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CASE

How the diabetic eye loses vision

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Abstract The objective is to review the most common causes of vision loss in patients with diabetes with the goal of better managing patients with diabetic eye disease. In this review, the causes of vision loss, and the clinical evaluation and management of diabetic retinopathy (DR) and diabetic macular edema (DME) are outlined. Patients with diabetes mellitus have an increased risk of vision loss and blindness. In patients with diabetes, the primary mechanism responsible for vision loss is centrally involved DME or clinically significant macular edema (CSME), defined as vascular leakage resulting in fluid accumulation that affects the center of the macula. DR and DME are thought to result from the effects of excessive blood glucose on the vessels that produces microvascular damage. The progression of DR can be slowed by intensive glycemic and blood pressure control. Severe visual loss from proliferative DR and moderate visual loss from DME can be reduced by laser photocoagulation. DR and DME are diagnosed on dilated retinal examination and confirmed with diagnostic testing. Many experts and associations recommend that patients with diabetes have an yearly, thorough, dilated eye exam. This manuscript describes the case history of a patient with diabetes and vision loss.

Keywords Diabetic retinopathy · Diabetic macular edema · Vision loss

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Abbreviations

ADA	American Diabetes Association
ARB	Angiotensin receptor blocker
COM	Center of the macula
CSME	Clinically significant macular edema
DR	Diabetic retinopathy
DME	Diabetic macular edema
ETDRS	Early treatment diabetic retinopathy study
HbA_{1c}	Hemoglobin A_{1c}
IRMA	Intraretinal microvascular abnormalities
MVL	Moderate visual loss
NPDR	Non-proliferative diabetic retinopathy
NCSME	Non-clinically significant diabetic macular edema
OCT	Optical coherence tomography
PDR	Proliferative diabetic retinopathy
VEGF	Vascular endothelial growth factor
TZD	Thiazolidinedione

Case history

Mr. VG is a 60 year-old white male with a 20-year history of documented type 2 diabetes mellitus. He comes to your

office for a routine follow-up visit, complaining of slowly worsening blurry vision for the past 3 months.

His list of medical problems includes coronary artery disease (s/p angioplasty and stent placement 1 year ago), diabetic retinopathy (DR), and hypertension. His medications include: maximal doses of a sulfonylurea, angiotensin receptor blocker (ARB), and a thiazolidinedione (TZD). According to his medical records, Mr. G's last hemoglobin A_{1c} (HbA_{1c}) was 7.8% several months ago.

On physical exam, his seated BP is 153/80, pulse 90, height 5′9″ and weight 270 pounds. His physical exam is unremarkable except for the presence of obesity. An eye exam found that both eyes appear normal externally. Visual acuity with a hand-held Snellen chart is 20/40 in both eyes. You do not have equipment to measure intraocular pressure.

His last ophthalmology consult from 8 months ago revealed that at that time, he had moderate non-proliferative retinopathy and non-clinically significant macular edema. The macular edema and DR was diagnosed with a combination of measures (e.g., slit-lamp biomicroscopy, stereoscopic fundus photography, fluorescein angiography, and optical coherence tomography [OCT]). The ophthalmologist stated that Mr. G has the beginnings of cataracts, and very small pupils, but you can see the optic discs, and there are no obvious hemorrhages visible.

Why has Mr. G lost vision?

Vision loss in patients with diabetes: differential diagnosis and top causes of vision loss

Visual impairment (defined as best-corrected visual acuity less than or equal to 20/40 in the better seeing eye) and legal blindness (defined as best-corrected visual acuity less than or equal to 20/200 in the better seeing eye) affects an estimated 3.4 million US adults aged ≥40 years (or 40% of this population) [1].

Diabetes affects approximately 20.8 million people in the USA (7% of the population; 14.6 million people are diagnosed and 6.2 million are undiagnosed) and is associated with a markedly increased risk for eye disease [2]. As the number of people with diabetes increases, due to the increasing prevalence of obesity, the number of patients with visual impairment due to diabetes will significantly increase [3].

Thus, it is not surprising that, overall, the leading causes of blindness and visual loss in the US are consequences of proliferative diabetic retinopathy (PDR), diabetic macular edema (DME) involving the foveal area and age-related eye diseases (e.g., cataracts, glaucoma and age-related macular degeneration) [see Table 1; 15].

Among working age adults (20–74-year-old), the leading cause of blindness is DR and 12% of new cases of blindness each year are caused by diabetic retinopathy [2]. The cumulative 14-year incidences in the diabetic population of visual impairment, doubling of the visual angle, and blindness were 12.7%, 14.2%, and 2.4%, respectively [16].

With regard to patient VG, among adults with type 2 diabetes and DR, the most common specific entity causing vision loss is DME involving the fovea (29% and 28% of individuals with type 1 and type 2 diabetes, respectively, after 20 years of diabetes) [6]. In DME, vascular leakage causes thickening or swelling of the retina, which disrupts retinal function. When this swelling occurs in the area of keenest vision (the fovea), DME significantly affects vision. DME which involves the fovea is known as "clinically significant macular edema" (CSME). Non-clinically significant diabetic macular edema (NCSME) and clinically significant DME (CSME) generally increase with duration of diabetes (Table 2) [17].

Stages of diabetic macular edema and DR

In 2003 the American Academy of Ophthalmology (AAO) and representatives from 16 countries met to develop clinical classification systems that would provide a means of appropriately staging DR and DME [18, 19]. Diabetic retinopathy was divided into two broad categories: non-proliferative diabetic retinopathy and PDR. Non-proliferative diabetic retinopathy was further subdivided into mild, moderate, and severe. This new classification system was a simplification of the research-oriented Early Treatment Diabetic Retinopathy Study (ETDRS) severity scale (Complete scale described in the appendix), which considers the number and severity of anatomical abnormalities such as: microaneurysms, hemorrhages, venous beading, and intraretinal microvascular abnormalities (IRMA) in assigning eyes to a particular level of severity [20].

Mild NPDR is characterized by microaneurysms only. Severe NPDR includes any of the following: more than 20 intraretinal hemorrhages in each of 4 quadrants, definite venous beading in at least two quadrants, or prominent IRMA in at least 1 quadrant and *no* signs of PDR. Moderate NPDR is characterized by more than just microaneurysms, but less than severe non-proliferative diabetic retinopathy. PDR is diagnosed if the patient has neovascularization or vitreous/preretinal hemorrhage.

Diabetic macular edema can occur at any level of DR, though generally, as DR worsens the likelihood of DME increases (see Fig. 1 for the incidence of DME by retinopathy severity). In the past, diabetic macular edema severity has been classified as either "clinically significant" (CSME) or "non-clinically significant" macular edema (NCSME). CSME is diagnosed, when edema begins to approach the fovea, specifically when retinal swelling with

Table 1 Most common causes of blindness and visual loss in adults [4, 5]

Condition	Prevalence
Diabetic macular edema	29% and 28% of individuals with type 1 and type 2 diabetes, respectively, after 20 years of diabetes [6]
Diabetic retinopathy	Vision-threatening retinopathy affects an estimated 8% of the 10.2 million adults age 40 years and older with diabetes mellitus [7, 8] • Patients with type 2 diabetes, 29% are affected in the first 5 years and 78% are affected after 15 or more years of systemic disease [9] • Patients with type 1 diabetes, 17% are affected in the first 5 years and 98% are affected after 15 or more years of systemic disease [10]
Refractive error	25–35% of adults aged 40–80 years of age [11]
Cataract	About 17% of adults aged >40 years (not all symptomatic) [6]
Primary open-angle glaucoma	Black patients aged >40 years of age (1.2–11.3%); White patients aged >40 years of age (0.9–2.1%) [12, 13]
Glaucoma	Worldwide 6.7 million people are blind due to glaucoma 2.2 million Americans [14]
Age-related macular degeneration	Late (symptomatic): 1.6 million US individuals aged >50 years of age [6]

Table 2 Incidence of macular edema by retinopathy level in the worse eye at baseline [17]

American Academy of Ophthalmology retinopathy severity level	ETDRS classification of retinopathy severity level (in worse eye)	Incidence of macular edema (%)
None	10 (no DR)	17.5
Mild NPDR	21	25.4
	31	30.5
Moderate NPDR	37 (microaneurysms and either soft or hard exudates[s])	36.7
	43	25.2
	47	40.4
Severe NPDR	53	50.0
PDR	60+ (PDR—untreated and evidence of treated PDR)	40.0

DR = Diabetic retinopathy; ETDRS = Early Treatment of Diabetic Retinopathy Study; PDR = Proliferative diabetic retinopathy

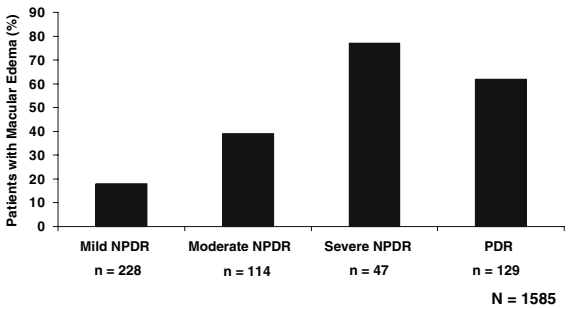

Fig. 1 Rate of diabetic macular edema by level of DR severity [21]

or without hard exudates is present within 500 microns of the center of the macula or edema greater than 1 optic disc area (1,500 microns) in size is present within 1,500 microns of the center [22]. However, the new international scale classifies DME as mild, moderate and severe. Mild diabetic macular edema is defined as some retinal thickening or hard exudates but distant or >2 disc diameters from the center of the macula. Moderate diabetic macular edema is defined as retinal thickening or hard exudates approaching the center of the macula but not involving the center, or greater than 300 microns. Severe diabetic macular edema is defined as retinal thickening or hard exudates involving the center of the macula.

The risk of developing visual loss increases as retinopathy becomes more severe, not only because the risk of proliferative DR increases, but also because the incidence of DME increases. In addition, the rate of progression to PDR and/or CSME, increases more rapidly with more advanced retinopathy. Patients with moderate NPDR have a 50% risk of vision loss due to PDR or CSME within 3 years [23], while approximately 50% of patients who had severe NPDR progressed within a year to PDR and/or CSME. Even with only mild NPDR at baseline, the 3-year risk for progression to PDR, and/or CSME, was 25%. Any kind of DME is associated with an increase in the risk of developing moderate visual loss and legal blindness and approximately one third of persons with CSME who are untreated have a significant loss of central vision within 3 years.

Diagnosis of DR, DME and visual acuity

Accurate diagnosis of DME and DR requires ophthalmologic consultation. An endocrinologist will have difficulty diagnosing progression of diabetic eye disease, especially macular edema; therefore, good communication between the ophthalmologists and the endocrinologists is essential for early diagnosis.

Typically, the eye examination begins with best-corrected visual acuity. Visual acuity is assessed by the clinician using the Snellen chart that uses a series of letters and numbers with the largest at the top. In clinical trials, the ETDRS chart is utilized and it has five letters on each line.

A test for intraocular pressure (to detect glaucoma) is also performed. Gonioscopy (an examination of the anterior chamber of the eye) may also be performed if neovascularization of the iris is present or suspected, or if intraocular pressure is elevated.

Once the risk of angle-closure is deemed to be low, the eyes are dilated. The ophthalmologist then uses a variety of methods to observe changes in the back of the eye: direct funduscopy (i.e., use of an ophthalmoscope) with a single eyepiece and a beam of light is convenient, but gives only a two dimensional, narrow view of the fundus. Slit-lamp funduscopy has an additional lens held close to the eye to provide a stereoscopic view, which can be helpful in detecting retinal swelling that is the hallmark of macular edema. Indirect funduscopy provides a wider view than direct or slit-lamp funduscopy, allowing the examiner to view the entire retina. In order to document structural changes in the retina and choroid, stereo fundus photography can be used. Contact lens biomicroscopy can also be used for the detection of macular edema and retinal thickening, and to examine the back of the retina to assess the stage of retinopathy.

The ophthalmologist may also elect to use one of more of a number of techniques to detect areas of vascular leakage in the retina that may require spot laser photocoagulation. These techniques include fluorescein angiography, OCT and ultrasonography (see Fig. 2 for examples of each).

Fluorescein angiography is a commonly performed retinal vascular assessment involving intravenous injection of fluorescein (an orange-colored, fluorescent dye), followed by rapid sequence black and white photography to analyze the retinal and underlying choroidal circulation in order to detect areas of vascular leakage and non-perfusion.

OCT is a non-invasive low-coherence interferometry imaging technology that provides in vivo retinal cross sectional images with a resolution of 10–17 microns. Using OCT, ophthalmologists can visualize retinal swelling in the anatomical layers of the eye in areas, such as the fovea, the foveal depression, internal limiting membrane, photoreceptor layer, and retinal pigment epithelium.

Ultrasonography is used to detect cataracts, vitreous hemorrhage, or other disorders that prevent direct visualization techniques from being used.

Discussion of the management

Medical management of retinopathy

Risk factors associated with DR and DME include long duration of diabetes, poorly controlled blood glucose levels, poorly controlled blood pressure, reduced kidney function, high cholesterol levels, and smoking. Studies, such as the Diabetes Control and Complications Trial (DCCT) showed that intensive control of blood glucose in patients with Type 1 diabetes, with preexisting retinopathy, reduced the risk of progression by 54% [24]. In patients with type 2 diabetes, both the U.K. Prospective Diabetes Study (UKPDS) and the Kumomoto study demonstrated a protective effect of glycemic control on the development of retinopathy [25]. Additionally, the UKPDS found that patients assigned to tight BP control with a 10/5 mmHg reduction in blood pressure had a 34% reduction in progression of retinopathy and a 47% reduced risk of deterioration in visual acuity by three lines. Therefore, the current standard of medical care for prevention or treatment of DR includes good metabolic control and tight control of blood pressure, as well as lipid lowering, and smoking cessation.

Surgical management of retinopathy

After the diagnosis of retinopathy is made and the extent of the lesions characterized, the ophthalmologist identifies areas within the eye that may require laser surgery. There are two types of laser photocoagulation: panretinal laser, which is used to treat proliferative retinopathy and focal or grid laser, which is used to treat DME.

Panretinal (scatter) photocoagulation, which is performed using a relatively high-energy laser, ablates large areas of retina in order to reduce the hypoxia of the remaining retina. It results in a decrease in the formation of proliferative vessels, and their sequelae of vitreal hemorrhage and retinal detachment and can reduce the risk for severe vision loss by 90% in patients with PDR [26].

In order to remove vitreous hemorrhage, pars plana vitrectomy, usually with an additional panretinal laser, is used in patients with PDR.

Focal/grid laser photocoagulation to the retina can reduce the risk of loss of vision by nearly 50% in patients

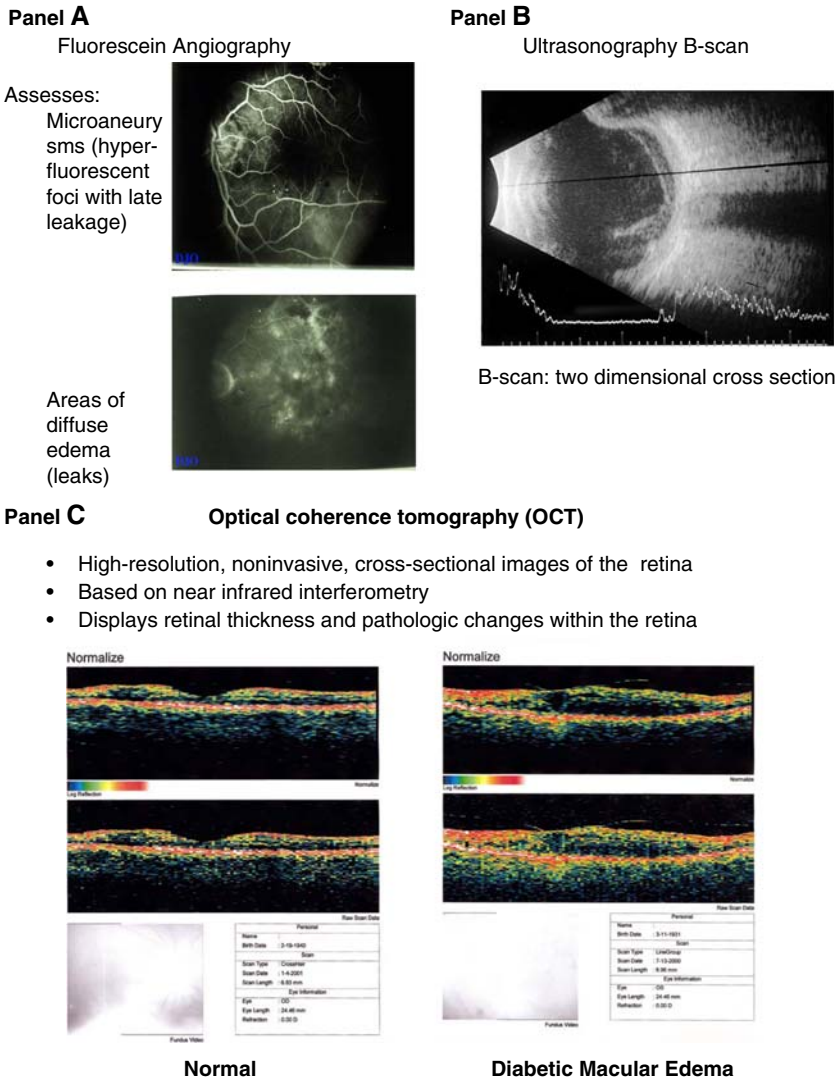

Fig. 2 Examples of fluorescein angiography (Panel **A**), ultrasonography (Panel **B**), and optical coherence tomography (Panel **C**)

with clinically significant DME (CSME), but is unlikely to restore vision [20, 22, 27].

Despite these valuable treatment options, vision loss still occurs at an alarming rate and laser photocoagulation is a late-stage, destructive intervention that does not specifically address the underlying etiology of DR [27].

Vision loss impact on quality of life

The most significant costs associated with diabetes result from treating the long-term chronic conditions arising from microvascular complications, such as DR and diabetic macular edema [28]. But DR and DME also significantly impact a patient's quality of life. The impact of 1–3-lines of visual loss on daily activities is described in Table 3 [29]. Recent data suggest that persons with DR are willing to trade off significant time from their life if they could eliminate their ocular condition (mean time tradeoff score = 0.77–0.8) and that laser photocoagulation can improve health-related quality of life (significant improvement noted in 8 out of 11 domains in the National Eye Institute Visual Function Questionnaire) [30]. Vision loss reduces independence and productivity, limits social interactions, and restricts ability to perform daily functions [31].

Guidelines for screening

The majority of associations and ophthalmic experts recommend yearly comprehensive eye examinations for most persons with diabetes [4, 5, 32–36]. The American Association of Clinical Endocrinologists (AACE), the American College of Endocrinology and the American Diabetes Association (ADA) guidelines suggest a dilated eye examination by an eye care professional 3–5 years after diagnosis for those with type 1 diabetes. For persons

Table 3 Impact of 1–3-line vision loss on a patient with diabetes daily activities

Impact of vision loss
1-line of vision loss
Greater difficulty with driving (e.g., driving during daytime in unfamiliar places; driving at night; driving in difficult conditions [rush hour, bad weather etc.])
Greater difficulty with distance vision (e.g., reading street signs; going down steps in dim light; going to see movies or sporting events)
Greater loss of independence (e.g., stay home more often; rely too much on what others say; need a lot of help from others)
2-lines of vision loss
Greater difficulty with near vision (e.g., reading newspaper; activities requiring up close vision [cooking, sewing, using hand tools])
Greater difficulty with role-specific functions (e.g., limited in how long you can work because of your eyesight)
3-lines of vision loss
Diminished color perception (e.g., difficulty picking and matching your clothes)

age 10–29 who have had diabetes for more than 5 years, a dilated examination is recommended yearly. For persons older than 30, a dilated examination is recommended near the time of diagnosis and at least yearly thereafter. Similar guidelines have been suggested by the American Optometric Association (AOA) and the AAO. Unfortunately, the rate of yearly screening visits to an ophthalmologist in the USA, and in the majority of countries outside of the United States (OUS), is <50% [37, 38].

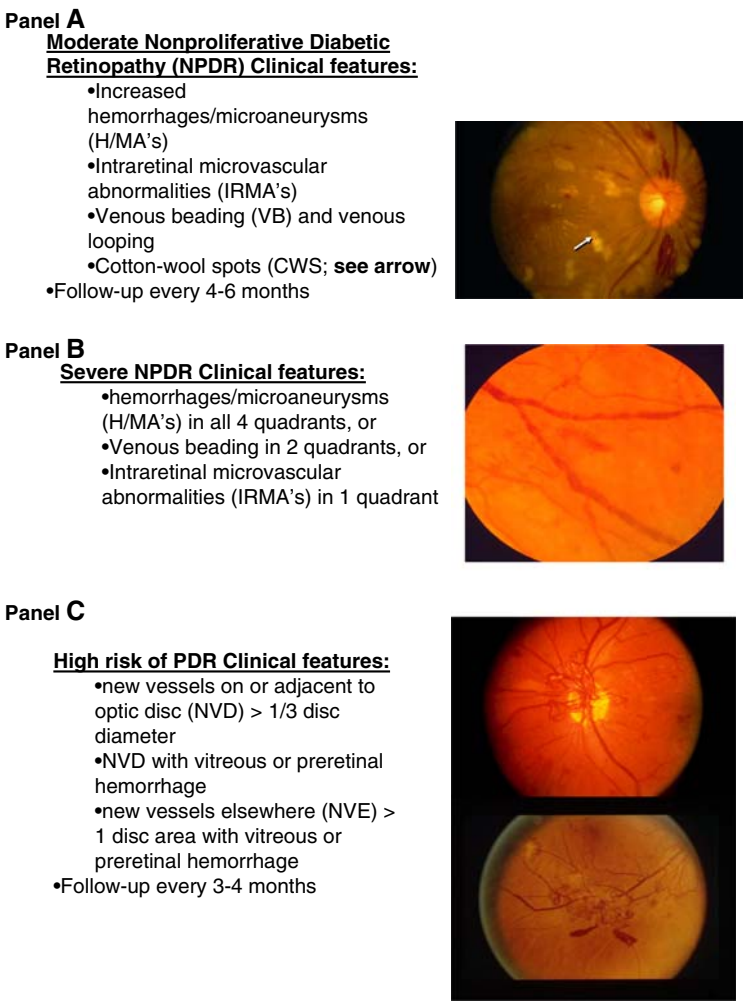

Fig. 3 Picture of moderate non-proliferative diabetic retinopathy (Panel **A**), proliferative diabetic retinopathy (Panel **B**) and high risk PDR (Panel **C**)

Pathological discussion

After examination by an ophthalmologist and/or retinal specialist, patient VG is found to have moderate DR, as evidenced by numerous microaneurysms and dot hemorrhages, as well as retinal thickening and hard exudates in the center of the macular area. Figure 3 contains some examples of these structural abnormalities. Based on OCT scans and photographs analyzed by the ophthalmologist, Mr. G's likely cause of vision loss is moderate non-proliferative diabetic retinopathy with center-involved diabetic macular edema.

The patient was treated with focal laser and was sent back to his endocrinologist for improved glycemic and blood pressure control. He will be seen by the ophthalmologist in 3 months for follow-up.

Causes of vision loss in patients with diabetes [39–41]

The retina is a highly specialized neural tissue that requires copious amounts of oxygen to function optimally. It receives oxygen-rich blood from the ophthalmic artery, which branches into a microvascular meshwork of arterioles and capillaries. The blood returns via venules into the ophthalmic vein. The microvasculature is normally made up of endothelial cells with tight junctions and supportive pericytes that form the blood–retinal barrier.

Persistent hyperglycemia, which is found in patients with poorly controlled diabetes, leads to biochemical changes that result in capillary basement membrane thickening, increased collagen and fibronectin deposition of the extracellular matrix, formation of microaneurysms, and the loss of pericytes. Collectively, these changes lead to altered retinal hemodynamics, including abnormal autoregulation of retinal blood flow, ultimately causing retinal hypoxia. In an effort to resolve the hypoxia, direct and indirect compensatory pathways are initiated, which ultimately leads to the structural changes of DR.

As DR progresses to PDR, vascular alterations can progress to retinal capillary non-perfusion leading to occlusion of retinal capillaries and the development of retinal ischemia. Subsequently, new blood vessels proliferate on the surface of the retina (e.g., neovascularization). These vessels are rendered fragile, and often shear when vitreous in the eye causes traction on them, leading to vitreous hemorrhages, which may acutely reduce visual acuity. Further consequences of PDR include the development of fibrous tissue on the surface of the retina with subsequent traction retinal detachment and possibly neovascular glaucoma (see Fig. 4 for images).

In contrast to PDR, the hallmark of DME is retinal thickening, which results from abnormal vascular permeability secondary to altered microvascular structure and the release of certain chemical growth factors, with leaking of fluid from capillaries into the surrounding

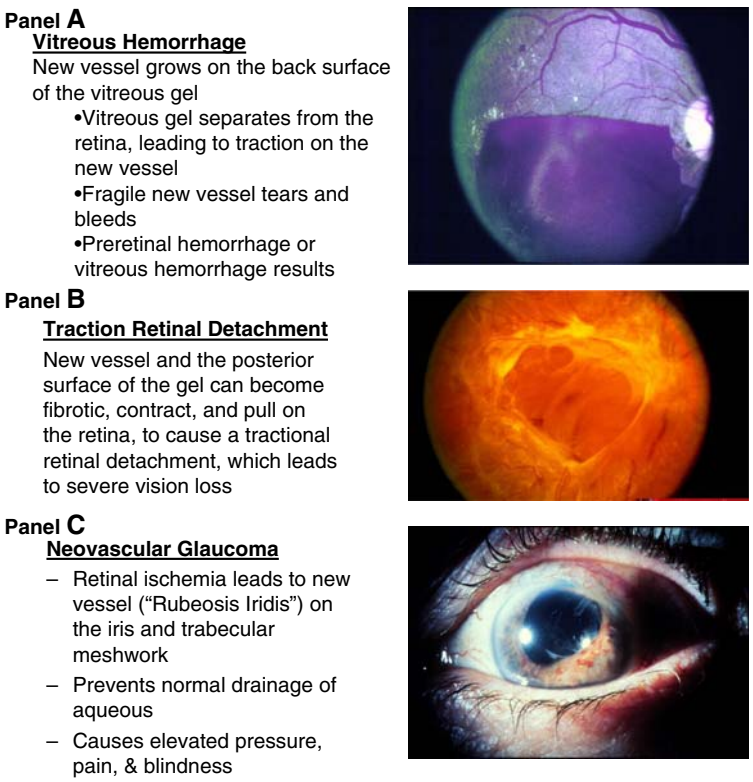

Fig. 4 Severe complications of diabetic retinopathy include vitreous hemorrhage (Panel **A**), traction retinal detachment (Panel **B**), or neovascular glaucoma (Panel **C**)

retinal tissue. When this retinal thickening occurs in the area of the fovea, it can disrupt vision. The area of retinal thickening is often surrounded by hard exudates, which are nothing more than accumulations of lipids, which have leaked from vessels along with other serum components.

In summary, the early changes of DR including retinal exudates, microinfarcts, microaneurysms, and/or localized hemorrhage within the retina can be entirely asymptomatic. Subsequently, DME and neovascularization can result in permanent vision loss, because edema alters the highly organized anatomical layers required for optimal retina functioning, and neovascularization can lead to hemorrhage, fibrosis, and ultimately retinal detachment. Early identification and intervention provide the best protection against loss of vision and preservation of function in DR, since vision loss is such a late and often irreversible finding. Subsequently, it is important to have open communication between endocrinologists and ophthalmologists or retinal specialists.

Appendix

Level	ETDRS severity	ETDRS definition	AAO severity ranking
10	DR absent	Microaneurysms and other characteristics absent	
12	Non-DR Abnormalities		
14[a]	DR questionable	14A HE definite; microaneurysms absent	
		14B SE definite; microaneurysms absent	
		14C IRMA definite; microaneurysms absent	
15[a]	DR questionable	Hemorrhage(s) definite; microaneurysms absent	
20	Microaneurysms only	Microaneurysms definite; other characteristics absent	Mild NPDR
35[b]	Mild NPDR	35A Venous loops ≥ D/1	Moderate NPDR
		35B SE, IRMA, or VB = Q	
		35C Retinal hemorrhages present	
		35D HE ≥ D/1	
		35E HE ≥ M/1	
		35F SE ≥ D/1	
43	Moderate NPDR	43A H/Ma = M/4–5 or S/1	Moderate NPDR
		43B IRMA = D/1–3	
47	Moderately severe NPDR	47A Both L43 characteristics	Moderate NPDR
		47B IRMA = D/4–5	
		47C H/Ma = S/2–3	
		47D VB = D/1	
53	Severe NPDR	53A ≥ 2 of the 3 L47 characteristics	Severe NPDR
		53B H/Ma ≥ S/4–5	
		53C IRMA ≥ M/1	
		53D VB ≥ D/2–3	
53E	Very Severe NPDR	53E ≥ 2 or 53B, 53C, and 53D	
61	Mild PDR	61A FPD and/or FPE only (regressed PDR)	PDR
		61B1 NVE < ¼ disc area in ≥ 1 field (Borderline PDR)	
		61B2 NVE ≥ ¼ but < ½ disc area in ≥ 1 field	
65	Moderate PDR	65A NVE ≥ M/1 (≥½ disc area in ≥ 1 field)	PDR
		65B NVD = D and VH or PRH = A or Q	
		65C VH or PRH = D and NVE < M/1 and NVD absent	
Level	Severity	Definition	
71, 75	High-risk PDR	71A VH or PRH ≥ M/1 (M = about 1 disc area)	PDR
		71B NVE ≥ M/1 and VH or PRH ≥ D/1	
		71C NVD = D and VH or PRH ≥ D/1	
		71D NVD ≥ M	
		75 NVD ≥ M and VH or PRH ≥ D/1	

Appendix continued

Level	ETDRS severity	ETDRS definition	AAO severity ranking
81	Advanced PDR: Fundus partially obscured, center of macula attached	NVD = cannot grade, or NVD < D and NVE = cannot grade in ≥ 1 field and absent in all others; and retinal detachment at center of macula < D	PDR
85	Advanced PDR: Posterior fundus obscured, or center of macula detached	85A VH = VS in Field 1 or 2 85B Retinal detachment at center of macula = D	PDR
90	Cannot grade, even sufficiently for level 81 or 85		PDR

[a] Levels 12, 14, and 15 are not considered separate steps in the scale, but are pooled with level 10 or 20 (or excluded)

[b] NPDR levels 35 and above all require presence of microaneurysms

Abbreviations: DR = Diabetic retinopathy; NPDR = Non-proliferative DR; PDR = Proliferative DR; HE = Hard exudates; SE = Soft exudates; IRMA = Intraretinal microvascular abnormalities; VB = Venous beading; H/Ma = Hemorrhages/microaneurysms; NVE = New vessels elsewhere; NVD = New vessels on or adjacent to optic disc; VH = Vitreous hemorrhage; PRH = Preretinal hemorrhage

Severity categories are of the form (maximum severity/extent), where maximum severity can be absent (A), questionable (Q), definitely present (D), moderate (M), severe (S), or very severe (VS) and extent is the number of photographic fields at that severity level. For example, M/2-3 means there are two or three fields from fields 3 to 7 with moderate severity and none with higher severity

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