DIABETIC

Review Article

# New advances in Diabetic Retinopathy: A Narrative Review

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**ABSTRACT**

Retinal vasculitis brought on by the consequences of diabetes mellitus is known as diabetic retinopathy. Globally, the prevalence of diabetic retinopathy has skyrocketed, making it a primary cause of blindness and visual impairment in individuals over 20. There are a number of risk factors for diabetic retinopathy including duration of diabetes, poor metabolic control, puberty, gender, hypertension, high lipid levels, nephropathy, and surgery. Clinical practice recommendations include 1) treating hyperlipidemia, 2) controlling arterial hypertension to levels below 130/80 mm Hg, and 3) bringing blood sugar levels down to levels to normal (HbA1c = 7.0%). It is possible to reduce the prevalence and incidence of diabetes mellitus and, consequently, its consequences by weight loss, exercise, and healthy eating.

**Keywords:** Diabetic Retinopathy, Ophthalmological Findings, Pharmacotherapy, Diabetic Control, Metabolic Control

## INTRODUCTION

Retinal vasculitis brought on by the consequences of diabetes mellitus is known as diabetic retinopathy [1]. Neovascularization and macular edema are two possible alterations, with the latter occurring more frequently. Globally, the prevalence of diabetic retinopathy has skyrocketed, making it a primary cause of blindness and visual impairment in persons over 20 [2].

### Risk Factors

### Duration of diabetes

The duration of diabetes is the main contributing factor [3]. Type 1 diabetes incidence is 2% in cases with less than two years of onset of disease, and up to 98% in cases with fifteen or more years of onset [3]. After five years, the incidence of type 2 diabetes treated with or without insulin is 20%; and after fifteen years, it rises to 80% [3]. The absence of an early diagnosis in asymptomatic patients is the cause of the apparent rise in the incidence of type 2 diabetes.



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### Poor metabolic control

Diabetic retinopathy can be prevented or delayed with early and effective glycemic management [3]. Elevation in glycated haemoglobin is linked to an increased risk of serious consequences [3].

### Puberty

Regardless of the length of diabetes, the risk of diabetic retinopathy is extremely low prior to puberty and increases in frequency and severity beyond the age of 13. This may be caused by hormonal changes [4].

### Gender

Another factor is the patient's gender. In addition to having a higher chance of diabetes than men, women are roughly twice as likely to be blind overall [5]. According to a study conducted by the Department of Ophthalmology at Marburg University, 446 women and 233 men with diabetes in the state of Hesse were blind or seriously visually impaired in 1997 and 1998 [6]. Moreover, there is a strong association between the risk of development of diabetic retinopathy and pregnancy due to factors including endocrinal and metabolic changes during pregnancy [5].

### Hypertension

One of the systemic aspects that has been studied the most is the direct relationship between high blood pressure to retinopathy [7]. However, it is uncertain if nephropathy causes hypertension, in which case both conditions would be consequences of diabetes [7].

### High lipid levels

It appears that retinopathy and elevated lipid levels are related [8]. Elevated amounts of hard exudates are correlated with high cholesterol levels. High levels of triglycerides are linked to the severity of retinopathy [8].

### Nephropathy

It has been noted in multicentric research that both type 1 and type 2 diabetes are accompanied by nephropathy and diabetic retinopathy. Possibly more frequent than nephropathy, diabetic retinopathy is a microvascular consequence of diabetes [9].

### Surgery

Diabetic patients who have surgery for early cataracts run the risk of developing proliferative diabetic retinopathy and macular edema [10]. In every case, laser therapy of proliferative diabetic retinopathy and retinal edema, as well as preoperative optimization of blood pressure and glucose control, are critical. Moreover, due to the cataract procedure, glucocorticoids or VEGF analogues are released into the vitreous body, which increases the risks [11].

### Pathogenesis

Diabetic retinopathy is a type of microangiopathy that impacts the arterioles, capillaries, venules, and tiny retinal arteries [12]. The vascular lesion is the root cause of the retinal problems. These lesions seem to be primarily caused by endothelial damage. The resultant clinical manifestation of diabetic retinopathy is caused by microvascular problems in addition to this. Anatomical alterations include thickening of the basal membrane and pericyte loss; physiological changes include decreased blood flow; biochemical changes include increased sorbitol and glucose metabolism end products; and blood-retinal barrier disruption [13].

### Classification of Diabetic Retinopathy

### Non-proliferative diabetic retinopathy

Microaneurysm development, or outward ballooning of the capillary wall, is the first morphological hallmark of non-proliferative diabetic retinopathy [14]. When these first appear, they are typically asymptomatic and are initially found on the temporal side of the fovea. However, they have the potential to rupture and cause intraretinal punctuates haemorrhages. Only ophthalmoscopy can identify them [14]. Macular edema is caused by leaking, which is shown by fluorescein angiography [14].

Additional indicators of non-proliferative diabetic retinopathy range in intensity from mild to severe, and include blot and flame-shaped hemorrhages, hard exudates, venous calibre fluctuations (venous beading), and intraretinal microvascular abnormalities [15]. The latter are ophthalmoscopically evident as capillary widening; they are dilated telangiectatic capillaries in the vicinity of capillary occlusions [15]. They are thought to be a well-known indicator of ischemia and an indication that proliferative retinopathy may soon proceed. Cotton wool spots or microinfarcts in the nerve-fiber layer may be a sign of poorly managed arterial hypertension [14].

### Proliferative diabetic retinopathy

Proliferative diabetic retinopathy develops when the hypoperfusion in the retinal capillary bed gets worse and extends across the retina [15]. Neovascularization develops in response to ischemia both on the retina outside of the papilla (neovascularization elsewhere, NVE) and at the papilla (neovascularization of the disc, NVD) [16].

Retinal vascular proliferation can be understood as an ineffective attempt to generate new arteries at the papilla, on the retina, and ultimately on the iris (neovascularization of the iris, or NVI) in an attempt to compensate for ischemia [16]. Neovascularization of the parenchyma and retina may result in membranes and cords arranged on the surface of the retina, as well as epiretinal and subhyaloid vitreous hemorrhages [15,16]. Later, tractional macular edema or tractional retinal detachment, both of which can result in blindness, are caused by the contraction of these diseased structures [15]. Neovascular glaucoma is the final and most serious consequence of diabetic retinopathy [17]. The aqueous humour cannot exist because of the newly developed vessels that extend from the pupil into the chamber angle [17]. Neovascularization glaucoma can cause excruciating blindness and eye shrinkage if left untreated [15,17].

**Diabetic macular edema**

When there is a zone of edema greater than the papilla at a distance of one papillary diameter, or when there is retinal thickening and/or hard exudates within 500 µm of the fovea, it is considered clinically significant macular edema [18]. Although the patient's vision is still pretty good at this point, diabetic retinopathy has already seriously compromised it. Lipids, proteins, and other substances seep into the sensory retina due to a malfunction in the inner blood-retinal barrier [18]. Hard exudates and retinal thickness are stereoscopically evident signs of this leaking [17-18]. It is not until the fovea itself is impacted that the patient realizes that their eyesight is getting worse. The location of the leak is localized using fluorescein angiography. Preventing irreversible loss of vision acuity requires early identification of clinically severe macular edema and laser treatment of the condition [19].

Another facet of diabetic macular degeneration is ischemic maculopathy [20]. This structure entails blocking the capillary network surrounding the fovea [20]. The prognosis for visual acuity is poor and there is no treatment for ischaemic maculopathy. Using fluorescein angiography, a diagnosis is made [20].

**Consequences**

Retinal edema and hard exudates are caused by increased vascular permeability that results in the loss of lipids and plasma proteins. Microthrombosis phenomena are accompanied by retinal microinfarcts that result in cotton wool patches, or soft exudates, which are indicative of hypoxia and ischemia. In the retina and iris, hypoxia causes the release of angiogenic factors and the development of new blood vessels (rubeosis iridis). Edema is caused by the extravasated fluids, particularly in the macular region. Under these conditions, multiple retinal cells, not just endothelium synthesize vascular endothelial growth factor (VEGF), which is produced 30 times more frequently under hypoxic conditions. There are two mechanisms for this being significant: It induces the creation of neovessels and increases edema and vascular permeability. As a result, abnormalities arise in all retinal cells, including glia, neurons, and arteries, which cause visual impairments.

**Treatment**

**Photo coagulation**

The evidence-based treatment for diabetic macular edema and diabetic retinopathy is laser photocoagulation [21]. The prospective, randomised, controlled ETDR trial, which was published in 1991 and for which 3711 patients in total were recruited, serves as the foundation for the recommendation for this type of treatment [6]. Consequently, the Working Group on Diabetes and the Eye (Arbeitsgemeinschaft Diabetes und Auge, AGDA) and the Initiative Group for the Early Detection of Diabetic Eye Diseases (Initiativgruppe zur Früherkennung diabetischer Augenerkrankungen, IFdA) have published national guidelines in Germany [22].

Currently, a double-frequency neodymium:yttrium-aluminum-garnet (Nd:YAG) laser produces light with a wavelength of 532 nm. With the use of a contact lens placed on the cornea, the laser is connected to a split-lamp microscope to administer the treatment. When there is advanced opacification of the cornea or lens, treatment with a Nd:YAG laser may not be feasible due to poor sight and light beam scattering from the therapeutic application. An 810 nm diode laser may be utilized in these circumstances, or the cataract may be treated first, with the laser treatment administered a few days after the cataract surgery [23]. Regression of the newly created vessels as a result of normalization of the partial pressure of oxygen in the peripheral avascular parts of the retina is the aim of pan-retinal laser photocoagulation for proliferative diabetic retinopathy

[23]. Thus, there is a decreased chance of membrane formation and vitreous hemorrhage [23]. Up to 2500 laser foci may be required to cover the whole surface of the retina; these foci are placed throughout the retina's periphery, sparing its center, and have a diameter of 500 µm [23]. The Diabetic Retinopathy Study (DRS), a prospective, randomized trial that included 1732 eyes, showed as early as 1976 that this type of treatment reduces the chance of severe visual loss by almost 50%. Just 56 of the untreated eyes experienced severe visual loss, compared to 129 of the treated eyes [6].

Targeted focal laser coagulation of leaky microaneurysms and capillaries in the vicinity of the fovea, with laser foci ranging in size from 100 to 200 µm, is the treatment for clinically severe diabetic macular edema [6]. In the 1985 EDTR research, 1490 eyes were in the untreated control group and 754 eyes received focal laser coagulation treatment [6]. When the first interim evaluation of the study results was conducted at one year, it was found that the risk of worsening vision due to significant macular edema had been so significantly reduced that further observation of the control group was deemed unethical, and patients in the control group were immediately offered laser coagulation [23]. For individuals with clinically severe macular edema who can be identified and treated promptly, this treatment is still the gold standard [22-23]. Visual acuity is rarely improved by laser treatment. Therefore, it is crucial to recognize the coming vision loss through a preventive checkup so that laser treatment can be administered to maintain acuity while the eye is still capable of seeing well. Visual acuity can deteriorate irreversibly.

**Surgery**

Non-resorbing vitreous hemorrhage, subhyaloid hemorrhage, ghost-cell glaucoma, tractional retinal detachment, and tractional macular edema are among the conditions that can be treated with pars plana vitrectomy (PPV) [24]. With a pars plana vitrectomy, the turbid vitreous body, scarred cords, and membranes can be removed, the retina can be properly repositioned, and the best laser photocoagulation treatment can be administered. An investigation that was prospective, randomized, controlled, and controlled (the Diabetic Retinopathy Vitrectomy Study, or DRVS) verified the benefits of pars plana vitrectomy and identified the best time point for treatment. Individuals who had their vitresections early on experienced noticeably superior vision than those who got them a year later [24].

The contemporary microsurgical techniques, vitrectomy has become a routine procedure [25]. In recent years, technical refinements have shortened the operative time and obviated the need for suturing. The diameter of the instruments that are currently introduced through trocars has been reduced from 1.0 to 0.6 mm. With vitrectomy, it is now possible to maintain at least rudimentary vision even in patients with advanced proliferative diabetic retinopathy. Painful neovascularization glaucoma is now a very rare event. In such cases, surgical removal of the blind eye may be necessary as a procedure of last resort to eliminate pain.

**Pharmacotherapy**

Treating diabetic macular edema is preferred using intraretinoid glucocorticoids [26]. Their anti-inflammatory and anti-angiogenic properties help prevent proliferative diabetic retinopathy and stabilize the inner blood-retina barrier [26]. Despite the lack of data from clinical trials, triamcinolone acetonide's off-label use has quickly proliferated due to its clear clinical benefit against diabetic macular edema. One drawback is that the impact is only temporary, lasting three months requiring repeated injections [26]. Additionally, one-third of individuals may develop secondary glaucoma [26]. Dexamethasone is utilized as a substitute medication as a result. Cataracts secondary to injury are also prevalent [27].

Since VEGF mediates vascular leakage, it bears some of the risks for the inner blood-retinal barrier's breakdown [28]. Inhibiting proliferation and leakage in diabetic macular edema is another benefit of using VEGF antagonists, which have been reported to be effective in treating wet age-related macular degeneration (AMD) [28]. One of its drawbacks is that their effects are only temporary, typically lasting four to six weeks [28].

The effects of pegaptanib (an aptamer), ranibizumab (a recombinant, humanised monoclonal antibody fragment), and bevacizumab (a humanised monoclonal antibody) are now being investigated through prospective, multicenter trials [6]. A randomised, double-blind trial conducted in 2005 previously demonstrated an effect on diabetic macular edema, with the retinal thickness significantly reduced by 68 µm and increasing by 4 µm in the control group. Additionally, the patients' visual acuity improved [6].

**Clinical practice recommendations**

Diabetic retinopathy can be prevented or delayed for many years

by treating hyperlipidemia, controlling arterial hypertension to levels below 130/80 mm Hg, and bringing blood sugar levels down to levels close to normal (HbA1c = 7.0%) [29]. It is possible to reduce the prevalence and incidence of diabetes mellitus and, consequently, its consequences by weight loss, exercise, and healthy eating [29]. Since diabetic retinopathy takes a long time to manifest symptoms, ophthalmologists must perform routine preventive examinations if permanent eye damage is to be prevented.

The German Diabetes Society (Deutsche Diabetes Gesellschaft, DDG) guidelines state that individuals with type 1 diabetes should have dilated pupil ophthalmoscopies starting five years after diagnosis, and children starting at age eleven [30]. The exams should be done annually as long as retinopathy has not yet developed, and otherwise on the advice of the ophthalmologist. As soon as type 2 diabetes is identified, a person should be referred to an ophthalmologist.

Because it is impossible to estimate how long a person has had diabetes, they should get an eye test after three months. Annual re-examination is sufficient if diabetic retinopathy has not yet occurred; if it has, re-examination should be conducted in accordance with the ophthalmologist's instructions.

When a female patient wants to get pregnant, she should have an ophthalmoscopy before getting pregnant, every three months while she is pregnant, or every month if she already has diabetic retinopathy. She should also have reexamined right away if she starts experiencing any new symptoms. From an ophthalmological perspective, a vaginal delivery is the preferred method of delivery and a caesarean section is not indicated.

It is advised that the ophthalmological findings be documented using standard forms, such as those provided in Germany by the Working Group on Diabetes and the Eye (Arbeitsgemeinschaft Diabetes und Auge, AGDA) and the Initiative Group for the Early Detection of Diabetic Eye Diseases (Initiativgruppe zur Früherkennung diabetischer Augenerkrankungen, IFdA) [31]. Transmitting a duplicate of the filled-out forms to the other attending physicians enhances the standard of interdisciplinary care, an essential aspect of managing the diabetic patient.

## DECLARATIONS

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### Competing interests

The authors declare that they have no competing interests.

### Authors' contributions

TA is a postgraduate ophthalmology student and this paper is part of his academic work. TA and AK carried out the literature review and wrote and finalized the manuscript.

### Ethics approval

Not Applicable

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