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Short Article

Diabetic Retinopathy: Pathogenesis, Clinical Features and the Role of Physical Activity in Prevention and Management

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Abstract

Background

Diabetic retinopathy (DR) is a vision-threatening microvascular complication of diabetes mellitus that affects the retina and is classified into non-proliferative (NDPR) and proliferative (PDR) forms with diabetic macular edema (DME) representing an additional sight-threatening manifestation.

Aim

This study provides a comprehensive overview of diabetic retinopathy, integrating current knowledge of its pathogenesis, risk factors, clinical features, diagnostic methods, treatment options and potential impact of physical activity on disease prevention and progression.

Material and methods

This study was conducted as a review of the selected literature on diabetic retinopathy available in the PubMed database. Keywords included “Diabetic retinopathy”, “Nonproliferative diabetic retinopathy”, “Proliferative diabetic retinopathy”, “Glycemic control”, “ Physical activity”.

Results

Diabetic retinopathy can remain asymptomatic for long periods, making regular eye examinations essential for its early detection. Strict control of blood glucose and blood pressure helps prevent the onset and slow the progression of diabetic retinopathy with inflammation playing a central role in its pathogenesis. In addition, physical activity is associated with a reduced risk of DR with a particularly strong protective effect against vision-threatening diabetic retinopathy (VTDR). Current treatments include intravitreal corticosteroids, anti-VEGF agents, vitrectomy and laser photocoagulation. Early diagnosis combined with optimized management can significantly reduce the risk of permanent visual loss.

Conclusion

Diabetic retinopathy is a primary contributor to vision loss in working-age adults in developed countries. Growing insights into its pathogenesis and the discovery of new therapeutic targets offer promising opportunities for improved treatment.

Keywords

Diabetic retinopathy, Nonproliferative diabetic retinopathy, Proliferative diabetic retinopathy, Glycemic control, Physical activity

Introduction

Diabetes mellitus (DM) is a chronic endocrine disorder characterized by persistent hyperglycemia and is associated with a range of microvascular and macrovascular complications, leading to increased morbidity and mortality. It ranks among the most prevalent and rapidly increasing diseases worldwide with an estimated 693 million adults projected to be affected by 2045- an increase of over 50% since 2017 [1, 2]. At present, 70% of the DM cases are concentrated in low- and middle- income countries, where annual per capita healthcare spending averages only $20 [3]. DM results either from insufficient insulin production, as observed in type 1 diabetes (T1DM) or from impaired insulin action, as seen in type 2 diabetes (T2DM) [4]. T1DM is relatively uncommon compared to T2DM, which accounts for approximately 90% of all cases worldwide. The term “diabetes epidemic” is commonly used to describe the rapidly increasing prevalence of diabetes, primarily T2DM, in both developed and developing countries. This increase is largely driven by sedentary lifestyle, poor dietary habits and rising obesity rates. After 20 years of disease, nearly all patients with T1DM exhibit some degree of retinopathy. Similarly, approximately 80% of insulin-dependent and 50% of non-insulin-dependent T2DM patients develop retinopathy within the same duration [5].

Definition

Diabetic retinopathy (DR) is the most common microvascular complication of diabetes and a leading cause of preventable blindness worldwide. Key risk factors for disease development include prolonged diabetes duration, poor glycemic control- indicated by elevated HbA1c levels and hypertension. Although the associations between classical lipid biomarkers and diabetic retinopathy remain inconsistent, lipid-lowering therapies may offer potential therapeutic benefits [6,23,31]. DR represents a retinal microangiopathy characterized by diabetes-induced alterations in vascular wall integrity and blood rheology, which together promote capillary occlusion, retinal ischemia, realising of vascular endothelial growth factor (VEGF) and angiographically detectable vascular leakage [7,10]. The exact mechanisms by which hyperglycemia induces vascular damage are complex and not yet completely understood. High intracellular glucose is thought to promote reactive oxygen species production, which in turn disrupts multiple downstream pathways, including polyol pathway flux, advanced glycation end-product formation and activation, protein kinase C activation and hexosamine pathway flux [2,8]. DR is commonly classified into two main clinical forms: non-proliferative (NPDR) and proliferative (PDR). The disease follows a characteristic progression, beginning with NPDR and advancing to PDR as retinal ischemia and neovascularization intensify [9]. Involvement of the macula, which threatens the central vision is referred to as diabetic maculopathy. Excessive vascular permeability in this region leads to diabetic macular edema (DME), which is the leading cause of vision loss in diabetes. Although DME can occur at any stage of retinopathy, it is most often observed in the later phases of the disease [5,9].

Non-proliferative diabetic retinopathy (NPDR)

Early non-proliferative diabetic retinopathy (NPDR) is characterized by endothelial injury, microaneurysm formation, and dot-blot intraretinal hemorrhages. Microaneurysms are focal outpouchings of the capillary wall, typically located on the temporal side of the fovea and initially asymptomatic, although rupture can lead to intraretinal hemorrhages. Disruption of the blood-retinal barrier, accompanied by leakage of inflammatory cytokines and plasma proteins, results in hard exudates visible on fundoscopic examination and fluorescein angiography can demonstrate vascular leakage contributing to macular edema. As NPDR progresses from mild to severe, additional signs appear, including flame-shaped and blot hemorrhages, venous beading, and intraretinal microvascular anomalies, which are dilated telangiectatic capillaries adjacent to areas of capillary occlusion. Capillary non-perfusion and vasoconstriction lead to retinal ischemia, which is often observed as cotton-wool spots. In the advanced stage, severe hypoxia triggers pathological neovascularization, which may culminate in vitreous hemorrhage and tractional retinal detachment, marking progression to proliferative diabetic retinopathy [10,11].

Proliferative diabetic retinopathy PDR

Proliferative diabetic retinopathy (PDR) develops as retinal capillary hypoperfusion worsens, triggering neovascularization at the optic disc, elsewhere on the retina and occasionally on the iris. These fragile new vessels can cause vitreous hemorrhage and form fibrous membranes, whose contraction may lead to tractional retinal detachment or macular edema, both of which can result in vision loss. The most severe complication is neovascular glaucoma, in which abnormal vessels obstruct aqueous outflow, potentially causing painful blindness if untreated [10,12].

Macular edema

Macular edema can occur at any stage of NPDR or PDR and is mainly caused by leakage from compromised retinal vessels or microaneurysms, resulting in fluid accumulation, thickening and cystoid edema often accompanied by hard exudates. It is typically defined as retinal thickening within approximately two disc diameters of the fovea. Additional mechanisms include parafoveal ischemia, fibrovascular traction, hemorrhage and macular hole formation, all of which can impair central vision [13, 14].

Screening

DR screening aims to detect sight-threatening complications like proliferative retinopathy and macular edema before irreversible vision loss [15]. In individuals with T1DM, regular eye examinations should start five years after diagnosis or from age 11 and be performed annually unless retinopathy requires closer follow-up. Patients with T2DM should be referred for ophthalmological assessment at diagnosis with an eye examination conducted within three months due to the uncertain duration of the disease [10]. Ophthalmic imaging is the primary method for screening for DR. The 7-field stereoscopic photography is regarded as the gold standard reference, offering the advantages of extensive retinal coverage and a detailed grading system specifically developed for this technique. A key limitation associated with the procedure

is the proportion of unassessable records. Images obtained using this method can be evaluated either on-site or remotely via telemedicine, providing flexible and accessible evaluation across a range of healthcare settings. Alternatively, slit-lamp biomicroscopy performed by an ophthalmologist is another accepted reference standard [16,17]. Another important imaging technique is optical coherence tomography (OCT) which can evaluate retinal morphology with microscopic resolution. In patients with diabetes, OCT is particularly valuable for measuring and quantifying macular edema making it an essential tool in patient management [18]. As an adjunctive imaging modality, fluorescein angiography is used ,valuable for assessing macular ischemia, capillary nonperfusion, leaking microaneurysms in DME and suspected neovascularization [20].

The Role of Physical Activity

PA is a key component of lifestyle interventions in diabetes management that improves glycemic control as reflected by reductions in HbA1c, which is strongly correlated with DR status. By helping maintain optimal blood glucose levels, regular PA can delay the onset of DR and slow its progression. Higher physical activity levels are associated with a lower risk of DR with a particularly pronounced protective effect against vision-threatening DR (VTDR). Moderate-intensity exercise appears especially beneficial, whereas sedentary behavior significantly increases the risk of DR with some evidence suggesting that the harmful effects of inactivity may outweigh the benefits of PA. Vigorous exercise, especially activities involving Valsalva-type maneuvers can transiently elevate systolic blood pressure and potentially increase the risk of ocular hemorrhage indicating that anaerobic or very intense exercise may carry specific risks compared with aerobic activity. PA also directly influences the retinal microvasculature by modulating retinal blood flow. Beyond glycemic regulation, exercise exerts antioxidant and anti-inflammatory effects counteracting oxidative stress and inflammation, which are key contributors to DR pathogenesis, thus providing additional protective mechanisms for the retinal health [21].

Therapeutic Strategies

Strict control of blood glucose levels and arterial blood pressure is essential to prevent the onset of DR and slow its progression. Emerging evidence indicates that inflammation plays a key role in DR pathogenesis [22]. Increased levels of vitreous inflammatory cytokines such as IL-6, VEGF, MCP-1, and IP-10 have been positively associated with both disease progression and DME severity [25].

Several therapeutic options are currently available for DR including intravitreal corticosteroids, anti-vascular endothelial growth factor (anti-VEGF) agents, vitrectomy and laser photocoagulation. For patients with severe NPDR or PDR, current guidelines recommend argon laser photocoagulation in combination with intravitreal anti-VEGF injections, whereas focal laser therapy is used selectively for DME. Panretinal photocoagulation (PRP) has been shown to reduce the risk of severe vision loss by approximately 60% over two years, particularly in patients with PDR [26].

Recent advances in laser technology, including pattern-scanning laser systems, have improved the treatment efficiency and patient comfort. Preliminary studies also suggest that subthreshold diode laser therapy and navigated laser systems (e.g., NAVILAS) may be beneficial in treating DME offering targeted therapy while minimizing retinal damage [27].

Vitrectomy remains an important surgical intervention for DR, especially in cases with non-clearing vitreous hemorrhage, tractional retinal detachment or extensive fibrovascular proliferation. The procedure involves the removal of the vitreous gel which occupies approximately two-thirds of the eye between the lens and retina. By excising the vitreous, vitrectomy can prevent recurrent hemorrhage and remove pathological neovascular tissue along with the associated fibrotic membranes. Although generally effective, the procedure is invasive and may be associated with complications such as postoperative hemorrhage, infection, retinal tears, cataract formation, and retinal detachment [27,28].

Pharmacological advances have significantly expanded the treatment options for DR. Intravitreal anti-VEGF agents and corticosteroids are the mainstay of medical therapy and pegaptanib, ranibizumab, bevacizumab and aflibercept have been extensively studied for their efficacy. However, conventional therapies are limited by nonspecific drug distribution, rapid clearance, suboptimal ocular absorption, and reduced bioavailability. To overcome these challenges, research has increasingly focused on nanocarrier-based drug delivery systems (DDSs). Nanotechnology offers multiple advantages, including enhanced ocular penetration, prolonged retention, sustained drug release and improved targeting. Various polymeric and lipid-based nanocarriers have been investigated to optimize ocular drug delivery systems. These systems also enable combination drug delivery in a single administration, reducing the need for repeated injections and invasive procedures while providing prolonged therapeutic effects [27,29].

Despite these advances, a subset of patients with DR continues to respond poorly to existing therapies, underscoring the need for more effective treatment strategies in this patient population. Progress in molecular biomarker-based analytical techniques is further enhancing our understanding of DR pathophysiology and may guide the development of novel therapeutic approaches [24].

CONCLUSION

The global increase in diabetes has intensified the need for the early prevention of DR and other complications. DR is an increasingly common cause of vision loss among working-age adults and delayed diagnosis can lead to severe and irreversible outcomes [30]. Given its substantial public health impact, strengthening primary and secondary prevention strategies is essential. Optimal management includes strict glycemic and blood pressure control, supported by lifestyle interventions such as weight loss, regular physical activity and healthy nutrition, which reduce the risk of diabetes and its complications. As DR often remains asymptomatic for prolonged periods, regular ophthalmological screening is crucial for early detection [9,19].

Disclosure

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