Diabetic Retinopathy

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Abstract

Diabetic retinopathy is a leading cause of blindness and visual impairment worldwide. The prevalence of diabetic retinopathy has been steadily increasing and is projected to continue to do so in the future. Diabetic retinopathy is a complex microvascular process with numerous associated risk factors and mediated through a multitude of metabolic pathways. Landmark clinical trials including the DRS and ETDRS were instrumental in establishing staging and treatment criteria. The clinical spectrum of disease is extremely varied and is broadly categorized into nonproliferative and proliferative forms. Nonproliferative disease represents the earliest clinical findings including retinal hemorrhages and hard and soft exudates. With increasing severity of retinopathy, there is a risk for the development of ischemic manifestations in the proliferative form with neovascularization, preretinal hemorrhage, and traction elevation of the retina. Both nonproliferative and proliferative stages of retinopathy can be associated with diabetic macular edema which is the most common cause of vision loss. The treatment of diabetic macular edema has been revolutionized with OCT-guided intravitreal therapy utilizing VEGF inhibitors and various forms of corticosteroids. Several clinical trials have recently demonstrated these novel therapies to be highly effective treatments in improving the long-term anatomic and visual outcomes in diabetic patients.

Keywords

Diabetic Retinopathy • Diabetic Maculopathy • Diabetic eye problems • Diabetes vision problems

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Epidemiology

Diabetes mellitus (DM) is a major medical problem in the United States and worldwide. The disease has tremendous social and economic impact as it affects individuals in their economically productive years. It is estimated that societal costs related to the disease exceed a 100 billion dollars per year [1]. Diabetes remains a leading cause of newly diagnosed blindness in the United States and worldwide today.

The prevalence of diabetes in the United States and worldwide is clearly increasing due to various environmental and behavioral factors [2, 3]. Ten to fifteen percent of patients with diabetes have type 1 diabetes mellitus and are typically diagnosed prior to 40 years of age. The vast majority of patients are diagnosed after the age of 40 and have type 2 diabetes. Both type 1 and type 2 diabetes patients can develop ocular complications of diabetes, although patients with type 2 diabetes make up the majority of cases due to the larger patient population. The ocular manifestations for both groups are similar, however, over a long-term follow-up period.

Roy et al. utilized prevalence data to estimate the prevalence of diabetic retinopathy by age, gender, and race among persons of 18 years and older having type 1 DM diagnosed before 30 years of age [4]. It was determined that among 209 million Americans of 18 years and older, an estimated 889,000 have type 1 diabetes mellitus diagnosed before age 30 years. Among persons with type 1 diabetes mellitus, the crude prevalence of diabetic retinopathy of any level (74.9% vs. 82.3% in black and white persons, respectively) and of vision-threatening retinopathy (30.0% vs. 32.2%, respectively) is high [4]. In another study [5], pooled analysis of data from eight population-based eye surveys was used to estimate the prevalence of diabetic retinopathy among adults 40 years of age and older in the United States. Among an estimated 10.2 million adults of 40 years and older included in the study, the estimated crude prevalence rates for retinopathy and vision-threatening retinopathy were 40.3 and 8.2%, respectively. The estimated US general population prevalence rates for retinopathy and vision-threatening retinopathy were 3.4% (4.1 million persons) and 0.75% (899,000 persons) [5].

It is important to note that the prevalence of diabetic retinopathy in the general population has been increasing and is related to the increase in patient's life expectancy due to better overall health care and treatment of comorbidities. Fortunately, advances in the treatment of diabetic retinopathy have allowed for improved prognosis and maintenance of visual potential in these patients.

Risk Factors of Diabetic Retinopathy

Duration of Diabetes

The single best predictor of diabetic retinopathy is the duration of the disease [21–28]. Among younger-onset patients with diabetes, the prevalence of any retinopathy was 8% at 3 years, 25% at 5 years, 60% at 10 years, and 80% at 15 years. The prevalence of proliferative diabetic retinopathy (PDR) was 0% at 3 years and increased to 25% at 15 years [2]. The incidence of retinopathy also increased with increasing duration. The incidence of developing proliferative retinopathy in the younger-onset group increased from 0% in the first 5 years to 27.9% in 13–14 years of diabetes [2].

Determining the role of duration of diabetes as a predictor of retinopathy in type 2 diabetes mellitus is more challenging because of the uncertainty of the time of onset and therefore duration in many patients. In a well-established study, Yanko et al. [6] found that the prevalence of

nonproliferative retinopathy was 23% after 11–13 years of the onset of disease and increased to 60% after 16 or more years. Klein found that 10 years after the diagnosis of type 2 diabetes, 67% of patients had retinopathy and 10% had PDR. The risk was determined to be lowest in patients not requiring insulin [7].

Glycemic Control

The effect of intensive glycemic control on the development of diabetic retinopathy was addressed by the Diabetes Control and Complications Trial (DCCT) [7, 8], involving 1,441 patients with type 1 diabetes across 29 medical centers in the United States and Canada. The DCCT enrolled patients with insulin-dependent diabetes mellitus with minimal (secondary progression cohort) or no (primary prevention cohort) evidence of diabetic retinopathy. Patients were assigned either to conventional treatment (one or two daily injections of insulin) or to intensive diabetes management with three or more daily insulin injections or a continuous subcutaneous insulin infusion.

The DCCT demonstrated that intensive therapy reduced clinically relevant diabetic retinopathy. In the primary-prevention cohort, intensive therapy reduced the adjusted mean risk for the development of retinopathy by 76% as compared with conventional therapy. In the secondary intervention cohort, intensive therapy slowed the progression of retinopathy by 54% and reduced the development of proliferative or severe nonproliferative retinopathy by 47%. In addition, intensive therapy reduced the occurrence of microalbuminuria, albuminuria, and that of clinical neuropathy in both cohorts [7, 8].

The United Kingdom Prospective Diabetes Study (UKPDS) [9] was a randomized, controlled clinical trial investigating the protective effects of glycemic control in newly diagnosed type 2 diabetic individuals. Patients were randomly assigned to intensive glycemic control with oral agents or insulin or to conventional control with diet. The study demonstrated that improved blood glucose control reduced the risk of developing retinopathy, nephropathy, and possibly neuropathy. The overall rate of microvascular complications was decreased by 25% in patients receiving intensive therapy versus conventional therapy [10].

Systemic Hypertension

The UKPDS also evaluated the effect of blood pressure control on the progression of diabetic retinopathy. With a median follow-up of 8.4 years, patients assigned to tight blood pressure control had a 34% reduction in progression of retinopathy and a 47% reduced risk of deterioration in visual acuity of three lines associated with a 10 mmHg reduction in systolic blood pressure [11].

The EURODIAB controlled trial of lisinopril in insulin-dependent diabetes (EUCLID) study group investigated the effect of lisinopril on retinopathy in type 1 diabetes. The study showed a statistically significant 50% reduction in the progression of retinopathy in those taking lisinopril over a 2-year period compared to those not on blood pressure medication, after the adjustment of glycemic control. The results of this study, however, are tempered by the small sample size.

Currently the utility of specific antihypertensive agents in preventing the incidence and progression of diabetic retinopathy cannot be addressed, and further investigation will be required.

Dyslipidemia

Elevated serum lipids have been associated with the occurrence and progression of diabetic ocular disease. According to the Early Treatment Diabetic Retinopathy Study (ETDRS), elevated triglycerides, low-density lipoproteins, and very low-density lipoproteins are related to an increased risk for the macular hard exudates that are associated with macular edema [12]. Independent of this association with macular edema, these exudates are associated with an increased risk for vision loss. Increased triglycerides also carry an increased risk for progression of retinopathy.

Pregnancy

Pregnancy is considered a risk factor for the progression of retinopathy. In one study of type 1 diabetes, 7.3% of pregnant women compared with only 3.7% of women who were not pregnant progressed to proliferative retinopathy [13]. The risk of progression, however, is low for pregnant women who have had type 1 diabetes for less than 10 years or who have mild retinopathy [14].

Pathophysiology of Diabetic Retinopathy

The precise mechanism resulting in diabetic retinopathy remains unknown. Several metabolic pathways have been implicated in the pathogenesis of diabetic retinopathy including protein kinase C activation, polyol accumulation, and vasoproliferative factors. The net result of these pathways is compromise of the retinal capillaries resulting in their functional incompetence.

Polyol Pathway

Polyol accumulation is linked to the pathogenesis of diabetic retinopathy. Polyol pathway is a two-step pathway in which glucose is initially converted to sorbitol and then to fructose. Experimental animal models have demonstrated that the accumulation of polyol has been associated with the development of basement membrane thickening, pericyte loss, and microaneurysm formation [15, 16]. Hyperglycemia leads to an elevation of intracellular sorbitol concentrations by utilization of aldose reductase, the first and rate-limiting enzyme in the polyol pathway. Accumulation of sorbitol causes an osmotic shift, drawing water into lens epithelial cells and producing cataracts in children [17]. Retinal capillary pericytes contain the enzyme aldose reductase, and the accumulation of excess sugar alcohol, catalyzed by aldose reductase in pericytes, has been linked to their degeneration and selective death [18, 19]. The efficacy of aldose reductase inhibitors (ARIs) has been evaluated for the prevention of retinal damage in diabetes. The results of several clinical trials, however, have not shown this class of medications to be useful in the management of the development or progression of diabetic retinopathy [20, 21].

Protein Kinase C Activation

Protein kinase C (PKC) is a family of related enzymes that function as signaling components for a variety of growth factors, hormones, neurotransmitters, and cytokines. PKC activation, specifically of the PKC-β2 isoform, has been implicated in causing hyperglycemia-related microvascular damage [22]. Changes in endothelial permeability, blood flow, and formation of angiogenic growth factors have been shown to be PKC mediated in experimental models of diabetic retinopathy and result in retinal leakage, ischemia, and neovascularization [23, 24]. PKC-beta has been shown to be an integral component of cellular signaling by vascular endothelial growth factor (VEGF), an important mediator of retinal neovascularization and vascular permeability [25–27].

PKC activation occurs with its binding to diacylglycerol (DAG) in the presence of calcium. Studies have demonstrated that the hyperglycemia of diabetes induces an early activation of PKC through de novo synthesis of DAG. Other factors including reactive oxygen species, advanced glycation end products, and oxidative stress are associated with DAG-independent activation of PKC [28]. Theoretically, PKC inactivation should suppress the stimuli for the inception and progression of diabetic retinopathy and macular edema. Clinical studies have shown that ruboxistaurin, a PKC-beta isoform selective inhibitor, normalized endothelial dysfunction, renal glomerular filtration rate, and prevented loss of visual acuity in diabetic patients [29, 30]. Thus, PKC activation involving several isoforms is likely to be responsible for some aspects of the pathogenesis of diabetic retinopathy, nephropathy, and cardiovascular disease. Ongoing prospective clinical trials investigate whether the treatment with the

specific PKC-beta inhibitor can prevent the progression of diabetic retinopathy and diabetic macular edema.

Growth Factors

PKC activation results in increased production of vasoconstrictive, angiogenic, and chemotactic growth factors including TGF-beta, vascular endothelial growth factor (VEGF), growth hormone, insulinlike growth factor I (IGF-I), transforming growth factor-β (TGF-beta), and pigment epithelium-derived growth factor (PEDF).

Vascular endothelial growth factor (VEGF) is an important signaling protein involved in vasculogenesis and angiogenesis. In vitro VEGF stimulates endothelial cell mitogenesis and cell migration. In addition, VEGF functions as a vasodilator and increases microvascular permeability. Its expression has been shown to be induced by hypoxia in both retinal pigment epithelial cells and retinal pericytes [31–33]. In an animal model, retinal neovascularization was suppressed utilizing soluble VEGF-neutralizing VEGF receptor chimera.

Aiello et al. [34] demonstrated the role of VEGF in the ocular ischemic neovascular response in proliferative diabetic retinopathy, ischemic central retinal vein occlusion, and retinopathy of prematurity. The authors measured intraocular VEGF concentrations of 164 patients undergoing intraocular surgery. They compared VEGF levels in patients with active neovascularization, quiescent neovascularization, and those without any underlying neovascular disorder. VEGF concentrations were highest in the subset of patients with active neovascularization. In addition, comparison of VEGF levels in vitreous humor to that found in the aqueous humor led them to suggest a gradient-driven diffusion of angiogenic factors from the posterior to the anterior segment of the eye in patients with ischemic retinal diseases. They also determined that treatment with panretinal photocoagulation caused regression of retinal neovascularization which coincided with lower VEGF levels [34]. The reduction in retinal ischemia after laser therapy, therefore, reduces the production of angiogenic factors, suppressing neovascularization through suppression of VEGF.

Growth hormone and IGF-I have been associated with the development of diabetic retinopathy since retinal neovascularization was found to regress following pituitary infarction [35]. IGF-I was one of the first growth factors to be directly associated with diabetic retinopathy because increased serum levels of IGF-I preceded the onset of proliferative diabetic retinopathy in animal models [36, 37]. Since then, increased IGF-I levels were measured in the vitreous fluid of patients with PDR indicating that IGF-I may play a role in retinal neovascularization [38]. Clinical trials are under way to determine the significance of IGF-I in the development of diabetic retinopathy.

TGF-beta is a multifunctional growth factor that can cause an accumulation of extracellular matrix. There are three known isoforms of TGF-beta (TGF-beta$_1$, TGF-beta$_2$, and TGF-beta3) in the human eye although TGF-beta$_2$ is the predominant isoform in the vitreous humor. There have been several reports of the action of TGF-beta$_2$ in the vitreous. Connor et al. [39] found that TGF-beta$_2$ levels were increased in proliferative vitreoretinopathy. Levels of TGF-beta$_2$ in the vitreous were correlated with the severity of fibrosis suggesting that TGF-beta$_2$ had a role in the formation of proliferating membranes in this disorder. Hirase et al. [40] determined that levels of TGF-beta$_2$ were increased in the vitreous of patients with PDR. In addition, there was also a direct correlation between intraocular fibrosis and TGF-beta$_2$ levels, suggesting that TGF-beta$_2$ plays a role in the pathogenesis of PDR by inducing the formation of proliferating membranes via its interaction with the extracellular matrix.

PEDF is produced by the retinal pigment epithelium and serves as a major inhibitor of intraocular angiogenesis. The vitreous humor, which is antiangiogenic and generally devoid of vessels, contains high concentrations of PEDF [41]. Dawson et al. [42] found that removal of PEDF from vitreous fluid abrogated its antiangiogenic activity and revealed an underlying angiogenic stimulatory activity. PEDF regulates blood vessel growth in the eye by altering its levels to the oxygen needs of the

eye thereby creating a permissive or inhibitory environment for angiogenesis. This process presumably occurs with regulation of VEGF levels.

Breakdown of Blood–Retinal Barrier

The blood–retinal barrier plays an important part in the pathophysiology of diabetic retinopathy. The blood–retinal barrier is composed of an inner and an outer component. The inner blood–retinal barrier is comprised of the tight junctions between endothelial cells of the retinal blood vessels. A competent inner blood–retinal barrier normally blocks the movement of macromolecules from the vessel lumen to the interstitial space. The outer blood–retinal barrier is comprised of the tight junctions of the retinal pigment epithelial cells (RPE) preventing leakage of fluid from the choroid into the retina.

The incipient stages of diabetic retinopathy are associated with an early breakdown of the blood–retinal barrier resulting in enhanced vascular permeability and macular edema. The breaching of the blood–retinal barrier is believed to represent the earliest known change in diabetic retinopathy occurring prior to the development of microaneurysms and capillary occlusion [43]. Although both the inner and outer components exhibit increased permeability in diabetes, the inner monolayer is the predominant site of leakage in diabetic retinopathy. Interestingly, the retinal vasculature comprising the inner blood–retinal barrier contains VEGF receptors, and early blood–retinal barrier breakdown in experimental diabetes is VEGF dependent [44].

Clinical Trials in Diabetic Retinopathy

Diabetic Retinopathy Study (DRS)

The Diabetic Retinopathy Study (DRS) was undertaken in 1971 to determine whether photocoagulation helps prevent severe visual loss from proliferative diabetic retinopathy and if there was a clinically significant difference in the efficacy and safety of argon versus xenon photocoagulation for proliferative diabetic retinopathy [45].

This randomized, controlled clinical trial involved more than 1,700 patients enrolled at 15 medical centers [45]. Eligibility criteria included patients younger than 70 years of age with best-corrected visual acuity of 20/100 or better in each eye in the presence of PDR in at least one eye or severe nonproliferative diabetic retinopathy in both eyes. Patients were excluded if they had prior treatment with photocoagulation or pituitary ablation, and both eyes had to be suitable for photocoagulation [45].

In the trial, one eye of each patient was randomly assigned to receive immediate photocoagulation with either argon laser or xenon arc photocoagulation. The fellow eye was observed without treatment [45]. Patients were subsequently monitored at 4-month intervals. Treatment with photocoagulation was carried out in a panretinal or scatter technique extending to or beyond the vortex veins. Argon photocoagulation treatment specified 800–1,600 burns, 500-μm in size with 0.1 s duration [45]. Direct treatment of retinal neovascularization was applied on or within one disk diameter of the optic disk (NVD) or beyond this zone (NVE). Photocoagulation with xenon was carried out in a similar manner with fewer burns of longer duration. Treatment with xenon photocoagulation was directed at NVE. Supplemental focal laser photocoagulation in the argon treatment group was applied when clinically necessary to treat macular edema.

The DRS demonstrated that both argon and xenon photocoagulation reduced the risk of severe visual loss (best-corrected visual acuity $< 5/200$) by more than 50% during a follow-up of over 5 years [46]. Adverse effects of laser photocoagulation included a modest reduction of visual acuity of one line and constriction of the peripheral visual field. The results indicated that these effects were more pronounced in the xenon arc-treated group. The study concluded that the risks of severe visual loss outweighed the adverse effect of treatment for two groups of patients: eyes with retinal neovascularization and preretinal or vitreous hemorrhage and eyes with new vessels on or within one disk diameter of the optic disk (NVD) equaling or exceeding 1/4–1/3 disk area in extent even in the absence of preretinal or vitreous

hemorrhage [46]. These eyes were considered at high risk for PDR and required prompt treatment as they had the highest risk of severe visual loss.

Early Treatment Diabetic Retinopathy Study (ETDRS)

The ETDRS was a multicenter, randomized clinical trial involving 3711 participants designed to evaluate the effectiveness of both argon laser photocoagulation and aspirin therapy in the management of patients with nonproliferative diabetic retinopathy and early PDR [47]. In addition, it was designed to determine the best time to initiate photocoagulation treatment in diabetic retinopathy.

The eligibility criteria for the ETDRS were broad, enrolling patients with a mild nonproliferative diabetic retinopathy through early PDR with visual acuity 20/200 or better in each eye [47]. Patients were randomly assigned to receive photocoagulation in one eye with the fellow eye observed. Follow-up examinations were scheduled at least every 4 months, and photocoagulation was initiated in the eyes assigned to deferral as soon as high-risk proliferative retinopathy was detected [47]. Furthermore, patients were randomly assigned to receive 650 mg per day of aspirin or a placebo. The primary outcome measured in the ETDRS was moderate visual loss (MVL) defined as a doubling of the visual angle, a drop of 15 or more letters on ETDRS visual acuity, or a drop of three or more lines of Snellen visual acuity [47].

The ETDRS defined clinically significant macular edema (CSME) as:

1. Retinal edema located at or within 500 μm of the center of the macula
2. Hard exudates at or within 500 μm of the center if associated with thickening of the adjacent retina
3. A zone of thickening larger than one disk area if located within one disk diameter of the center of the macula

The ETDRS determined that focal laser photocoagulation reduced the risk of MVL by 50%. Treatment increased the chance of visual improvement and was associated in minor losses of visual field. Treatment consisted of argon laser photocoagulation of individual-leaking microaneurysms and grid treatment to areas of diffuse leakage and capillary nonperfusion [48].

The ETDRS also concluded that early panretinal photocoagulation with or without focal photocoagulation compared with deferral of photocoagulation was associated with a small reduction in the incidence of severe visual loss (visual acuity less than 5/200 at two consecutive visits), but 5-year rates were low in both the early treatment and deferral groups (2.6 and 3.7%, respectively) [49]. It was determined that scatter photocoagulation is not recommended for the eyes with mild or moderate nonproliferative diabetic retinopathy provided appropriate follow-up care can be maintained. Patients with severe nonproliferative diabetic retinopathy or high-risk PDR should receive prompt photocoagulation. The ETDRS defined severe nonproliferative diabetic retinopathy as follows:

1. Diffuse intraretinal hemorrhages and microaneurysms in four quadrants
2. Venous beading in two quadrants
3. Intraretinal microvascular abnormalities (IRMA) in one quadrant

Aspirin treatment did not alter the course of diabetic retinopathy in patients enrolled in ETDRS. Aspirin did not prevent the development of high-risk proliferative retinopathy and did not reduce the risk of visual loss, nor did it increase the risk of vitreous hemorrhage in both eyes assigned for laser photocoagulation and deferral of treatment. Furthermore, it was determined that aspirin had no deleterious effects for diabetic patients with retinopathy [50].

Diabetic Retinopathy Vitrectomy Study (DRVS)

The DRVS was a randomized, multicenter clinical trial designed to compare two therapies, early vitrectomy and conventional management, for

recent severe vitreous hemorrhage secondary to diabetic retinopathy [51]. The early vitrectomy group had vitrectomy within 6 months of the onset of vitreous hemorrhage. The conventional management group underwent vitrectomy if hemorrhage failed to clear during a waiting period of 6–12 months or if retinal detachment involving the center of the macula developed at any time [51].

The results of the DRVS clearly demonstrated the benefit of early vitrectomy for patients with severe PDR. After 2 years of follow-up, 25% of the early vitrectomy group had visual acuity of 10/20 or better compared with 15% in the deferral group [52]. This benefit was most evident for patients with type 1 diabetes, as they represented a younger subset of patients with a relatively more severe PDR. This trend continued at the 4-year follow-up, with 44% of patients in the early vitrectomy group achieving 10/20 visual acuity versus 28% for the conventional management group [53].

Clinical and Fundus Findings

Nonproliferative Diabetic Retinopathy (NPDR)

Diabetic retinopathy is a retinal vascular disorder characterized by typical microvascular funduscopic changes. These typical funduscopic lesions can be broadly characterized as either nonproliferative or proliferative retinopathy with varying degrees of severity in each subset. They can either precede or follow alterations in retinal function thereby highlighting the importance of timely examinations to detect incipient changes.

The characteristic fundus lesions associated with nonproliferative diabetic retinopathy include cotton wool spots, microaneurysms, dot and blot hemorrhages, retinal vascular caliber changes, hard exudate formation, retinal capillary closure, and macular edema.

Microaneurysms represent saccular outpouchings of the retinal capillary bed. They can present as concentrated lesions in the posterior pole or with widespread distribution throughout the fundus. Their formation is nonspecific to diabetes and can occur in a variety of disorders including hypertension and sickle cell disease. Although their precise pathogenesis remains unknown, they are attributed to pericyte degeneration, endothelial cell proliferation, and retinal capillary closure. They represent the earliest clinical changes of the retinal vasculature in NPDR detectable with ophthalmoscopy. They are best detected with fluorescein angiography in which they typically surround areas of capillary nonperfusion. In the earliest stages, the increase or decrease in microaneurysm formation can be used as an indicator for progression or regression of disease. The microaneurysm count at baseline examination can be used as an important predictor of progression of diabetic retinopathy [54]. They become visually significant when there is an associated leakage of serous contents leading to macular edema.

Cotton wool spots represent retinal nerve fiber layer infarcts associated with stasis of axoplasmic flow. They occur early in the course of NPDR and may be evident prior to the development of microaneurysms and retinal hemorrhages. They are evanescent in nature, usually resolving in several months though they may persist much longer. Their effect on visual acuity and the visual field is dependent on their size and location. Although most commonly seen in diabetic retinopathy, they are also seen in a variety of retinal vascular disorders including hypertensive retinopathy, central retinal vein occlusion, and drug toxicities such as with interferon retinopathy.

The presence of intraretinal microvascular abnormalities and capillary permeability may lead to the formation of retinal hemorrhages. The morphology of the hemorrhages is related to the topography of the anatomical retinal layer from which they are derived. Superficial hemorrhages assume a flame-shaped appearance due to the parallel arrangement of the nerve fiber layer to the retinal surface. Deeper hemorrhages assume a dot and blot appearance due to the perpendicular arrangement of cells in the deeper retinal tissue. Occasionally, these hemorrhages may attain a white center, representing fibrin deposition. White-centered hemorrhages are more commonly

seen in other conditions such as subacute bacterial endocarditis and acute leukemia. Intraretinal hemorrhages are significant in that they generally parallel the severity of NPDR. Intraretinal hemorrhages are not typically visually significant unless they assume a subfoveal location.

Intraretinal microvascular abnormalities or IRMA are evident in NPDR. They represent dilated vascular segments in a partially occluded capillary bed and represent intraretinal neovascularization or the formation of shunts in areas on nonperfusion. They are clinically significant in that they may leak and cause macular edema and impart a greater risk for the development of PDR.

The venous caliber abnormalities in NPDR include vascular dilation, beading, and the formation of loops. They are indicative of retinal ischemia and may be associated with central or branch retinal venous occlusions, which are both seen more commonly in the diabetic population.

The primary mechanism of visual loss in nonproliferative retinopathy is through macular edema. The edema can be a result of focal vascular leakage from microaneurysms in the macular or via diffuse vascular leakage. The edema may be associated with hard exudates or cystoid changes in the macula. If the edema is classified as clinically significant macular edema (CSME), as outlined by the ETDRS, focal laser photocoagulation is performed to avoid precipitous vision loss. Laser photocoagulation is directed at microaneurysms for focal leakage and is applied in a grid pattern for diffuse leakage. Concomitant cardiovascular and renal disease leading to fluid retention and hypertension can further exacerbate the edema. Treatment, therefore, of systemic abnormalities using a multidisciplinary approach should be included in the care of the patient with macular edema.

NPDR can be classified into mild, moderate, and severe forms, with each imparting its own degree of severity and progression to proliferative retinopathy. *Mild* NPDR is characterized by microaneurysms only and impart a 5% risk of developing PDR in 1 year (Fig. 1(1)) [55]. *Moderate* NPDR is characterized by less than four quadrants of scattered microaneurysms and hemorrhages along with cotton wool spots, venous beading, or IRMA (Fig. 1(2)). The risk of progression to PDR within 1 year is between 12 and 27% [55]. Patients with mild and moderate NPDR are treated by medically optimizing glycemic control and any associated hypertension or dyslipidemia. Patients with clinically significant macular edema are treated with focal laser therapy. These patients are not candidates for scatter laser photocoagulation. *Severe* NPDR is characterized by the "4-2-1" rule of four quadrants of hemorrhages and microaneurysms, two quadrants of venous caliber abnormalities, or one quadrant of IRMA (Fig. 1(3)). These patients are at high risk for developing PDR with a 52% risk within 1 year [55]. These patients are candidates for panretinal photocoagulation (PRP); the timing of which is determined at the discretion of the retinal specialist.

Proliferative Diabetic Retinopathy (PDR)

Proliferative diabetic retinopathy is an advanced form of diabetic retinopathy characterized by the growth of abnormal blood vessels, which extend over the surface of the retina and along the "scaffold" provided by the posterior vitreous hyaloid. These new blood vessels may present as neovascularization of the optic disk (NVD) or anywhere along the retinal periphery (NVE), vitreous hemorrhage, and fibrous proliferation. Active neovascularization commonly occurs at the border of perfused and nonperfused retina and is most severe in the eyes with extensive nonperfusion. The newly formed vessels are fragile commonly resulting in vitreous hemorrhage and precipitous vision loss.

The formation of new blood vessels in PDR occurs as a consequence of progressive damage to the retinal blood vessels in NPDR. Eventually, with cumulative damage, there is capillary occlusion resulting in a relative oxygen-deficient or ischemic environment. This results in the release of various angiogenic growth factors; the most significant of which is believed to be vascular endothelial growth factor or VEGF. VEGF release serves as the stimulus for the proliferation of new vessels resulting in NVD, NVE, and potential

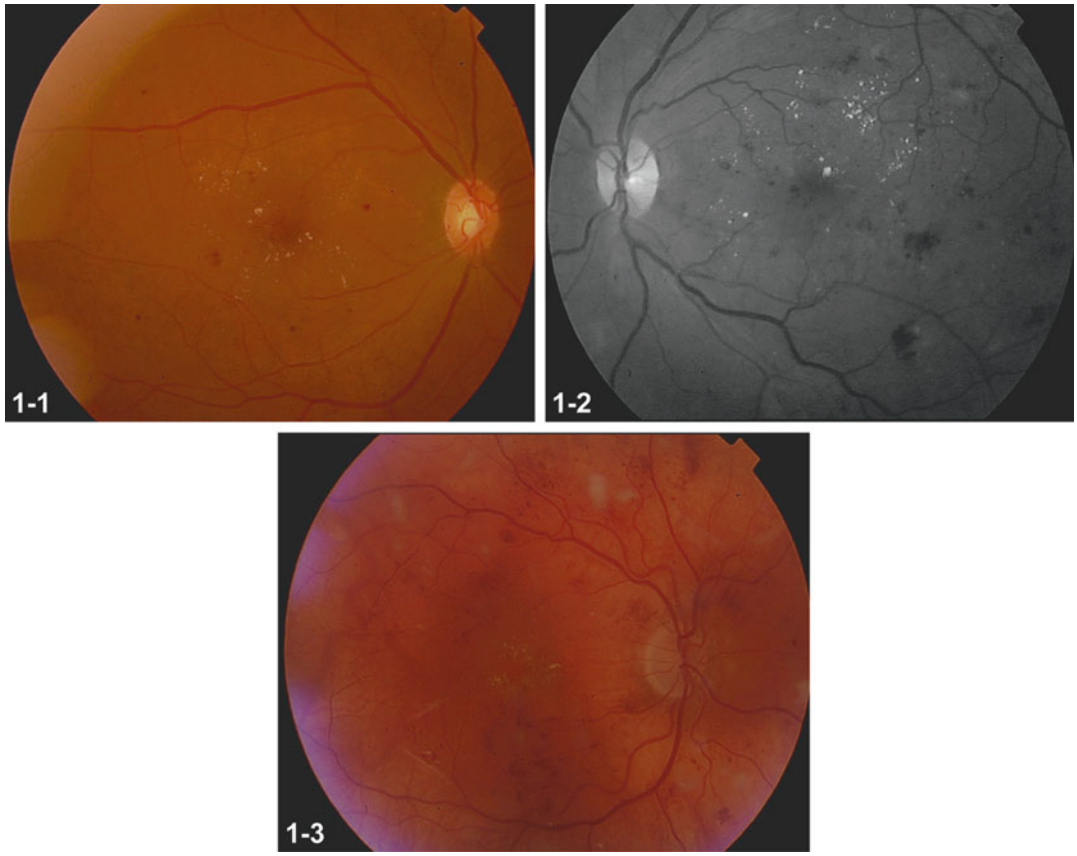

Fig. 1 Stages of nonproliferative diabetic retinopathy. Mild NPDR (*1*) with few dot and blot hemorrhages and intraretinal lipid. Red-free photograph of moderate NPDR (*2*) depicting a greater number of dot and blot hemorrhages and microaneurysms with associated lipid exudation. Severe NPDR (*3*) characterized by extensive four-quadrant distribution of intraretinal hemorrhages and lipid along with infarctions of the nerve fiber layer (cotton wool spots)

neovascularization within the anterior chamber along the surface of the iris. Neovascularization along the iris surface most commonly occurs at the pupillary margin and is significant in that these fine-arborizing vessels can progress along the iris margin and into the trabecular meshwork accompanied by a fibrous membrane. Subsequent contracture of the fibrous membrane leads to synechiae within the trabecular meshwork and secondary angle-closure glaucoma.

Clinicians treating PDR assess for the presence of new vessels, their location, and severity when determining the timing of panretinal photocoagulation. Early PDR is that which does not meet the criteria for high-risk PDR. Patients with early PDR have a 75% risk of developing high-risk PDR within a 5-year period. Patients with early PDR and severe NPDR may require treatment with early PRP. Initiation of PRP should be considered for patients with severe NPDR with any new vessels or early PDR with elevated new vessels or NVD.

High-risk PDR is characterized by any of the following:

1. NVD 1/4–1/3 disk area or more in size (Fig. 2(1))
2. NVD less than 1/4 disk area in size with concurrent vitreous hemorrhage
3. NVE greater than or equal to 1/2 disk area in size with concurrent vitreous hemorrhage (Fig. 2(2))

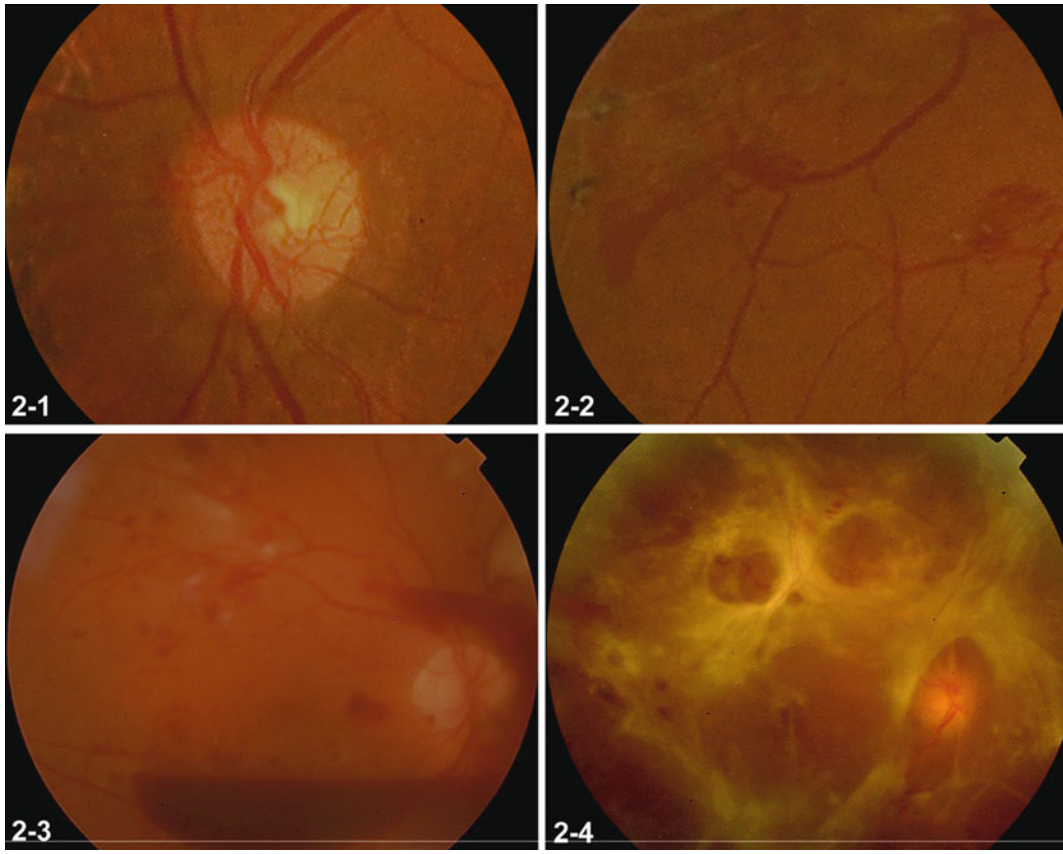

Fig. 2 Sequelae of proliferative diabetic retinopathy. Color photographs depicting neovascularization of the optic disk or NVD (*1*) and neovascularization elsewhere in the retinal periphery or NVE (*2*). Note the development of preretinal hemorrhage in the subhyaloidal space with progression of PDR (*3*). Severe proliferation of tractional membranes resulting in detachment of the macula; tractional retinal detachment (*4*)

Patients with high-risk characteristics require prompt treatment with laser photocoagulation to prevent further progression of retinopathy.

Patients with advanced PDR may require vitrectomy surgery to clear an otherwise non-clearing vitreous hemorrhage. Vitreous hemorrhage may occur as a result of vitreous traction on new vessels (Fig. 2(3)). Contracture of the vitreous or fibrovascular proliferation can result in the shearing of a new vessel and subsequent vitreous hemorrhage.

In time, retinal neovascularization may become fibrotic, contract, and lead to tractional retinal detachment (Fig. 2(4)). The fibrovascular proliferation in PDR typically occurs along the temporal vascular arcades and on the optic disk and may exhibit tractional forces resulting in macular striae and edema. The tractional retinal detachments that result can involve or spare the macula. They may be associated with both atrophic and tractional retinal breaks resulting in a combined rhegmatogenous–tractional retinal detachment. Patients with posterior tractional retinal detachments not involving the macula may be observed without vitrectomy surgery and can be stable for years. Upon encroachment of the macula, however, tractional retinal detachments can result in profound visual compromise and are therefore an indication for prompt vitrectomy. These tractional forces may be relieved with pars plana vitrectomy utilizing segmentation and delamination techniques.

Fluorescein Angiography

Fluorescein angiography is a technique for examining the integrity of the retinal circulation using the dye-tracing method. Sodium fluorescein dye is injected into an antecubital vein, and then an angiogram is obtained with multiple sequential photographs to monitor dye transit. Sodium fluorescein is a yellow-red dye with a molecular weight of 376.67 Da with a spectrum of absorption at 465–490 nm (blue wavelength) and excitation at 520–530 nm (yellow-green wavelength). The angiogram is performed with a camera with exciter and barrier filters that allow for the illumination of the retina with blue light because only yellow-green light (from the fluorescence) can reach the camera. The dye is metabolized within the liver and kidney within 24–36 h turning the patient's urine a yellow-green color. The most common adverse reactions to fluorescein dye are mild including nausea, vomiting, and pruritus and are typically transient. However, severe reactions requiring immediate intervention such as bronchospasm and anaphylaxis can occur and must be monitored. Although there are no adverse effects reported during pregnancy, all efforts are undertaken to avoid fluorescein angiography unless deemed critical in directing diagnosis and management.

Fluorescein angiography is an invaluable tool that aids in the diagnosis and directs management of diabetic retinopathy. By allowing the clinician to identify the spectrum of funduscopic changes prevalent in diabetic retinopathy, fluorescein angiography can be used to monitor the severity of retinopathy and identify risk factors for progression. Various angiographic risk factors have been identified including fluorescein leakage, capillary dilation, and capillary loss [56, 57].

Diabetic retinopathy can result in both hyper- and hypofluorescent patterns of angiography, and their distinction and interpretation are essential in identifying treatable lesions. In the setting of clinically significant macular edema (CSME), angiography is utilized to better identify leaking microaneurysms, which may appear as either focal or diffuse areas of permeability (Fig. 3(1)). Treatment with laser photocoagulation then can be directed to the selected microaneurysms or to a cluster of microaneurysms in a grid pattern with diffuse permeability alterations (Fig. 3(2)). Marked ischemia can result in areas of capillary closure within the macula potentially limiting vision or further peripherally. These vascular filling defects are well delineated on angiography as hypofluorescent patches representing nonperfused segments (Fig. 3(4)). Furthermore, angiography can be used to identify and monitor leaf-like formation of new blood vessels referred to as fronds of neovascularization along the optic disk or elsewhere in the retinal periphery. Areas of neovascularization are easily identified in the early frames of the angiogram and exhibit late hyperfluorescence signaling leakage of dye from these newly formed, incompetent vessels (Fig. 3(3)). Other high-risk vascular abnormalities such as *IRMA* are clearly demonstrated with angiography. The use of fluorescein angiography is essential as an adjunct to clinical ophthalmoscopy in the diagnosis and management of diabetic retinopathy.

Optical Coherence Tomography (OCT)

Optical coherence tomography (OCT) captures reflected light from retinal structures to create a cross-sectional image of the retina. Optical coherence tomography (OCT) greatly enhances the ability to detect macular thickening and has brought new insights into the efficacy of various treatments. Use of this imaging modality allows for the quantitative measurement of macular thickness and objective analysis of the foveal architecture. OCT has gained widespread acceptance as an additional modality to help identify and evaluate macular pathology and allows for a reproducible way to monitor macular edema.

The use of OCT with micrometer resolution was first devised by Huang et al. in 1991 [58]. The ability to obtain cross-sectional retinal images with micrometer resolution has allowed for better morphological tissue imaging and analysis compared to other imaging modalities. OCT utilizes the principle of low-coherence interferometry where distance information concerning various ocular

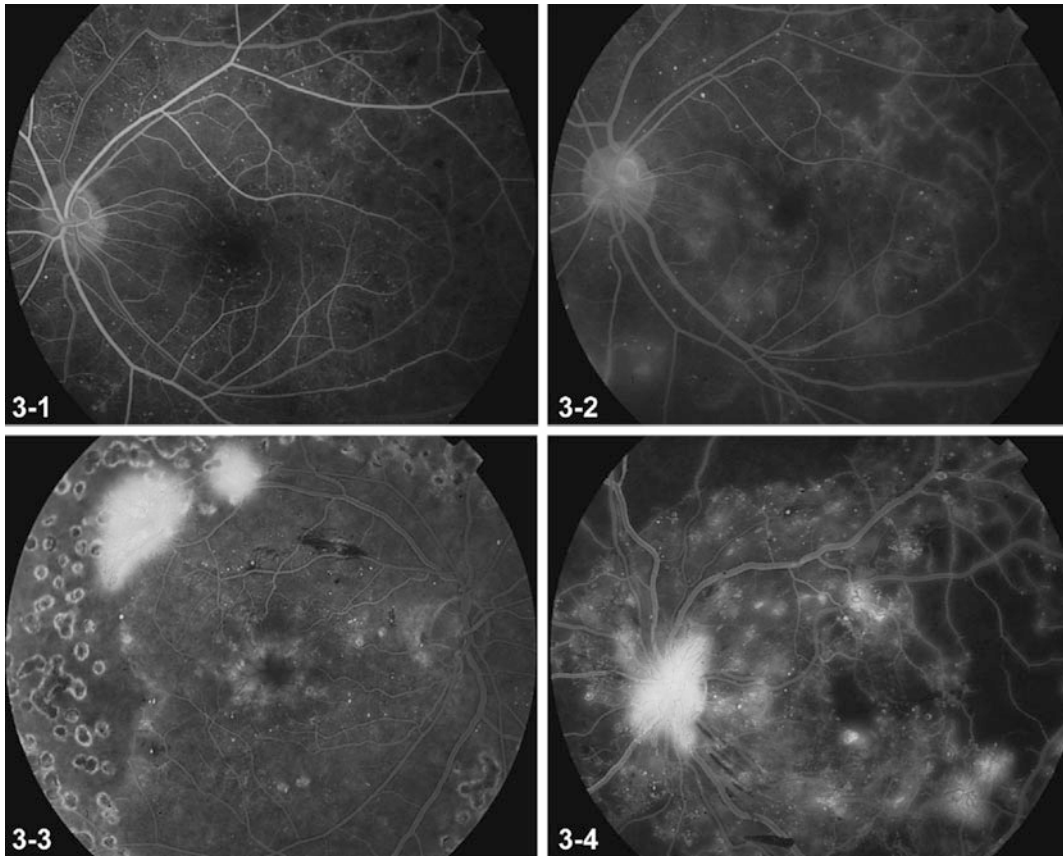

Fig. 3 Fluorescein angiographic characteristics. Early frame of fluorescein angiography (*1*) highlighting multiple areas of hyperfluorescence corresponding to microaneurysms which demonstrate prominent leakage in the late frame (*2*). Late-frame fluorescein angiogram showing an area of hyperfluorescence along the supero-temporal arcade corresponding to retinal neovascularization and within the macula representing pronounced leakage from the perifoveal capillaries (*3*). Multiple areas of hyperfluorescence in the late-frame angiogram (*4*) representing fronds of active retinal neovascularization. Hypofluorescent areas (*4*) seen temporally and superiorly representing ischemic zones of capillary nonperfusion

structures is extracted from time delays of reflected signals. The interference pattern of light is measured over a distance of micrometers in OCT using broadband light sources. In OCT, interferometry is utilized in a noninvasive, noncontact manner to produce high-resolution cross-sectional images of the retina. It is particularly useful in evaluating the extent of diabetic macular edema and in monitoring the efficacy of a given treatment (Fig. 4(1–4)). Topographic mapping protocol can be utilized for longitudinally monitoring and objectively quantifying the development of macular edema and for following the resolution of edema after laser treatment.

Novel Therapeutic Approaches

Various novel medical approaches in conjunction with laser photocoagulation are currently being explored for the treatment of diabetic retinopathy and diabetic macular edema. One such treatment is with ruboxistaurin, a selective PKC-beta inhibitor. Hyperglycemia activates protein kinase C, and the beta-isoform of protein kinase C mediates early diabetes-induced microvascular complications, including diabetic macular edema. Animal models have suggested that ruboxistaurin ameliorates hyperglycemia-induced complications. Initial results of the 30-month data of the randomized

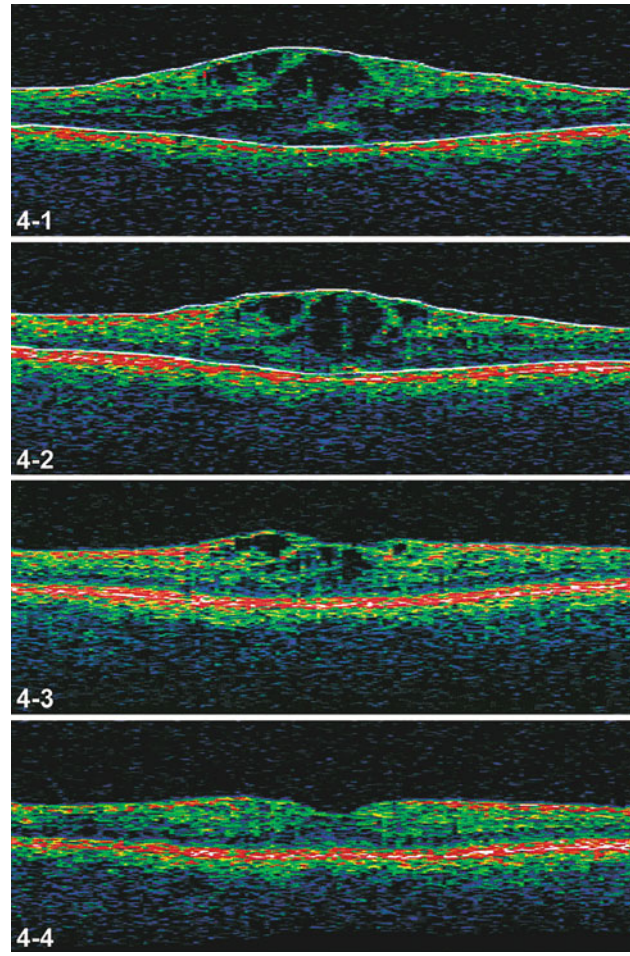

Fig. 4 Optical coherence tomography (OCT). OCT demonstrating persistent macular edema in a patient with diabetic retinopathy (*1*). Note the collection of cystic spaces throughout the retina. Following treatment with intravitreal bevacizumab at monthly intervals, there is progressive resolution of the macular edema at 1 month (*2*) and 2 months (*3*) from baseline with ultimate restitution of the normal foveal architecture at the 3-month interval (*4*)

Protein Kinase C-b Inhibitor Diabetic Macular Edema Study (PKC-DMES) indicated that treatment with 32 mg of ruboxistaurin daily did not reduce the risk of progression to sight-threatening diabetic macular edema or focal/grid photocoagulation in diabetic patients [59]. However, subgroup analysis of the data revealed that those treated with ruboxistaurin daily appeared to have slower progression to sight-threatening diabetic macular edema than those taking placebo when the end point excluded photocoagulation, as different practitioners had different thresholds for initiating photocoagulation [59]. Thus, the results of this clinical trial demonstrated that daily treatment with ruboxistaurin is an effective therapy for diabetic macular edema and diabetic retinopathy.

Pharmacologic inhibition of VEGF is an effective strategy for diabetic macular edema, due to its anti-permeability and inflammatory effects. Introduction of VEGF into normal primate eyes induces the same pathologic processes as those seen in diabetic retinopathy, including microaneurysm formation and increased vascular permeability [60]. Furthermore, elevated VEGF levels have been found from the analysis of vitreous samples from patients with diabetic macular edema [61]. Therefore, VEGF inhibition has garnered interest in ameliorating diabetic retinopathy and diabetic macular edema, and the development of anti-VEGF therapy has revolutionized treatment [62]. The utilization of anti-VEGF pharmacotherapy allowed for an alternative to focal laser treatment. Although it has been the mainstay of

DME treatment for decades, laser monotherapy has some important limitations including the development of scotomas or "blind spots" and altered contrast sensitivity. The first prospective study to compare laser monotherapy to combined laser and anti-VEGF was undertaken by the DRCRnet protocol I [63]. The trial evaluated intravitreal ranibizumab (Lucentis, Genentech) or triamcinolone acetonide plus prompt or deferred focal/grid laser versus laser alone in 854 eyes of patients with DME. Intravitreal ranibizumab with prompt versus deferred focal/grid laser was shown to be superior to laser alone. A greater percentage of the eyes in the ranibizumab groups achieved a substantial improvement in best-corrected visual acuity of two or more lines (10 or more letters) at 1 year. (Fifty percent in the deferred laser group and 47% in the prompt laser group, compared with 30% in the laser alone group.) Loss of two or more lines of best-corrected visual acuity was determined to be less common for the ranibizumab groups than for laser alone. These visual acuity gains were corroborated anatomically by OCT where the ranibizumab groups had the most rapid decrease in macular edema.

The RESTORE study, conducted in Europe, directly compared ranibizumab monotherapy or in combination with focal laser to focal laser alone [64]. In the trial, three initial monthly injections of ranibizumab were followed by as-needed (prn) injections of ranibizumab, with the primary end point at 1 year. Patients were randomized to either ranibizumab plus sham laser, ranibizumab plus laser, or sham injection plus laser. It was determined that ranibizumab injections either solely or in conjunction with laser were superior to laser alone.

The RISE and RIDE trials were similar phase 3 clinical trials in which monthly ranibizumab injections were compared to sham injections for patients with diabetic macular edema [65]. In RISE, at 24 months, 18.1% of sham patients gained $\geq$15 letters versus 44.8% of ranibizumab (0.3 mg) patients. In RIDE, significantly more ranibizumab-treated patients gained $\geq$15 letters: 12.3% of sham patients versus 33.6% of ranibizumab (0.3 mg) patients. It was determined that in addition to visual acuity gains, patients treated with ranibizumab had less progression in the severity of their retinopathy. VISTA and VIVID were similarly matched studies that compared aflibercept (Eylea, Regeneron, Tarrytown, NY) to macular laser for DME, and they demonstrated more than a 10-letter mean improvement in VA in the aflibercept group, compared to the laser group [66]. Data from these multicenter trials was used to support US Food and Drug Administration (FDA) approval of ranibizumab (RISE/RIDE) and Eylea (VISTA/VIVID) for treatment of diabetic macular edema.

Anti-VEGF therapy in the treatment of DME has been shown to be highly effective in ameliorating anatomical and visual outcomes and is first-line therapy for center-involving macular edema. However, the development of diabetic macular edema is complex integrating multiple intracellular signaling pathways and thus limiting the effectiveness of anti-VEGF monotherapy. Even when effective, monotherapy with anti-VEGF therapy exerts a significant treatment burden for patients and providers alike due to its transient effects on edema and potential associated risks of intraocular infection and retinal detachment with multiple, repeat injection. Although highly effective, anti-VEGF monotherapy can often result in refractory macular edema. Inflammation is well known to be implicated in the pathogenesis of diabetes and in the formation of macular edema [67, 68]. Numerous inflammatory mediators have been involved in diabetic retinopathy and edema including tumor necrosis factor α (TNF-α), a pro-inflammatory cytokine, and interleukin-6 [69]. Two intravitreal implantable steroid devices have been recently approved by the FDA. The MEAD study demonstrated that treatment with a 0.7-mg dexamethasone intravitreal implant (Ozurdex, Allergan, Irvine, CA) every 6 months (as needed) was effective in visual and anatomical gains for DME. The percentage of patients with $\geq$15-letter improvement in BCVA from baseline at study end was greater with dexamethasone implant 0.7 mg (22.2%) and DEX implant 0.35 mg (18.4%) than sham (12%) [70]. Similarly, the FAME study showed yearly treatment (as needed) with the 0.2 μg/d fluocinolone

acetonide (Iluvien, Alimera Sciences, Alpharetta, GA) effective for DME. At 36 months, 27.8% (0.5 ug/day) and 28.7% (0.2 ug/day) of implant-treated eyes versus 18.9% of sham eyes demonstrated an improvement of 15 or more letters [71, 72]. Subgroup analysis showed particular benefit among patients with DME for three or more years. Corticosteroid-related side effects were noted in both studies with increased risk of needing incisional glaucoma surgery and progression of cataracts. The treatment paradigm for DME is rapidly evolving with the development and FDA approval of multiple highly effective drugs. Due to the complex interplay of multiple pathways in the development of DME, combination therapy of anti-VEGF, intravitreal steroids, and laser treatment is appealing in providing the most effective long-term visual and anatomical outcomes.

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