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DIABETIC RETINAL NEURODEGENERATION

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Abstract

Diabetic retinopathy (DR) is widely recognized as one of the leading causes of blindness and low vision among people of working age. Its high prevalence among patients with diabetes mellitus (DM) makes this disease a key problem in ophthalmology. Diagnosis and grading of DR are traditionally based on the detection of vascular changes in the retina: microaneurysms, hemorrhages, avascular zones and neovascularization. These signs serve as important markers for assessing the severity of the disease and choosing treatment tactics.

However, in recent decades, research has significantly expanded our understanding of the pathogenesis of DR. Compelling evidence has accumulated indicating that retinal neurodegeneration may precede vascular changes. This early neuronal damage includes dysfunction and death of retinal ganglion cells, changes in photoreceptors, and activation of microglia, indicating the complex nature of the disease. Oxidative stress, inflammation, and impaired glucose metabolism are key triggers for these changes.

The early onset of neurodegeneration suggests that damage to neural tissue may play an equally important role in the progression of DR as vascular disorders. Moreover, neurodegeneration is considered as an independent therapeutic target, which opens up new prospects for the development of treatment methods. Neuroprotective approaches aimed at preserving neuronal function are already attracting the attention of researchers, and their inclusion in therapeutic strategies may significantly improve treatment outcomes.

Introduction

Diabetes mellitus (DM) continues to rapidly spread worldwide, becoming one of the most significant global epidemics of the 21st century. According to the International Diabetes Federation (IDF), in 2021, the number of people with diabetes exceeded 537 million, and projections indicate a possible increase to 783 million by 2045. The increase in diabetes incidence is associated with both increasing life expectancy and global lifestyle changes, including decreased physical activity, increased body weight, and poor diet [1].

Diabetic retinopathy (DR), one of the most severe complications of diabetes, remains the leading cause of blindness and visual impairment among people of working age. It is estimated that about one third of patients with diabetes have some degree of retinopathy, and 10% of them develop vision-threatening forms of the disease, such as proliferative diabetic retinopathy or diabetic

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macular edema. In developed countries, DR is the leading cause of vision loss, especially in patients aged 20 to 64 years [2].

In addition to the personal health consequences of patients, diabetes and its complications, including DR, have a significant impact on society and the economy. Reduced vision or blindness makes it difficult to perform daily tasks, limits work capacity, and reduces quality of life. This leads to additional costs for medical care, rehabilitation, and social security [3].

Given the scale of the problem, the World Health Organization (WHO) and other international organizations emphasize the importance of prevention, early detection, and effective treatment of diabetic retinopathy. Innovative technologies such as automated screening systems, neuroprotection methods , and anti-VEGF therapy offer new opportunities to combat this complication, which is especially relevant in the context of the growing diabetes epidemic[4].

According to traditional concepts, diabetic retinopathy was considered and is still perceived as a disease affecting the microcirculatory bed of the retina. Diagnosis and staging of DR are also based on the detection of microvascular changes: microaneurysms , cotton-wool spots, intraretinal hemorrhages, venous loops and tortuosity, intraretinal microvascular anomalies (IRMA) and newly formed vessels [5]. However, modern diagnostic methods, such as optical coherence tomography (OCT) and OCT angiography, allow a more accurate assessment of the state of the retina, revealing not only minimal changes at the microvascular level, but also changes that are not recorded by ophthalmoscopy. Among them are changes such as neurodegeneration and damage to glial cells, which also play an important role in the pathogenesis of the disease [6, 7].

Thus, although DR continues to be viewed through the lens of microcirculatory disorders, the integration of data on neurodegenerative and inflammatory processes helps to better understand the mechanisms of disease development and suggests new therapeutic approaches.

The stage of diabetic retinopathy (DR) plays a key role in determining the treatment tactics and frequency of patient observations. As the disease progresses, the risk of vision loss increases significantly, which makes early diagnosis and classification of DR extremely important. Dividing the disease into stages allows for an effective assessment of the degree of retinal damage, predicting the development of complications, and developing individualized recommendations for each patient.

A study conducted on the basis of the Intelligent registry Research inSight (IRIS) study of the American Academy of Ophthalmology confirmed the importance of the initial stage of DR as a predictor of subsequent vision loss. The data showed that in patients with good visual acuity at diagnosis, the severity of DR was already a significant risk factor for developing blindness or low vision. This highlights the clinical importance of the DR classification and its use for long-term treatment planning. This study highlights the need for strict adherence to surveillance recommendations, as timely diagnosis and treatment can significantly reduce the risk of vision loss. The introduction of a systematic approach based on the DR classification helps to improve the effectiveness of treatment and the prognosis for patients [8].

In recent years, increasing evidence has accumulated indicating that retinal neurodegeneration is an additional and important component in the development of diabetic retinopathy. It is clearly evident that diabetic retinal neurodegeneration may precede vascular manifestations of the disease [9]. Studying early, "preclinical" manifestations of diabetic retinopathy, their onset, pathogenetic mechanisms and progression will open up new opportunities for early diagnosis and treatment. This review will examine evidence of early retinal neurodegeneration in patients with diabetes,

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analyze experimental models, propose possible molecular mechanisms and cell types involved in this process, and focus on the implications for the diagnosis and therapy of diabetic retinopathy.

Retinal neurodegeneration in the early and preclinical stages of DR . More recently, we have used ophthalmoscopy, fundus photography, and fluorescein angiography to detect signs of DR. In many countries, the diagnostic criteria for DR are based on these instruments. The advent of optical coherence tomography (OCT) has significantly changed and expanded our understanding of DR and its progression. Optical coherence tomography and, more recently, angio-OCT have allowed non-invasive and rapid cross-sectional imaging of the retina, revealing changes in its structure even before signs of DR appear. Many studies now use OCT to demonstrate thinning of the inner retinal layers such as the retinal nerve fiber layer (RNFL), ganglion cell layer (GCL), and in some cases the inner plexiform layer (IPL) in patients with type 1 and type 2 diabetes, as well as in other diseases. Thinning of the retinal layers in patients with diabetes is often recorded even before visible changes appear on the retina [10; 11]. Similar changes in the retinal structure were recorded not only in the macular region. A decrease in the thickness of the peripapillary retinal nerve fiber layer was recorded in patients with and without diabetic retinopathy. Moreover, the thickness of the peripapillary retinal nerve fiber layer inversely correlates with the level of glycated hemoglobin (HbA1c), the duration of diabetes, and the severity of retinopathy [12; 13].

In addition to the thinning of the inner retinal layers, diabetic patients without diabetic retinopathy or with very early manifestations of it also experience functional impairments such as decreased contrast sensitivity, abnormalities in perimetric test results, multifocal electroretinogram (mfERG) and dark adaptation [14; 15]. A correlation was found between ganglion cell layer (GCL) thinning and visual field deficits on perimetry in patients with type 1 DM without signs of retinopathy [16]. Another recent large cohort study of patients with DM demonstrated an association between functional impairments detected by perimetry and mesopic microperimetry, and retinal ganglion cell number as measured by OCT [17]. However, although Park J . C . et al. showed decreased microperimetry sensitivity and thinning of the inner retinal layers (including the GCL/IPL/inner nuclear layer complex in their study) in patients with type 2 diabetes with or without early signs of DR, the relationship between these functional and structural changes was weak. This suggests that early retinal dysfunction in diabetes may be caused by factors other than retinal thinning [18]. One example is disorganization of the inner retinal layers (DRIL), which can independently cause visual field and contrast sensitivity deficits in patients with diabetes [19].

It is noteworthy that neuronal dysfunction in the early stages of diabetic retinal damage may contribute to the subsequent development and progression of diabetic retinopathy. It was found that deterioration of ERG parameters was accompanied by the subsequent development of DR within a year. Also, progressive thinning of the RNFL and GCL in patients with type 1 diabetes without signs of DR was accompanied by the appearance of DR over the next 6 years [20; 21].

In conclusion, it can be noted that the decrease in the thickness of the inner retinal layers and the deterioration of visual functions occur in patients with diabetes mellitus even before the appearance of clinical signs of diabetic retinopathy. This indicates the presence of a neurodegenerative component in the development of retinal disease, which may be either independent of vascular changes or accompany them.

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Pathogenetic mechanisms of diabetic retinal neurodegeneration

Data from various animal models, in vitro experiments , and, most importantly, from the ocular fluids of diabetic patients have identified various molecular mechanisms that may be responsible for retinal neuronal damage in diabetes. Some of these pathways have long been associated with the pathogenesis of diabetic retinopathy, but recent studies link them more specifically to retinal neurodegeneration.

Hyperglycemia can cause cellular damage through activation of protein kinase C (PKC), oxidative stress, upregulation of the polyol pathway of glucose oxidation, in which glucose is converted to sorbitol via aldose reductase, and formation of advanced glycation end products (AGEs). A study in streptozotocin-induced diabetes in rats demonstrated that mitochondrial swelling in retinal ganglion cells and decreased retinal superoxide dismutase activity were observed 4 weeks after induction of hyperglycemia, suggesting that oxidative stress may contribute to retinal ganglion cell death [22].

The inflammatory component of DR development in diabetes mellitus (DM) has been well studied, and there is a large body of evidence for the pathological role of inflammation in retinal damage. Activation of microglia and increased expression of proinflammatory proteins have been detected in the retina of streptozocin- treated rats. cytokines such as TNF-alpha and IL-1beta. Activated microglia produced substances capable of inducing retinal neuronal death in cell cultures. Furthermore, histological analysis of the retina of postmortem samples from patients with different stages of DR also showed microglia activation. A recent study found that streptozocin- induced diabetes in animals aggravates retinal ganglion cell dysfunction and loss, and is accompanied by increased expression of oxidative stress markers, as well as IL-6 and TNF-alpha. Finally, several studies have found increased levels of inflammatory cytokines such as TNF-alpha, IL-6, IL-1beta and MCP in the aqueous humor or vitreous of patients at different stages of diabetic retinopathy, further emphasizing the role of inflammation in the pathogenesis of diabetic retinal disease [23; 24; 25].

Decreases in the thickness of the RNFL, GCL, and GC/IPL complexes detected by OCT in diabetic patients have been associated with diabetic peripheral neuropathy, suggesting similarities in key molecular mechanisms of neuronal injury [20]. Particularly in light of the growing evidence describing inner retinal thinning in patients with Alzheimer's and Parkinson's disease, there is interest in possible parallels in the molecular mechanisms involved in these neurodegenerative diseases [26]. One possible common cause may be glutamate excitotoxicity, which causes cell death in postsynaptic neurons through multiple molecular pathways due to increased intracellular calcium levels. In rats with streptozocin- induced hyperglycemia, elevated retinal glutamate levels were detected after 3 months, likely due to decreased expression of the glutamate transporter and impaired uptake by Müller cells, as well as decreased conversion of glutamate to glutamine by Müller glia [27]. Elevated glutamate levels have also been found in the vitreous of patients with proliferative diabetic retinopathy [28]. In addition, a study by ZhuH, ZhangW , ZhaoY , et al . found elevated levels of phosphorylated tau protein in the retina of mice fed a high-fat diet, which correlated with dysregulation of synaptic proteins. Their results, both in a high -fat diet mouse model and in primary RGC cells in culture, showed an upregulation of the IRS-1/ Akt /GSK3b signaling pathway in early diabetic neuronal dysfunction [29]. Also, diabetic rats treated with streptozocin showed increased staining for key components of pathways regulating mitochondrial dynamics, which has been well studied in the context of Parkinson's disease [30].

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Conclusions

The use of high-tech and sensitive devices for assessing the retinal structure in patients with diabetes without signs of diabetic retinopathy continues to demonstrate the complexity of diabetic retinal damage and expands our understanding of the impact of diabetes on this organ. Although the traditional concept of DR, its diagnosis and staging, as well as existing therapeutic methods are based on the hypothesis of vascular genesis of this disease, it is now becoming apparent that thinning of the inner retinal layers occurs in patients with diabetes even before the detection of clinical signs of DR. This indicates that diabetic retinal neurodegeneration is a significant and, possibly, an independent manifestation of diabetic damage, and, possibly, its early stage. Studies in animal models and analysis of intraocular fluid in patients with diabetes have identified key molecular mechanisms, such as oxidative stress, hyperglycemic formation of advanced glycation end products, glutamate excitotoxicity and inflammation, which can cause dysfunction and death of retinal neurons. Targeting these pathways or administering neurotrophic factors may offer neuroprotective strategies. OCT angiography has provided a more detailed view of the retinal capillary networks and has demonstrated preclinical vascular changes in patients with DS. However, it remains unclear whether these vascular abnormalities precede, follow, or occur simultaneously with neuronal degeneration. Despite this, current diagnostic criteria for DR do not take into account these early “preclinical” retinal changes, which not only affect visual function but may also contribute to the subsequent development of DR. Recognition and understanding of retinal neurodegeneration in DS may open opportunities for earlier diagnosis and development of new treatment approaches, ultimately helping to reduce the incidence of blindness caused by this serious disorder.

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