BOROWIEC, Kinga, BOROWIEC, Agnieszka, KWAŚNIEWSKA, Paulina, BIERNIKIEWICZ, Julia, WILEWSKA, Anna, BIERNIKIEWICZ, Milena, POMIRSKI, Bartosz, POMIRSKA, Agata, ALABRUDZIŃSKI, Konstanty and KAŁACHURSKA, Miszela. The Silent Threat: Understanding and Managing Diabetic Retinopathy. Journal of Education, Health and Sport. 2024;76:56642. eISSN 2391-8306.
https://dx.doi.org/10.12775/JEHS.2024.76.56642
https://apcz.umk.pl/JEHS/article/view/56642

The journal has had 40 points in Minister of Science and Higher Education of Poland parametric evaluation. Annex to the announcement of the Minister of Education and Science of 05.01.2024 No. 32318. Has a Journal's Unique Identifier: 201159. Scientific disciplines assigned: Physical culture sciences (Field of medical and health sciences); Health Sciences (Field of medical and health sciences).
Punkty Ministerialne 40 punktów. Załącznik do komunikatu Ministra Nauki i Szkolnictwa Wyższego z dnia 05.01.2024 Lp. 32318. Posiada Unikatowy Identyfikator Czasopisma: 201159. Przypisane dyscypliny naukowe: Nauki o kulturze fizycznej (Dziedzina nauk medycznych i nauk o zdrowiu); Nauki o zdrowiu (Dziedzina nauk medycznych i nauk o zdrowiu).© The Authors 2024;
This article is published with open access at Licensee Open Journal Systems of Nicolaus Copernicus University in Torun, Poland

The authors declare that there is no conflict of interests regarding the publication of this paper.
Received: 04.12.2024. Revised: 18.12.2024. Accepted: 18.12.2024. Published: 18.12.2024.

The Silent Threat: Understanding and Managing Diabetic Retinopathy

Kinga Borowiec
Faculty of Medicine, Medical University of Warsaw, Żwirki i Wigury 61, 02-091 Warsaw, Poland
https://orcid.org/0009-0000-5546-9787
kingaborowiec07@gmail.com

Agnieszka Borowiec
The Regional Specialist Hospital in Biala Podlaska Terebelska 57-65 21-500 Biala Podlaska, Poland
https://orcid.org/0000-0002-1428-170X
borowiec.agn@gmail.com

Paulina Kwaśniewska
Faculty of Medicine, Medical University of Warsaw, Żwirki i Wigury 61, 02-091 Warsaw, Poland
https://orcid.org/0009-0009-4677-3387
paulinakwasniewska12@gmail.com

Julia Biernikiewicz
Faculty of Medicine, Medical University of Warsaw, Żwirki i Wigury 61, 02-091 Warsaw, Poland
https://orcid.org/0009-0004-1192-9365
biernikiewiczjulia@gmail.com

Anna Wilewska
Faculty of Medicine, Medical University of Warsaw, Żwirki i Wigury 61, 02-091 Warsaw, Poland
https://orcid.org/0009-0001-5136-4598
wilewskaanna2000@gmail.com

Milena Biernikiewicz
Faculty of Medicine Wroclaw Medical University, wybrzeże Ludwika Pasteura 1 50-367 Wroclaw, Poland
https://orcid.org/0009-0006-7288-6965
milenabiernikiewicz@gmail.com

Bartosz Pomirski
Faculty of Medicine, Medical University of Warsaw, Żwirki i Wigury 61, 02-091 Warsaw, Poland
https://orcid.org/0009-0004-4868-0073
Bartosz.pomirski@gmail.com

Agata Pomirska
Faculty of Medicine, Medical University of Warsaw żwirki i wigury 61, 02-091 Warsaw, Poland
https://orcid.org/0009-0009-5367-7123
pomirska.agata@gmail.com
Konstanty Alabrudziński
School of Medicine Collegium Medicum University of Warmia and Mazury in Olsztyn, ul. Oczapowskiego 2, 10-719 Olsztyn, Poland
https://orcid.org/0009-0008-4729-0937
konstanty.alabrudzinski@gmail.com
Miszela Kałachurska
Faculty of Medicine, Pomeranian Medical University of Szczecin, Rybacka 1, 70-204 Szczecin
https://orcid.org/0009-0006-0687-638X
miszela.kaachurska@gmail.com

Keywords: Diabetic retinopathy pathogenesis and risk factors; Diabetic retinopathy treatment; Vascular endothelial growth factor inhibitors; Intravitreal injections; Laser photocoagulation;

Abstract

Introduction and purpose: Diabetic retinopathy (DR) is a common complication of diabetes mellitus, characterized by damage to the blood vessels in the retina. It is one of the leading causes of blindness in adults worldwide. This article aims to explore the pathophysiology, risk factors, basic rules of patient screening, DR classification and current treatment approaches for DR, with the goal of improving awareness and understanding of this vision threatening condition.

Materials and methods: A review was conducted in PubMed and Google Scholar including publications regarding diabetic retinopathy and its' pathogenesis, risk factors, classification, screening and treatment. Literature was searched using the following terms: "diabetic retinopathy pathogenesis and treatment", "diabetic retinopathy screening", "diabetic retinopathy risk factors", "vascular endothelial growth factor inhibitors", "laser photocoagulation" and "vitrectomy".

Brief description of the state of knowledge: DR is typically classified into two stages: non-proliferative DR, where the retinal vessels leak fluid or bleed and proliferative DR, characterized by the growth of abnormal blood vessels that can lead to retinal detachment or hemorrhaging. Treatment for DR aims to slow disease progression and preserve vision. Modern therapies include laser therapy, anti-VEGF injections and vitrectomy.

Conclusions: Prevention is the most effective way to avoid vision loss from DR. Maintaining a healthy lifestyle, controlling blood glucose and blood pressure, as well as regular eye examinations are essential for managing DR. Therapeutic interventions such as anti-VEGF intravitreal injections, laser photocoagulation and vitrectomy proved to be very effective in DR management. Early intervention with modern therapies, patients education and treatment adherence are main factors in preventing severe outcomes of DR.

Introduction

Diabetes mellitus (DM) is such a worldwide prevalent disease that it has been considered a civilization disease. It has a significant impact not only on life expectancy but especially on its quality. Diabetic retinopathy (DR) is an ocular manifestation of organ failure associated

with prolonged high blood glucose levels and the leading cause of new cases of blindness in working-age adults with DM worldwide. It is a common complication of both type 1 and type 2 diabetes. Diabetic eye disease affects as many as 34.6% of patients with diabetes. Vision-threatening diabetic retinopathy affects 10.2% of this group [1]. As a general rule, more frequent and severe ocular complications are seen in individuals with type 2 diabetes. With the increasing global prevalence of DM, the burden of diabetic retinopathy continues to rise, highlighting the importance of effective prevention, early detection, and advanced treatment options. This article explores the pathophysiology, risk factors and current treatment strategies for diabetic retinopathy, aiming to enhance awareness and understanding of this sight-threatening condition.

Pathogenesis

Diabetic retinopathy (DR) is a microangiopathy in which hyperglycemia plays a crucial role in the pathogenesis of retinal microvascular damage. The initial reaction of retinal blood vessels to high blood glucose levels is their dilation [2]. Apart from that, hyperglycemia leads to thinning of the superficial layer of the endothelial cells (glycocalyx). This results in the loss of their antithrombotic, profibrinolytic and vasodilatory functions. Pericyte loss is another key early event in diabetic retinopathy. Studies have shown that high glucose levels trigger apoptosis of pericytes, both in vitro and in vivo [3,4]. Pericytes are essential for providing structural support to capillaries, so their loss leads to regional bulging of capillary walls. This process is linked to the development of microaneurysms, which is considered to be the first noticeable clinical indicator of DR. As a consequence, the pericytes and endothelial cells can no longer perform their protective roles leading to impairment of the blood-retina barrier (BRB), which is critical for maintaining the integrity of the retinal vasculature. These aforementioned factors contributes to the development of vascular abnormalities such as increased permeability, capillary occlusion, ischaemia and the formation of microaneurysms, all of which are characteristic features and one of the earliest clinical signs of diabetic retinopathy.

Another important factor that plays an enormous role in diabetic retinopathy, specifically in proliferative diabetic retinopathy (PDR) and diabetic macular edema (DME) pathogenesis and progression is vascular endothelial growth factor (VEGF). Retinal ischemia or hypoxia triggers the upregulation of VEGF through the activation of hypoxia-inducible factor 1 (HIF-1), which leads to the development of abnormal blood vessels in the retina [5]. VEGF is known to contribute to this process by affecting tight junction proteins (such as occludin and zonula occludens-1) causing their phosphorylation and thus increasing vascular permeability.

Additionally, VEGF stimulates mitogen-activated protein (MAP), which is responsible for promoting the proliferation of endothelial cells [6]. The activation of these signaling pathways is crucial for stimulating endothelial cell growth, contributing to the formation of new blood vessels, a process known as neovascularization. This abnormal growth of new blood vessels is a characteristic feature of PDR, a more advanced stage of DR, and is also associated with DME, which causes fluid buildup in the macula and leads to vision problems. Increased VEGF expression has been detected in various studies, including in the retina of diabetic mouse models and in the vitreous of patients suffering from DME and PDR [7-9]**.** This suggests that VEGF plays a significant role in driving the pathological changes seen in these conditions.

In addition to VEGF, there are other angiogenic factors, which are also involved in regulating the retinal vasculature. One such group includes angiopoietins (Ang-1 and Ang-2), which are critical for the stability and function of blood vessels. These factors act through the interaction with the endothelial receptor tyrosine kinase Tie2, which is found on the surface of endothelial cells lining the blood vessels. Ang-1 generally functions to promote vessel stability and protect endothelial cells, helping maintain vascular integrity. It binds to Tie2, leading to the stabilization of blood vessels. Ang-2, on the other hand, acts as an antagonist to Ang-1 by binding to the Tie2 [10] receptor resulting in promoting vascular leakage and destabilization of the vasculature. In the context of diabetic retinopathy, Ang-2 has been shown to contribute to the increased vascular permeability observed in the retina, particularly under conditions of retinal ischemia or hypoxia. Studies in diabetic rat models have demonstrated that elevated levels of Ang-2 can induce vascular leakage in the retina, leading to the development of retinal edema, a characteristic feature of DME [11].

Inflammation is a crucial factor in the development of diabetic retinopathy. Persistent, low-level inflammation has been observed at various stages of DR both in diabetic animal models as well as in human patients [12,13]. A key early event in DR is leukostasis, which refers to the accumulation of leukocytes in the retinal microvasculature, which can impair retinal blood flow and lead to further complications like retinal hypoxia. Schröder and colleagues were the first to describe that monocytes and granulocytes obstructs retinal blood vessels in rats with streptozotocin (STZ) induced diabetes [14,15]. They found that leukocyte adherence to retinal blood vessels occurred as soon as three days after diabetes was induced in the rats. Furthermore, they observed that this increased leukostasis was closely associated with endothelial damage contributing to the breakdown of the BRB, causing the leakage of fluid

and proteins into the retina. Further research revealed that leukostasis plays a significant role in endothelial cell damage and the breakdown of the BRB via the Fas (CD95)/Fas-ligand pathway [16]. Moreover, the expression of leukocyte adhesion molecules b2-integrins (such as CD11a, CD11b, and CD18) on leukocytes is increased, allowing leukocytes to bind tightly to endothelial cells, which results in leukostasis both in diabetic rats and patients [14,15]. On the endothelial cells themselves, molecules like ICAM-1 (intercellular adhesion molecule-1), VCAM-1 (vascular cell adhesion molecule-1), and E-selectin are also upregulated [12,17,18]. These molecules interact with the leukocyte adhesion molecules and facilitate the binding of leukocytes to the vessel walls. E-selectin and VCAM-1 are especially significant because their expression in the plasma of diabetic patients has been shown to correlate with the severity of DR [12]. High levels of these molecules indicate more severe inflammation and greater leukocyte adhesion, both of which contribute to retinal damage and disease progression.

Chemokines are a subset of cytokines that primarily function to attract and activate immune cells such as monocytes, neutrophils, and T cells. In the context of DR, chemokines contribute to the inflammatory response by promoting the recruitment of leukocytes to the retinal vasculature, where they can cause further endothelial damage and break down the BRB. Monocyte chemotactic protein-1 (MCP-1) is one of the most studied chemokines in DR. It binds to the CCR2 receptor on monocytes, promoting their migration across the endothelial layer of retinal blood vessels into the retina. In diabetic patients, MCP-1, as well as macrophage inflammatory protein-1 alpha (MIP-1α) and MIP-1β levels are significantly elevated [19], contributing to leukocyte infiltration into the retina and subsequent damage to the retinal microvasculature and exacerbation of the vascular leakage. The increase in MCP-1 expression correlates with the severity of DR, suggesting that it plays a role in a disease progression. Studies have shown that mice deficient in MCP-1 exhibit reduced retinal vascular leakage and less leukocyte infiltration [20]. This suggests that targeting MCP-1 or its receptor could offer potential therapeutic benefits for reducing inflammation and vascular damage in DR. Additionally, the levels of inflammatory cytokines such as tumor necrosis factor alpha (TNF-α), interleukin 6 (IL-6), IL-8, and interleukin 1 beta (IL-1β) were found to be noticeably elevated in diabetic patients, and their expression level was closely correlated with the severity of diabetic retinopathy [21,22].

What is also worth elaborating on is that retinal glial cells like microglia, Müller cells, and astrocytes are believed to contribute to retinal inflammation and thus play critical role in

maintaining retinal homeostasis [23]. Under normal conditions, these retinal glial cells work together to maintain retinal health and homeostasis. They protect neurons from damage, regulate blood flow, and help with waste disposal. Müller cells take part in recycling neurotransmitters and controlling water balance. Astrocytes ensure the integrity of the BRB, while microglia are quick to become activated in response to injury or disease. In diabetic retinopathy, especially under conditions of hyperglycemia, these glial cells become dysregulated and contribute to inflammation. Once activated, microglia shift from their protective functions to inflammatory roles. They begin to secrete proinflammatory cytokines such as TNF-α, IL-6, MCP-1, and VEGF [24]. As the disease progresses, other retinal glial cells, such as Müller cells and astrocytes, become involved in the response by producing proinflammatory mediators [23]. Additionally, Müller cells are involved in the formation of "gliosis" (a scar-like tissue formation) in the retina which can disrupt its normal function and further exacerbate the inflammatory response.

Risk Factors

The risk factors for diabetic retinopathy include a combination of modifiable and non-modifiable factors. The duration of the underlying disease is initially the most important non-modifiable risk factor for the development of diabetic retinopathy. The main modifiable risk factors, on the other hand, are the level of blood glucose and blood pressure. Effective control of these factors can prevent or delay the onset or progression of diabetic eye disease. Prolonged hyperglycemia with high values has a crucial impact on the progression of retinopathy. The longer it lasts and the higher its levels, the greater the risk of worsening the patient's condition. After changes are diagnosed in the retina, the duration of the disease is considered a less significant factor in predicting progression to later stages of DR than blood glucose control [25,26]. Increased levels of glycated hemoglobin (HbA1c) are associated with an increased risk of DR progression and macular edema development [27, 28]. Maintaining strict control of blood sugar is critical for reducing the risk of developing or worsening diabetic retinopathy. The Diabetes Control and Complications Trial found a significant link between the risk of DR and average HbA1c levels: a reduction of about 10% in HbA1c was associated with a 39% decrease in the risk of retinopathy progression [29]. Additionally, a long-term follow-up demonstrated that tight blood glucose control reduce the incidences of progression of severe non-proliferative diabetic retinopathy (NPDR), proliferative diabetic retinopathy and macular edema [30]. For most people with diabetes, a level of HbA1c of ≤7% is recommended [31].

What is more, uncontrolled high blood pressure increases the risk of developing diabetic retinopathy and can accelerate its development. Intensive and tight management of blood pressure through medication and lifestyle changes is critical for reducing risk and delaying the progression of DR [32,33]. However, the Cochrane review indicated that, although intensive blood pressure control reduced the risk of developing DR, it had no significant effect on the progression of existing DR when compared to less strict blood pressure control measures [32].

Elevated serum cholesterol and triglyceride levels are a known risk factor for the development and progression of diabetic retinopathy. Moreover, the presence of hard exudates in the retina correlates with elevated cholesterol levels in the serum. Hard exudates in the macula promote the development of subretinal fibrosis, increasing the risk of vision loss. The ACCORD (Action to Control Cardiovascular Risk in Diabetes) trial examined the effects of tight blood sugar control and treatment for dyslipidemia in patients with type 2 diabetes [34]. The results showed that combining strict glycemic control with fenofibrate and simvastatin therapy slowed the progression of DR, compared to the combination of simvastatin and a placebo. The FIELD (Fenofibrate Intervention and Event Lowering in Diabetes) study also proved that fenofibrate treatment led to a reduced need for laser treatments in patients with DR [35].

The mechanism of retinopathy development during puberty is associated with the release of certain growth-related hormones, including insulin-like growth factor 1 (IGF-1) and growth hormone. It was shown that in patients with type 1 diabetes, the severity of DR is inversely related to serum IGF-1 levels, meaning that lower IGF-1 levels are associated with more severe DR [36]. Adjusted IGF-1 levels, considering disease, age, and sex, could complement HbA1c in predicting long-term outcomes for children and adolescents with type 1 diabetes [37].

Being overweight or obese increases the risk of developing type 2 diabetes and worsens diabetes control. Weight loss and maintaining a healthy body weight and corrects body mass index can significantly reduce the risk of DR [38]. Smoking damages blood vessels and can exacerbate the development of diabetic retinopathy [39]. Smokers with diabetes are more likely to develop DR, and quitting smoking is highly beneficial in reducing this likelihood. Another risk factor associated with the detrimental effect (threatening diabetic macular edema and reducing the effectiveness of laser therapy) is connected with kidney damage accompanied by albuminuria and anemia [40]. It is believed that the progression of macular

edema in these cases is due to a decrease in osmotic pressure and autoregulatory vessel dilation as a result of chronic retinal hypoxia.

During pregnancy, retinopathy may progress due to hormonal changes and the associated poorer metabolic control. Pregnancy is sometimes the cause of rapid progression of DR. Predisposing factors include ineffective glycemic control before pregnancy, overly intensive control in early pregnancy, as well as the development of preeclampsia and fluid balance disturbances [41]. The risk of progression depends on the severity of DR in the first trimester. Monitoring for DR during pregnancy should be performed monthly. Diabetic macular edema usually resolves spontaneously after delivery and does not require treatment if it develops in the later stages of pregnancy. Regular monitoring is important during pregnancy to catch early signs of progression [42].

Diabetic Retinopathy Classification

The classification of DR is typically based on the severity of the retinal changes, which range from mild signs of disease to severe stages with risk of vision loss. The two main classification systems used are the Early Treatment Diabetic Retinopathy Study (ETDRS) grading system and the International Clinical Diabetic Retinopathy (ICDR) scale. The ETDRS grading system is widely used to classify diabetic retinopathy based on the appearance of retinal changes observed during clinical examination, particularly through fundus photography. While the ETDRS grading scale provides an accurate and structured approach to assessing diabetic retinopathy, its complexity limits its practical use in daily clinical settings. It is particularly beneficial in research environments where precision and consistency are paramount. However, for routine clinical practice, simpler, faster grading systems such as ICDR are often preferred, allowing ophthalmologists to make decisions in real-time without the need for extensive training or detailed image analysis [43].

Table 1. The Early Treatment Diabetic Retinopathy Study (ETDRS) Grading System

Grade	Stage of Diabetic Retinopathy	Description
10	No Diabetic Retinopathy	No detectable signs of diabetic retinopathy. Retina appears normal, no hemorrhages, microaneurysms, or other changes.
20	Mild NPDR	Presence of microaneurysms. No other significant retinal changes. No hemorrhages, exudates, or macular edema.
35	Moderate NPDR	Increased microaneurysms, retinal hemorrhages, and slight vascular changes. No neovascularization or macular edema.
43	Severe NPDR	Significant microaneurysms**,** retinal hemorrhages**,** venous beading (widening of blood vessels). Presence of cotton wool spots and hard exudates. No proliferative changes.
60-85	Proliferative Diabetic Retinopathy (PDR)	Neovascularization at the optic disc or retina. Risk of vitreous hemorrhages, retinal detachment, and severe vision impairment.
DME	Diabetic Macular Edema	Swelling or fluid leakage in the macula (central retina), leading to blurred central vision. DME can occur at any stage of diabetic retinopathy, but particularly concerning in advanced stages.

The ICDR classification is another common method used for grading DR, with a focus on clinical and fundoscopic findings. The ICDR scale was developed to make the classification of DR more accessible and practical for daily clinical use by ophthalmologists and primary care physicians. The ICDR scale condenses the 14 levels of the ETDRS scale into just 5 severity levels, making it easier to apply in clinical settings. It helps clinicians assess the severity of the disease, plan appropriate treatments, and track the progression of DR. The

ICDR scale was created through an international consensus workshop held in 2002, which involved experts from various countries. It was based on the data from the ETDRS and WESDR (Wisconsin Epidemiologic Study of Diabetic Retinopathy) and was designed to simplify the process of diagnosing and managing DR. The system divides DR into non-proliferative (NPDR) and proliferative stages (PDR), with diabetic macular edema as a separate complication**.**

The first subcategory of non-proliferative DR is Mild NPDR with the presence of microaneurysms (small, localized bulges or swellings in the walls of the retinal blood vessels appearing as tiny red dots scattered in the retina) without other significant changes and no visual impairment at this stage. The second one is Moderate NPDR with increased microaneurysms, hemorrhages (dot/blot), and retinal edema, which can affect vision. The last stage of NPDR is Severe NPDR with marked retinal hemorrhages, cotton wool spots (microinfarctions of the retinal nerve fiber layer) and extensive areas of ischemia. Venous beading or large areas of non-perfused retina may be seen. What is worth mentioning is that there is a risk of significant vision loss, requiring close monitoring and potential intervention. Proliferative Diabetic Retinopathy (PDR) divides into Early PDR characterized by neovascularization (growth of new, abnormal blood vessels) forming on the retina (NVE – neovascularisation elswhere) or optic disc (NVD – neovascularisation of the disc). The new vessels are fragile and prone to bleeding. There is a risk of vitreous hemorrhage, which can obscure vision. The second subcategory is High-risk PDR with extensive neovascularization, leading to vitreous hemorrhages, retinal detachment, and possible scar tissue formation that distorts the retina. This stage requires immediate medical intervention (e.g., laser photocoagulation, anti-VEGF therapy). Without treatment, there is a high likelihood of serious vision impairment or severe vision loss.

Diabetic Macular Edema (DME) is a complication of DR that can occur at any stage but is most often seen in more advanced stages of DR (especially moderate to severe NPDR and PDR).

It refers to the swelling or edema of the macula (the central part of the retina responsible for sharp, detailed vision). DME can lead to central vision loss resulting in great difficulty with tasks that require fine vision, like reading, thus making it a major cause of visual impairment. Macular edema is classified separately because it can occur in isolation, without other signs of diabetic eye disease. It can also affect all types of retinopathy. As a result of the damage to the

BRB, fluid accumulates around the macula. There are two types: diffuse edema, where massive leakage occurs from capillaries, and localized edema [44], caused by focal leakage from grouped microaneurysms. Hard exudates indicate the presence of current or previous macular edema.

Table 2. The International Clinical Diabetic Retinopathy (ICDR) Scale

Stage	Description	Clinical Findings
Stage 0: No Diabetic Retinopathy	No signs of diabetic retinopathy.	Retina appears normal with no abnormalities.
Stage 1: Mild Non-Proliferative Diabetic Retinopathy (NPDR)	Early stage of DR with minimal retinal changes.	- Microaneurysms (small, localized dilations of blood vessels).
Stage 2: Moderate Non-Proliferative Diabetic Retinopathy (NPDR)	Moderate retinal changes, with some visual disturbances possible.	- Microaneurysms more numerous. - Dot and blot hemorrhages. - Hard exudates. - Venous beading.
Stage 3: Severe Non-Proliferative Diabetic Retinopathy (NPDR)	Significant damage to the retina with a high risk of progression to proliferative diabetic retinopathy (PDR).	- More than 20 intraretinal hemorrhages in each of four quadrants. - Extensive venous beading in two or more quadrants. - Intraretinal microvascular abnormalities (IRMA) in one or more quadrants.
Stage 4: Proliferative Diabetic Retinopathy (PDR)	Advanced DR with new, abnormal blood vessel growth (neovascularization).	- Neovascularization. - Vitreous hemorrhage. - Retinal fibrosis and scarring.
Stage 5: Diabetic Macular Edema (DME)	Fluid accumulation in the macula leading to vision impairment. Can occur at any stage of DR but is most common in later stages.	- Swelling of the macula. - Blurred or distorted central vision.

DR progresses in a sequential manner – from the mildest changes to the most advanced stages if appropriate medical interventions are not implemented. A large area of retinal changes, elevated vessels, and fibrosis contribute to a poor prognosis. Advanced neovascularization leads to the development of tractional retinal detachment and neovascular glaucoma. Hemorrhages into the eyeball are associated with hypoglycemic episodes, physical exertion, and direct trauma.

Screening

Screening for DR is essential for early detection and timely treatment to prevent vision loss. The primary goal of screening is to identify patients with DR before symptoms develop. Individuals receiving treatment for diabetes should undergo an eye examination at least once a year. For those with type 1 diabetes, the first annual eye exam is recommended 5 years after diagnosis. Due to the difficulty in determining the exact onset of type 2 diabetes, eye exams for these patients should take place as soon as the condition is diagnosed. If any abnormalities are found in the fundus, the frequency of follow-up visits is typically increased.

Severe NPDR follows a similar course to PDR, and both are characterized by a very high risk of progression. For this reason, follow-up visits every 2-4 months are essential to initiate treatment at the appropriate time. Particular attention should be given to high-risk PDR, which can be identified based on three out of the following four changes: neovascularization at any location, neovascularization on the optic disc or in its immediate vicinity, neovascularization of at least moderate degree (defined as new retinal vessels covering an area at least the size of half the optic disc, new vessels on the optic disc and/or within a radius of one optic disc diameter, covering an area between one-quarter and one-third of the optic disc surface) or intraretinal hemorrhage or hemorrhage into the vitreous body [63]. Visit schedules should be adjusted individually, taking into account the rate of retinopathy progression, the patient's overall condition, and the presence of other complications.

Pregnancy can increase the risk for the development and progression of DR in women with preexisting diabetes (both type 1 and type 2). As far as pregnant women with diabetes are concerned, they should undergo preconception eye exam and then should be monitored every trimester throughout the pregnancy for the development or progression of DR [43]. For women who develop gestational diabetes mellitus (GDM) during pregnancy (diabetes that is first diagnosed during pregnancy and typically resolves after childbirth), the risk of developing DR is not significantly higher compared to women who do not have diabetes. As such, eye exams are generally not required for women with GDM unless other risk factors for eye disease are present. GDM typically does not cause the same long-term retinal damage as preexisting diabetes, as the condition usually resolves after delivery. However, these women should still be monitored for the development of type 2 diabetes in the future, as they are at higher risk of developing diabetes later in life.

Table 3. Screening recommendations for diabetic retinopathy in different patient populations

Diabetes Type	When to Start Screening	Frequency
Type 1 Diabetes	After 5 years of diagnosis (or age 10)	Annually, or more frequently if needed
Type 2 Diabetes	At the time of diagnosis	Annually, or more frequently if needed
Women with pre-existing diabetes who plan pregnancy or who have become pregnant	Before pregnancy or in the first trimester	Every trimester during pregnancy to monitor DR progression
Gestational Diabetes Mellitus (GDM)	No routine eye exams needed, as GDM typically does not cause DR or retinal complications. Eye exams only if there are additional risk factors or signs of DR.	
High Risk/Progression	Severe NPDR or PDR present	Every 3-6 months

Treatment

In modern times, the most commonly performed procedures for treating diabetic retinopathy are retinal laser therapy, intravitreal injections of anti-VEGF or corticosteroids, and vitrectomy. To achieve the best possible outcomes, therapies are often combined, thereby intensifying the treatment. The selection of the appropriate therapy depends on the severity of the retinopathy symptoms and the presence and extent of macular edema.

It is often observed that visual acuity remains good despite the presence of macular edema. In such cases, intervention is typically withheld unless vision deteriorates to a level of 0.7. These patients should be monitored every 2 to 4 months [45]. Currently, the main treatment for

macular edema is intravitreal injections of anti-VEGF agents. VEGF is a pro-inflammatory factor that stimulates the formation of new blood vessels in the retina and increases vascular permeability, leading to fluid accumulation in the macula. The most commonly used VEGF inhibitors in ophthalmology are bevacizumab (Avastin), aflibercept (Eylea), and ranibizumab (Lucentis). A new drug that has been introduced for the treatment of DR is brolucizumab (Beovu). The goal of intravitreal injections is to reduce or eliminate macular edema and improve vision. Numerous studies have shown that anti-VEGF therapy is more effective than the previously used focal laser therapy as a first-line treatment. The Diabetic Retinopathy Clinical Research (DRCR) Protocol T, a randomized clinical trial conducted at multiple centers, compared the effectiveness of bevacizumab, aflibercept, and ranibizumab. The study demonstrated that these medications are effective treatments for DME. No significant difference was found between the drugs in terms of vision loss to a level of 0.5 due to macular edema. However, aflibercept proved to be most effective when the vision deterioration ranged from 0.4 to 0.06 [46]. According to DRCR guidelines, if macular edema is detected, it is recommended to begin monthly injections of aflibercept for 4 to 6 months. Treatment can be stopped if the macular edema is eliminated or visual acuity reaches 1.0 and no further improvement in vision or central retinal thickness is observed. If vision or central retinal thickness worsens during follow-up visits, injections should be reinitiated. If there are no indications for further injections, monitoring appointments may be scheduled every 4 months. As mentioned before, intravitreal anti-VEGF injections remain the first-line treatment for DME. In some cases, focal laser therapy may be considered afterward if persistent areas of edema are observed. Gross et al. [47] demonstrated that anti-VEGF treatment is at least as effective as photocoagulation in patients with and without DME, while Sivaprasad et al. [48] found that anti-VEGF treatment is more effective in patients without DME. Apart from that, it has been demonstrated that therapy with ranibizumab, aflibercept or bevacizumab, in combination with or without focal laser therapy, leads to better outcomes than using laser treatment alone [49-52]. On January 2022, the U.S. Food and Drug Administration (FDA) approved a new drug, faricimab (Vabysmo) for the treatment of DME. The YOSEMITE and RHINE studies showed comparable therapeutic effects when administering aflibercept and faricimab every 8 weeks [53]. This new drug is a humanized monoclonal antibody that works in two ways, inhibiting angiopoietin-2 and VEGF. On July 2022, the European Medicines Agency (EMA) gave a positive opinion on Vabysmo, recommending the drug for market authorization in Europe.

A serious complication of intravitreal anti-VEGF injections is endophthalmitis (infection inside the eye), which has been reported in clinical trials with an incidence ranging from 0.019% to 0.09% of cases [54]. The local application of povidone-iodine during the injection is necessary to effectively reduce the risk of endophthalmitis. Routine use of antibiotic eye drops before or after the intravitreal injection is not recommended, as it has not been proven to prevent the development of endophthalmitis [55]. Other complications, such as increased intraocular pressure, cataract development, or worsening of retinal traction, are rarely observed.

Laser photocoagulation has long been known as the standard treatment for both DME and PDR prior to the introduction of anti-VEGF therapies. As demonstrated in the Early Treatment Diabetic Retinopathy Study (ETDRS), focal/grid macular laser treatment has proven effective in reducing macular edema and lowering the risk of significant vision loss by 50% over three years [56]. Panretinal photocoagulation (PRP) has also been commonly used to manage PDR, significantly lowering the risk of severe vision loss, particularly in high-risk cases involving complications like vitreous hemorrhage [57]. While the exact mechanisms by which laser therapy alleviates DME and promotes neovascular regression remain unclear, it is believed that the therapy works by directly closing leaking microaneurysms, decreasing retinal blood flow (which reduces retinal tissue damage and improves oxygenation), and possibly stimulating the retinal pigment epithelium (RPE) [58,59].

In the case of focal macular edema diagnosed outside the foveal area, focal laser treatment is recommended. A moderate laser beam intensity should be used, targeting specific microaneurysms and avoiding the foveal vasculature within a radius of at least 500 μm [60]. A rare but dangerous complication of focal laser therapy is the development of subretinal fibrosis and choroidal neovascularization, which can lead to permanent vision loss [61]. Paracentral scotomas may also form if the laser was applied too close to the fovea, or central scotomas may occur due to human error. In some cases, after many years, the area treated with the laser may expand. For this reason, some authors believe that the use of micropulse laser causes less damage to the macula. However, a recent meta-analysis by Wu et al. did not show any differences in visual acuity outcomes between conventional and micropulse laser therapy [62].

Rapid and effective panretinal photocoagulation (PRP) prevents significant vision deterioration in patients with high-risk proliferative diabetic retinopathy - neovascular

changes are usually observed to regress [63]. The DRCR Protocol S study, based on a 2-year follow-up, demonstrated that a series of anti-VEGF injections could yield comparable results to PRP [47]. In patients receiving anti-VEGF injections, macular edema and peripheral vision loss were less frequently observed compared to those who underwent PRP. Nevertheless, in patients who continued treatment but had insufficiently administered anti-VEGF injections, visual acuity and anatomical outcomes were poorer than in the PRP group [64]. What is more, individuals with PDR who received PRP and were lost to follow-up for more than 6 months showed better anatomical and functional outcomes compared to those treated with anti-VEGF therapy [65]. This indicates that anti-VEGF therapy, as an alternative to PRP, is a risky choice, as treatment success is directly related to patient adherence to scheduled follow-up visits. The Early Treatment Diabetic Retinopathy Study (ETDRS) guidelines for PRP recommend performing 1200 to 1600 laser burns spaced half a disc diameter apart, with a laser duration of 0.1 seconds, creating a moderate whitening of the retina. When narrowing the area of PRP, it is crucial to ensure that the lesions are made at least two disc diameters from the fovea [66]. Additional PRP treatments or anti-VEGF injections are recommended when neovascularization does not regress - if it becomes more severe, appears in new locations, or when recurrent hemorrhage into the vitreous occurs. ETDRS studies also showed that early use of laser therapy reduces the risk of severe vision loss and the need for vitrectomy by 50%. The side effects of PRP, due to its destructive nature and permanent damage to retinal cells, include macular edema, visual field constriction, delayed dark adaptation, reduced accommodation, and mydriasis. Combining laser therapy with anti-VEGF injections is a possible treatment option for patients with concurrent macular edema.

DME can also be treated with intravitreal corticosteroids. Topical administration in the form of eye drops or peribulbar injections do not show therapeutic effects [67]. Intravitreal injections of triamcinolone acetonide and long-acting drug release implants such as dexamethasone (Ozurdex; duration of action up to 6 months) and fluocinolone acetonide (Iluvien; duration of action up to 3 years) are used. However, steroids remain a second-line treatment due to frequent complications, cataract progression, and elevated intraocular pressure (IOP). In the two-year follow-up of the DRCR Protocol I trial, intravitreal administration of triamcinolone increased IOP in 50% of patients, and cataract surgery was required in 59% of patients [68]. They are primarily administered to pseudophakic patients who have contraindications to other methods of treating macular edema or in whom other therapies have not been effective.

Vitrectomy should be considered when there is a suspicion that the lack of transparency in the central areas is affecting vision quality and treatment outcomes. Observations may include non-resolving vitreous or intraretinal hemorrhages, as well as massive fibrovacular proliferations and tractional retinal detachments that threaten or involve the macula.

The benefits of performing vitrectomy earlier are greater the more extensive the neovascularization is [67]. Surgical intervention is also indicated when disease activity is observed despite proper PRP treatment or anti-VEGF injections. In the case of vitreous hemorrhage, an ultrasound examination is recommended to detect any potential retinal detachment. Additionally, the preoperative administration of an intravitreal anti-VEGF agent provides benefits such as a shorter surgery time, reduced intraoperative bleeding, and a lower risk of postoperative vitreous hemorrhage [69,70]. It is important to consider the potential complications associated with vitrectomy, including vitreous hemorrhage, retinal tear or detachment, worsening visual acuity, cataract progression and endophthalmitis.

Conclusions

Despite the availability of advanced modern treatments, prevention remains the most effective approach to avoiding vision loss in diabetic eye disease. If left untreated, DR leads to blindness, which has a significant social and economic consequences for patients and their families. It is essential to remember that in treating patients with DR, maintaining a healthy lifestyle, controlling blood glucose levels, managing blood pressure, and conducting regular eye exams are of utmost importance. When therapy is necessary, it should be initiated as early as possible using modern treatment methods to prevent the severe outcomes of disease progression. Early intervention is most effective, so patients should be made aware that treatment is most successful during the initial stages of the condition. Diabetic patients often see multiple specialists, making clear communication and coordination of care vital to achieving the best treatment results. General practitioners and diabetologists should be aware of the need to refer diabetic patients to an ophthalmologist for routine monitoring. Given that current therapies often require multiple visits and continuous monitoring, educating patients about the benefits of regular eye exams is critical. A lack of patient engagement in the treatment process leads to poorer adherence to medical recommendations. Patients need to understand what DR is and be aware of the consequences associated with neglecting ophthalmologist advice. Proper patient education can also reduce the need for more invasive medical interventions, yielding significant savings for both the patient and the healthcare

system. There is no doubt that proper education, prevention, and modern treatment methods play a crucial role in reducing the consequences of diabetic eye disease, including decreased productivity and human suffering.

Disclosure

Author Contributions:
Conceptualization: Agnieszka Borowiec
Methodology: Bartosz Pomirski
Validation: Paulina Kwaśniewska
Formal Analysis: Julia Biernikiewicz
Investigation: Anna Wilewska
Resources: Milena Biernikiewicz
Data Curation: Konstanty Alabrudziński
Writing - Original Draft Preparation: Kinga Borowiec, Agnieszka Borowiec
Writing - Review & Editing: Kinga Borowiec, Agnieszka Borowiec, Agata Pomirska
Visualization: Miszela Kałachurska
Supervision: Kinga Borowiec, Agnieszka Borowiec

All authors have read and agreed to the published version of the manuscript.

Funding statement: The study received no financial support.
Institutional review board statement: Not applicable.
Informed consent statement: Not applicable.
Data availability statement: Not applicable.
Conflict of interest: The authors declare no conflict of interest.

List of References:

1. Zheng Y, He M, Congdon N. The worldwide epidemic of diabetic retinopathy. Indian J Ophthalmol. 2012 Sep-Oct;60(5):428-31. doi: 10.4103/0301-4738.100542. PMID: 22944754; PMCID: PMC3491270.
2. Bek T. Diameter Changes of Retinal Vessels in Diabetic Retinopathy. Curr Diab Rep. 2017 Aug 8;17(10):82. doi: 10.1007/s11892-017-0909-9. PMID: 28791532.
3. Naruse K, Nakamura J, Hamada Y, Nakayama M, Chaya S, Komori T, Kato K, Kasuya Y, Miwa K, Hotta N. Aldose reductase inhibition prevents glucose-induced apoptosis in cultured bovine retinal microvascular pericytes. Exp Eye Res. 2000 Sep;71(3):309-15. doi: 10.1006/exer.2000.0882. PMID: 10973739.
4. Romeo G, Liu WH, Asnaghi V, Kern TS, Lorenzi M. Activation of nuclear factor-kappaB induced by diabetes and high glucose regulates a proapoptotic program in retinal pericytes. Diabetes. 2002 Jul;51(7):2241-8. doi: 10.2337/diabetes.51.7.2241. PMID: 12086956.
5. Huang H, He J, Johnson D, Wei Y, Liu Y, Wang S, Lutty GA, Duh EJ, Semba RD. Deletion of placental growth factor prevents diabetic retinopathy and is associated with Akt activation and HIF1α-VEGF pathway inhibition. diabetes 2015;64:200-212. Diabetes. 2015 Mar;64(3):1067. doi: 10.2337/db15-er03. Erratum for: Diabetes. 2015 Jan;64(1):200-12. doi: 10.2337/db14-0016. PMID: 25713201; PMCID: PMC4876739.
6. Rousseau S, Houle F, Landry J, Huot J. p38 MAP kinase activation by vascular endothelial growth factor mediates actin reorganization and cell migration in human endothelial cells. Oncogene. 1997 Oct;15(18):2169-77. doi: 10.1038/sj.onc.1201380. PMID: 9393975.

7. Li J, Wang JJ, Yu Q, Chen K, Mahadev K, Zhang SX. Inhibition of reactive oxygen species by Lovastatin downregulates vascular endothelial growth factor expression and ameliorates blood-retinal barrier breakdown in db/db mice: role of NADPH oxidase 4. Diabetes. 2010 Jun;59(6):1528-38. doi: 10.2337/db09-1057. Epub 2010 Mar 23. PMID: 20332345; PMCID: PMC2874715.

8. Aiello LP, Avery RL, Arrigg PG, Keyt BA, Jampel HD, Shah ST, Pasquale LR, Thieme H, Iwamoto MA, Park JE, et al. Vascular endothelial growth factor in ocular fluid of patients with diabetic retinopathy and other retinal disorders. N Engl J Med. 1994 Dec 1;331(22):1480-7. doi: 10.1056/NEJM199412013312203. PMID: 7526212.

9. Adamis AP, Miller JW, Bernal MT, D'Amico DJ, Folkman J, Yeo TK, Yeo KT. Increased vascular endothelial growth factor levels in the vitreous of eyes with proliferative diabetic retinopathy. Am J Ophthalmol. 1994 Oct 15;118(4):445-50. doi: 10.1016/s0002-9394(14)75794-0. PMID: 7943121.

10. Patel JI, Hykin PG, Gregor ZJ, Boulton M, Cree IA. Angiopoietin concentrations in diabetic retinopathy. Br J Ophthalmol. 2005 Apr;89(4):480-3. doi: 10.1136/bjo.2004.049940. PMID: 15774928; PMCID: PMC1772595.

11. Rangasamy S, Srinivasan R, Maestas J, McGuire PG, Das A. A potential role for angiopoietin 2 in the regulation of the blood-retinal barrier in diabetic retinopathy. Invest Ophthalmol Vis Sci. 2011 Jun 1;52(6):3784-91. doi: 10.1167/iovs.10-6386. PMID: 21310918; PMCID: PMC3109054.

12. Miyamoto K, Khosrof S, Bursell SE, Rohan R, Murata T, Clermont AC, Aiello LP, Ogura Y, Adamis AP. Prevention of leukostasis and vascular leakage in streptozotocin-induced diabetic retinopathy via intercellular adhesion molecule-1 inhibition. Proc Natl Acad Sci U S A. 1999 Sep 14;96(19):10836-41. doi: 10.1073/pnas.96.19.10836. PMID: 10485912; PMCID: PMC17969.

13. Yuuki T, Kanda T, Kimura Y, Kotajima N, Tamura J, Kobayashi I, Kishi S. Inflammatory cytokines in vitreous fluid and serum of patients with diabetic vitreoretinopathy. J Diabetes Complications. 2001 Sep-Oct;15(5):257-9. doi: 10.1016/s1056-8727(01)00155-6. PMID: 11522500.

14. Barouch FC, Miyamoto K, Allport JR, Fujita K, Bursell SE, Aiello LP, Luscinskas FW, Adamis AP. Integrin-mediated neutrophil adhesion and retinal leukostasis in diabetes. Invest Ophthalmol Vis Sci. 2000 Apr;41(5):1153-8. PMID: 10752954.

15. Chibber R, Ben-Mahmud BM, Coppini D, Christ E, Kohner EM. Activity of the glycosylating enzyme, core 2 GlcNAc (beta1,6) transferase, is higher in polymorphonuclear leukocytes from diabetic patients compared with age-matched control subjects: relevance to capillary occlusion in diabetic retinopathy. Diabetes. 2000 Oct;49(10):1724-30. doi: 10.2337/diabetes.49.10.1724. PMID: 11016457.

16. Joussen AM, Poulaki V, Mitsiades N, Cai WY, Suzuma I, Pak J, Ju ST, Rook SL, Esser P, Mitsiades CS, Kirchhof B, Adamis AP, Aiello LP. Suppression of Fas-FasL-induced endothelial cell apoptosis prevents diabetic blood-retinal barrier breakdown in a model of streptozotocin-induced diabetes. FASEB J. 2003 Jan;17(1):76-8. doi: 10.1096/fj.02-0157fje. Epub 2002 Nov 15. PMID: 12475915.

17. Kasza M, Meleg J, Vardai J, Nagy B Jr, Szalai E, Damjanovich J, Csutak A, Ujhelyi B, Nagy V. Plasma E-selectin levels can play a role in the development of diabetic retinopathy. Graefes Arch Clin Exp Ophthalmol. 2017 Jan;255(1):25-30. doi: 10.1007/s00417-016-3411-1. Epub 2016 Jul 4. PMID: 27377657.

18. Limb GA, Hickman-Casey J, Hollifield RD, Chignell AH. Vascular adhesion molecules in vitreous from eyes with proliferative diabetic retinopathy. Invest Ophthalmol Vis Sci. 1999 Sep;40(10):2453-7. PMID: 10476819.

19. Suzuki Y, Nakazawa M, Suzuki K, Yamazaki H, Miyagawa Y. Expression profiles of cytokines and chemokines in vitreous fluid in diabetic retinopathy and central retinal vein occlusion. Jpn J Ophthalmol. 2011 May;55(3):256-263. doi: 10.1007/s10384-011-0004-8. Epub 2011 May 3. PMID: 21538000.

20. Rangasamy S, McGuire PG, Franco Nitta C, Monickaraj F, Oruganti SR, Das A. Chemokine mediated monocyte trafficking into the retina: role of inflammation in alteration of the blood-retinal barrier in diabetic retinopathy. PLoS One. 2014 Oct 20;9(10):e108508. doi: 10.1371/journal.pone.0108508. PMID: 25329075; PMCID: PMC4203688.

21. Koleva-Georgieva DN, Sivkova NP, Terzieva D. Serum inflammatory cytokines IL-1beta, IL-6, TNF-alpha and VEGF have influence on the development of diabetic retinopathy. Folia Med (Plovdiv). 2011 Apr-Jun;53(2):44-50. doi: 10.2478/v10153-010-0036-8. PMID: 21797106.

22. Boss JD, Singh PK, Pandya HK, Tosi J, Kim C, Tewari A, Juzych MS, Abrams GW, Kumar A. Assessment of Neurotrophins and Inflammatory Mediators in Vitreous of Patients With Diabetic Retinopathy. Invest Ophthalmol Vis Sci. 2017 Oct 1;58(12):5594-5603. doi: 10.1167/iovs.17-21973. PMID: 29084332; PMCID: PMC5667399.

23. Sorrentino FS, Allkabes M, Salsini G, Bonifazzi C, Perri P. The importance of glial cells in the homeostasis of the retinal microenvironment and their pivotal role in the course of diabetic retinopathy. Life Sci. 2016 Oct 1;162:54-9. doi: 10.1016/j.lfs.2016.08.001. Epub 2016 Aug 3. PMID: 27497914.

24. Abcouwer SF. Müller Cell-Microglia Cross Talk Drives Neuroinflammation in Diabetic Retinopathy. Diabetes. 2017 Feb;66(2):261-263. doi: 10.2337/dbi16-0047. PMID: 28108606; PMCID: PMC5248992.

25. Davis MD, Fisher MR, Gangnon RE, Barton F, Aiello LM, Chew EY, Ferris FL 3rd, Knatterud GL. Risk factors for high-risk proliferative diabetic retinopathy and severe visual loss: Early Treatment Diabetic Retinopathy Study Report #18. Invest Ophthalmol Vis Sci. 1998 Feb;39(2):233-52. PMID: 9477980.

26. Kilpatrick ES, Rigby AS, Atkin SL, Frier BM. Does severe hypoglycaemia influence microvascular complications in Type 1 diabetes? An analysis of the Diabetes Control and Complications Trial database. Diabet Med. 2012 Sep;29(9):1195-8. doi: 10.1111/j.1464-5491.2012.03612.x. PMID: 22332940.

27. Hainsworth DP, Bebu I, Aiello LP, Sivitz W, Gubitosi-Klug R, Malone J, White NH, Danis R, Wallia A, Gao X, Barkmeier AJ, Das A, Patel S, Gardner TW, Lachin JM; Diabetes Control and Complications Trial (DCCT)/Epidemiology of Diabetes Interventions and Complications (EDIC) Research Group. Risk Factors for Retinopathy in Type 1 Diabetes: The DCCT/EDIC Study. Diabetes Care. 2019 May;42(5):875-882. doi: 10.2337/dc18-2308. Epub 2019 Mar 4. PMID: 30833368; PMCID: PMC6489114.

28. Song KH, Jeong JS, Kim MK, Kwon HS, Baek KH, Ko SH, Ahn YB. Discordance in risk factors for the progression of diabetic retinopathy and diabetic nephropathy in patients with type 2 diabetes mellitus. J Diabetes Investig. 2019 May;10(3):745-752. doi: 10.1111/jdi.12953. Epub 2018 Nov 7. PMID: 30300472; PMCID: PMC6497586.

29. Flaxel CJ, Adelman RA, Bailey ST, Fawzi A, Lim JI, Vemulakonda GA, Ying GS. Diabetic Retinopathy Preferred Practice Pattern®. Ophthalmology. 2020 Jan;127(1):P66-P145. doi: 10.1016/j.ophtha.2019.09.025. Epub 2019 Sep 25. Erratum in: Ophthalmology. 2020 Sep;127(9):1279. doi: 10.1016/j.ophtha.2020.06.047. PMID: 31757498.

30. Correction: Retinopathy and Nephropathy in Patients with Type 1 Diabetes Four Years after a Trial of Intensive Therapy. N Engl J Med. 2000 May 4;342(18):1376. doi: 10.1056/nejm200005043421820. PMID: 10793172.

31. American Diabetes Association. Standards of medical care in diabetes--2013. Diabetes Care. 2013 Jan;36 Suppl 1(Suppl 1):S11-66. doi: 10.2337/dc13-S011. PMID: 23264422; PMCID: PMC3537269.

32. Do DV, Han G, Abariga SA, Sleilati G, Vedula SS, Hawkins BS. Blood pressure control for diabetic retinopathy. Cochrane Database Syst Rev. 2023 Mar 28;3(3):CD006127. doi: 10.1002/14651858.CD006127.pub3. PMID: 36975019; PMCID: PMC10049880.

33. UK Prospective Diabetes Study Group. Tight blood pressure control and risk of macrovascular and microvascular complications in type 2 diabetes: UKPDS 38. UK Prospective Diabetes Study Group. BMJ. 1998 Sep 12;317(7160):703-13. Erratum in: BMJ 1999 Jan 2;318(7175):29. PMID: 9732337; PMCID: PMC28659.

34. ACCORD Study Group; ACCORD Eye Study Group; Chew EY, Ambrosius WT, Davis MD, Danis RP, Gangaputra S, Greven CM, Hubbard L, Esser BA, Lovato JF, Perdue LH, Goff DC Jr, Cushman WC, Ginsberg HN, Elam MB, Genuth S, Gerstein HC, Schubart U, Fine LJ. Effects of medical therapies on retinopathy progression in type 2 diabetes. N Engl J Med. 2010 Jul 15;363(3):233-44. doi: 10.1056/NEJMoa1001288. Epub 2010 Jun 29. Erratum in: N Engl J Med. 2011 Jan 13;364(2):190. Erratum in: N Engl J Med. 2012 Dec 20;367(25):2458. PMID: 20587587; PMCID: PMC4026164.

35. Keech A, Simes RJ, Barter P, Best J, Scott R, Taskinen MR, Forder P, Pillai A, Davis T, Glasziou P, Drury P, Kesäniemi YA, Sullivan D, Hunt D, Colman P, d'Emden M, Whiting M, Ehnholm C, Laakso M; FIELD study investigators. Effects of long-term fenofibrate therapy on cardiovascular events in 9795 people with type 2 diabetes mellitus (the FIELD study): randomised controlled trial. Lancet. 2005 Nov 26;366(9500):1849-61. doi: 10.1016/S0140-6736(05)67667-2. Erratum in: Lancet. 2006 Oct 21;368(9545):1420. Erratum in: Lancet. 2006 Oct 21;368(9545):1415. doi: 10.1016/S0140-6736(06)69594-9. PMID: 16310551.

36. Raman P, Singal AK, Behl A. Effect of Insulin-Like Growth Factor-1 on Diabetic Retinopathy in Pubertal Age Patients With Type 1 Diabetes. Asia Pac J Ophthalmol (Phila). 2019 Jul-Aug;8(4):319-323. doi: 10.1097/APO.0000000000000250. PMID: 31369407; PMCID: PMC6727916.

37. Öberg D, Salemyr J, Örtqvist E, Juul A, Bang P. A longitudinal study of serum insulin-like growth factor-I levels over 6 years in a large cohort of children and adolescents with type 1 diabetes mellitus: A marker reflecting diabetic retinopathy. Pediatr Diabetes. 2018 Aug;19(5):972-978. doi: 10.1111/pedi.12681. Epub 2018 May 2. PMID: 29663652.

38. Kaštelan S, Tomić M, Gverović Antunica A, Ljubić S, Salopek Rabatić J, Karabatić M. Body mass index: a risk factor for retinopathy in type 2 diabetic patients. Mediators Inflamm. 2013;2013:436329. doi: 10.1155/2013/436329. Epub 2013 Nov 20. PMID: 24347825; PMCID: PMC3853039.

39. Su Z, Wu Z, Liang X, Xie M, Xie J, Li H, Wang X, Jiang F. Diabetic retinopathy risk in patients with unhealthy lifestyle: A Mendelian randomization study. Front Endocrinol (Lausanne). 2023 Jan 17;13:1087965. doi: 10.3389/fendo.2022.1087965. PMID: 36733810; PMCID: PMC9887126.

40. Estacio RO, McFarling E, Biggerstaff S, Jeffers BW, Johnson D, Schrier RW. Overt albuminuria predicts diabetic retinopathy in Hispanics with NIDDM. Am J Kidney Dis. 1998 Jun;31(6):947-53. doi: 10.1053/ajkd.1998.v31.pm9631838. PMID: 9631838.

41. Chandrasekaran PR, Madanagopalan VG, Narayanan R. Diabetic retinopathy in pregnancy - A review. Indian J Ophthalmol. 2021 Nov;69(11):3015-3025. doi: 10.4103/ijo.IJO_1377_21. PMID: 34708737; PMCID: PMC8725079.

42. Vujosevic S, Aldington SJ, Silva P, Hernández C, Scanlon P, Peto T, Simó R. Screening for diabetic retinopathy: new perspectives and challenges. Lancet Diabetes Endocrinol. 2020 Apr;8(4):337-347. doi: 10.1016/S2213-8587(19)30411-5. Epub 2020 Feb 27. PMID: 32113513.

43. Yang Z, Tan TE, Shao Y, Wong TY, Li X. Classification of diabetic retinopathy: Past, present and future. Front Endocrinol (Lausanne). 2022 Dec 16;13:1079217. doi: 10.3389/fendo.2022.1079217. PMID: 36589807; PMCID: PMC9800497.

44. Chong DD, Das N, Singh RP. Diabetic retinopathy: Screening, prevention, and treatment. Cleve Clin J Med. 2024 Aug 1;91(8):503-510. doi: 10.3949/ccjm.91a.24028. PMID: 39089852.

45. Photocoagulation for diabetic macular edema. Early Treatment Diabetic Retinopathy Study report number 1. Early Treatment Diabetic Retinopathy Study research group. Arch Ophthalmol. 1985 Dec;103(12):1796-806. PMID: 2866759.

46. Cai S, Bressler NM. Aflibercept, bevacizumab or ranibizumab for diabetic macular oedema: recent clinically relevant findings from DRCR.net Protocol T. Curr Opin Ophthalmol. 2017 Nov;28(6):636-643. doi: 10.1097/ICU.0000000000000424. PMID: 28837425.

47. Writing Committee for the Diabetic Retinopathy Clinical Research Network; Gross JG, Glassman AR, Jampol LM, Inusah S, Aiello LP, Antoszyk AN, Baker CW, Berger BB, Bressler NM, Browning D, Elman MJ, Ferris FL 3rd, Friedman SM, Marcus DM, Melia M, Stockdale CR, Sun JK, Beck RW. Panretinal Photocoagulation vs Intravitreous Ranibizumab for Proliferative Diabetic Retinopathy: A Randomized Clinical Trial. JAMA. 2015 Nov 24;314(20):2137-2146. doi: 10.1001/jama.2015.15217. Erratum in: JAMA. 2016 Mar 1;315(9):944. doi: 10.1001/jama.2016.1591. Erratum in: JAMA. 2019 Mar 12;321(10):1008. doi: 10.1001/jama.2019.0265. PMID: 26565927; PMCID: PMC5567801.

48. Sivaprasad S, Prevost AT, Vasconcelos JC, Riddell A, Murphy C, Kelly J, Bainbridge J, Tudor-Edwards R, Hopkins D, Hykin P; CLARITY Study Group. Clinical efficacy of intravitreal aflibercept versus panretinal photocoagulation for best corrected visual acuity in patients with proliferative diabetic retinopathy at 52 weeks (CLARITY): a multicentre, single-blinded, randomised, controlled, phase 2b, non-inferiority trial. Lancet. 2017 Jun 3;389(10085):2193-2203. doi: 10.1016/S0140-6736(17)31193-5. Epub 2017 May 7. PMID: 28494920.

49. Elman MJ, Bressler NM, Qin H, Beck RW, Ferris FL 3rd, Friedman SM, Glassman AR, Scott IU, Stockdale CR, Sun JK; Diabetic Retinopathy Clinical Research Network. Expanded 2-year follow-up of ranibizumab plus prompt or deferred laser or triamcinolone plus prompt laser for diabetic macular edema. Ophthalmology. 2011 Apr;118(4):609-14. doi: 10.1016/j.ophtha.2010.12.033. PMID: 21459214; PMCID: PMC3096445.

50. Nguyen QD, Shah SM, Khwaja AA, Channa R, Hatef E, Do DV, Boyer D, Heier JS, Abraham P, Thach AB, Lit ES, Foster BS, Kruger E, Dugel P, Chang T, Das A, Ciulla TA, Pollack JS, Lim JI, Eliott D, Campochiaro PA; READ-2 Study Group. Two-year outcomes of the ranibizumab for edema of the mAcula in diabetes (READ-2) study. Ophthalmology. 2010 Nov;117(11):2146-51. doi: 10.1016/j.ophtha.2010.08.016. Epub 2010 Sep 19. Erratum in: Ophthalmology. 2011 Jun;118(6):1016. Eliot, Dean [corrected to Eliott, Dean]. PMID: 20855114.

51. Rajendram R, Fraser-Bell S, Kaines A, Michaelides M, Hamilton RD, Esposti SD, Peto T, Egan C, Bunce C, Leslie RD, Hykin PG. A 2-year prospective randomized controlled trial of intravitreal bevacizumab or laser therapy (BOLT) in the management of diabetic macular edema: 24-month data: report 3. Arch Ophthalmol. 2012 Aug;130(8):972-9. doi: 10.1001/archophthalmol.2012.393. PMID: 22491395.

52. Do DV, Nguyen QD, Boyer D, Schmidt-Erfurth U, Brown DM, Vitti R, Berliner AJ, Gao B, Zeitz O, Ruckert R, Schmelter T, Sandbrink R, Heier JS; da Vinci Study Group. One-year outcomes of the da Vinci Study of VEGF Trap-Eye in eyes with diabetic

macular edema. Ophthalmology. 2012 Aug;119(8):1658-65. doi: 10.1016/j.ophtha.2012.02.010. Epub 2012 Apr 24. PMID: 22537617.

53. Wykoff CC, Abreu F, Adamis AP, Basu K, Eichenbaum DA, Haskova Z, Lin H, Loewenstein A, Mohan S, Pearce IA, Sakamoto T, Schlottmann PG, Silverman D, Sun JK, Wells JA, Willis JR, Tadayoni R; YOSEMITE and RHINE Investigators. Efficacy, durability, and safety of intravitreal faricimab with extended dosing up to every 16 weeks in patients with diabetic macular oedema (YOSEMITE and RHINE): two randomised, double-masked, phase 3 trials. Lancet. 2022 Feb 19;399(10326):741-755. doi: 10.1016/S0140-6736(22)00018-6. Epub 2022 Jan 24. PMID: 35085503.
54. Lau PE, Jenkins KS, Layton CJ. Current Evidence for the Prevention of Endophthalmitis in Anti-VEGF Intravitreal Injections. J Ophthalmol. 2018 Jul 24;2018:8567912. doi: 10.1155/2018/8567912. PMID: 30174946; PMCID: PMC6098904.
55. Parke DW 2nd, Coleman AL, Rich WL 3rd, Lum F. Choosing Wisely: five ideas that physicians and patients can discuss. Ophthalmology. 2013 Mar;120(3):443-444. doi: 10.1016/j.ophtha.2013.01.017. PMID: 23714602.
56. Treatment techniques and clinical guidelines for photocoagulation of diabetic macular edema. Early Treatment Diabetic Retinopathy Study Report Number 2. Early Treatment Diabetic Retinopathy Study Research Group. Ophthalmology. 1987 Jul;94(7):761-74. doi: 10.1016/s0161-6420(87)33527-4. PMID: 3658348.
57. Photocoagulation treatment of proliferative diabetic retinopathy: the second report of diabetic retinopathy study findings. Ophthalmology. 1978 Jan;85(1):82-106. doi: 10.1016/s0161-6420(78)35693-1. PMID: 345173.
58. Arnarsson A, Stefánsson E. Laser treatment and the mechanism of edema reduction in branch retinal vein occlusion. Invest Ophthalmol Vis Sci. 2000 Mar;41(3):877-9. PMID: 10711707.
59. Ogata N, Tombran-Tink J, Jo N, Mrazek D, Matsumura M. Upregulation of pigment epithelium-derived factor after laser photocoagulation. Am J Ophthalmol. 2001 Sep;132(3):427-9. doi: 10.1016/s0002-9394(01)01021-2. PMID: 11530069.
60. Writing Committee for the Diabetic Retinopathy Clinical Research Network; Fong DS, Strauber SF, Aiello LP, Beck RW, Callanan DG, Danis RP, Davis MD, Feman SS, Ferris F, Friedman SM, Garcia CA, Glassman AR, Han DP, Le D, Kollman C, Lauer AK, Recchia FM, Solomon SD. Comparison of the modified Early Treatment Diabetic Retinopathy Study and mild macular grid laser photocoagulation strategies for diabetic macular edema. Arch Ophthalmol. 2007 Apr;125(4):469-80. doi: 10.1001/archopht.125.4.469. PMID: 17420366; PMCID: PMC2536574.
61. Guyer DR, D'Amico DJ, Smith CW. Subretinal fibrosis after laser photocoagulation for diabetic macular edema. Am J Ophthalmol. 1992 Jun 15;113(6):652-6. doi: 10.1016/s0002-9394(14)74789-0. PMID: 1376019.
62. Wu Y, Ai P, Ai Z, Xu G. Subthreshold diode micropulse laser versus conventional laser photocoagulation monotherapy or combined with anti-VEGF therapy for diabetic macular edema: A Bayesian network meta-analysis. Biomed Pharmacother. 2018 Jan;97:293-299. doi: 10.1016/j.biopha.2017.10.078. Epub 2017 Nov 6. PMID: 29091878.
63. Indications for photocoagulation treatment of diabetic retinopathy: Diabetic Retinopathy Study Report no. 14. The Diabetic Retinopathy Study Research Group. Int Ophthalmol Clin. 1987 Winter;27(4):239-53. doi: 10.1097/00004397-198702740-00004. PMID: 2447027.
64. Obeid A, Gao X, Ali FS, Talcott KE, Aderman CM, Hyman L, Ho AC, Hsu J. Loss to Follow-Up in Patients with Proliferative Diabetic Retinopathy after Panretinal Photocoagulation or Intravitreal Anti-VEGF Injections. Ophthalmology. 2018 Sep;125(9):1386-1392. doi: 10.1016/j.ophtha.2018.02.034. Epub 2018 Mar 29. PMID: 29606377.
65. Obeid A, Su D, Patel SN, Uhr JH, Borkar D, Gao X, Fineman MS, Regillo CD, Maguire JI, Garg SJ, Hsu J. Outcomes of Eyes Lost to Follow-up with Proliferative Diabetic Retinopathy That Received Panretinal Photocoagulation versus Intravitreal Anti-Vascular Endothelial Growth Factor. Ophthalmology. 2019 Mar;126(3):407-413. doi: 10.1016/j.ophtha.2018.07.027. Epub 2018 Aug 2. PMID: 30077614.
66. Early photocoagulation for diabetic retinopathy. ETDRS report number 9. Early Treatment Diabetic Retinopathy Study Research Group. Ophthalmology. 1991 May;98(5 Suppl):766-85. PMID: 2062512.
67. Diabetic Retinopathy Clinical Research Network; Chew E, Strauber S, Beck R, Aiello LP, Antoszyk A, Bressler N, Browning D, Danis R, Fan J, Flaxel C, Friedman S, Glassman A, Kollman C, Lazarus H. Randomized trial of peribulbar triamcinolone acetonide with and without focal photocoagulation for mild diabetic macular edema: a pilot study. Ophthalmology. 2007 Jun;114(6):1190-6. doi: 10.1016/j.ophtha.2007.02.010. PMID: 17544778; PMCID: PMC2465806.
68. Diabetic Retinopathy Clinical Research Network; Elman MJ, Aiello LP, Beck RW, Bressler NM, Bressler SB, Edwards AR, Ferris FL 3rd, Friedman SM, Glassman AR, Miller KM, Scott IU, Stockdale CR, Sun JK. Randomized trial evaluating

ranibizumab plus prompt or deferred laser or triamcinolone plus prompt laser for diabetic macular edema. Ophthalmology. 2010 Jun;117(6):1064-1077.e35. doi: 10.1016/j.ophtha.2010.02.031. Epub 2010 Apr 28. PMID: 20427088; PMCID: PMC2937272.

69. Zhao XY, Xia S, Chen YX. Antivascular endothelial growth factor agents pretreatment before vitrectomy for complicated proliferative diabetic retinopathy: a meta-analysis of randomised controlled trials. Br J Ophthalmol. 2018 Aug;102(8):1077-1085. doi: 10.1136/bjophthalmol-2017-311344. Epub 2017 Dec 15. PMID: 29246890; PMCID: PMC6059039

70. Smith JM, Steel DH. Anti-vascular endothelial growth factor for prevention of postoperative vitreous cavity haemorrhage after vitrectomy for proliferative diabetic retinopathy. Cochrane Database Syst Rev. 2015 Aug 7;2015(8):CD008214. doi: 10.1002/14651858.CD008214.pub3. Update in: Cochrane Database Syst Rev. 2023 May 31;5:CD008214. doi: 10.1002/14651858.CD008214.pub4. PMID: 26250103; PMCID: PMC6599827.