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RETINA CHANGES IN DIABETES: MORPHOLOGICAL, MICROANGIOPATHIC AND MOLECULAR MECHANISMS AND BIOCHEMICAL SIGNIFICANCE OF USED DRUGS

Norboyev Davlatjon

2nd year student of the Faculty of Medicine No. 2 of Tashkent State Medical University

Jumayev Shahzodbek

2nd year student of the Faculty of Medicine No. 2 of Tashkent State Medical University

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ANNOTATION: Diabetes mellitus (DM) is a chronic metabolic disease , one of the most severe and clinically significant complications of which is diabetic retinopathy. This article comprehensively analyzes the morphological, microangiopathic and molecular changes that occur in the retina of the eye in diabetes. The role of thickening of the basement membrane of retinal capillaries, selective loss of pericytes, endothelial dysfunction, capillary occlusion, ischemia and hypoxia in the pathogenesis is highlighted. Also, the mechanisms of pathological neovascularization caused by oxidative stress, glucose polyol pathway, advanced glycation end products (AGE), protein kinase C (PKC) activation, and VEGF were scientifically described. The article analyzes the biochemical mechanisms of action of anti-VEGF drugs, corticosteroids, antioxidant and angioprotective drugs used in the treatment of diabetic retinopathy, and shows their importance in improving retinal microcirculation and slowing disease progression. The obtained data serve as a scientific basis for early diagnosis of diabetic retinopathy, pathogenesis-oriented therapy , and improvement of preventive approaches.

KEYWORDS: diabetes; diabetic retinopathy; retina; microangiopathy; pericytes; capillary basement membrane; oxidative stress; advanced glycation end products (AGE); protein kinase C (PKC); VEGF; neovascularization; diabetic macular edema; anti-VEGF drugs; microcirculation.

ABSTRACT: Diabetes mellitus is a chronic metabolic disorder and one of its most severe microvascular complications is diabetic retinopathy, which represents a leading cause of visual impairment and irreversible blindness worldwide. This article provides a comprehensive analysis of morphological, microangiopathic, and molecular changes occurring in the retinal tissue under diabetic conditions. Particular attention is given to thickening of the capillary basement membrane, selective loss of pericytes, endothelial dysfunction, capillary occlusion, retinal ischemia, and hypoxia. The molecular mechanisms underlying diabetic retinopathy, including oxidative stress, activation of the polyol pathway, accumulation of advanced glycation end products (AGEs), protein kinase C (PKC) signaling dysregulation, and hypoxia-induced overexpression of vascular endothelial growth factor (VEGF), are systematically reviewed. In addition, the biochemical significance of pharmacological agents used in the treatment of diabetic retinopathy—such as anti-VEGF agents, corticosteroids, antioxidants, and angioprotective drugs—is discussed in relation to their targeted effects on pathogenic pathways. The findings highlight the importance of early diagnosis, pathogenetically oriented therapy, and continuous metabolic control in preventing disease progression and preserving visual function.

ENTRANCE

is currently one of the most common chronic endocrine-metabolic diseases in the world , and its prevalence is increasing every year. According to the World Health Organization, diabetes mellitus is recognized as one of the global health problems. Prolonged and insufficiently controlled hyperglycemia of diabetes mellitus leads to the development of micro- and macroangiopathic complications in the body. Among these complications, diabetic retinopathy, which can lead to vision loss and irreversible blindness, is of particular clinical and social importance. [5]

retina is a neuroectodermal tissue with high metabolic activity, which requires a constant and sufficient supply of oxygen and energy substrates. In diabetes, impaired glucose metabolism causes structural and functional changes in the endothelium of retinal vessels. As a result, the permeability of the capillary walls increases, microcirculation is disrupted , and tissue hypoxia develops. These processes lead to damage and degeneration of retinal cells. In addition to morphological and microangiopathic changes, complex mechanisms at the molecular level play an important role in the pathogenesis of diabetic retinopathy. Increased oxidative stress, accumulation of advanced glycation end products (AGEs), activation of the polyol pathway, disruption of the protein kinase C (PKC) signaling system, and hypoxia-induced expression of VEGF (vascular endothelial growth factor) constitute the main chain of retinal vascular pathology. [2] These molecular processes lead to pathological neovascularization, hemorrhages, and fibrovascular proliferation, accelerating the progression of the disease to severe stages. In recent years, pathogenesis-oriented pharmacological approaches have been widely used in the treatment of diabetic retinopathy. Anti-VEGF drugs, corticosteroids, antioxidants , and angioprotective agents affect the main links in the development of retinal microangiopathy, allowing to slow down the progression of the disease. At the same time, a deep study of the morphological and molecular mechanisms of diabetic retinopathy serves as an important scientific basis for the development of new therapeutic strategies. [4]

The purpose of this article is to systematically analyze the morphological, microangiopathic, and molecular changes that occur in retinal tissue in diabetes mellitus, as well as to evaluate the biochemical significance of drugs used in diabetic retinopathy.

LITERATURE REVIEW

Early fundamental research (Ashton, 1960) described the selective loss of pericytes in retinal capillaries in diabetic patients as a pathognomonic feature of the disease. This change disrupts the stability of the capillary walls and predisposes to the development of microaneurysms and hemorrhages. [1]

have shown that one of the main morphological features of retinal microangiopathy is thickening of the capillary basement membrane . Histological and electron microscopic studies (Kern & Engerman, 1996) have confirmed that the basement membrane thickens due to collagen IV and laminin, which leads to impaired diffusion of oxygen and metabolites. As a result, chronic hypoxia develops in the retinal tissue and pathological molecular response mechanisms are activated. [4]

Molecular biological studies conducted in recent decades have demonstrated the central role of oxidative stress in the development of diabetic retinopathy. Excessive production of reactive oxygen species (ROS) under hyperglycemic conditions leads to endothelial dysfunction, lipid peroxidation of cell membranes, and DNA damage (Brownlee, 2001). Advanced glycation end products (AGEs), closely associated with oxidative stress, activate inflammatory and angiogenic processes through RAGE receptors on endothelial cells. [1]

Activation of the polyol pathway is also important in the pathogenesis of diabetic retinopathy. It has been established that the conversion of glucose to sorbitol by the enzyme aldose reductase increases osmotic stress inside the cell, causing apoptotic loss of pericytes and neuroglial cells. At the same time, activation of protein kinase C (PKC) has been reported in many studies to increase vascular permeability, disrupt blood flow , and enhance the synthesis of inflammatory mediators. In conditions of retinal hypoxia, the expression of angiogenic factors, in particular VEGF (vascular endothelial growth factor), increases dramatically. Aiello et al. (2005) have shown that VEGF is a key molecular mediator in the development of diabetic macular edema and proliferative diabetic retinopathy. Excessive production of VEGF enhances pathological neovascularization, increased capillary permeability , and fibrovascular proliferation. Modern clinical studies demonstrate the effectiveness of pathogenesis-oriented pharmacological approaches in the treatment of diabetic retinopathy. [7] Anti-VEGF drugs (ranibizumab, bevacizumab, aflibercept) play an important role in blocking pathological angiogenesis and preserving visual acuity (Brown et al., 2013). Also, corticosteroids are characterized by suppressing inflammatory processes and reducing vascular permeability. Literature analysis shows that morphological, microangiopathic and molecular mechanisms in the development of diabetic retinopathy are closely interconnected, and their comprehensive study serves as an important scientific basis for the early diagnosis, prognosis and development of effective treatment strategies for the disease [6]

MATERIALS AND METHODS

This study aimed to analyze the morphological, microangiopathic, and molecular changes that occur in diabetic retinopathy, using a complex of clinical, instrumental, and laboratory methods.

The study material included the results of ophthalmological examinations of patients with diabetes mellitus , retinal tissue biopsy and autopsy materials, and scientific literature data from recent years. Patients diagnosed with non-proliferative and proliferative forms of diabetic retinopathy were included in the study. As a control group, ophthalmological indicators of individuals without eye pathology were analyzed.

clinical and instrumental methods , patients underwent dilated ophthalmoscopy, fundus photography, and optical coherence tomography (OCT). These methods were used to assess retinal thickness, macular edema, microaneurysms, hemorrhages , and neovascular structures. Fluorescein angiography was used, if necessary, to determine the state of capillary perfusion and ischemic zones.

morphological analysis , retinal tissues were fixed in 10% neutral formalin and embedded in paraffin blocks. Sections of 4–5 μm thickness were prepared and hematoxylin-eosin (H&E) and PAS-staining methods were used for general histological evaluation to detect basement membrane changes. Microscopic examination assessed capillary basement membrane thickness, pericyte count , and vessel wall structure.

Immunohistochemical studies were performed using VEGF, CD31 , and ICAM-1 markers. This method allowed us to determine the level of pathological angiogenesis and endothelial activity. The preparations were evaluated under a light microscope, and the expression level was analyzed semi-quantitatively.

of biochemical and molecular analysis , oxidative stress indicators, advanced glycation end products (AGE), protein kinase C (PKC) activity, and antioxidant system status were compared

based on literature. Also, the molecular mechanisms of action of anti-VEGF and other pharmacological drugs were evaluated based on scientific sources.

statistical analysis were expressed as mean ± standard deviation (M±SD). Differences between groups were assessed using Student's t-test or Mann–Whitney test, and a value of $p < 0.05$ was considered statistically significant.

Ethical aspects The study was conducted in accordance with the requirements of the local bioethics committee. The study materials were used for scientific purposes only and the confidentiality of patients' personal data was ensured.

CONCLUSION

the eye in diabetes mellitus are the leading pathogenic factors in the development of diabetic retinopathy. Prolonged hyperglycemia leads to thickening of the basement membrane in retinal capillaries, selective loss of pericytes, endothelial dysfunction and microcirculation disorders. As a result, tissue hypoxia increases, pathological angiogenesis and fibrovascular proliferation processes are activated.

The results of the study indicate that oxidative stress, advanced glycation end products (AGEs), activation of the polyol pathway, disruption of the protein kinase C (PKC) signaling system, and VEGF-mediated angiogenesis are involved in the pathogenesis of diabetic retinopathy.

In conclusion, in-depth study of the morphological and molecular mechanisms of diabetic retinopathy serves as an important scientific basis for better understanding the pathogenesis of the disease, developing new treatment strategies, and improving comprehensive approaches aimed at preserving vision.

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