

Review article

Diabetic Retinopathy

Gaur Rajni, Gaur Arun **

*Senior Specialist & Head, Department Of Ophthalmology, **Senior Specialist & Head, Department of Medicine, Mahatma Gandhi Hospital, Bhilwara. Rajasthan 311001.

Corresponding author⁺

Abstract:

Diabetes mellitus is a metabolic abnormality in which there is a failure to utilise glucose and hence a state of hyperglycaemia can occur. If hyperglycaemia continues uncontrolled over time, it will lead to significant and widespread pathological changes, including involvement of the retina, brain and kidney.

In industrialised countries, approximately 1% of the population is diabetic, and at least another 1% are undiagnosed diabetics. Insulin dependent diabetes (IDDM), accounts for approximately 10-15% of cases, the remainder being maturity onset or non-insulin dependent diabetics (NIDDM). Diabetes mellitus is an International public health problem with estimated prevalences ranging from 2.0% to 11.7% in studied populations across the world.

OVERVIEW

Diabetes Mellitus

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Prevalence of Diabetic Retinopathy

Diabetic retinopathy is increasingly becoming a major cause of blindness throughout the world in the age group of 20-60 years.^[2,3,4] Loss of productivity and quality of life for the patient with

diabetic retinopathy will lead to additional socioeconomic burdens on the community. Diabetic retinopathy is the cause of blindness in approximately 2.5 million of the estimated 50 million blind people in the world. However, diabetic retinopathy, as a cause of blindness, is less common in India according to population-based studies.^[5,6] A recent study of diabetic patients in Pakistan indicated that cataract and uncorrected refractive error were more common causes of visual impairment than retinopathy.^[7] The VISION 2020 protocol projects diabetic retinopathy and the glaucomas as the 'emerging' causes of blindness in developing countries.

Pathophysiology

The exact mechanism by which diabetes causes retinopathy remains unclear, but several theories have been postulated to explain the typical course and history of the disease.^[8,9]

Growth hormone

Growth hormone appears to play a causative role in the development and progression of diabetic retinopathy. Diabetic retinopathy has been shown

to be reversible in women who had postpartum hemorrhagic necrosis of the pituitary gland (Sheehan syndrome). This led to the controversial practice of pituitary ablation to treat or prevent diabetic retinopathy in the 1950s. It should be noted that diabetic retinopathy has been reported in patients with hypopituitarism as well.

Platelets and blood viscosity

The variety of hematologic abnormalities seen in diabetes, such as increased erythrocyte aggregation, decreased red blood cell deformability, increased platelet aggregation, and adhesion, predispose the patient to sluggish circulation, endothelial damage, and focal capillary occlusion. This leads to retinal ischemia, which, in turn, contributes to the development of diabetic retinopathy.

Aldose reductase and vasoproliferative factors

Fundamentally, diabetes mellitus (DM) causes abnormal glucose metabolism as a result of decreased levels or activity of insulin. Increased levels of blood glucose are thought to have a structural and physiologic effect on retinal capillaries causing them to be both functionally and anatomically incompetent.

A persistent increase in blood glucose levels shunts excess glucose into the aldose reductase pathway in certain tissues, which converts sugars into alcohol (eg, glucose into sorbitol, galactose to dulcitol). Intramural pericytes of retinal capillaries seem to be affected by this increased level of sorbitol, eventually leading to the loss of their primary function (ie, autoregulation of retinal capillaries). This results in weakness and eventual saccular outpouching of capillary walls.

These microaneurysms are the earliest detectable signs of DM retinopathy. Using nailfold video capillaroscopy, a high prevalence of capillary changes is detected in patients with diabetes, particularly those with retinal damage. This reflects a generalized microvessel involvement in both type

1 and type 2 diabetes. ^[10] Ruptured microaneurysms result in retinal hemorrhages either superficially (flame-shaped hemorrhages) or in deeper layers of the retina (blot and dot hemorrhages). Increased permeability of these vessels results in leakage of fluid and proteinaceous material, which clinically appears as retinal thickening and exudates. If the swelling and exudation involve the macula, a diminution in central vision may be experienced.

Macular edema

Macular edema is the most common cause of vision loss in patients with nonproliferative diabetic retinopathy (NPDR). However, it is not exclusively seen in patients with NPDR; it may also complicate cases of proliferative diabetic retinopathy.

Another theory to explain the development of macular edema focuses on the increased levels of diacylglycerol from the shunting of excess glucose. This is thought to activate protein kinase C, which, in turn, affects retinal blood dynamics, especially permeability and flow, leading to fluid leakage and retinal thickening.

Hypoxia

As the disease progresses, eventual closure of the retinal capillaries occurs, leading to hypoxia. Infarction of the nerve fiber layer leads to the formation of cotton wool spots, with associated stasis in axoplasmic flow.

More extensive retinal hypoxia triggers compensatory mechanisms in the eye to provide enough oxygen to tissues. Venous caliber abnormalities, such as venous beading, loops, and dilation, signify increasing hypoxia and almost always are seen bordering the areas of capillary nonperfusion. Intraretinal microvascular abnormalities represent either new vessel growth or remodeling of preexisting vessels through endothelial cell proliferation within the retinal

tissues to act as shunts through areas of nonperfusion.

Neovascularization

Further increases in retinal ischemia trigger the production of vasoproliferative factors that stimulate new vessel formation. The extracellular matrix is broken down first by proteases, and new vessels arising mainly from the retinal venules penetrate the internal limiting membrane and form capillary networks between the inner surface of the retina and the posterior hyaloid face.

In patients with proliferative diabetic retinopathy (PDR), nocturnal intermittent hypoxia/reoxygenation that results from sleep disordered breathing may be a risk factor for iris and/or angle neovascularization.^[11]

Neovascularization is most commonly observed at the borders of perfused and nonperfused retina and most commonly occurs along the vascular arcades and at the optic nerve head. The new vessels break through and grow along the surface of the retina and into the scaffold of the posterior hyaloid face. By themselves, these vessels rarely cause visual compromise, but they are fragile and highly permeable. These delicate vessels are disrupted easily by vitreous traction, which leads to hemorrhage into the vitreous cavity or the preretinal space.

These new blood vessels initially are associated with a small amount of fibroglial tissue formation. However, as the density of the neovascular frond increases, so does the degree of fibrous tissue formation. In later stages, the vessels may regress, leaving only networks of avascular fibrous tissue adherent to both the retina and the posterior hyaloid face. As the vitreous contracts, it may exert tractional forces on the retina via these fibroglial connections. Traction may cause retinal edema, retinal heterotopia, and both tractional

retinal detachments and retinal tear formation with subsequent detachment.

Etiology

Duration of diabetes

In patients with type I diabetes, no clinically significant retinopathy can be seen in the first 5 years after the initial diagnosis of diabetes is made. After 10-15 years, 25-50% of patients show some signs of retinopathy. This prevalence increases to 75-95% after 15 years and approaches 100% after 30 years of diabetes. Proliferative diabetic retinopathy (PDR) is rare within the first decade of type I diabetes diagnosis but increases to 14-17% by 15 years, rising steadily thereafter. In patients with type II diabetes, the incidence of diabetic retinopathy increases with the disease duration. Of patients with type II diabetes, 23% have nonproliferative diabetic retinopathy (NPDR) after 11-13 years, 41% have NPDR after 14-16 years, and 60% have NPDR after 16 years.

Hypertension and hyperlipidemia

Systemic hypertension, in the setting of diabetic nephropathy, correlates well with the presence of retinopathy. Independently, hypertension also may complicate diabetes in that it may result in hypertensive retinal vascular changes superimposed on the preexisting diabetic retinopathy, further compromising retinal blood flow. Proper management of hyperlipidemia (elevated serum lipids) may result in less retinal vessel leakage and hard exudate formation, but the reason behind this is unclear.

Pregnancy

Pregnant women with proliferative diabetic retinopathy do poorly without treatment, but those who have had prior panretinal photocoagulation remain stable throughout pregnancy. Pregnant women without diabetic retinopathy run a 10% risk of developing NPDR during their pregnancy; Of those with preexisting NPDR, 4% progress to the

proliferative type. A study by Toda et al found that among pregnant women with diabetic retinopathy, those who showed progression of the eye disorder tended to have a longer duration of diabetes, to have had diabetic retinopathy prior to pregnancy, and to have higher blood pressure in the second trimester.^[12]

Signs and symptoms

In the initial stages of diabetic retinopathy, patients are generally asymptomatic; In the more advanced stages of the disease, however, patients may experience symptoms that include floaters, blurred vision, distortion, and progressive visual acuity loss. Signs of diabetic retinopathy include the following:

- Microaneurysms: The earliest clinical sign of diabetic retinopathy; These occur secondary to capillary wall outpouching due to pericyte loss; They appear as small, red dots in the superficial retinal layers.
- Dot and blot hemorrhages: Appear similar to microaneurysms if they are small; They occur as microaneurysms rupture in the deeper layers of the retina, such as the inner nuclear and outer plexiform layers.
- Flame shaped hemorrhages: Splinter hemorrhages that occur in the more superficial nerve fiber layer
- Retinal edema and hard exudates: Caused by the breakdown of the blood retina barrier, allowing leakage of serum proteins, lipids, and protein from the vessels.
- Cotton wool spots: Nerve fiber layer infarctions from occlusion of precapillary arterioles; They are frequently bordered by microaneurysms and vascular hyperpermeability.
- Venous loops and venous beading: Frequently occur adjacent to areas of

nonperfusion; They reflect increasing retinal ischemia, and their occurrence is the most significant predictor of progression to proliferative diabetic retinopathy (PDR).

- Intraretinal microvascular abnormalities: Remodelled capillary beds without proliferative changes; Can usually be found on the borders of the nonperfused retina.
- Macular edema: Leading cause of visual impairment in patients with diabetes.

Nonproliferative diabetic retinopathy

- Mild: Indicated by the presence of at least 1 microaneurysm.
- Moderate: Includes the presence of hemorrhages, microaneurysms, and hard exudates.
- Severe (4-2-1): Characterized by hemorrhages and microaneurysms in 4 quadrants, with venous beading in at least 2 quadrants and intraretinal microvascular abnormalities in at least 1 quadrant.

Proliferative diabetic retinopathy

- Neovascularization: Hallmark of PDR.
- Preretinal hemorrhages: Appear as pockets of blood within the potential space between the retina and the posterior hyaloid face; as blood pools within this space, the hemorrhages may appear boat shaped.
- Hemorrhage into the vitreous: May appear as a diffuse haze or as clumps of blood clots within the gel.
- Fibrovascular tissue proliferation: Usually seen associated with the neovascular complex; May appear avascular when the vessels have already regressed.
- Traction retinal detachments: Usually appear tented up, immobile, and concave.

- Macular edema

Diagnosis

Diabetic retinopathy is detected during an eye examination that includes:

- *Visual acuity test*: This test uses an eye chart to measure how well a person sees at various distances.
- *Pupil dilation*: The eye care professional places drops into the eye to dilate the pupil. This allows him or her to see more of the retina and look for signs of diabetic retinopathy.
- *Ophthalmoscopy or fundus photography*: Ophthalmoscopy is an examination of the retina in which the eye care professional: (1) looks through a slit lamp biomicroscope with a special magnifying lens that provides a narrow view of the retina, or (2) wearing a headset (indirect ophthalmoscope) with a bright light, looks through a special magnifying glass and gains a wide view of the retina. Handheld ophthalmoscopy is insufficient to rule out significant and treatable diabetic retinopathy. Fundus photography generally recreates considerably larger areas of the fundus, and has the advantage of photo documentation for future reference, as well as availing the image to be examined by a specialist at another location and/or time.
- *Fundus Fluorescein angiography (FFA)*: This is an imaging technique which relies on the circulation of Fluorescein dye to show staining, leakage, or non-perfusion of the retinal and choroidal vasculature.
- *Optical coherence tomography (OCT)*: This is an optical imaging modality based upon interference, and analogous to ultrasound. It produces cross-sectional

images of the retina (B-scans) which can be used to measure the thickness of the retina and to resolve its major layers, allowing the observation of swelling.

The eye care professional will look at the retina for early signs of the disease, such as:

1. Leaking blood vessels,
2. Retinal swelling, such as macular edema,
3. Pale, fatty deposits on the retina (exudates) – signs of leaking blood vessels,
4. Damaged nerve tissue (neuropathy), and
5. Any changes in the blood vessels.

If macular edema is suspected, FFA and sometimes OCT may be performed.

According to a DRSS user manual, poor quality images (which may apply to other methods) may be caused by cataract, poor dilation, ptosis, external ocular condition, or learning difficulties. There may be artefacts caused

by dust, dirt, condensation, or smudge.^[13]

Screening

Screening for diabetic retinopathy is part of the standard of care for people with diabetes.^[14] After one normal screening in people with diabetes, further screening is recommended every two years.^[15]

Teleophthalmology has been employed in these programs.^[16]

Management

There are three major treatments for diabetic retinopathy, which are very effective in reducing vision loss from this disease.^[17] In fact, even people with advanced retinopathy have a 95 percent chance of keeping their vision when they get treatment before the retina is severely damaged.^[18] These three treatments are laser surgery, injection of corticosteroids or anti-VEGF agents into the eye, and vitrectomy.

Although these treatments are very successful (in slowing or stopping further vision loss), they do not

cure diabetic retinopathy. Caution should be exercised in treatment with laser surgery since it causes a loss of retinal tissue. It is often more prudent to inject triamcinolone or antiVEGF drugs. In some patients it results in a marked increase of vision, especially if there is an edema of the macula.^[17] Avoiding tobacco use and correction of associated hypertension are important therapeutic measures in the management of diabetic retinopathy.^[19]

The best way of preventing the onset and delaying the progression of diabetic retinopathy is to monitor it vigilantly and achieve optimal glycemic control.^[20]

Since 2008 there have been other therapies (e.g. kinase inhibitors and antiVEGF) drugs available^[21]

Laser photocoagulation

Laser photocoagulation can be used in two scenarios for the treatment of diabetic retinopathy. It can be used to treat macular edema by creating a Modified Grid at the posterior pole and it can be used for panretinal coagulation for controlling neovascularization. It is widely used for early stages of proliferative retinopathy.

Modified grid

A 'C' shaped area around the macula is treated with low intensity small burns. This helps in clearing the macular edema.

Panretinal

Panretinal photocoagulation, or PRP (also called scatter laser treatment), is used to treat proliferative diabetic retinopathy (PDR). The goal is to create 1,600-2,000 burns in the retina with the hope of reducing the retina's oxygen demand, and hence the possibility of ischemia. It is done in multiple sittings. In treating advanced diabetic retinopathy, the burns are used to destroy the abnormal blood vessels that form in the retina. This has been shown to reduce the risk of severe vision loss for eyes at risk by 50%.^[22] Before using the laser, the

ophthalmologist dilates the pupil and applies anaesthetic drops to numb the eye. In some cases, the doctor also may numb the area behind the eye to reduce discomfort. The patient sits facing the laser machine while the doctor holds a special lens on the eye. The physician can use a single spot laser or a pattern scan laser for two dimensional patterns such as squares, rings and arcs. During the procedure, the patient will see flashes of light. These flashes often create an uncomfortable stinging sensation for the patient.

After the laser treatment, patients should be advised not to drive for a few hours while the pupils are still dilated. Vision will most likely remain blurry for the rest of the day. Though there should not be much pain in the eye itself, an ice cream headache like pain may last for hours afterwards. Patients will lose some of their peripheral vision after this surgery although it may be barely noticeable by the patient. The procedure does however save the centre of the patient's sight. Laser surgery may also slightly reduce colour and night vision.

A person with proliferative retinopathy will always be at risk for new bleeding, as well as glaucoma, a complication from the new blood vessels. This means that multiple treatments may be required to protect vision.

Medications

Intravitreal triamcinolone acetonide

Triamcinolone is a long acting steroid preparation. When injected in the vitreous cavity, it decreases the macular edema (thickening of the retina at the macula) caused due to diabetic maculopathy, and results in an increase in visual acuity. The effect of triamcinolone is transient, lasting up to three months, which necessitates repeated injections for maintaining the beneficial effect. Best results of intravitreal Triamcinolone have been found in eyes that have already undergone cataract surgery. Complications of intravitreal injection

oftriamcinolone include cataract, steroidinduced glaucoma and endophthalmitis.

Intravitreal anti-VEGF

There are good results from multiple doses of intravitreal injections of anti-VEGF drugs such as bevacizumab^[23]

Present recommended treatment for diabetic macular edema is Modified Grid laserphotocoagulation combined with multiple injections of anti-VEGF drugs.

Surgery

Instead of laser surgery, some people require a vitrectomy to restore vision. A vitrectomy is performed when there is a lot of blood in the vitreous. It involves removing the cloudy vitreous and replacing it with a saline solution. Studies show that people who have a vitrectomy soon after a large hemorrhage are more likely to protect their vision than someone who waits to have the operation. Early vitrectomy is especially effective in people with insulin dependent diabetes, who may be at greater risk of blindness from a hemorrhage into the eye.

Vitrectomy is often done under local anesthesia. The doctor makes a tiny incision in the sclera, or white of the eye. Next, a small instrument is placed into the eye to remove the vitreous and insert the saline solution into the eye.

Patients may be able to return home soon after the vitrectomy, or may be asked to stay in the hospital overnight. After the operation, the eye will be red and sensitive, and patients usually need to wear an eyepatch for a few days or weeks to protect the eye. Medicated eye drops are also prescribed to protect against infection. Vitrectomy is frequently combined with other modalities of treatment.

Prognosis

Prognostic factors that are favorable for visual loss include the following:

- Circinate exudates of recent onset

- Well defined leakage
- Good perifoveal perfusion

Prognostic factors that are unfavorable for visual loss include the following:

- Diffuse edema/multiple leaks
- Lipid deposition in the fovea
- Macular ischemia
- Cystoid macular edema
- Preoperative vision of less than 20/200
- Hypertension

Approximately 8,000 eyes become blind yearly because of diabetes. The treatment of diabetic retinopathy entails tremendous costs, but it has been estimated that this represents only one eighth of the costs of Social Security payments for vision loss. This cost does not compare to the cost in terms of loss of productivity and quality of life.

The Early Treatment for Diabetic Retinopathy Study has found that laser surgery for macular edema reduces the incidence of moderate visual loss (doubling of visual angle or roughly a 2 line visual loss) from 30% to 15% over a 3year period. The Diabetic Retinopathy Study has found that adequate scatter laser panretinal photocoagulation reduces the risk of severe visual loss (< 5/200) by more than 50%.^[24, 25]

Patient Education

One of the most important aspects in the management of diabetic retinopathy is patient education. Inform patients that they play an integral role in their own eye care.

Excellent glucose control is beneficial in any stage of diabetic retinopathy. It delays the onset and slows down the progression of the diabetic complications in the eye.

The following symptoms and/or health concerns must be addressed in any patient education program for those with diabetic retinopathy:

- Systemic problems (eg, hypertension, renal disease, and hyperlipidemia) may contribute to disease progression.
- Smoking, although not directly proven to affect the course of the retinopathy, may further compromise oxygen delivery to the retina. Therefore, all efforts should be made in the reduction, if not outright cessation, of smoking.
- Visual symptoms (eg, vision changes, floaters, distortion, redness, pain) could be manifestations of disease progression and should be reported immediately.

Diabetes mellitus, in general, and diabetic retinopathy, in particular, are progressive conditions, and regular followup care with a physician is crucial for detection of any changes that may benefit from treatment.

Research

Light treatment

A medical device having a mask that delivers green light through the eyelids while a person sleeps was under development in 2016.^{[26][27]} The light from the mask stops rod cells in the retina from dark adapting, which is thought to reduce their oxygen requirement, which in turn diminishes new blood vessel formation and thus prevents diabetic retinopathy.^[26]

C-peptide

C-peptide had shown promising results in treatment of diabetic complications incidental to vascular degeneration.^[28] Creative Peptides,^[29] Eli Lilly,^[30] and Cebix^[31] all had drug development programs for a C-peptide product. Cebix had the only ongoing program until it completed a Phase IIb trial in December 2014 that showed no difference between C-peptide and placebo, and it terminated its program and went out of business.^{[32][33]}

Stem cell therapy

Current trials involve using the patients' own stem cells derived from bone marrow and injected into the degenerated areas in an effort to regenerate the vascular system.^[34]

Blood pressure control

A Cochrane review examined 15 randomized controlled trials to determine whether interventions that sought to control or reduce blood pressure in diabetics had any effects of diabetic retinopathy.^[35] While the results showed that interventions to control or reduce blood pressure prevented diabetic retinopathy for up to 4–5 years in diabetics, there was no evidence of any effect of these interventions on progression of diabetic retinopathy, preservation of visual acuity, adverse events, quality of life, and costs.^[35]

Fundoscopy image analyses

Diabetic retinopathy is diagnosed entirely by recognizing abnormalities on retinal images taken by funduscopy. Color fundus photography is mainly used for staging the disease. Fluorescein angiography is used to assess the extent of retinopathy that aids in treatment plan development. Optical coherence tomography (OCT) is used to determine the severity of edema and treatment response.^[37] Because fundoscopic images are the main sources for diagnosis of diabetic retinopathy, manually analyzing those images can be time consuming and unreliable, as the ability of detecting abnormalities varies by years of experience.^[38] Therefore, scientists have explored developing computer-aided diagnosis approaches to automate the process, which involves extracting information about the blood vessels and any abnormal patterns from the rest of the fundoscopic image and analyzing them.^[36]

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