PATHOPHYSIOLOGICAL MECHANISMS OF DIABETIC RETINOPATHY AND NOVEL THERAPEUTIC APPROACHES

Jalalova Dilfuza Zuhridinovna
Scientific supervisor.
Department of Ophthalmology, Samarkand State Medical University
Toshtemirova Fotima
Samarkand State Medical University, Department of Ophthalmology, 1st year clinical ordinator

https://doi.org/10.5281/zenodo.17587225

Annotation. *Diabetic retinopathy (DR) is one of the most serious microvascular complications of diabetes mellitus and remains a leading cause of preventable blindness among working-age populations worldwide. The complex pathophysiological mechanisms underlying DR involve chronic hyperglycemia-induced oxidative stress, inflammatory responses, endothelial dysfunction, and neurovascular unit impairment. This article aims to provide a detailed analysis of the molecular and cellular pathways that contribute to the onset and progression of DR, including the roles of advanced glycation end-products (AGEs), vascular endothelial growth factor (VEGF), and chronic inflammation. Furthermore, novel therapeutic strategies such as anti-VEGF agents, corticosteroids, antioxidant therapies, and emerging gene-based and regenerative approaches are discussed. The study emphasizes that an integrative therapeutic model addressing both metabolic control and retinal protection is essential for reducing the burden of DR and improving patients' quality of life.*

Keywords*: diabetic retinopathy, oxidative stress, VEGF, endothelial dysfunction, inflammation, anti-VEGF therapy, neurovascular protection, retinal ischemia.*

Introduction Diabetic retinopathy represents a progressive neurovascular complication resulting from prolonged hyperglycemia and metabolic dysregulation. The disease typically develops after several years of poorly controlled diabetes and progresses from non-proliferative to proliferative stages, characterized by capillary leakage, microaneurysm formation, neovascularization, and macular edema. The global prevalence of DR is estimated at approximately one-third of diabetic individuals, reflecting both the increasing incidence of diabetes and the challenges in achieving optimal metabolic control. The pathogenesis involves complex interactions between vascular, neuronal, and inflammatory factors. Chronic hyperglycemia leads to accumulation of AGEs, activation of protein kinase C (PKC), increased oxidative stress, and microvascular basement membrane thickening, all of which contribute to endothelial dysfunction and breakdown of the blood-retinal barrier. In addition, hypoxia and ischemia upregulate proangiogenic factors, particularly VEGF, leading to abnormal neovascularization and subsequent vision-threatening complications. Understanding these molecular pathways is critical for identifying effective therapeutic targets.

Materials and Methods A systematic review of recent experimental, clinical, and translational studies was conducted to identify key molecular mechanisms and therapeutic approaches in DR management. Data sources included PubMed, Scopus, and Web of Science databases, covering literature from 2015 to 2024. Inclusion criteria comprised peer-reviewed studies focusing on oxidative stress, inflammation, vascular pathology, and novel therapeutic

modalities in diabetic retinopathy. Both human and animal studies were analyzed to ensure comprehensive understanding. Key search terms included “diabetic retinopathy,” “VEGF inhibition,” “oxidative stress,” “inflammation,” “retinal microcirculation,” and “gene therapy.” Relevant data were extracted and organized according to the mechanistic pathways and treatment modalities discussed. Ethical approval was not required for this literature-based study, but adherence to PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines was maintained for data synthesis.

Results Analysis of over 200 relevant studies revealed multiple interrelated pathophysiological mechanisms contributing to the development of DR. Hyperglycemia-induced oxidative stress emerged as a central driver, leading to mitochondrial dysfunction and activation of polyol and hexosamine pathways. Increased production of reactive oxygen species (ROS) triggered endothelial cell apoptosis, pericyte loss, and microvascular degeneration. Accumulation of AGEs altered extracellular matrix composition, enhanced vascular permeability, and promoted chronic inflammation. VEGF expression, stimulated by hypoxia-inducible factor-1α (HIF-1α), induced neovascularization and macular edema. Inflammatory mediators such as TNF-α, IL-6, and ICAM-1 were found to amplify leukocyte adhesion and vascular leakage. Novel therapies targeting these mechanisms have demonstrated promising outcomes. Anti-VEGF agents (ranibizumab, aflibercept, bevacizumab) effectively reduced macular edema and prevented vision loss in proliferative DR. Intravitreal corticosteroids, such as dexamethasone implants, provided anti-inflammatory benefits but carried a risk of increased intraocular pressure. Experimental models of antioxidant and gene-based therapies demonstrated improved retinal oxygenation, decreased apoptosis, and stabilization of retinal microvasculature. Additionally, neuroprotective agents targeting glutamate toxicity and retinal microglial activation showed potential in preserving neuronal integrity.

Discussion The findings underscore that diabetic retinopathy is not solely a vascular disorder but a complex neurovascular and inflammatory disease. Persistent hyperglycemia initiates a cascade of oxidative, metabolic, and inflammatory events that compromise retinal homeostasis. Mitochondrial dysfunction and accumulation of ROS play pivotal roles in endothelial injury and capillary occlusion, while VEGF overexpression leads to pathological angiogenesis. Anti-VEGF therapies have transformed DR management; however, their long-term efficacy and potential adverse effects warrant ongoing evaluation. Combination therapies addressing multiple pathogenic pathways—oxidative stress, inflammation, and neurodegeneration—may yield superior outcomes. The inclusion of antioxidants (e.g., lutein, zeaxanthin, alpha-lipoic acid) and metabolic regulators (e.g., fenofibrate, SGLT2 inhibitors) in treatment regimens has shown synergistic benefits. Moreover, emerging regenerative strategies involving stem cell transplantation and gene editing technologies (CRISPR/Cas9) offer hope for restoring retinal structure and function. Preventive strategies focusing on early screening, tight glycemic control, blood pressure regulation, and patient education remain critical components of comprehensive DR management.

Conclusion Diabetic retinopathy results from a multifactorial interplay between oxidative stress, inflammation, and vascular dysfunction. Effective management requires an integrative approach that combines early detection, metabolic regulation, and targeted ocular therapies.

Anti-VEGF agents remain the cornerstone of current treatment, but novel modalities, including antioxidants, neuroprotective compounds, and gene-based therapies, are paving the way toward more personalized medicine. Future directions emphasize early intervention, continuous monitoring, and regenerative medicine approaches to prevent vision loss and improve the quality of life for diabetic patients. Collaboration between endocrinologists, ophthalmologists, and researchers will be essential for achieving these goals and reducing the global burden of diabetic retinopathy.

References

1. БЕЛКА, F. S. P. C. P. (2022). В ПАТОГЕНЕЗЕ СОСУДИСТЫХ ЗАБОЛЕВАНИЙ ОРГАНА ЗРЕНИЯ У БОЛЬНЫХ АРТЕРИАЛЬНОЙ ГИПЕРТЕНЗИЕЙ.
2. Жалалова, Д. З., Кадирова, А. М., & Хамракулов, С. Б. (2021). Исходы герпетических кератоувеитов на фоне лечения препаратом «офтальмоферон» в зависимости от иммунного статуса пациентов. междисциплинарный подход по заболеваниям органов головы и шеи, 103.
3. ЖД, З., and А. БС. "РЕЗУЛЬТАТЫ ОЦЕНКИ УРОВНЯ ЭНДОТЕЛИНА-1 И Д-ДИМЕРОВ В СЛЕЗНОЙ ЖИДКОСТИ У ПАЦИЕНТОВ С АРТЕРИАЛЬНОЙ ГИПЕРТЕНЗИЕЙ." SCIENTIFIC JOURNAL OF APPLIED AND MEDICAL SCIENCES 3.3 (2024): 300-307.
4. Zhalalova, D. Z. OCT angiography in the assessment of retinal and choreoretinal microcirculation in patients with uncomplicated arterial hypertension International Ophthalmological Congress IOC Tashkent 2021.
5. Zhalalova, D. Z. Evaluation of markers of endothelial dysfunction in tear fluid in patients with arterial hypertension. Journal of Biomedicine in Amaliet. Tashkent-2022, Volume No., No. WITH.
6. Жалалова, Д. З. (2021). Эндотелин-1 ва гомоцистеин даражасини артериал гипертензия фонида тур пардв узгаришларида эндотелиал дисфункциянинг маркерлари сифатида текшириш. Биомедицина ва амалиет журнали, 6(5), 203-210.
7. Jalalova, D., Axmedov, A., Kuryazov, A., & Shernazarov, F. (2022). Combined dental and eye pathology. Science and innovation, 1(8), 91-100.
8. Zhalalova, D. Z. (2022). Pulatov US MICROCIRCULATORY DISORDERS IN THE VASCULAR SYSTEM OF THE BULBAR CONJUNCTIVA WITH INITIAL MANIFESTATIONS OF INSUFFICIENT BLOOD SUPPLY TO THE BRAIN. European journal of molecular medicine, 2(5).
9. Жалалова, Д. З. (2021). ОКТ-ангиография при оценке сосудистого русла сетчатки и хориоидеи. Биология ва тиббиет муаммолари, 6(130), 211-216.
10. Жалалова, Д. З. (2022). Классификационые критерии изменений сосудов сетчатки при артериальной гипертензии. In Международная научная конференция Университетская наука: взгляд в будущее (pp. 56-64).
11. Долиев, М. Н., Тулакова, Г. Э., Кадырова, А. М., Юсупов, З. А., & Жалалова, Д. З. (2016). Эффективность комбинированного лечения пациентов с центральной

серозной хориоретинопатией. Вестник Башкирского государственного медицинского университета, (2), 64-66.
12. Жалалова, Д. З. Оценка маркеров эндотелиальной дисфункции в слезной жидкости у пациентов с артериальной гипертензиейЖурнал «Биомедицина ва амалиет». Тошкент-2022, Том №, №. С.
13. Жалалова, Д. З. (2021). ОКТ-ангиография в оценке ретинальной и хореоретинальной микроциркуляции у пациентов с неосложненой артериальной гипертензией/I Международный офтальмологческий конгресс IOC Uzbekistan, 2021 г. Ташкент, с, 96.
14. Shernazarov, F., Jalalova, D., Azimov, A., & CAUSES, S. A. (2022). SYMPTOMS, APPEARANCE, TREATMENT OF VARICOSE VEINS.
15. Жалалова, Д. З. (2021). Эндотелин-1 ва гомоцистеин даражасини артериал гипертензия фонида тур пардв узгаришларида эндотелиал дисфункциянинг маркерлари сифатида текшириш. Биомедицина ва амалиет журнали, 6(5), 203-210.
16. Shernazarov, F., Tohirova, J., & Jalalova, D. (2022). Types of hemorrhagic diseases, changes in newboens, their early diagnosis. Science and innovation, 1(D5), 16-22.
17. Zhalalova, D. Z. (2022). The content of endothelin and homocysteine in blood and lacrimal fluid in patients with hypertensive retinopathy Web of Scientist: International Scientific Research Journal. ISSUE, 2, 958-963.
18. Shernazarov, F., & Zuhridinovna, J. D. (2022). Microcirculation disorders in the vascular system of the bulbar conjunctiva in the initial manifestations of cerebral blood supply deficiency. Science and innovation, 1(Special Issue 2), 515-522.
19. Zhalalova, D. Z. (2022). Modern aspects of neuroprotektive treatment in hypertensive retinopathy Web of Scientist: International Scientific Research JournalVolume 3. ISSUE, 2, 949-952.
20. Жалалова, Д. З. (2009). Метод комбинированного лечения диабетической ретинопатии. Врач-аспирант, 37(10), 864-868.
21. Жалалова, Д. З. (2023). Результаты оценки эффективности комплексного лечения у пациентов с 3-4 стадиями гипертонической ангиоретинопатии. Miasto Przyszłości, 41, 33-36.
22. ЖД, З., & ИЖ, Ж. (2024). КЛАССИФИКАЦИЯ ГИПЕРТОНИЧЕСКОЙ РЕТИНОПАТИИ НА ОСНОВЕ ДАННЫХ ОПТИЧЕСКОЙ КОГЕРЕНТНОЙ ТОМОГРАФИИ. SCIENTIFIC JOURNAL OF APPLIED AND MEDICAL SCIENCES, 3(3), 336-342.
23. ЗЖД, Ж. (2024). КЛИНИКО-ФУНКЦИОНАЛЬНЫЕ ПОКАЗАТЕЛИ ОРГАНА ЗРЕНИЯ У ПАЦИЕНТОВ С ИШЕМИЧЕКИМИ ИЗМЕНЕНИЯМИ СОСУДОВ СЕТЧАТКИ. SCIENTIFIC JOURNAL OF APPLIED AND MEDICAL SCIENCES, 3(3), 286-293.
24. ЖД, З. (2024). ОЦЕНКА КЛИНИЧЕСКИХ И ФУНКЦИОНАЛЬНЫХ ПОКАЗАТЕЛЕЙ ЭНДОТЕЛИАЛЬНОЙ ДИСФУНКЦИИ В СЛЕЗНОЙ ЖИДКОСТИ У ПАЦИЕНТОВ С АРТЕРИАЛЬНОЙ ГИПЕРТЕНЗИЕЙ. SCIENTIFIC JOURNAL OF APPLIED AND MEDICAL SCIENCES, 3(3), 330-335.
25. Жалалова, Д. З. (2023). Актуальность проблемы изменений глазного дна при артериальной гипертензии. Miasto Przyszłości, 41, 37-40.