Chapter

Treating Diabetic Retinopathy: Challenges and the Way Forward

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Abstract

Diabetic retinopathy is a well-known complication of long-standing diabetes and is frequently encountered by ophthalmologists. While early changes may not impact vision, it is important to understand the need to follow up these patients regularly to avoid sight-threatening vision loss with timely management. Timely referral by physicians and increasing awareness about diabetic retinopathy is crucial to achieve this goal. Moreover, the advent of newer pharmacotherapeutics and better machinery and instrumentation for safe vitreoretinal surgery has played a significant role in changing the dynamics of the treatment of diabetic retinopathy. This chapter focuses on the difficulties faced in managing patients with diabetic retinopathy, as well as treatment options in practice and areas of future research.

Keywords: diabetic retinopathy, diabetic macular edema, photocoagulation, anti-vascular endothelial growth factor (VEGF) injections, diabetic vitrectomy

1. Introduction

Diabetes is a well-known metabolic disorder with an estimated global prevalence of 536.6 million (10%) in 20 to 79-year-olds in 2021. This is expected to rise to 783.2 million (12.2%) in 2045 [1]. With the increasing disease burden, the prevalence of people with microvascular complications such as nephropathy, neuropathy and retinopathy is on the rise. Diabetic retinopathy (DR) is a major ocular complication of this disease with known visual repercussions. With a global prevalence of more than 100 million, DR is known to cause significant sight-threatening complications that lead to blindness and visual impairment [2]. This is projected to increase significantly to 161 million in 2045 [3].

The prevalence of diabetic retinopathy has been noted in both type 1 and type 2 diabetics. In the former variant, 13% develop retinopathy after 5 years, and it increases to 90% after 10 to 15 years. After 15 years, proliferative retinopathy may be seen in about 25% of patients with type 1 diabetes [4]. Forty percent of type 2 diabetics treated with insulin develop retinopathy after 5 years as compared to 24% when treated with oral hypoglycemic agents. The prevalence increases to 84 and 53%, respectively, after 15 to 19 years of diabetes. Proliferative retinopathy has been detected in 2% of type 2 diabetics within 5 years of diagnosis and 25% after 25 years or more [5].

Although DR is preventable and treatable with appropriate screening strategies, newer imaging modalities and advances in pharmacotherapy, there are still several challenges that need to be faced to decrease the burden of the disease. This chapter shall discuss the problems encountered, current treatment strategies and key areas of further research. It will not only improve our insight on DR but also help us tackle this public health problem in a better manner.

2. Challenges of treating diabetic retinopathy

Although diabetic retinopathy and its pathogenesis is well-understood now, its management is fraught with challenges. Since the burden of the disease is high, it is important to screen established diabetics properly to detect retinopathy before it gets sight-threatening. Unfortunately, the degree of awareness regarding diabetic retinopathy in the community is still low, which can pose a hindrance to the detection and further management of retinopathy. Even when it is diagnosed, compliance issues, lack of motivation for blood sugar control, and failure to treat other microvascular complications like nephropathy can further aggravate retinopathy and pose problems for the patient as well as the physician.

Treatment of diabetic retinopathy complications includes retinal laser, anti-VEGF injections and surgical management in those with established retinal detachment and vitreous hemorrhage. This has been explained lucidly in **Figure 1**. While intravitreal anti-VEGF injections can work wonders, economic issues involving affordability remain. The advent of microincision vitreoretinal surgery (MIVS) may have made the lives of vitreoretinal surgeons better, but diabetic vitrectomy is not without challenges.

In the subsequent sections, the management of diabetic retinopathy and the challenges faced thereof shall be discussed.

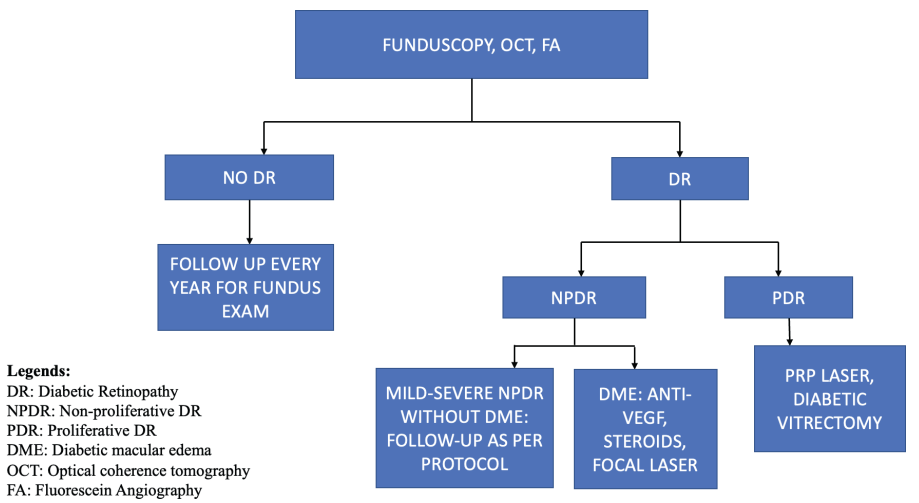

Figure 1.
A simplistic flowchart on approach to management in diabetic retinopathy.

3. Role of glycemic control

Glycemic control has an important role in the management of diabetic retinopathy. Several studies have highlighted the importance of glycated hemoglobin (HbA1c) in predicting the course of retinopathy. The Wisconsin Epidemiologic Study reported that HbA1c levels at baseline had a significant correlation with the incidence and progression of proliferative retinopathy in diabetic individuals younger than 30 years and in those who were older and treated with oral hypoglycemic agents and insulin [6].

The Diabetes Control and Complications Trial (DCCT) studied the effects of intensive glycemic control on the incidence and progression of retinopathy and its management in type 1 diabetes [7]. Participants treated with conventional therapy had a mean HbA1c of 9.2% at follow-up as compared to 7.2% in the intensive control group. There was a risk reduction of 70% for clinically important sustained retinopathy, 56% for laser photocoagulation and 60% for sustained microalbuminuria. Even after 4 years of completion of study, the intensive control group not only reported lower HbA1c but also a reduction in proliferative retinopathy, macular edema and need for laser therapy by 74, 77% and 77%, respectively [8].

The United Kingdom Prospective Diabetes Study (UKPDS) also achieved lower HbA1c levels in the intensive therapy group in type 2 diabetic individuals [9, 10]. A risk reduction of 27% for retinal photocoagulation was reported at 12 years in the intensive treatment group. In addition, the effects of blood pressure control in type 2 diabetics with hypertension were also studied. Those with tight blood pressure control experienced a 34% reduction in two-step deterioration of retinopathy, a 35% reduction in retinal photocoagulation, and a 47% risk reduction in three-line deterioration in Early Treatment of Diabetic Retinopathy Study (ETDRS) visual acuity over 7.5 years [11, 12].

Therefore, not only should one understand the need for strict glycemic control but also the requirement for blood pressure control in patients with coexisting hypertension.

4. Diabetic retinopathy study (DRS) and ETDRS studies: stepping stones in diabetic retinopathy treatment

Two major landmark trials made a huge impact on the classification and management of diabetic retinopathy. They were the Diabetic Retinopathy Study (DRS) and the Early Treatment of Diabetic Retinopathy Study (ETDRS).

4.1 Diabetic retinopathy study (DRS)

The DRS was a randomized, controlled clinical trial funded by the National Eye Institute (NEI) to evaluate photocoagulation for the treatment of proliferative diabetic retinopathy (PDR). The main aim of the DRS was to determine whether photocoagulation helps prevent severe vision loss (SVL) in PDR, with SVL being defined as visual acuity (VA) defined as less than 5/200 at two or more consecutively completed 4-month follow-up visits [13]. The results of DRS showed that the 2-year incidence of SVL was reduced by photocoagulation in more than half of eyes with PDR with or without high-risk characteristics (HRCs), which were described as follows:

- Moderate or severe new vessels on or within one disc diameter (DD) of the optic disc.
- Mild new vessels on or within one DD of the optic disc if fresh vitreous or pre-retinal hemorrhage is present.
- Moderate or severe new vessels elsewhere (NVE), if fresh vitreous or pre-retinal hemorrhage is present, and if the area of NVE was half DD or more.

On the contrary, in eyes with non-proliferative diabetic retinopathy (NPDR), photocoagulation reduced the risk of SVL to only 2.8% compared to 3.2% in the untreated NPDR subjects. Therefore, in NPDR, the risks of photocoagulation outweigh the benefits [13].

In conclusion, the DRS firmly established the benefits of laser photocoagulation in patients with PDR with HRCs and advised prompt treatment in such cases. It did not, however, include the effects of focal laser on macular edema [14].

4.2 The early treatment diabetic retinopathy study

The ETDRS was a multicenter, randomized clinical trial, funded by the NEI, to evaluate argon laser photocoagulation in the management of patients with non-proliferative or early PDR [15]. They not only studied the effects of scatter photocoagulation but also that of focal laser in patients with macular edema [16].

The ETDRS recommended that scatter photocoagulation should be considered without delay if the eye has already reached a high-risk proliferative stage. It is not recommended for mild to moderate NPDR cases as the side effects outweigh the benefits in those cases. It also showed that in eyes with macular edema, an immediate focal laser showed a statistically significant beneficial effect [17].

However, there were many gray areas that this study could not answer. Moreover, with the advent of modern pharmacotherapeutic agents for macular edema, many recommendations have changed over time.

5. Present role of laser photocoagulation

With the advent of anti-VEGF therapy in the management of PDR and diabetic macular edema (DME), several trials have been conducted to study the effect of pharmacologic therapy vis-à-vis laser therapy or combined therapy. Even corticosteroid agents have been the focus of certain clinical trials. The Diabetic Retinopathy Clinical Research Network (DRCR.net) has conducted many of these studies [18]. They establish the efficacy and benefits of intravitreal anti-VEGF therapy, either alone or in combination with laser, for the treatment of PDR and DME.

However, in the real-world scenario, various other factors also come into play. There might be several personal, social, financial or even medical constraints to seeking therapy by multiple intravitreal injections [19]. It is in these conditions that laser therapy emerges as the better option, considering that it not only reduces the number of injections required but also provides a lasting therapeutic effect [20].

Laser treatment in the form of Panretinal Photocoagulation (PRP) remains the gold standard for PDR as it offers a definitive and long-lasting therapeutic effect that prevents severe vision loss or complications of PDR. It also minimizes the number of intravitreal injections for treatment and reduces the number of follow-up visits.

Similarly, a focal laser can be done to treat leaking microaneurysms that cause persistent DME in patients with DR. However, it should be noted that only fovea-sparing microaneurysms can be lasered.

In addition, newer laser techniques and instrumentation are being introduced that can lead to better clinical efficacy and improvements in patient management. Examples include pattern scanning laser technology (PASCAL), which reduces the time taken to laser a patient as well as improves patient comfort levels. Selective Retinal Therapy (SRT) treats retinal pigment epithelial cells selectively, thus limiting damage to the neurosensory retina. Similarly, subthreshold laser induces a therapeutic effect without any visible tissue damage. Other innovations including End Point Management and Navigated Laser have improved the safety and efficacy of laser photocoagulation [21].

6. Anti-VEGF agents in diabetic retinopathy

Anti-VEGF agents were first developed in the 1990s and worked by blocking the vascular endothelial growth factor (VEGF) that is known to cause angiogenesis. Although they were majorly introduced as anti-cancer therapy, the beneficial effects of these agents were soon discovered in a range of eye conditions like diabetic macular edema and age-related macular degeneration [22]. Bevacizumab was the first anti-VEGF agent that was tried for treatment and is still used off-label [23]. Later, many anti-VEGF drugs were formulated that are FDA-approved and have been summarized in **Table 1**.

6.1 Mechanism of action

The major factor that drives angiogenesis in an eye with diabetic retinopathy is VEGF and its isoforms. Studies have shown that VEGF-A is the most significant of all in promoting vascular permeability and angiogenesis by interacting with the receptor

Name	Mechanism of action	FDA approval
Bevacizumab	149 KDa recombinant humanized monoclonal antibody targeting VEGF-A	Metastatic colorectal cancer (2004), Off-label use in Ophthalmology
Ranibizumab	48KDa recombinant monoclonal antibody fragment with one VEGF-A binding site	Wet AMD[#] (2006), DME[*] (2012), DR[$] (2017)
Aflibercept	115 KDa soluble decoy receptor with two VEGF binding domains for VEGFR-1 and VEGFR-2	Wet AMD[#] (2011), DME[*] (2014), DR[$] (2019)
Newer agents		
Brolucizumab	26KDa humanized monoclonal single-chain variable fragment that binds VEGF-A	Wet AMD[#] (2019), DME[*] (2022), not approved for DR[$]
Faricimab	149 KDa dual mechanism antibody that works against VEGF-A and Ang-2	Wet AMD[#] (2022), DME[*] (2022)

[#]*Age-related macular degeneration.*
[*]*Diabetic macular edema.*
[$]*Diabetic retinopathy.*

Table 1.
List of anti-VEGF agents and their mechanism of action.

VEGFR-2 on vascular endothelial cells [24]. This leads to destruction of capillary endothelium tight junction that leads to endothelial cell fenestration and weakened blood vessels. It also stimulates endothelial proliferation and migration associated with the early stages of angiogenesis [25]. Different agents, however, differ in their specific actions.

6.2 Use of anti-VEGF agents

Anti-VEGF agents are popularly used to decrease the central macular thickness in cases of DME. Studies like the RISE and ranibizumab in diabetic macular edema studies (RIDE) evaluated ranibizumab as therapy for DME. Later Intravitreal Aflibercept injection in vision impairment due to DME (VIVID) and study of intravitreal aflibercept injection (IAI; EYLEA®; BAY86-5321) in patients with diabetic macular edema (VISTA) studied the effects of aflibercept [26, 27]. Both studies showed improvement in the eyes with injection. Comparison of anti-VEGF agents like bevacizumab, ranibizumab and aflibercept was done by the Protocol T. Post-hoc analysis after 2 years did not show any significant difference between the three groups [28]. At least a minimum of three injections every month is required following which the number of injections and duration of follow-up can be adjusted as per response.

In PDR, anti-VEGF agents can be used as an adjunct or as primary therapy. Protocol S demonstrated that ranibizumab was non-inferior to PRP laser therapy, with outcomes showing improvement in DME, reduction in rates of DME development and decrease in the need for rescue laser therapy [29]. Eyes with proliferative retinopathy that develop vitreous hemorrhage can also benefit from anti-VEGF therapy. They can be used to buy time for surgery or as therapy while waiting for media to clear up [30].

6.3 Safety and precautions of anti-VEGF agents

Ocular adverse events often associated anti-VEGF agents include cataracts, retinal detachment, endophthalmitis, elevated intraocular pressure, vitreous hemorrhage, uveitis, ocular inflammation, floaters, retinal vessel changes and risks of glaucomatous optic atrophy [31, 32]. Systemic side effects like thromboembolism, myocardial infarction, stroke, hypertension and bowel perforation [33]. Although most of the systemic adverse events have been associated with cancer trials, they have not been confirmed with low dose or intravitreal route of drug delivery. No difference has been noted between the anti-VEGF agents [34].

Another serious complication that can occur is the development of tractional detachment in cases of PDR with pre-existing membranes. It is hypothesized that when anti-VEGF medications are used, angiogenesis is suppressed, but connective tissue growth factor (CTGF) mediated fibrosis is not checked. This leads to the acceleration of fibrosis, which produces traction on the underlying retina [35, 36]. Long-standing diabetes and poorly controlled diabetic retinopathy are major risk factors [37].

7. Corticosteroid therapy in treatment of diabetic retinopathy

Corticosteroid therapy has mostly been used to treat diabetic macular edema, especially those refractory to anti-VEGF treatment. It has been found that apart from upregulation in VEGF, there is an increase in the levels of various growth factors and cytokines like interleukin-6, interleukin-8, interleukin-1β, monocyte chemotactic

protein-1 and tumor necrosis factor α [38]. Sometimes, even after six consecutive monthly injections of anti-VEGF, 40-50% of the eyes can still have persistent DME, thus suggesting that in certain eyes, cytokines dominate over VEGF upregulation [39].

Triamcinolone acetonide (TA) was the first corticosteroid to be widely used for DME as an intravitreal pharmacotherapy [40]. Currently, apart from TA, the dexamethasone implant and the fluocinolone acetonide implant are in use.

Triamcinolone acetonide was first tried by Jonas et al. at a dose of 20 mg injected intravitreally in an eye with persistent DME following macular photocoagulation. The DME regressed visual gains were maintained for 5 months in the patient [40]. Thereafter, most retina specialists started using 4 mg for the dose of intravitreal TA as the commercial formulation was 40 mg/ml and it is readily available.

Dexamethasone implant was studied in the dexamethasone in macular edema (MEAD) trial that randomized patients to 0.7 mg dexamethasone (DEX) implant, 0.35 mg DEX implant and sham injections [41]. The DEX-treated eyes gained eight letters compared to two letters in the sham group. At around 15 months, development of cataract led to reduction in the visual improvement in the DEX-treated eyes. These were treated and cataract extraction and gained vision toward 3-year visit. About a third of patients who were treated with the DEX implant required medication for increased intraocular pressure (IOP) and 0.3% required incisional surgery for the same [42].

The fluocinolone acetonide implant is known to deliver drugs for 3 years and has the potential to reduce frequent injections and associated endophthalmitis [43]. The fluocinolone acetonide in macular edema (FAME) study assigned individuals with persistent DME to three groups: 0.2 μg Iluvien-fluorescein angiography (FA) per day, 0.5 μg Iluvien-FA per day, or sham injection. After 3 years, 28.7, 27.8, and 18.9% gained ≥15 letters, respectively [44]. Despite 0.2 μg Iluvien-FA per day implantation, rescue photocoagulation therapy was required in 40% of the eyes. Iluvien-FA has been approved for chronic DME in Europe. It was also found through a cost-effectiveness analysis in the United Kingdom that the Iluvien-FA implant provided good value for patients with persistent DME, specifically pseudophakic patients [45, 46].

Although several head-on trials with anti-VEGF have proved that corticosteroids are non-inferior, they are still associated with a number of side effects such as increased IOP and cataract that make them a less popular drug for the first line of treatment in phakic patients [47, 48].

8. Considerations in treating diabetic macular edema

While the efficacy of intravitreal anti-VEGF agents and corticosteroids is well established, there are certain factors that one must keep in mind while treating patients with DME. It is also advisable to obtain a fundus fluorescein angiogram (FFA) and optical coherence tomography (OCT) of the patient to tailor treatment as per individual needs. OCT further classifies DME into center-involving (CI) and non-center-involving (NCI), as discussed in **Table 2**, which can again lead to differences in therapeutic approach.

8.1 Non-center-involving DME

In a naïve case of NCI-DME, one can observe if the vision is good enough (6/6-6/9). However, if the vision is worse, one can consider lasering any leaking microaneurysm 500-3000 microns away from the fovea if it meets the Clinically significant

Clinically significant macular edema (CSME)	Retinal thickening at or within 500 microns from the center of fovea
	Hard exudates at or within 500 microns from the center of fovea with associated retinal thickening
	An area or areas of retinal thickening 1 disc area in size, a part of which is within 1 disc diameter of the center of macula
Center-involving DME (CI-DME)	Diagnosed on SD-OCT[#] when the central subfoveal thickness (CST) on the macular map is 305 microns or worse in women and 315 microns or worse in men on Heidelberg (or equivalent thickness on other SD-OCT machines)
Non-center-involving DME (NCI-DME)	Diagnosed on SD-OCT[#] when the central subfoveal thickness (CST) on the macular map is less than 305 microns in women and less than 315 microns in men on Heidelberg (or equivalent thickness on other SD-OCT machines) with increased thickness in inner and outer ETDRS subfields

[#]*SD-OCT: Spectral domain optical coherence tomography.*

Table 2.
Classification of Diabetic Macular Edema.

macular edema (CSME) criteria, as given in **Table 2** [49]. Sometimes, NCI-DME may result after treatment of CI-DME. In such cases, one can opt to observe every 2 months if the vision is more than equal to 6/9. If it is less than that, leaking microaneurysms may be lasered, as discussed above [50, 51]. However, it must be kept in mind that if there is a plaque of hard exudates near fovea, it often carries a poor prognosis and the patient must be counseled thusly [52].

8.2 Center-involving DME

Intravitreal anti-VEGF agents are often the first choice of treatment for center-involving DME. The drug doses commonly administered are – bevacizumab – 1.25 mg/0.05 ml, ranibizumab – 0.5 mg/0.05 ml and aflibercept – 2 mg/0.05 ml [51, 53].

Treatment usually involves monthly injections for 4-6 months initially followed by changing regimen as per response [54]. No further improvement has been described as a less than 10% decrease in the central subfield thickness on OCT and no more than a line improvement of visual acuity [49]. Treatment can be withdrawn and patients are observed if visual acuity improves to 6/7.5 despite persistent DME. Therapy can be reinstituted if there is worsening on follow-up [55].

In cases with sub-optimal response to anti-VEGF injections, focal macular laser or switch to corticosteroid therapy may be considered depending on the case [56, 57].

8.3 DME in special situations

DME in pregnancy has been reported to spontaneously regress. However, it is important to maintain a close follow-up [49, 58]. If vision is worsened, dexamethasone implants may be considered. Intravitreal anti-VEGF injections are not recommended owing to potential side effects on the developing embryo/fetus. It is also advised not to conceive immediately after the last intravitreal injection. A waiting time of 3 months is recommended in these cases [59].

In vitrectomized eyes, it has been reported that intravitreal anti-VEGF therapy may not be as effective. Instead, an intravitreal dexamethasone implant has been found to be effective in such a scenario. However, both these agents are preferred in vitrectomized eyes based on current evidence [60, 61].

Caution should also be practiced when dealing with DME patients with cardiovascular diseases. If there is a recent history of stroke or myocardial infarction (event less than 3 months), it is better to refrain from anti-VEGF agents; steroids or laser treatment should be used instead. If the event occurred more than 3 months ago, then anti-VEGF agents can be injected, although it is better to consult with the treating physician before proceeding if a high risk of thromboembolism is suspected [49].

9. Surgical treatment for diabetic retinopathy

Common indications for vitrectomy in diabetic retinopathy include vitreous hemorrhage, tractional retinal detachment involving or approaching fovea, combined rhegmatogenous and tractional detachment, pre-macular hemorrhage and diabetic macular edema due to vitreomacular traction [62].

The Diabetic Retinopathy Vitrectomy Study has shown a clear benefit of early vitrectomy in type 1 diabetics with vitreous hemorrhage. Since then, there has been a lower threshold for vitrectomy, with more and more ophthalmologists opting for early vitrectomy [63]. Current guidelines include managing conservatively for a month before proceeding for vitrectomy. The risk of intra-operative bleeding is usually reduced with the injection of anti-VEGF agent a week before surgery. However, care should be taken so that the gap between injection and surgery is not too long to avoid Crunch syndrome [64].

Tractional retinal detachment (TRD) is usually operated upon if it involves the fovea or if there is a risk of foveal involvement if not treated. Contraction of the TRD may also lead to breaks in the atrophic retina that can further result in a combined tractional and rhegmatogenous retinal detachment. Although better equipment and improvements in vitrectomy machinery have made these surgeries easier, they still have a variable prognosis. Older age, anterior segment neovascularization, poor preoperative visual acuity, greater extent of retinal detachment and macular heterotopia are the reasons for worse prognosis [65, 66].

Pars plana vitrectomy (PPV) with internal limiting membrane (ILM) peeling is considered if there is persistent macular edema with a taut posterior hyaloid or vitreomacular traction. However, there has been contrasting evidence in relation to this subject. While some studies show favorable outcomes, others do not show a clear benefit [67].

10. Challenges and the way forward

The major challenge with any disease with a long-term course is compliance issues. Even though the early treatment of DR can improve quality of life, a significant proportion fails to comply with follow-ups, thus leading to recommended screening exams in only 18 to 60% [68]. Therefore, awareness and outreach camps in diabetic screening should not only be organized but also should be compulsorily included in the national health policy. Moreover, various therapeutic options in diabetic retinopathy come with their own set of complications and limitations. This has been summarized in **Table 3**.

Treatment options	Limitations
Anti-VEGF Agents	Relative contraindication in patients with cerebrovascular accident and myocardial infarction. Cost prohibitive
Steroids	Can lead to increase in intraocular pressure, secondary glaucoma and cataract formation. Contraindicated in glaucoma patients. Implant migration can occur in patients with posterior capsular defect
Laser Photocoagulation	Precipitates macular edema. It can cause constriction of field of vision and consecutive optic atrophy
Diabetic Vitrectomy	Foveal contour may not return to normal even after the removal of tractional membranes. Not advocated in extramacular tractional retinal detachment

Table 3.
Limitations of treatment strategies for diabetic retinopathy.

Another major factor is the economic burden of the disease. While the advent of intravitreal injections has made treating DME a lot easier, at the same time, it has increased the cost burden by several notches [69]. Therefore, economically marginalized sections of society are deprived of treatment, which increases the burden of disease. To tackle this, progress is being made in formulating more long-acting preparations or drug delivery systems like the ranibizumab port delivery system and the verisome system. Both act as long-acting systems of drug delivery into the vitreous [70, 71].

The lack of skilled retina specialists for screening is also another challenge in treating diabetic retinopathy. Therefore, several training sessions need to be organized so that ophthalmologists can identify cases that require further evaluation and urgent attention. The use of teleophthalmology can also be helpful in such cases. Fundus photographs can be screened by experts, thus aiding management [72]. The use of artificial intelligence can also augment patient care with precision and reduce human errors [73].

11. Areas of future research

There are still many unanswered questions with regard to diabetic retinopathy and its future prospects. Certain areas that require clarification and provide scope for further research have been outlined below [74].

11.1 Diabetic retinal neurodegeneration

While the primary focus of research in DR was on its vascular pathophysiology, evidence of neuronal degeneration has been collected over the years [75]. OCT of retinal inner layers including nerve fiber layer (RNFL) and ganglion cell layer (GCL) has demonstrated significant thinning over a period of time that may even precede the appearance of microangiopathic lesions [76, 77]. This has been termed as "diabetic retinal neurodegeneration" and has been corroborated histologically [78]. However, it is yet to be known as to how it affects the quality of life in diabetics and what more this information can contribute. It remains to be seen if the knowledge of retinal neurodegeneration in diabetics will help in prognosis or play a role in response to treatment of the disease.

11.2 Ultrawide field angiography and optical coherence tomography angiography

Ultrawide field (UWF) imaging with a field of view of 110 degrees to 220 degrees allows the visualization of retinal periphery as far as the anterior edge of the ampullae of the vortex veins [79]. They provide not only color fundus photography but also other investigation modalities like fluorescein angiography (FA) and indocyanine green angiography (ICGA). They are non-contact and allow photography without mydriasis. The most significant advantage of these modalities is their ability to assess the retinal periphery, covering about 80% of the retinal area [80]. Assessment of the peripheral retina can help detect lesions that are otherwise missed and help in the prognosis of the disease [81]. Moreover, cohort studies also show that peripheral lesions are independently associated with a greater risk of progression of DR [82]. However, the widespread application of this technology and its role in the classification and prognosis of DR remains to be seen.

Optical coherence tomography angiography (OCTA) is another imaging modality that is increasingly gaining importance in DR assessment and prognostication. OCTA is a non-invasive, non-contact system that provides angiographic information of the retina. Advantages of OCTA include no requirement of invasive dye administration, better visualization of the capillary microvasculature, and depth-resolved segmentation of the superficial, middle and deep capillaries plexuses, which is affected differently in eyes with DR [83, 84]. Since OCTA can provide metric quantification and analysis of retinal vasculature, there is scope for research as to how these metrics can be applied to further prognosticate and give valuable information regarding clinical outcome of DR patients [85].

11.3 Artificial intelligence

Artificial Intelligence (AI) algorithms in ophthalmology, using machine learning algorithms, for automated diagnosis or detection of DR from color fundus photograph (CFP) images have been under development since 2016 [86]. Preliminary studies demonstrated that AI algorithms developed on large datasets reach significantly high levels of diagnostic performance for detection of referable DR and vision-threatening DR [87]. There are now multiple AI-based systems for DR screening that have been approved for clinical use. IDx-DR (IDx LLC, Coralville, IA, USA) and EyeArt (Eyenuk, Inc., Woodlands Hills, CA, USA) have both received approval from the USA Food and Drug Administration (FDA) and are already in clinical use [88, 89]. By 2030, it is projected that AI in diabetic retinopathy screening will be in widespread use. However, certain aspects pertaining to image quality and medicolegal issues need to be dealt with before AI gets worldwide acceptance [90].

Apart from fundus photography, AI can be used to incorporate other imaging modalities such as OCT and OCTA, that already have inbuilt segmentation software, which is amenable to machine learning [91]. This can be another area of groundbreaking research.

12. Conclusion

Diagnosing and managing diabetic retinopathy may not be as simple as it sounds. A lot of effort goes into acquiring the skillset required for the treatment of patients

suffering from the consequences of diabetic retinopathy. However, with newer innovations and changing times, a lot of things are slowly becoming plausible and easier to imagine. Newer imaging modalities and the incorporation of AI in detection and prognostication will be a gamechanger in the near future. Nevertheless, we still have a long way to go before applying research from these areas into clinical practice. We can only hope that the unmet needs for managing diabetic retinopathy will slowly disappear in the generations to come.

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