71] Early Treatment Diabetic Retinopathy Study Research Group. Grading diabetic retinopathy from stereoscopic color fundus photographs--an extension of the modified Airlie House classification. ETDRS report number 10 Ophthalmology 1991; 98: 786-806.

[72] Panozzo G, Parolini B, Gusson E, Mercanti A, Pinackatt S et al. Diabetic macular edema: an OCT-based classification. Seminars in Ophthalmology 2004, 19: 13-20

[73] Wilkinson CP, Ferris FL 3rd, Klein RE, Lee PP, Agardh CD et al. Proposed international clinical diabetic retinopathy and diabetic macular edema disease severity scales. Ophthalmology 2003; 110(9): 1677-1682

[74] Nicoară SD. Spectral Domain Optical Coherence Tomography in the Diagnosis and Monitoring of Diabetic Macular Edema. In. Intechopen. OCT-applications in ophthalmology [book on the internet].

[75] Chung Y, Kim KY, Ha SJ, Byeon H, Cho C, Kim JH, Lee K. Role of Inflammation in Classification of Diabetic Macular Edema by Optical Coherence Tomography. Journal of Diabetes Research. 2019: 1-8

[76] Alia OM, Saada MS, Hazema HAM, Dawood MN. Optical coherence tomography patterns of diabetic macular edema and their correlation with visual acuity. Journal of Current Medical Research and Practice 2020, 5:365-370

[77] Leng T, Tripathy K, Bhagat N, Lim JI. Diabetic Macular Edema. https://eyewiki.aao.org

[78] Schmidt-Erfurth U, Garcia-Arumi J, Bandello F, Berg K, Chakravarthy U, et al. Guidelines for the Management of Diabetic Macular Edema by the European Society of Retina Specialists (EURETINA). Ophthalmologica. 2017; 237:185-222.

[79] Aiello LP, Cahill MT, Wong JS: Systemic considerations in the management of diabetic retinopathy. Am J Ophthalmol. 2001; 132:760-776.

[80] Diabetes Control and Complications Trial Research Group: The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. N Engl J Med. 1993; 329:977-986.

[81] Ciulla TA, Amador AG, Zinman B. Diabetic Retinopathy and Diabetic Macular Edema: Pathophysiology, screening, and novel therapies. Diabetes care. 2003; 2653-2664.

[82] Cole ED, Novais EA, Louzada RN, Waheed NK. Contemporary retinal imaging techniques in diabetic retinopathy: a review. Clinical and Experimental Ophthalmology 2016; 44: 289-299

[83] Cohen SR, Gardner TW. Diabetic Retinopathy and Diabetic Macular Edema. Dev Ophthalmol. 2016; 55: 137-146

[84] Fenner BJ, Wong RLM, Lam W, Tan GSW, Cheung GCM. Advances in Retinal Imaging and Applications in Diabetic Retinopathy Screening: A Review. Ophthalmol Ther. 2018 7:333-346

[85] Bresnick GH. Diabetic maculopathy. A critical review highlighting diffuse macular edema. Ophthalmology. 1983; 90:1301-1317

[86] Cheung N, Wang JJ, Klein R, Couper DJ, Sharrett AR, Wong TY. Diabetic retinopathy and the risk of coronary heart disease: the Atherosclerosis Risk in Communities Study. Diabetes Care 2007; 30: 1742-6.

[87] Kawasaki R, Cheung N, Islam FM, et al. Is diabetic retinopathy related to subclinical cardiovascular disease? Ophthalmology 2011; 118: 860-5.

[88] Alex D, Giridhar A, Gopalakrishnan M, Madan S, Indurkhya S, Haridas S, et al. Emerging retinal diseases and newer terminologies in spectral domain optical coherence tomography. Kerala JOphthalmol 2020; 32:234-43.

[89] Michl M, Fabianska M, Seeböck P, Sadeghipour A, Haj Najeeb B et al. Automated quantification of macular fluid in retinal diseases and their response to anti-VEGF therapy. Br J Ophthalmol. 2020: 317416.

[90] Lee H, Kang KE, Chung H, Kim HC. Prognostic Factors for Functional and Anatomic Outcomes in Patients with Diabetic Macular Edema Treated with Dexamethasone Implant. Korean J Ophthalmol. 2018; 32(2):116-125.

[91] Das R, Spence G, Hogg RE, Stevenson M, Chakravarthy U. Disorganization of Inner Retina and Outer Retinal Morphology in Diabetic Macular Edema. JAMA Ophthalmol. 2018; 136(2):202-208.

[92] Rasendran C, Conti TF, Hom GL, Babiuch AS, Conti FF, Singh RP. Current Understanding of the Pathophysiology of Disorganization of the Retinal Inner Layers and Relationship to Visual Acuity. Am J Ophthalmic Clin Trials 2019, 2(5) 1-10

[93] Sampani K, Abdulaal M, Peiris T, Lin MM, Pitoc C, et al. Comparison of SDOCT scan types for grading disorganization of retinal inner layers and other morphologic features of diabetic macular edema. Trans Vis Sci Tech. 2020; 9(8):45

[94] Sun JK, Lin MM, Lammer J, et al. Disorganization of the retinal inner layers as a predictor of visual acuity in eyes with center-involved diabetic macular edema. JAMA Ophthalmol. 2014; 132(11):1309-1316

[95] Sun JK, Radwan SH, Soliman AZ, et al. Neural retinal disorganization as a

robust marker of visual acuity in current and resolved diabetic macular edema. Diabetes 2015; 64(7):2560-2570

[96] Radwan SH, Soliman AZ, Tokarev J, Zhang L, van Kuijk FJ, Koozekanani DD. Association of disorganization of retinal inner layers with vision after resolution of center-involved diabetic macular edema. JAMA Ophthalmol. 2015; 133(7):820-825

[97] Salz DA, de Carlo TE, Adhi M, Moult E, Choi W, et al. Select features of diabetic retinopathy on swept-source optical coherence tomographic angiography compared with fluorescein angiography and normal eye. JAMA Ophthalmol. 2016; 134(6): 644-650.

[98] Suciu C, Suciu V, Nicoara S. Optical Coherence Tomography (Angiography) Biomarkers in the assessment and monitoring of diabetic macular edema. Journal of Diabetes Research. 2020; 20: 1-10

[99] Sousa CD, O'Keefe GD, Breda J, Tripathy K, Pinto LA, et al. Optical Coherence Tomography Angiography. https://eyewiki.aao.org.

[100] Greig EC, Duker JS, Waheed NK. A practical guide to optical coherence tomography angiography interpretation. Int J Retin Vitr. 2020; 6(55): 1-17.

[101] Moraes G, Faes L, Pal B. Optical Coherence Tomography Angiography: Principles and Application in Retinal Diseases. Delhi J Ophthalmol 2018; 29: 43-48

[102] Atta AHR, Mohamed AAM, Ali MA. Macular vessels density in diabetic retinopathy: quantitative assessment using optical coherence tomography angiography. International Ophthalmology. 2019; 39(8): 1845-1859

[103] Tang FY, Chan EO, Sun Z et al. Clinically relevant factors associated with quantitative optical coherence tomography angiography metrics in deep capillary plexus in patients with diabetes. Eye and Vision. 2020; 7 (1):1-7

[104] Sun Z, Tang F, Wong R, Lok J, Szeto SKH et al. OCT Angiography Metrics Predict Progression of Diabetic Retinopathy and Development of Diabetic Macular Edema. Ophthalmology 2019; 126:1675-1684

[105] Lee J, Moon BG, Cho AR, Yoon YH. Optical Coherence Tomography Angiography of DME and Its Association with Anti-VEGF Treatment Response. Ophthalmology. 2016; 123 (11):2368 – 2375

[106] Hsieh Y, Alam MN, Le D, Hsiao C, Yang C, Chao DL, Yao X. OCT Angiography Biomarkers for Predicting Visual Outcomes after Ranibizumab Treatment for Diabetic Macular Edema. Ophthalmol Retina. 2019; 3(10): 826-834.

[107] Russell JF, Shi Y, Hinkle JW, Scott NL, Fan KC, et al. Longitudinal Wide Field Swept Source OCT Angiography of Neovascularization in Proliferative Diabetic Retinopathy After Panretinal Photocoagulation. Ophthalmol Retina. 2019; 3(4): 350-361

[108] Bontzos G, Kabanarou SA, Garnavou-Xirou C, Kontou E, Triantafyllou D, Xirou T. Segmentation errors and motion artifacts in OCT-A associated with epiretinal membranes. Canadian Journal of Ophthalmology. 2020; 55 (4): 293 – 300

[109] Midena E, Vujosevic S. Microperimetry in diabetic retinopathy. Saudi Journal of Ophthalmology. 2011; 25:131-135.

[110] Laishram M, Srikanth K, Rajalakshmi AR, Nagarajan S, Ezhumalai G. Microperimetry – A New Tool for Assessing Retinal Sensitivity in Macular Diseases. Journal of Clinical and Diagnostic Research. 2017; 11(7): 8-11.

[111] Pereira F, Godoy BR, Maia M, Regatieri CV. Microperimetry and OCT

angiography evaluation of patients with ischemic diabetic macular edema treated with monthly intravitreal bevacizumab: a pilot study. Int J Retin Vitr. 2019; 5(24): 1-7

[112] Tehrani NM, Riazi-Esfahani H, Jafarzadehpur E, et al. Multifocal Electroretinogram in Diabetic Macular Edema; Correlation with Visual Acuity and Optical Coherence Tomography. J Ophthalmic Vis Res. 2015; 10(2):165-171.

[113] Baget-Bernaldiz M, Romero-Aroca P, Bautista-Perez A, Mercado J. Multifocal electroretinography changes at the 1-year follow up in a cohort of diabetic macular edema patients treated with ranibizumab. Doc Ophthalmol. (2017; 135:85-96.

[114] Singh R, Abhiramamurthy V, Gupta V, Gupta A, Bhansali A. Effect of multifactorial intervention on diabetic macular edema. Diabetes Care 2006; 29:463-4.

[115] Progression of retinopathy with intensive versus conventional treatment in the diabetes control and complications trial. Diabetes control and complications trial research group. Ophthalmology 1995; 102:647-61

[116] Early worsening of diabetic retinopathy in the diabetes control and complications trial. Arch Ophthalmol 1998; 116:874-86.

[117] Chew EY, Ambrosius WT, Davis MD, Danis RP, Gangaputra S, Greven CM, et al. Effects of medical therapies on retinopathy progression in type 2 diabetes. N Engl J Med 2010; 363:233-244.

[118] Klein BE, Moss SE, Klein R, Surawicz TS. The Wisconsin Epidemiologic Study of Diabetic Retinopathy. XIII. Relationship of serum cholesterol to retinopathy and hard exudate. Ophthalmology 1991; 98(8):1261-5.

[119] Chew EY, Klein ML, Ferris FL et al. Association of elevated serum lipid levels with retinal hard exudate in diabetic retinopathy. Early Treatment Diabetic Retinopathy Study (ETDRS) Report 22. Arch Ophthalmol 1996; 114(9):1079-84.

[120] Gupta A, Gupta V, Thapar S, Bhansali A. Lipid-lowering drug atorvastatin as an adjunct in the management of diabetic macular edema. Am J Ophthalmol 2004; 137(4):675-82.

[121] Baker CW, Glassman AR, Beaulieu WT, Antoszyk AN, Browning DJ, Chalam KV, et al. Effect of initial management with Aflibercept vs laser photocoagulation vs observation on vision loss among patients with diabetic macular edema involving the center of the macula and good visual acuity: a randomized clinical trial. JAMA. 2019; 321:1880-94.

[122] Nguyen, Q. D. et al. Ranibizumab for diabetic macular edema: results from 2 phase III randomized trials: RISE and RIDE. Ophthalmology 119, 789-801 (2012).

[123] The Diabetic Retinopathy Clinical Research Network. Aflibercept, bevacizumab, or ranibizumab for diabetic macular edema. N. Engl. J. Med. 372, 1193-1203 (2015).

[124] Wells, J. A. et al. Aflibercept, bevacizumab, or ranibizumab for diabetic macular edema: two-year results from a comparative effectiveness randomized clinical trial. Ophthalmology 123, 1351-1359 (2016).

[125] Heier, J. S. et al. Intravitreal aflibercept for diabetic macular edema: 148-week results from the VISTA and VIVID studies. Ophthalmology 123, 2376-2385 (2016).

[126] Brown DM, Nguyen QD, Marcus DM, Boyer DS, Patel S, Feiner L, et al. Long-term outcomes of ranibizumab therapy for diabetic macular edema: The 36-month results from two phase III trials: RISE and

RIDE. Ophthalmology. 2013; 120(10):2013-22

[127] Cunningham ET Jr., Adamis AP, Altaweel M, Aiello LP, Bressler NM, D'Amico DJ, et al. A phase II randomized double-masked trial of pegaptanib, an anti-vascular endothelial growth factor aptamer, for diabetic macular edema. Ophthalmology 2005; 112:1747-57.

[128] A Phase II Randomized Double-Masked Trial of Pegaptanib, an Anti–Vascular Endothelial Growth Factor Aptamer, for Diabetic Macular Edema. Ophthalmology 2005; 112(10):1747-57.

[129] Ahmadi MA, Lim JI (2008) Pharmacotherapy of age-related macular degeneration. Expert Opin Pharmacother 9:3045-3052

[130] J. C. Cilley, K. Barfi, A. B. Benson 3rd., and M. F. Mulcahy, "Bevacizumab in the treatment of colorectal cancer," Expert Opinion on Biological Therapy, vol. 7, no. 5, pp. 739-749, 2007.

[131] Rajendram R, Fraser-Bell S, Kaines A, Michaelides M, Hamilton RD, Esposti SD, Peto T, Egan C, Bunce C, Leslie RD, Hykin PG. A 2-year prospective randomized controlled trial of intravitreal bevacizumab or laser therapy (BOLT) in the management of diabetic macular edema: 24-month data: report 3. Arch Ophthalmol. 2012 Aug; 130(8):972-9. Doi: 10.1001/archophthalmol.2012.393. PMID: 22491395

[132] Diabetic Retinopathy Clinical Research Network, Wells JA, Glassman AR, Ayala AR, Jampol LM, Aiello LP, et al. Aflibercept, bevacizumab, or ranibizumab for diabetic macular edema. N Engl J Med 2015; 372:1193-203.

[133] Stein JD, Newman-Casey PA, Kim DD, Nwanyanwu KH, Johnson MW, Hutton DW, et al. Cost-effectiveness of various interventions for newly diagnosed diabetic macular edema. Ophthalmology 2013; 120:1835-42.

[134] Pershing S, Enns EA, Matesic B, Owens DK, Goldhaber-Fiebert JD. Cost-effectiveness of treatment of diabetic macular edema. Ann Intern Med 2014; 160:18-29.

[135] L. Wu, M. A. Mart'ınez-Castellanos, H. Quiroz-Mercado et al., "Pan American collaborative retina group (PACORES). Twelve-month safety of intravitreal injections of bevacizumab (avastin): results of the Pan-American collaborative retina study group (PACORES)," Graefe's Archive for Clinical and Experimental Ophthalmology, vol.246, no. 1, pp. 81-87, 2008.

[136] N. Ferrara, L. Damico, N. Shams, H. Lowman, and R. Kim, "Development of ranibizumab, an anti-vascular endothelial growth factor antigen binding fragment, as therapy for neovascular age-related macular degeneration," Retina, vol. 26, no. 8, pp. 859-870, 2006.

[137] Brown DM, Nguyen QD, Marcus DM, et al.: Long-term outcomes of ranibizumab therapy for diabetic macular edema: the 36-month results from two phase III trials: RISE and RIDE. Ophthalmology. 2013; 120(10): 2013-22.

[138] Campochiaro P, et al. Primary analysis results of the phase 3 Archway trial of the port delivery system with ranibizumab for patients with neovascular AMD. American Society of Retina Specialists Annual Meeting; 2020 July 24-26.

[139] Campochiaro PA, Marcus DM, Awh CC, et al. The port delivery system with Ranibizumab for neovascular age-related macular degeneration: results from the randomized Phase 2 ladder clinical trial.Ophthalmology. 2019; 126(8):1141-1154. doi:10.1016/j. ophtha.2019.03.03620.

[140] ClinicalTrials.gov. This study will evaluate the efficacy, safety, and

pharmacokinetics of the port delivery system with ranibizumab in participants with diabetic macular edema compared with intravitreal ranibizumab (PAGODA). clinicaltrials.gov/ct2/show/NCT04108156. Accessed June 9, 2021.

[141] ClinicalTrials.gov. A multicenter, randomized study in participants with diabetic retinopathy without center-involved diabetic macular edema to evaluate the efficacy, safety, and pharmacokinetics of ranibizumab delivered via the port delivery system relative to the comparator arm (PAVILION). clinicaltrials.gov/ct2/show/NCT04503551. Accessed June 9, 2021

[142] Holash J, Davis S, Papadopoulos N, et al. VEGF-Trap: a VEGF blocker with potent antitumor effects. Proc Natl Acad Sci USA 2002; 99(17):11393-8.

[143] Yog Raj Sharma, Koushik Tripathy, Pradeep Venkatesh and Varun Gogia. Aflibercept – How does it compare with other Anti–VEGF Drugs? Austin J Clin Ophthalmol 2014; 1(3):8.

[144] Chappelow AV, Kaiser PK. Neovascular age-related macular degeneration: potential therapies. Drugs 2008; 68(8):1029-36.

[145] Brown DM, Schmidt-Erfurth U, Do DV, et al.: Intravitreal Aflibercept for Diabetic Macular Edema: 100-Week Results From the VISTA and VIVID Studies. Ophthalmology. 2015; 122(10): 2044-52.

[146] Wells JA, Glassman AR, Ayala AR, et al.: Aflibercept, Bevacizumab, or Ranibizumab for Diabetic Macular Edema: Two-Year Results from a Comparative Effectiveness Randomized Clinical Trial. Ophthalmology. 2016; 123(6): 1351-9

[147] Wells JA, Glassman AR, Ayala AR, Jampol LM, Bressler NM, Bressler SB, et al. Aflibercept, bevacizumab, or ranibizumab for diabetic macular edema: Two-year results from a comparative effectiveness randomized clinical trial. Ophthalmology 2016; 123:1351-9.

[148] Brown DM, Schmidt-Erfurth U, Do DV, Holz FG, Boyer DS, Midena E, et al. Intravitreal aflibercept for diabetic macular edema: 100-week results from the VISTA and VIVID studies. Ophthalmology 2015; 122:2044-52.

[149] Kim JT, Lee DH, Joe SG, Kim JG, Yoon YH. Changes in choroidal thickness in relation to the severity of retinopathy and macular edema in type 2 diabetic patients. Invest Ophthalmol Vis Sci 2013; 54:3378-84.

[150] Lee SH, Kim J, Chung H, Kim HC. Changes of choroidal thickness after treatment for diabetic retinopathy. Curr Eye Res 2014; 39:736-44.

[151] Dugel PU, Singh RP, Koh A, et al. Hawk and harrier: Ninety-Six-Week outcomes from the phase 3 trials of Brolucizumab for neovascular age-related macular degeneration. Ophthalmology 2021; vasculitis, and retinal Occlusion-Related events with Brolucizumab: post hoc review of hawk and harrier. Ophthalmology 2020. doi:doi:10.1016/j.ophtha.2020.11.011.

[152] Dugel PU, Jaffe GJ, Sallstig P, et al. Brolucizumab versus aflibercept in participants with neovascular age-related macular degeneration: a randomized trial. Ophthalmology 2017;124:1296-304.doi:10.1016/j.ophtha.2017.03.057pmid:http://www.ncbi.nlm.nih.gov/pubmed/28551167

[153] Holz FG, Dugel PU, Weissgerber G, et al. Single-Chain antibody fragment VEGF inhibitor RTH258 for neovascular age-related macular degeneration: a randomized controlled study. Ophthalmology2016;123:10809. doi:10.1016/j.ophtha.2015.12.030pmid:http://www.ncbi.nlm.nih.gov/pubmed/26906165

[154] Baumal CR, Spaide RF, Vajzovic L, et al. Retinal vasculitis and intraocular inflammation after intravitreal injection of Brolucizumab. Ophthalmology 2020;127:1345-59.doi:10.1016/j.ophtha.2020.04.017pmid:http://www.ncbi.nlm.nih.gov/pubmed/32344075

[155] Holz FG, Heinz C, Wolf A. Intraocular inflammation with brolucizumab use: patient management, diagnosis, therapy. Ophthalmologe 2021;118:1-3.doi:10.1007/s00347-021-01321-8pmid:http://www.ncbi.nlm.nih.gov/pubmed/33007521

[156] Brown D, Wolf S, Garweg JG, et al. Brolucizumab for the treatment of visual impairment due to diabetic macular edema: 52-week results from the KESTREL & KITE studies. Presented at: The Association for Research in Vision and Ophthalmology (ARVO) 2021 Annual Meeting. May 2021.

[157] Novartis reports one year results of Phase III MERLIN study evaluating Beovu® every four week dosing and provides update on Beovu clinical program .https://www.novartis.com.

[158] Regula J.T. Lundh von Leithner P. Foxton R. et al. Targeting key angiogenic pathways with a bispecific CrossMAb optimized for neovascular eye diseases. EMBO Mol Med. 2016; 8: 1265-1288

[159] Foxton R.H. Uhles S. Gruener S. et al Evaluation of the effects of VEGF/ANG-2 neutralization on vascular, neuronal and inflammatory pathologies in a spontaneous choroidal neovascularization (CNV) mouse model.

[160] Schaefer W. Regula J.T. Bähner M. et al Immunoglobulin domain crossover as a generic approach for the production of bispecific IgG antibodies. Proc Nat Acad Sci U S A. 2011; 108: 11187-11192

[161] .Khan M, et al. Targeting Angiopoietin in retinal vascular diseases: A literature review and summary of clinical trials involving faricimab. Cells. 2020; 9:1869.

[162] Heier JS, et al. The Angiopoietin/Tie pathway in retinal vascular diseases: a review. Retina-J Ret Vit Dis. 2021; 41:1-19.

[163] Khanani AM, Patel SS, Ferrone PJ, et al. Efficacy of Every Four Monthly and Quarterly Dosing of Faricimab vs Ranibizumab in Neovascular Age-Related Macular Degeneration: The STAIRWAY Phase 2 Randomized Clinical Trial. JAMA Ophthalmol. 2020; 138(9):964-972. doi:10.1001/jamaophthalmol.2020.2699

[164] Arshad M. Khanani, Jeffrey Heier, Carlos Quezada Ruiz, Hugh Lin, David Silverman, Christopher Brittain, Jane Ives, Balakumar Swaminathan, Karen Basu, Tien Y Wong; Faricimab in Neovascular Age-Related Macular Degeneration: 1-Year Efficacy, Safety, and Durability in the Phase 3 TENAYA and LUCERNE Trials. Invest. Ophthalmol. Vis. Sci. 2021; 62(8):428.

[165] John A Wells, Charles Clifton Wykoff, Jeffrey R Willis, Zdenka Haskova, Hugh Lin, David Silverman, Anthony P Adamis, Jane Ives, Francis Abreu, Karen Basu, Ramin Tadayoni; Efficacy, durability, and safety of faricimab in diabetic macular edema (DME): one-year results from the phase 3 YOSEMITE and RHINE trials. Invest. Ophthalmol. Vis. Sci. 2021; 62(8):1037.

[166] Lalwani GA, Rosenfeld PJ, Fung AE, Dubovy SR, Michels S, Feuer W, Davis JL, Flynn HW Jr, Esquiabro M (2009) A variable-dosing regimen with intravitreal ranibizumab for neovascular age-related macular degeneration: year 2 of the PrONTO Study. Am J Ophthalmol 148(1):43-58 e41

[167] Flaxel CJ, Adelman RA, Bailey ST et al. Age-related macular degeneration preferred practice Pattern R. Ophthalmology 127(1), P1–p65 (2020).

[168] Maguire MG, Martin DF, Ying G-S, Jaffe GJ, Daniel E, Grunewald JE,

Toth CA, Ferris FL III, Fine SL, Group CoA-rMDTTR (2016) Five-year outcomes with anti–vascular endothelial growth factor treatment of neovascular age-related macular degeneration: the comparison of age-related macular degeneration treatments trials. Ophthalmology 123(8):1751-1761

[169] Spaide, R. Ranibizumab according to need: a treatment for age-related macular degeneration. Am. J. Ophthalmol. 143, 679-680 (2007).

[170] Kim, Y.C., Shin, J.P., Pak, K.Y. et al. Two-year outcomes of the treat-and-extend regimen using aflibercept for treating diabetic macular oedema. Sci Rep 10, 22030 (2020). https://doi.org/10.1038/s41598-020-78954-3

[171] Ghasemi Falavarjani, K., Nguyen, Q. Adverse events and complications associated with intravitreal injection of anti-VEGF agents: a review of literature. Eye 27, 787-794 (2013). https://doi.org/10.1038/eye.2013.107

[172] Witkin A, Hahn P, Murray T, et al. Occlusive Retinal Vasculitis Following Intravitreal Brolucizumab. Journal of VitreoRetinal Diseases 2020: 247412642093086. doi.org/10.1177/2474126420930863

[173] Kondapalli SSA. Retinal Vasculitis after Administration of Brolucizumab Resulting in Severe Loss of Visual Acuity. JAMA Ophthalmol 2020.doi: 400 10.1001/jamaophthalmol.2020.2810

[174] Schargus M, Frings A. Issues with Intravitreal Administration of Anti-VEGF Drugs. Clin Ophthalmol. 2020; 14:897-904 https://doi.org/10.2147/OPTH.S207978

[175] M. I. van der Reis, E. C. La Heij, Y. De Jong-Hesse, P. J. Ringens, F. Hendrikse, and J. S. A. G. Schouten, "A systematic review of the adverse events of intravitreal antivascular endothelial growth factor injections,"Retina,vol.31, no. 8, pp. 1449-1469, 2011.

[176] R. Nuzzi and F. Tridico, "Local and systemic complications after intravitreal administration of anti-vascular endothelial growth factor agents in the treatment of different ocular diseases: a five-year retrospective study," Seminars in Ophthalmology, vol. 30, no. 2, pp. 129-135, 2015

[177] .Das A, McGuire PG, Rangasamy S. Diabetic Macular Edema: Pathophysiology and Novel Therapeutic Targets. Ophthalmology [Internet]. 2015; 122(7):1375-94. Available from: 10.1016/ j.ophtha.2015.03.024

[178] Brown DM, Nguyen QD, Marcus DM, Boyer DS, Patel S, Feiner L, et al. Long-term outcomes of ranibizumab therapy for diabetic macular edema: The 36-month results from two phase III trials: RISE and RIDE. Ophthalmology [Internet]. 2013; 120(10):2013-22. Available from: 10.1016/ j.ophtha.2013.02.034.

[179] Antonetti DA, Wolpert EB, DeMaio L, et al: Hydrocortisone decreases retinal endothelial cell water and solute flux coincident with increased content and decreased phosphorylation of occludin. J Neurochem 2002; 80: 667-677.

[180] Silva PS, Sun JK, Aiello LP: Role of steroids in the management of diabetic macular edema and proliferative diabetic retinopathy. Semin Ophthalmol 2009;

[181] Bhisitkul RB, Winn BJ, Lee OT, et al: Neuroprotective effect of intravitreal triamcinolone acetonide against photoreceptor apoptosis in a rabbit model of subretinal haemorrhage. Invest Ophthalmol Vis Sci 2008; 49: 4071-4077.

[182] Dinah Zur, Matias Iglicki, Anat Loewenstein. The Role of Steroids in the Management of Diabetic Macular Edema. Ophthalmic Res 2019; 62: 231-236 DOI: 10.1159/000499540

[183] Pessoa B, Coelho J, Correia N, Ferreira N, Beirão M, Meireles A, et al. Fluocinolone acetonide intravitreal implant 190 μg (ILUVIEN®) in vitrectomized versus nonvitrectomized eyes for the treatment of chronic diabetic macular edema. Ophthalmic Res 2018; 59:68-75.

[184] Boyer DS, Faber D, Gupta S, Patel SS, Tabandeh H, Li XY, et al. Dexamethasone intravitreal implant for treatment of diabetic macular edema in vitrectomized patients. Retina 2011; 31:915-23

[185] Diabetic Retinopathy Clinical Research Network. A randomized trial comparing intravitreal triamcinolone acetonide and focal/grid photocoagulation for diabetic macular edema. Ophthalmology. 2008; 115:1447-9.

[186] Elman MJ, Bressler NM, Qin H, Beck RW, Ferris FL 3rd, Friedman SM, et al.; Diabetic Retinopathy Clinical Research Network. Expanded 2-year follow-up of ranibizumab plus prompt or deferred laser or triamcinolone plus prompt laser for diabetic macular edema. Ophthalmology. 2011 Apr; 118(4): 609-14

[187] Maturi RK, Glassman AR, Liu D, Beck RW, Bhavsar AR, Bressler NM, et al. Effect of adding dexamethasone to continued ranibizumab treatment in patients with persistent diabetic macular edema: a DRCR network phase 2 randomized clinical trial. JAMA Ophthalmol. 2018; 136:29-38.

[188] N. Haghjou, M. Soheilian, and M. J. Abdekhodaie, "Sustained release intraocular drug delivery devices for treatment of uveitis," Journal of Ophthalmic & Vision Research, vol. 6, no. 4, pp. 317-329, 2011.

[189] J.-E. Chang-Lin, M. Attar, A. A. Acheampong et al., "Pharmacokinetics and pharmacodynamics of a sustained release dexamethasone intravitreal implant," Investigative Ophthalmology & Visual Science, vol. 52, no. 1, pp. 80-86, 2011.

[190] D. S. Boyer, Y. H. Yoon, R. Belfort Jr. et al., "Three-year, randomized, sham-controlled trial of dexamethasone intravitreal implant in patients with diabetic macular edema," Ophthalmology, vol. 121, no. 10, pp. 1904-1914, 2014

[191] Whitcup SM, Cidlowski JA, Csaky KG, Ambati J. Pharmacology of corticosteroids for diabetic macular edema. Invest Ophthalmol Vis Sci. 2018 Jan; 59(1): 1-12.

[192] Chang-Lin JE, Burke JA, Peng Q, Lin T, Orilla WC, Ghosn CR, et al. Pharmacokinetics of a sustained-release dexamethasone intravitreal implant in vitrectomized and nonvitrectomized eyes. Invest Ophthalmol Vis Sci. 2011 Jun; 52(7): 4605-9

[193] Iglicki M, Busch C, Zur D, Okada M, Mariussi M, Chhablani JK, et al. Dexamethasone implant for diabetic macular edema in naive compared with refractory eyes: The International Retina Group Real-Life 24-Month Multicenter Study. The IRGREL-DEX Study. Retina. 2019 Jan; 39(1): 44-51

[194] Malclès A, Dot C, Voirin N, Agard É, Vié AL, Bellocq D, et al. Real-life study in diabetic macular edema treated with dexamethasone implant: The Reldex Study. Retina. 2017 Apr; 37(4): 753-60.

[195] Busch C, Zur D, Fraser-Bell S, Laíns I, Santos AR, Lupidi M, et al.; International Retina Group. Shall we stay, or shall we switch? Continued anti-VEGF therapy versus early switch to dexamethasone implant in refractory diabetic macular edema. Acta Diabetol. 2018 Aug; 55(8): 789-96.

[196] Cantrill HL, Waltman SR, Palmberg PF, Zink HA, Becker B. In vitro determination of relative corticosteroid potency. J Clin Endocrinol Metab. 1975 Jun; 40(6): 1073-7. doi: 10.1210/jcem-40-6-1073.

[197] Veritti D, Sarao V, Diplotti L, Samassa F, Lanzetta P. Fluocinolone

acetonide for the treatment of diabetic macular edema. Expert Opin Pharmacother. 2017 10; 18(14):1507-16.

[198] Syed YY. Fluocinolone Acetonide Intravitreal Implant 0.19 mg (ILUVIEN®): A Review in Diabetic Macular Edema. Drugs. 2017; 77(5):575-83.

[199] Haritoglou C, Mayer W, Wolf A. Fluocinolone acetonide for the treatment of diabetic macular edema. Expert Rev Clin Pharmacol [Internet]. 2016;9(3):367-74. Available from: 10.1080/14656566.2017.1363182

[200] Schmit-Eilenberger VK, Augustin AJ. Early experience with Iluvien for the treatment of chronic DME. Retina Today 2013: 34-37. http://retinatoday.com/2013/08/early-experience-with-iluvien-for-the-treatment-of-chronic-dme/

[201] Alimera Sciences Inc. Iluvien (fluocinolone acetonide intravitreal implant) 0.19 mg for intravitreal injection: US prescribing information. 2014.

[202] Campochiaro PA, Brown DM, Pearson A, Ciulla T, Boyer D, Holz FG, et al.; FAME Study Group. Long-term benefit of sustained-delivery fluocinolone acetonide vitreous inserts for diabetic macular edema. Ophthalmology. 2011 Apr; 118(4): 626-635.e2.

[203] Campochiaro PA, Brown DM, Pearson A, Chen S, Boyer D, Ruiz-Moreno J, et al.; FAME Study Group. Sustained delivery fluocinolone acetonide vitreous inserts provide benefit for at least 3 years in patients with diabetic macular edema. Ophthalmology. 2012 Oct; 119(10): 2125-32.

[204] Mansoor S, Kuppermann BD, Kenney MC. Intraocular sustained-release delivery systems for triamcinolone acetonide. Pharm Res 2009; 26:770-84.

[205] Jonas JB, Söfker A. Intraocular injection of crystalline cortisone as adjunctive treatment of diabetic macular edema. Am J Ophthalmol 2001; 132:425-7.

[206] Martidis A, Duker JS, Greenberg PB, Rogers AH, Puliafito CA, Reichel E, et al. Intravitreal triamcinolone for refractory diabetic macular edema. Ophthalmology. 2002 May; 109(5): 920-7.

[207] Massin P, Audren F, Haouchine B, Erginay A, Bergmann JF, Benosman R, et al. Intravitreal triamcinolone acetonide for diabetic diffuse macular edema: preliminary results of a prospective controlled trial. Ophthalmology. 2004 Feb; 111(2): 218-24.

[208] Audren F, Lecleire-Collet A, Erginay A, Haouchine B, Benosman R, Bergmann JF, et al. Intravitreal triamcinolone acetonide for diffuse diabetic macular edema: phase 2 trial comparing 4 mg vs 2 mg. Am J Ophthalmol. 2006 Nov; 142(5): 794-9.

[209] Beer PM, Bakri SJ, Singh RJ, Liu W, Peters GB 3rd, Miller M, et al. Intraocular concentration and pharmacokinetics of triamcinolone acetonide after a single intravitreal injection. Ophthalmology 2003; 110:681-6.

[210] Mason JO 3rd, Somaiya MD, Singh RJ. Intravitreal concentration and clearance of triamcinolone acetonide in nonvitrectomized human eyes. Retina 2004; 24:900-4.

[211] Elman MJ, Aiello LP, Beck RW, et al; Diabetic Retinopathy Clinical Research Network: Randomized trial evaluating ranibizumab plus prompt or deferred laser or triamcinolone plus prompt laser for diabetic macular edema. Ophthalmology 2010; 117: 1064-1077.e35

[212] Elman MJ, Bressler NM, Qin H, Beck RW, Ferris FL 3rd, Friedman SM, et al.; Diabetic Retinopathy Clinical Research Network. Expanded 2-year

follow-up of ranibizumab plus prompt or deferred laser or triamcinolone plus prompt laser for diabetic macular edema. Ophthalmology. 2011 Apr; 118(4): 609-14

[213] Chawan-Saad J, Wu M, Wu A, Wu L. Corticosteroids for diabetic macular edema. Taiwan J Ophthalmol 2019; 9:233-42. DOI: 10.4103/tjo.tjo_68_19

[214] Jones R 3rd, Rhee DJ. Corticosteroid-induced ocular hypertension and glaucoma: A brief review and update of the literature. Curr Opin Ophthalmol 2006; 17:163-7.

[215] Razeghinejad MR, Katz LJ. Steroid-induced iatrogenic glaucoma. Ophthalmic Res 2012; 47:66-80.

[216] Papastavrou VT, Zambarakji H, Dooley I, Eleftheriadis H, Jackson TL. Observation: Fluocinolone acetonide (Iluvien) implant migration into the anterior chamber. Retin Cases Brief Rep 2017; 11:44-6.

[217] Gonçalves MB, Alves BQ, Moura R, Magalhães O Jr., Maia A, Belfort R Jr., et al. Intravitreal dexamethasone implant migration into the anterior chamber: A multicenter study from the Pan-American Collaborative Retina Study Group. Retina 2019. doi: 10.1097/IAE.0000000000002475.

[218] Chalioulias K, Muqit MM. Vitreoretinal surgery for inadvertent intralenticular Ozurdex implant. Eye (Lond) 2014; 28:1523-4.

[219] Gillies MC, Lim LL, Campain A, Quin GJ, Salem W, Li J et al. A randomized clinical trial of intravitreal bevacizumab versus intravitreal dexamethasone for diabetic macular edema: The BEVORDEX Study. Ophthalmology 2014; 121 (12): 2473-2481.

[220] Meyer-Schwickerath G. History and development of photocoagulation. Am J Ophthalmol. 1967; 63:1812-4.

[221] Photocoagulation for diabetic macular edema. Early Treatment Diabetic Retinopathy Study report number 1. Early Treatment Diabetic Retinopathy Study research group. Arch Ophthalmol. 1985; 103:1796-806.

[222] Stefansson E (2006) Ocular oxygenation and the treatment of diabetic retinopathy. Surv Ophthalmol 51:364-380

[223] Matsumoto M, Yoshimura N, Honda Y (1994) Increased production of transforming growth factor-beta 2 from cultured human retinal pigment epithelial cells by photocoagulation. Invest Ophthalmol Vis Sci 35:4245-4252

[224] Schatz H, Madeira D, McDonald HR, Johnson RN. Progressive enlargement of laser scars following grid laser photocoagulation for diffuse diabetic macular edema. Arch Ophthalmol. 1991; 109:1549-51. [PubMed] [Google Scholar]

[225] Rutledge BK, Wallow IH, Poulsen GL. Sub-pigment epithelial membranes after photocoagulation for diabetic macular edema. Arch Ophthalmol. 1993; 111:608-13.

[226] Writing Committee for the Diabetic Retinopathy Clinical Research Network, Fong DS, Strauber SF, Aiello LP, Beck RW, et al. (2007) Comparison of the modified Early Treatment Diabetic Retinopathy Study and mild macular grid laser photocoagulation strategies for diabetic macular edema. Arch Ophthalmol 125: 469-480.

[227] Crosson JN, Mason L, Mason JO. The Role of Focal Laser in the Anti-Vascular Endothelial Growth Factor Era. Ophthalmol Eye Dis. 2017 Nov 21; 9:1179172117738240. doi: 10.1177/1179172117738240.

[228] Diabetic Retinopathy Clinical Research Network: The course of

response to focal/grid photocoagulation for diabetic macular edema. Retina. 2009; 29(10): 1436-43.

[229] The Diabetic Retinopathy Study Research Group, "Preliminary report on effects of photocoagulation therapy," American Journal of Ophthalmology, vol. 81, pp. 383-396, 1976.

[230] Laursen ML, Moeller F, Sander B, Sjoelie AK. Subthreshold micropulse diode laser treatment in diabetic macular oedema. Br J Ophthalmol 2004; 88:1173-9.

[231] Luttrull JK, Musch DC, Mainster MA. Subthreshold diode micropulse photocoagulation for the treatment of clinically significant diabetic macular oedema. Br J Ophthalmol 2005; 89:74-80.

[232] Akduman L, Olk RJ. Subthreshold (invisible) modified grid diode laser photocoagulation in diffuse diabetic macular edema (DDME) Ophthalmic Surg Lasers 1999; 30:706-14.

[233] Luttrull, J. K.Dorin, G. Subthreshold diode micropulse laser photocoagulation (SDM) as invisible retinal phototherapy for diabetic macular edema: a review. Curr Diabetes Rev 8, 274-284 (2012).

[234] Chhablani, J. et al. Restorative retinal laser therapy: Present state and future directions. Survey Ophthalmol 63, 307-328, https://doi.org/10.1016/j.survophthal.2017.09.008 (2018).

[235] Yu, A. K. et al. The comparative histologic effects of subthreshold 532- and 810-nm diode micropulse laser on the retina. Invest Ophthalmol Vis Sci 54, 2216-2224, https://doi.org/10.1167/iovs.12-11382 (2013).

[236] Luttrull JK, Sramek C, Palanker D, Spink CJ, Musch DC. Long-term safety, high-resolution imaging, and tissue temperature modeling of subvisible

diode micropulse photocoagulation for retinovascular macular edema. Retina 2012; 32:375-86.

[237] Lavinsky D, Cardillo JA, Melo LA Jr, Dare A, Farah ME, Belfort R Jr: Randomized clinical trial evaluating mETDRS versus normal or high-density micropulse photocoagulation for diabetic macular edema. Invest Ophthalmol Vis Sci 2011; 52: 4314-4323.

[238] Figueira J, Khan J, Nunes S, Sivaprasad S, Rosa A, de Abreu JF, Cunha-Vaz JG, Chong NV: Prospective randomised controlled trial comparing sub-threshold micropulse diode laser photocoagulation. Available: 10.1016/j.ophtha.2013.02.034. and conventional green laser for clinically significant diabetic macular oedema. Br J Ophthalmol 2009; 93: 1341-1344.

[239] Abouhussein MA, Gomaa AR. Aflibercept plus micropulse laser versus aflibercept monotherapy for diabetic macular edema: 1-year results of a randomized clinical trial. Int Ophthalmol. 2020 May; 40(5):1147-1154. doi: 10.1007/s10792-019-01280-9.

[240] Furashova O, Strassburger P, Becker KA, Engelmann K. Efficacy of combining intravitreal injections of ranibizumab with micropulse diode laser versus intravitreal injections of ranibizumab alone in diabetic macular edema (ReCaLL): a single center, randomised, controlled, non-inferiority clinical trial. BMC Ophthalmol. 2020; 20(1):308. Published 2020 Jul 29. doi: 10.1186/s12886-020-01576-w

[241] Roider J, Brinkmann R, Wirbelauer C, Laqua H, Birngruber R (1999) Retinal sparing by selective retinal pigment epithelial photocoagulation. Arch Ophthalmol 117:1028-1034

[242] Brinkmann R, Roider J, Birngruber R (2006) Selective retina therapy (SRT): a review on methods, techniques,

preclinical and first clinical results. Bull Soc Belge Ophtalmol 302:51-69

[243] Roider J, Liew SH, Klatt C, Elsner H, Poerksen E, Hillenkamp J, Brinkmann R, Birngruber R (2010) Selective retina therapy (SRT) for clinically significant diabetic macular edema. Graefes's Arch Clin Exp Ophthalmol 248:1263-1272

[244] Park YG, Kim JR, Kang S, Seifert E, Theisen-Kunde D, Brinkmann R, Roh YJ (2016) Safety and efficacy of selective retina therapy (SRT) for the treatment of diabetic macular edema in Korean patients. Graefes's Arch Clin Exp Ophthalmol 254:1703-1713

[245] Jain A, Blumenkranz MS, Paulus Y, Wiltberger MW, Andersen DE, Huie P, et al. Effect of pulse duration on size and character of the lesion in retinal photocoagulation. Arch Ophthalmol. 2008; 126:78-85.

[246] Muqit MM, Gray JC, Marcellino GR, Henson DB, Young LB, Patton N, et al. In vivo laser-tissue interactions and healing responses from 20- vs 100-millisecond pulse Pascal photocoagulation burns. Arch Ophthalmol. 2010; 128:448-55.

[247] Muqit MM, Gray JC, Marcellino GR, Henson DB, Young LB, Patton N, et al. Barely visible 10-millisecond pascal laser photocoagulation for diabetic macular edema: Observations of clinical effect and burn localization. Am J Ophthalmol. 2010; 149:979-986.e2.

[248] Blumenkranz MS, Yellachich D, Andersen DE, Wiltberger MW, Mordaunt D, Marcellino GR, et al. Semiautomated patterned scanning laser for retinal photocoagulation. Retina 2006; 26:370-6

[249] Chappelow AV, Tan K, Waheed NK, Kaiser PK. Panretinal photocoagulation for proliferative diabetic retinopathy:

Pattern scan laser versus argon laser. Am J Ophthalmol 2012; 153:137-42.e2.

[250] Kernt M, Cheuteu R, Vounotrypidis E, Haritoglou C, Kampik A, Ulbig MW, et al. Focal and panretinal photocoagulation with a navigated laser (NAVILAS®) Acta Ophthalmol. 2011; 89:e662-4.

[251] Neubauer AS, Langer J, Liegl R, Haritoglou C, Wolf A, Kozak I, et al. Navigated macular laser decreases retreatment rate for diabetic macular edema: A comparison with conventional macular laser. Clin Ophthalmol. 2013; 7:121-8.

[252] Kozak I, Oster SF, Cortes MA, Dowell D, Hartmann K, Kim JS, et al. Clinical evaluation and treatment accuracy in diabetic macular edema using navigated laser photocoagulator NAVILAS. Ophthalmology. 2011; 118:1119-24.

[253] Kernt M, Ulbig M, Haritoglou C. Seattle, Washington: The Association for Research in Vision and Ophthalmology; 2013. Combination of ranibizumab and navigated retinal photocoagulation vs ranibizumab mono-therapy for diabetic macular oedema: Twelve month results.

[254] Barteselli G, Kozak I, El-Emam S, Chhablani J, Cortes MA, Freeman WR. 12-month results of the standardised combination therapy for diabetic macular oedema: Intravitreal bevacizumab and navigated retinal photocoagulation. Br J Ophthalmol. 2014; 98:1036-41

[255] Gaucher D, Tadayoni R, Erginay A, Haouchine B, Gaudric A, Massin P, et al. Optical coherence tomography assessment of the vitreoretinal relationship in diabetic macular edema. Am J Ophthalmol 2005; 139:807-13.

[256] Nasrallah FP, Jalkh AE, Van Coppenolle F, et al. The role of the

vitreous in diabetic macular edema. Ophthalmology. 1988; 95(10):1335-9.

[257] Todorich, B., Mahmoud, T.H. Vitrectomy for Diabetic Macular Edema. Curr Ophthalmol Rep 2, 167-174 (2014). https://doi.org/10.1007/s40135-014-0052-6

[258] Lewis H, Abrams GW, Blumenkranz MS, Campo RV. Vitrectomy for diabetic macular traction and edema associated with posterior hyaloid traction. Ophthalmology 1992; 99:753-9.

[259] Gandorfer A, Messmer EM, Ulbig MW, Kampik A. Resolution of diabetic macular edema after surgical removal of the posterior hyaloid and the inner limiting membrane. Retina 2000; 20:126-33

[260] Hartley KL, Smiddy WE, Flynn HW Jr., Murray TG. Pars plana vitrectomy with internal limiting membrane peeling for diabetic macular edema. Retina 2008; 28:410-9.

[261] Yang CM. Surgical treatment for severe diabetic macular edema with massive hard exudates. Retina 2000; 20:121-5.

[262] Mochizuki Y, Hata Y, Enaida H, Yoshiyama K, Miyazaki M, Ueno A, et al. Evaluating adjunctive surgical procedures during vitrectomy for diabetic macular edema. Retina 2006; 26:143-8.

[263] Landers MB 3rd, Graversen VA, Stewart MW. Early vitrectomy for DME: Does it have a role? Sometimes Vitrectomy can be First-Line Treatment. Part 1 of 2. Retina Physician; 2013

[264] Patel JI, Hykin PG, Schadt M, Luong V, Fitzke F, Gregor ZJ, et al. Pars plana vitrectomy with and without peeling of the inner limiting membrane for diabetic macular edema. Retina 2006; 26:5-13.

[265] Thomas D, Bunce C, Moorman C, Laidlaw DA. A randomised controlled feasibility trial of vitrectomy versus laser for diabetic macular oedema. Br J Ophthalmol 2005; 89:81-6.

[266] Terasaki H, Kojima T, Niwa H, Piao CH, Ueno S, Kondo M, et al. Changes in focal macular electroretinograms and foveal thickness after vitrectomy for diabetic macular edema. Invest Ophthalmol Vis Sci 2003; 44:4465-72.

[267] Higuchi A, Ogata N, Jo N, Wada M, Matsumura M. Pars plana vitrectomy with removal of posterior hyaloid face in treatment of refractory diabetic macular edema resistant to triamcinolone acetonide. Jpn J Ophthalmol 2006; 50:529-31.

[268] Kadonosono K, Itoh N, Ohno S. Perifoveal microcirculation before and after vitrectomy for diabetic cystoid macular edema. Am J Ophthalmol 2000; 130:740-4.

[269] Shah SP, Laidlaw DA. Vitrectomy for diabetic macular edema. Am J Ophthalmol 2006; 141:225

[270] Kita T, Clermont AC, Murugesan N, et al. Plasma kallikrein-kinin system as a VEGF-independent mediator of diabetic macular edema. Diabetes. 2015 10; 64(10):3588-3599.

[271] Ashay D. Bhatwadekara, Viral S. Kansarab, Thomas A. Ciulla. Investigational plasma kallikrein inhibitors for the treatment of diabetic macular edema: an expert assessment. Expert Opin Investig Drugs. 2020 March; 29(3): 237-244. doi:10.1080/13543784.2020.1723078