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DIABETIC RETINOPATHY AND RETINAL VASCULAR DISEASES

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Abstract

According to WHO, the number of people living with diabetes has increased from 200 to 830 million in the past thirty-five years (since 1990). In 2020, more than a million people became blind due to diabetic retinopathy (DR), and almost 3.28 million suffered from moderate to severe visual impairment (MSI). DR is recognized as one of the most common causes of blindness and visual impairment among the working-age population worldwide. At the same time, early detection and treatment of MVI can reduce the risk of severe vision loss by approximately 90 percent.

The scientific novelty of the article is that it substantiates the need for a combination of anti-VEGF, glucocorticosteroids, laser therapy and systemic treatment, taking into account the pathogenesis features of a particular patient. Particular attention is paid to the development of prolonged forms of anti-VEGF delivery, including implants - a direction that has strategic importance in reducing the frequency of injections. The article emphasizes the relationship between molecular, inflammatory, hemodynamic and neurovascular mechanisms in the development of diabetic retinopathy.

Keywords: Diabetic retinopathy, diabetes mellitus (DM), hyperglycemia, diabetic macular edema (DME), blood-retinal barrier (BRB), VEGF, cytokines, chemokines, angiopoietin-2, panretinal photocoagulation.

Introduction

Diabetes mellitus, hypertension, hyperlipidemia, obesity, smoking - all these factors contribute to the development of DR and other retinal vascular diseases. There is a close connection between retinal vascular diseases and diabetic

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retinopathy (DR), since diabetic retinopathy is one of the forms of retinopathy associated with damage to the retinal vessels. DR develops against the background of chronic hyperglycemia, which causes endothelial dysfunction, damage to pericytes and increased vascular permeability. It is based on microangiopathy - damage to small blood vessels of the retina. This is a classic example of retinal vascular pathology, along with occlusions of the veins and arteries of the retina.

Oxidative stress, inflammation, neovascularization and tissue hypoxia are common features between DR, retinal vein occlusions (CRVO/BRVO), hypertensive retinopathy and age-related macular degeneration (in its neovascular form). Increased levels of VEGF (vascular endothelial growth factor) play a key role in both DR and other retinal vasculopathies.

1. Molecular mechanisms of pathogenesis of diabetic retinopathy

Recent advances in understanding the complex pathophysiology of DR have allowed the identification of many cell types involved in the pathogenesis.

VEGF. Vascular endothelial growth factor (VEGF) is the most widely studied factor in altering the blood-retinal barrier (BRB). VEGF levels are significantly elevated in patients with DME compared to non-diabetic eye diseases. VEGF is a potent vasoactive cytokine that causes increased vascular permeability. It affects endothelial tight junction proteins, leading to plasma leakage and retinal edema. Studies have shown that it induces phosphorylation of VE-cadherin, occludin, and ZO-1, thereby further causing barrier disruption. VEGF also stimulates increased leukostasis in retinal microvessels, and subsequently leukocytes release cytokines that cause BRB disruption.

Cytokines. The role of inflammation in the development and progression of DR has been studied for a long time, but currently the number of studies in this area is growing. This is explained by the importance of molecular mechanisms for the development of new therapeutic approaches and treatments.

There are common sets of inflammatory cytokines that are elevated in both serum and vitreous and aqueous humor samples in patients with DR, and these cytokines may have multiple interactions that influence disease pathogenesis.

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Hyperglycemia. The pathogenesis of hyperglycemia-induced DR involves four major biochemical changes: increased polyol pathway flux; increased formation of advanced glycation end products; activation of protein kinase C isoforms; and increased hexosamine flux. These pathways lead to vascular dysfunction and inflammation, followed by increased vascular permeability, vascular occlusion, and focal ischemia. In addition, these processes upregulate proangiogenic and inflammatory factors such as VEGF, insulin-like growth factor (IGF), angiopoietins (Ang-2), stromal-derived growth factor-1 (SDF-1), basic fibroblast growth factor-2 (bFGF), hepatocyte growth factor (HGF), tumor necrosis factor (TNF), and interleukin (IL-6).

Chemokines. Complex scientific studies conducted at different periods using a panel of cytokines have shown that the levels of IL-6, IL-8 (CXCL8), IL-10 (CXCL10), IL-13, IP-10, MCP-1 (CCL2), MIP-1β (CCL4), PDGF and VEGF in the vitreous fluid are significantly higher than normal in patients with DR. In addition, inflammatory factors IP-10 and MCP-1 were detected in tears of patients with DM. However, selective blockade of VEGF by injections of bevacizumab (anti-VEGF) does not affect the control of other immunogenic cytokines, such as MCP-1 and IL-6 in the aqueous humor. Monocyte chemotactic protein-1 (MCP-1), also known as chemokine ligand 2 (CCL2), is produced by retinal vascular endothelial cells, pigment epithelial cells, and Müller glial cells in response to hyperglycemia.

Research conducted in the laboratory led by N. Katakami showed that genetic knockout of the CCL2 gene in diabetic mice prevents changes in BHR. The findings suggest that selective inhibition of the CCL2 gene can prevent changes in BHR.

Leukostasis. S. Schröder first described leukostasis in the retinal vasculature as an important phenomenon associated with increased numbers of neutrophils and monocytes, which are associated with retinal vascular abnormalities in rat models of diabetes. Increased neutrophil density has been found in the retinal vasculature in diabetes, particularly around the optic disc and macula. Leukocyte adhesion in the diabetic retina is promoted by increased expression of adhesion molecules such as ICAM-1 and P-selectin on the endothelium and its leukocyte counter-

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receptor CD18. This leads to endothelial cell loss and destruction of the intrinsic BHR. Normal intrinsic BHR is impermeable to leukocytes, but leukocyte activation results in its transient disintegration, which becomes
an impetus to strengthen the pro-inflammatory reaction in the retina of the eye.

Angiopoietins are a family of inflammatory growth factors. They bind to the receptor tyrosine kinase TIE2 and are important modulators of angiogenesis. Vitreous angiopoietin-2 (Ang-2) levels are significantly elevated in patients with clinically significant macular edema, suggesting a role for angiopoietin-2 in modulating BHR.

There is increased expression of Ang-2 mRNA and proteins in the retina of animals with diabetes. In addition, scientists administered Ang-2 intravitreal to rats without diabetes, which showed a threefold increase in retinal vascular permeability.

Other studies have shown that Ang-2 promotes monocyte adhesion by sensitizing endothelial cells to TNF-α and modulates TNF-α-induced endothelial cell adhesion molecule expression and induces loss of VE-cadherin. This finding identifies Ang-2 as an autocrine regulator of endothelial cell inflammatory responses, thereby becoming an important therapeutic target for the treatment of patients with DR.

Hemodynamic changes. Many scientific papers describe the high frequency of detection of arterial hypertension in individuals with SD. It has been established, that after successful photocoagulation, the blood flow to the retina decreases, which was interpreted as correction of hemodynamic autoregulation.

Arterial hypertension influences the progression of DR through two mechanisms. First, mechanical stretch and sheer tension, exerted on endothelial cells by high blood pressure and increased retinal perfusion, and also higher blood viscosity, lead to endothelial dysfunction. Secondly, the renin-angiotensin-aldosterone system (RAAS), involved in regulation of blood pressure, also independently involved in pathogenesis DR. It also turned out that that the expression of RAAS receptors and signaling molecules, namely renin, angiotensin-converting enzymes I and II (ACE I and ACE II), and angiotensin receptors, is increased in

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the retina of patients with DR. These data provide new insights into the value of RAAS blockade as a new treatment for DR.

Disturbances in the BHR are a hallmark of the pathogenesis of DR. Normally, this barrier at the level of retinal capillaries includes endothelial intercellular junctions, the basement membrane, and pericytes that coat the vessels externally. In DM, the following changes occur: loss of endothelial intercellular junctions, thickening of the basement membrane, and selective loss of pericytes. The latter is one of the early histopathological lesions observed in DR. Normally, pericytes (modified smooth muscle cells) contract and maintain capillary blood flow in the retina. Their loss leads to focal weakening of the capillary wall, as well as uninhibited focal proliferation of endothelial cells, which causes the formation of microaneurysms. Later, endothelial cells also die, which causes impaired retinal perfusion. The breakdown of the BHR leads to intraretinal hemorrhages, hard exudates, and macular edema.

2. Prevention and treatment of DR: systemic factors and targeted therapy

Strict glycemic and blood pressure (BP) control is the basis for preventing and slowing the progression of ocular complications of diabetes mellitus (DM). Large studies have shown that a decrease in glycated hemoglobin levels (<6.5%) is associated with a low risk of developing retinopathy. In the DCCT study in patients with type 1 DM, intensive glycemic control reduced the progression of DR by 76%. Blood pressure control is also important: in the UKPDS it reduced the risk of vision loss, but the ACCORD Eye study did not confirm a significant effect. In terms of lipid metabolism, a link has been established between high LDL and triglyceride levels and the severity of DR. Fenofibrate (200 mg/day) in combination with statins (ACCORD Eye) slows the progression of DR and reduces the need for laser therapy. The target blood pressure is below 140 mmHg.

Anti-VEGF therapy. Intravitreal drugs that inhibit VEGF have become the mainstay of therapy for diabetic macular edema (DME). Ranibizumab (Lucentis), pegaptanib (Macugen), and bevacizumab (Avastin) are effective in reducing swelling and improving visual acuity. Large studies (READ-2, RESTORE, RISE, RIDE, BOLT) have confirmed the effectiveness of ranibizumab and bevacizumab

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monotherapy compared with laser therapy. Aflibercept has a potentially longer-lasting effect.

The use of anti-VEGF agents has significantly improved the treatment options for DR. However, the use of focal/retinal macular laser therapy still plays a crucial role in the treatment of this disease.

Glucocorticosteroids (eg, triamcinolone) have anti-inflammatory and anti-VEGF effects. In some cases, they are comparable in efficacy to ranibizumab, especially in combination with laser. However, their use is limited by the risk of cataracts and increased IOP. In the FAME study, intravitreal fluocinolone acetonide improved vision in DME, especially chronic DME, but was associated with complications, including glaucoma.

Because of the need for frequent anti-VEGF injections, studies are underway on prolonged forms: biodegradable implants, microspheres, and drug delivery systems. A phase I clinical trial showed that a non-degradable ranibizumab implant provided stable vision improvement over a year **.**

Panretinal photocoagulation (PRP) remains the current standard treatment for DR and significantly reduces the risk of vision loss. There is strong evidence for the use of focal macular laser photocoagulation to prevent vision loss due to DME. In this procedure, larger, higher intensity burns (500 μm) are placed in the mid-periphery of the retina over 360° in one or two sessions. The treatment causes regression of new vessels in about six weeks, but side effects should be considered, namely worsening of pre-existing macular edema and impairment of peripheral retinal function and night vision.

The use of PRP has not changed fundamentally until the introduction of PASCAL in recent years. The goal of this device was to reduce the time of laser treatment and reduce patient pain by reduction of stimulation ciliary nerves in the choroid, while providing the same therapeutic results. S. Al-Hussainy et al. in their studies found that PASCAL requires a shorter duration of photocoagulation, but higher power, which was shown to actually reduce pain in patients with similar results compared to traditional PRP.

Despite significant advances in conservative therapy in the treatment of DR, surgery remains an indispensable treatment option for patients with

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complications, including non-resolving vitreous hemorrhages and tractional retinal detachments.

3. Review of modern diagnostic methods

Prevention of vision loss requires a better understanding of the fundamental processes that impair vision and improved diagnostic tests that can define parameters to assess response to pharmacological intervention. Retinal dysfunction in diabetes begins before the onset of microvascular lesions. Recent technological advances allow new imaging techniques to be applied to retinal diseases in clinical practice.

Dilated fundoscopy is the most important clinical examination in patients with diabetes during screening examination by an ophthalmologist. Pupil dilation is necessary to ensure correct stereoscopic image, which is necessary for assessing macular edema, as well as for visualization of the peripheral part of the retina.

Ultra-wide-field (up to 200°) scanning laser ophthalmoscopy , using two lasers and without mydriasis, is a modern and effective method for retinal imaging. It can be supplemented with fluorescein angiography to assess peripheral ischemia and neovascularization, which is especially important in diabetic retinopathy. According to recent studies, wide-field images and traditional color fundus photography with mydriasis correlate with DR classification and DME visualization.

Optical coherence tomography (OCT) is a diagnostic examination of the eye structures using special equipment - a coherence tomograph. The examination provides data on the volume of the retina and the configuration of the macular area. In recent years, the resolution and recording speed have been significantly improved using the method

Spectral domain OCT (SD-OCT). The high resolution available with spectral domain OCT allows detailed study of the retinal layers and cells in SD and its response to treatment. In DME, SD-OCT is a very valuable diagnostic tool to compare follow-up visits with baseline data, as modern OCT devices use eye tracking to find the same image position during follow-up examinations. Macular

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thickness maps and OCT images provide guidance for determining response to anti-VEGF and macular laser therapy and are widely used in large clinical trials.

Artificial Intelligence and Automated Screening: In recent years, the diagnosis of diabetic retinopathy (DR) and diabetic macular edema (DME) has advanced significantly thanks to the introduction of new imaging technologies and artificial intelligence (AI).

Automated platforms based on artificial intelligence (AI) algorithms are successfully integrated into screening programs. **The IDx-DR (** FDA, USA) and **EyeArt systems** have demonstrated high sensitivity (>90%) and specificity (>85%) in large multicenter studies in 2022-2024. Their use allows for autonomous analysis of digital fundus images and the detection of referable DR without the participation of a physician, which is especially important in regions with limited access to ophthalmological care.

Optical coherence tomography angiography (OCT-A) has become an important tool in the assessment of retinal microcirculation in DR. Unlike fluorescein angiography, the method does not require intravenous contrast, providing high resolution and safety for repeated examinations. OCT-A allows visualization of areas of capillary nonperfusion, microneovascularization, and early vascular changes in the macular region, previously inaccessible to other methods.

Since 2024, there has been an increase in the use of **portable retinal cameras** (Peek Retina, Remidio FOP), compact OCT devices, and mobile applications compatible with smartphones. In combination with cloud platforms (e.g. EyePACS, CloudRetina™), this has enabled the introduction of remote DR screening in remote and socially vulnerable populations with low ophthalmological surveillance coverage.

Recent studies show that in diabetes, dysfunction of neuronal elements of the retina (in particular, ganglion cells) occurs before visible vascular damage occurs. SD-OCT allows us to assess the thickness of the inner nuclear layer and the nerve fiber layer as potential biomarkers of early diabetic neurodegeneration. This opens the way to identifying so-called subclinical (invisible) retinopathy and highlights the need to revise the criteria for initiating therapy.

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