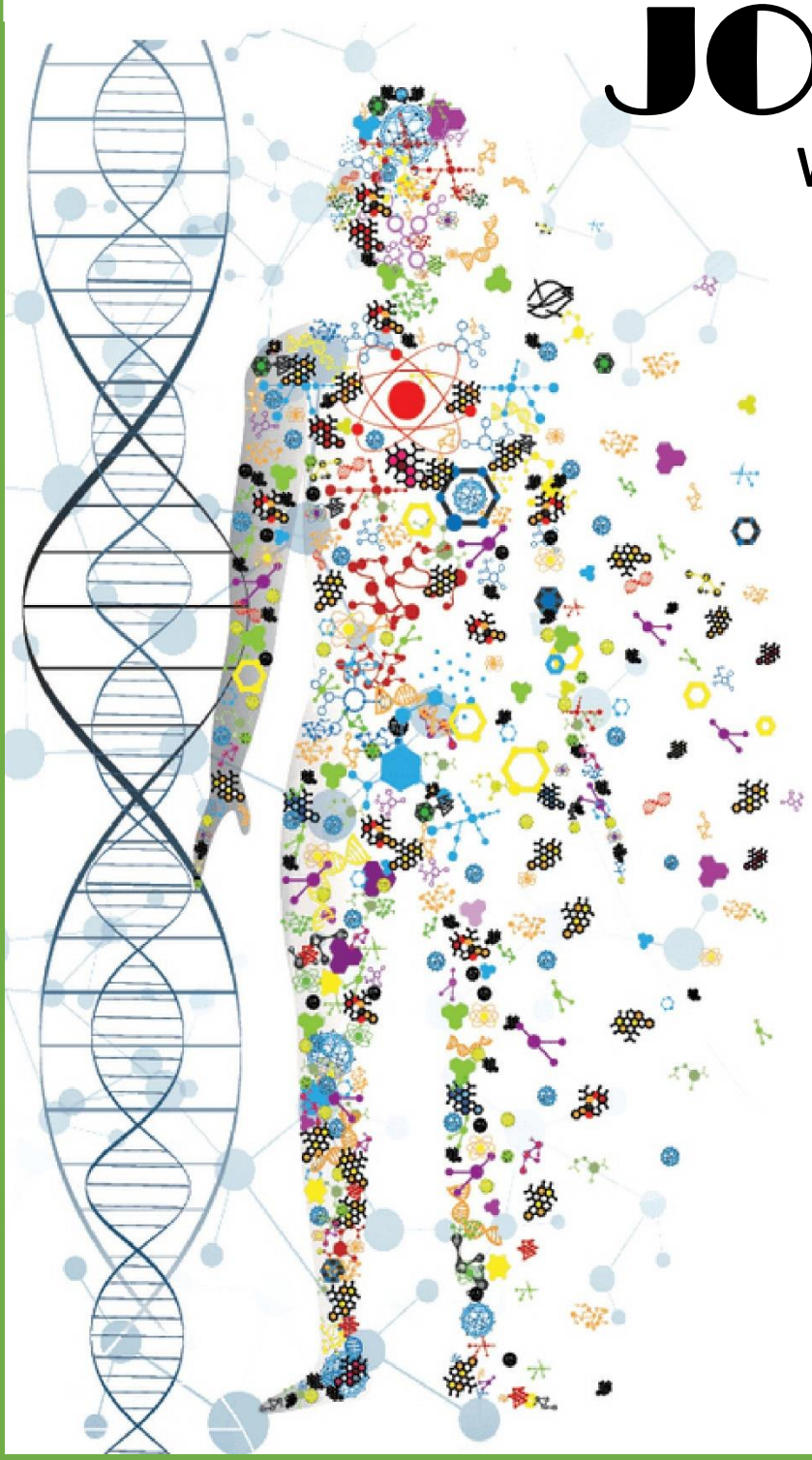
ECO SCIENCE JOURNALS

We care for Health & Natures

Volume 2



INTERNATIONAL STANDARD SERIAL NUMBER UNITED STATES

ISSN:3067-1221; CODEN: USA

ECO SCIENCE JOURNALS
We care for health & Nature

PHARMACOTHERAPY OF DIABETIC RETINOPATHY: BEYOND THE EYE

Marianne Levon Shahsuvaryan[1*]

1.MD, PhD, Dr of Sc., Professor, Department of Ophthalmology, Yerevan State Medical University, Yerevan, Armenia

ARTICLE INFO

Received 06 May 2025

Revised 08 Jun 2025

Accepted 17 Jun 2025

Available 21 Jun 2025

KEYWORDS

Diabetic retinopathy

Pharmacotherapy

Eye

Intravitreal

Systemic Therapies

CORRESPONDING AUTHOR

Yerevan State Medical University, Yerevan, Armenia.

✉ mar_shah@hotmail.com

ORCID0000-0003-3627-4137

ABSTRACT

Diabetic retinopathy (DR), which is still one of the main causes of vision impairment in the world, is directly correlated with the rising incidence of diabetes. The purpose of this review is to assess the available data and offer a critical evaluation of the justification for contemporary pharmacotherapeutic approaches for DR around the globe. From intravitreal injections of corticosteroids and anti-VEGF medicines to new systemic and multitarget therapies, a thorough evaluation of recent clinical trials, observational studies, and expert advice shows a changing landscape of therapeutic options. These tactics are becoming more and more concentrated on treating the underlying pathophysiological mechanisms, such as inflammation, oxidative stress, and neurodegeneration, in addition to stopping the progression of the disease. This analysis emphasizes the need for customized, affordable therapies, access and compliance issues, and regional differences in treatment acceptance. In order to maximize patient results and lessen the worldwide disease burden, current research supports a multifaceted approach to DR medication that integrates both local and systemic Therapies.

INTRODUCTION:

Diabetes as a chronic disease represents “a substantial public health issue” [1]. No country, age group and gender are immune to it. The forecast for the year 2050 indicates that the number of people with diabetes will reach more than 1.31 billion [2].

Diabetic Retinopathy (DR) is “a highly specific neurovascular complication of diabetes” [2], which occurs in more than one-third [2] persons with diabetes. DR is the most challenging cause of blindness worldwide [3]. DR is classified as Mild Non-Proliferative DR (Mild NPDR), Moderate Non-Proliferate DR (Moderate NPDR), Severe Non-Proliferate DR (Severe NPDR), Proliferative DR (PDR), Any type of DR with Clinically Significant Diabetic Macular Edema (CSDME). Sight-threatening DR was defined as Severe NPDR or higher severity with/without Clinically Significant Diabetic Macular Edema (CSDME).

The prevalence and incidence of DR are exponentially growing due to increased life expectancy over the past century highlighting not only medical issues including public health problem, but also an economic burden, representing a medico-social challenge, to meet which it is extremely important to identify a disease as soon as possible and successfully treat it. DR management poses challenges because of the incompletely understood pathogenesis.

Recent studies have implicated neurovascular unit (NVU) formed by different neuron cells (horizontal cells, bipolar cells ganglion cells, amacrine cells), glial cells (microglia, astrocytes, Müller cells) and vascular cells (pericytes, endothelial cells) in pathophysiology of DR, suggesting that the cardinal position belongs to primary neurodegeneration manifesting before microvascular abnormalities[4].

Multifactorial genesis of DR includes a cascade of biochemical events with initial neurodegeneration followed by microvascular dysfunction, inflammation, oxidative stress, and angiogenesis[5-8].

Tissue hypoxia is the most common driver of vascular endothelial growth factor (VEGF) synthesis [8]. VEGF as a key regulator of angiogenesis and vascular permeability, is involved also in the pathogenesis of retinal diseases associated with neovascularization and edema, such as neovascular age-related macular degeneration (nAMD), retinal vein occlusion, DR with or without diabetic macular edema (DME) [9].

AIM:

The aim of this review is to evaluate the evidence and discuss the rationale behind the recent pharmacotherapy of DR worldwide. based on the currently available findings.

METHODOLOGY:

For this review, a literature search was conducted using PubMed®/Medline® and Google Scholar for studies published up to May 2025. The following keywords were used in various combinations: “diabetic retinopathy”, “pharmacotherapy of diabetic retinopathy”, “antiangiogenics in diabetic retinopathy”, “intravitreal pharmacotherapy of diabetic retinopathy by anti-VEGF”. Articles with high or medium clinical relevance were selected for this review.

The development of intraocular therapy with antiangiogenics or vascular endothelial growth factor inhibitors (anti-VEGF) opens a new avenue in eye diseases treatment [10]. The term antiangiogenic therapy was introduced by J. Folkman more than 50 years ago [11]. Bevacizumab (a full-length humanized monoclonal antibody) became the first therapy approved by the US - FDA designed to inhibit angiogenesis in tumors, and since 2004 widely used off-label (it has not been officially approved) in ophthalmology [12].

Another antiangiogenic, specially designed for use in ophthalmology, ranibizumab is a humanized, affinity-matured VEGF antibody fragment derived from bevacizumab, making it safer due to shorter half lifetime [12]. It neutralizes all isoforms of VEGF and is FDA approved in 2006 for use in nAMD, DR, DME. Several studies have pointed out ranibizumab 's efficacy in treating DR with or without DME [12]. Despite this, however, there is no expert consensus on treatment regimen and impact on the progression of retinal ischemia [13].

New antiangiogenic aflibercept was approved by the FDA in 2015 for the treatment of DR with DME. It is a recombinant fusion protein, which binds to VEGF-A and placental growth factor [12]. The most influential trials underscore the efficacy of aflibercept for aforementioned indications [12].

Interventional, retrospective, single-center study conducted at Al-Azhar University Hospitals, Egypt between March 2023 and January 2024 comparing ranibizumab and aflibercept in DME have shown equal anatomical and functional efficacy for both drugs in short-term (at 6 months post-injection) [14] and long-term follow up to 36 months in four hundred three eyes of 235 patients [15]. Another retrospective comparative study [16] of ranibizumab and aflibercept in 534 eyes with DME of 402 patients based on the data from the Fight Retinal Blindness! Registry have documented similar outcomes up to 36 months of treatment, however aflibercept should be used in cases with initial severe visual deterioration. Ma et al [17].

conducted a randomized study of ninety-four patients with DR admitted to Sunshine Union Hospital to compare the difference in the effectiveness of ranibizumab and aflibercept in 47 and 47 patients respectively. All patients underwent 25G vitrectomy after intravitreal injection of any antiangiogenic agent. Results evidenced no difference in intraoperative bleeding, the occurrence of medically induced fissures, the operative time, best corrected visual acuity, Central Macular Thickness, prognosis of DR recurrence rate between both groups, but at the same time aflibercept have shown more prominent anti-inflammatory effect at 2 months after surgery.

Evaluation of antiangiogenic therapy in non-proliferative DR evidenced that despite prevention of retinal neovascularization and DME, it was no positive impact on vision over 2 years, that is why anti-VEGF agents are not recommended in such cases. Currently intraocular pharmacotherapy by anti-VEGF is the first-line treatment approach for majority center-involved DME cases, and also in some proliferative DR cases could serve as an alternative to pan retinal laser photocoagulation reducing vision loss risk [18].

However, despite DR therapy advances by antiangiogenics real-world evidence reveals significant rate of suboptimal therapeutic effect [19] and underscores the need for new anti-VEGF agents with better durability. Brolucizumab and faricimab representing a new generation of antiangiogenics received FDA-approvement for the treatment of DME in 2022 [20]. The first long acting anti-VEGF is brolucizumab. Many papers have reported therapeutic efficacy of this drug [21], however visually disabling cases of retinal vasculitis were reported [21]. Faricimab is a bispecific monoclonal antibody targeting VEGF-A and angiopoietin-2 [22]. It remains to be seen its long-term efficacy in real world [23].

Another new multitarget antiangiogenic developed and presently approved only in China is conbercept, directed to block all isoforms of VEGF-A, and also placental growth factor (PlGF) and VEGF-B.

The systematic review by Yao and colleagues [24] based on meta-analysis of 1606 patients from 20 retrospective studies and evaluating comparative efficacy of ranibizumab, aflibercept, bevacizumab and conbercept in DME with cystoid macular edema, diffuse retinal thickening and serous retinal detachment verified by OCT, have shown the best visual outcomes for conbercept, ranibizumab, and bevacizumab. The greatest reduction in Central Macular Thickness in all subtypes of DME was evidenced after conbercept use, highlighting a therapeutic potential of this VEGF inhibitor. Despite substantial advancements in the therapy of DR with or without DME by anti-VEGF, a significant proportion of DR and DME patients do not respond to antiangiogenics [25,26], from 30% to 60% of DME cases [27]. Currently available therapeutic option targets only VEGF, but it is obvious an involvement of other pathogenetic pathways [26] indicating that multiple pathways causing DR require targeting, such as an oxidative stress, inflammation, neurodegeneration [25,26,28].

Growing body of evidence suggests some undesirable effects in antiangiogenic intraocular pharmacotherapy. Real-world experience underscores the need for comprehensive evaluation of systemic and ocular adverse effects, including local injection-related and ocular chemical compound-related [29,30]. AntiVEGF-related adverse events in DR have been studied [29]. Ocular chemical compound-related side effect includes also a tolerance/tachyphylaxy due to required regular injections over long periods of time [31]. To overcome this challenge, it is advised to switch to another anti-VEGF. Systemic side effects of antiangiogenics include myocardial infarction, cerebrovascular accidents, transient ischemic attacks, pulmonary embolism, deep vein thrombosis, thrombophlebitis and recently documented renal disfunction [32,33]. Importantly, nephrotoxicity deserves a special attention in people with diabetes taking into account renal vulnerability. It is well-known that not only DR, but also Diabetic nephropathy (DN) is a microvascular complication of diabetes [34], which directly correlates with the severity of retinopathy [35].

It must be taken into consideration that in aging population endless intraocular injections of antiangiogenics will cause a social challenge with an economic burden [36], highlighting the urgent need for alternative noninvasive cost-effective drug delivery route. To address medical and social challenges Boyer and colleagues [37] advocate oral use of Amine oxidase copper-containing 3 (AOC3) inhibitors with antioxidant, antiischemic and antiedematous effects, however in further testing in a randomized, double-masked, placebo-controlled Phase IIa study in patients with non-proliferative DR without center-involved DME clinically meaningful change was not documented [38]. Pharmacotherapy intended to suppress just one chemical substance is inadequate to successfully treat DR. Besides, accumulating evidence has suggested that DR could manifest as a neural disfunction followed by vascular abnormalities [39] indicating a role of preventive neuroprotection. Thoughtful pharmacotherapy of DR will be multidimensional and directed to augmenting neuroprotection, attenuating inflammation, ameliorating oxidative stress and restoring retinal microcirculation. An ideal therapeutic drug will have a multimodal activity.

CONCULSION:

Diabetic retinopathy, as a most common neuromicrovascular complication of diabetes, represent disease with bilateral involvement, which underscores a need for oral systemic therapy targeting both eyes simultaneously, as a cost-effective approach, in contrast to monocular local topical or invasive intraocular drug delivery. At the same time it is a need for multitarget drug directed on prevention of other complications of diabetes, such as diabetic nephropathy, ischemic heart disease, etc. The continued research have the potential to enhance diabetic retinopathy druggability.

ACKNOWLEDGEMENT:

This article is derived in part from an Article published in Cutan Ocul Toxicol 2025 Mar 14 <copyright Taylor & Francis>, available online: http://www.tandfonline.com DOI:10.1080/15569527.2025.2475445.

Author contributions: Marianne L. Shahsuvaryan was involved in the conception and design, analysis and interpretation of the data; the drafting of the paper and revising it critically for intellectual content; and the final approval of the version to be published; and agree to be accountable for all aspects of the work.

BIOBILOGRAPHY:

1. GBD 2021 Diabetes Collaborators. “Global, regional, and national burden of diabetes from 1990 to 2021, with projections of prevalence to 2050: a systematic analysis for the Global Burden of Disease Study 2021,” Lancet. 2023;402(10397):203-34. doi: 10.1016/S0140-6736(23)01301-6. Epub 2023 Jun 22. Erratum in: Lancet. 2023 Sep 30;402(10408):1132. doi: 10.1016/S0140-6736(23)02044-5.

2. Matuszewski W, Baranowska-Jurkun A, Stefanowicz-Rutkowska MM, Gontarz-Nowak K, Gątarska E, Bandurska-Stankiewicz E. “The Safety of Pharmacological and Surgical Treatment of Diabetes in Patients with Diabetic Retinopathy-A Review,” J Clin Med. 2021;10(4):705. doi: 10.3390/jcm10040705.

3. Kaur A, Kumar R, Sharma A. “Diabetic Retinopathy Leading to Blindness- A Review,” Curr Diabetes Rev. 2024; doi: 10.2174/0115733998274599231109034741. Epub ahead of print.

4. Oshitari T. Neurovascular Cell Death and Therapeutic Strategies for Diabetic Retinopathy. Int J Mol Sci. 2023 Aug 18;24(16):12919. doi: 10.3390/ijms241612919.

5. Shyam M, Sidharth S, Veronica A, Jagannathan L, Srirangan P, Radhakrishnan V, Sabina EP. Diabetic retinopathy: a comprehensive review of pathophysiology and emerging treatments. Mol Biol Rep. 2025 Apr 10;52(1):380. doi: 10.1007/s11033-025-10490-7.

6. Ramegowda LB, Maheshwari S, Ramachandra SC, Kempegowda SN, Vishwanath P, Prashant A. Exploring Diabetic Retinopathy: Pathogenesis, Therapeutic Advances, and Genetic Influences. Current Ophthalmology Reports. 2025 Apr 11;13(1):5.

7. Zhu H, Li B, Huang T, Wang B, Li S, Yu K, Cai L, Ye Y, Chen S, Zhu H, Xu J, Lu Q, Ji L. Update in the molecular mechanism and biomarkers of diabetic retinopathy. Biochim Biophys Acta Mol Basis Dis. 2025 Jun;1871(5):167758. doi: 10.1016/j.bbadis.2025.167758. Epub 2025 Mar 5.

8. Wal P, Wal A, Gupta D, Mantry S, Mahajan KC, Rathore S, Behl T. "Diabetic retinopathy: Stressing the function of angiogenesis, inflammation and oxidative stress," In: Behl T, Singh S, Sharma N,editors. Targeting Angiogenesis, Inflammation, and Oxidative Stress in Chronic Diseases; 2024.p. 323-348. Academic Press. ISBN 9780443135873, doi:10.1016/B978-0-443-13587-3.00002-3.

9. Wang L, Liu WQ, Broussy S, Han B, Fang H. "Recent advances of anti-angiogenic inhibitors targeting VEGF/VEGFR axis," Front Pharmacol. 2024;14:1307860. doi: 10.3389/fphar.2023.1307860.

10. Kwong TQ, Mohamed M. "Anti-vascular endothelial growth factor therapies in ophthalmology: current use, controversies and the future," Br J Clin Pharmacol. 2014;78(4):699-706. doi: 10.1111/bcp.12371.

11. Folkman J. "Tumor angiogenesis: therapeutic implications," N Engl J Med. 1971;285(21):1182-6. doi: 10.1056/NEJM197111182852108.

12. Cheema AA, Cheema HR. "Diabetic Macular Edema Management: A Review of Anti-Vascular Endothelial Growth Factor (VEGF) Therapies," Cureus. 2024;16(1):e52676. doi: 10.7759/cureus.52676.

13. Chatziralli I. "Ranibizumab for the treatment of diabetic retinopathy," Expert Opin Biol Ther. 2021;21(8):991-997. doi: 10.1080/14712598.2021.1928629.

14. Ali Ali MA, Hegazy HS, Abdelkhalek Elsayed MO, Tharwat E, Mansour MN, Hassanein M, Ezzeldin ER, GadElkareem AM, Abd Ellateef EM, Elsayed AA, Elabd IH, Abd Rbu MH, Amer RS, Gabbar AGAE, Mahmoud H, Abdelhameed HM, Abdelkader AME. "Aflibercept or ranibizumab for diabetic macular edema," Med Hypothesis Discov Innov Ophthalmol. 2024;13(1):16-26. doi: 10.51329/mehdiophthal1490.

15. Akbas YB, Alagoz C, Cakmak S, Demir G, Alagoz N, Artunay HO. "Three year outcomes of intravitreal ranibizumab and aflibercept treatment of patients with diabetic macular edema: A comparative study," Ther Adv Ophthalmol. 2023;15:25158414231195174. doi: 10.1177/25158414231195174.

16. Gabrielle PH, Nguyen V, Creuzot-Garcher C, Arnold JJ, Mehta H, Duran MA, Bougamha W, Carreño E, Viola F, Squirrell D, Barthelmes D, Gillies M. "THREE-YEAR TREATMENT OUTCOMES OF AFLIBERCEPT VERSUS RANIBIZUMAB FOR DIABETIC MACULAR EDEMA: Data from the Fight Retinal Blindness! Registry," Retina. 2022;42(6):1085-1094. doi: 10.1097/IAE.0000000000003428.

17. Ma X, Ma N, Zhang Q, Wang Y, Sun H, Yang Z. "Effectiveness Differences of Ranibizumab and Aflibercept Action in the Treatment of Diabetic Retinopathy," Altern Ther Health Med. 2024;30(1):441-445.

18. American Diabetes Association Professional Practice Committee. “12. Retinopathy, Neuropathy, and Foot Care: Standards of Care in Diabetes-2024,” Diabetes Care. 2024 ;47(Suppl 1):S231-S243. doi: 10.2337/dc24-S012.

19. Boscia F, Veritti D, Iaculli C, Lattanzio R, Freda S, Piergentili B, Varano M. ‘Management of treatment-naïve diabetic macular edema patients: Review of real-world clinical data,” Eur J Ophthalmol. 2024 ;11206721241237069. doi: 10.1177/11206721241237069.

20. Almony A. “Treatment approaches for neovascular age-related macular degeneration and diabetic macular edema,” Am J Manag Care. 2023;29(6 Suppl):S81-S89. doi: 10.37765/ajmc.2023.89386.

21. Abu Serhan H, Taha MJJ, Abuawwad MT, Abdelaal A, Irshaidat S, Abu Serhan L, Abu Salim QF, Awamleh N, Abdelazeem B, Elnahry AG. “Safety and Efficacy of Brolucizumab in the Treatment of Diabetic Macular Edema and Diabetic Retinopathy: A Systematic Review and Meta-Analysis,” Semin Ophthalmol. 2024;39(4):251-60. doi: 10.1080/08820538.2023.2271095.

22. Kusuhara S, Kishimoto-Kishi M, Matsumiya W, Miki A, Imai H, Nakamura M. “Short-Term Outcomes of Intravitreal Faricimab Injection for Diabetic Macular Edema,” Medicina (Kaunas). 2023;59(4):665. doi: 10.3390/medicina59040665.

23. Wong TY, Haskova Z, Asik K, Baumal CR, Csaky KG, Eter N, Ives JA, Jaffe GJ, Korobelnik JF, Lin H, Murata T, Ruamviboonsuk P, Schlottmann PG, Seres AI, Silverman D, Sun X, Tang Y, Wells JA, Yoon YH, Wykoff CC; YOSEMITE and RHINE Investigators. “Faricimab Treat-and-Extend for Diabetic Macular Edema: Two-Year Results from the Randomized Phase 3 YOSEMITE and RHINE Trials,” Ophthalmology. 2024;131(6):708-723. doi: 10.1016/j.ophtha.2023.12.026.

24. Yao J, Huang W, Gao L, Liu Y, Zhang Q, He J, Zhang L. “Comparative efficacy of anti-vascular endothelial growth factor on diabetic macular edema diagnosed with different patterns of optical coherence tomography: A network meta-analysis,” PLoS One. 2024;19(6):e0304283. doi: 10.1371/journal.pone.0304283.

25. Gurung RL, FitzGerald LM, Liu E, McComish BJ, Kaidonis G, Ridge B, Hewitt AW, Vote BJ, Verma N, Craig JE, Burdon KP. “Predictive factors for treatment outcomes with intravitreal anti-vascular endothelial growth factor injections in diabetic macular edema in clinical practice,” Int J Retina Vitreous. 2023;9(1):23. doi: 10.1186/s40942-023-00453-0.

26. Zhang X, Hu Q, Peng H, Huang J, Sang W, Guan J, Huang Z, Jiang B, Sun D. “Therapeutic potential of flavopiridol in diabetic retinopathy: Targeting DDX58,” Int Immunopharmacol. 2024;137:112504. doi: 10.1016/j.intimp.2024.112504.

27. Chen-Li G, Martinez-Archer R, Coghi A, Roca JA, Rodriguez FJ, Acaba-Berrocal L, Berrocal MH, Wu L. “Beyond VEGF: Angiopoietin-Tie Signaling Pathway in Diabetic Retinopathy,” J Clin Med. 2024;13(10):2778. doi: 10.3390/jcm13102778.

28. Shughoury A, Bhatwadekar A, Jusufbegovic D, Hajrasouliha A, Ciulla TA. “The evolving therapeutic landscape of diabetic retinopathy,” Expert Opin Biol Ther. 2023;23(10):969-985. doi: 10.1080/14712598.2023.2247987.

29. Zehden JA, Mortensen XM, Reddy A, Zhang AY. “ Systemic and Ocular Adverse Events with Intravitreal Anti-VEGF Therapy Used in the Treatment of Diabetic Retinopathy: a Review,” Curr Diab Rep. 2022;22(10):525-536. doi: 10.1007/s11892-022-01491-y.

30. Cheema AA, Cheema HR. “Diabetic Macular Edema Management: A Review of Anti-Vascular Endothelial Growth Factor (VEGF) Therapies,” Cureus. 2024;16(1):e52676. doi: 10.7759/cureus.52676.

31. Binder S. “Loss of reactivity in intravitreal anti-VEGF therapy: tachyphylaxis or tolerance?” Br J Ophthalmol. 2012;96(1):1-2. doi: 10.1136/bjophthalmol-2011-301236.

32. Del Cura Mar P, Carballés MJC, Sastre-Ibáñez M. “Risk of renal damage associated with intravitreal anti-VEGF therapy for diabetic macular edema in routine clinical practice,” Indian J Ophthalmol. 2023;71(8):3091-3094. doi: 10.4103/IJO.IJO_44_23.

33. Lye LF, Chou RH, Wu TK, Chuang WL, Tsai SC, Lin HJ, Tsai FJ, Chang KH. “Administration of Bevacizumab and the Risk of Chronic Kidney Disease Development in Taiwan Residents: A Population-Based Retrospective Cohort Study,” Int J Mol Sci. 2023;25(1):340. doi: 10.3390/ijms25010340.

34. Meir J, Huang L, Mahmood S, Whiteson H, Cohen S, Aronow WS. “The vascular complications of diabetes: a review of their management, pathogenesis, and prevention,” Expert Rev Endocrinol Metab. 2024;19(1):11-20. doi: 10.1080/17446651.2023.2279533.

35. Tang S, An X, Sun W, Zhang Y, Yang C, Kang X, Sun Y, Jiang L, Zhao X, Gao Q, Ji H, Lian F. “Parallelism and non-parallelism in diabetic nephropathy and diabetic retinopathy,” Front Endocrinol (Lausanne). 2024 ;15:1336123. doi: 10.3389/fendo.2024.1336123.

36. Ruiz-Moreno JM, Gámez Lechuga M, Calvo P, Merino M, Martín Lorenzo T, Maravilla-Herrera P, Gil Jiménez B, Abraldes MJ. “Burden of Disease Study of Patients with Diabetic Macular Oedema in Spain,” Ophthalmol Ther. 2024;13(7):1937-53. doi: 10.1007/s40123-024-00959-2.

37. Boyer DS, Rippmann JF, Ehrlich MS, Bakker RA, Chong V, Nguyen QD. “Amine oxidase copper-containing 3 (AOC3) inhibition: a potential novel target for the management of diabetic retinopathy,” Int J Retina Vitreous. 2021 Apr 12;7(1):30. doi: 10.1186/s40942-021-00288-7.

38. Dong Nguyen Q, Ehlers JP, Boyer DS, et al. Jin X, Giani A, Ehrlich MS; ROBIN study investigators. “ROBIN: a randomised, double-masked, placebo-controlled Phase IIa study of the AOC3 inhibitor BI 1467335 in diabetic retinopathy,” Eye (Lond). 2024 Jul;38(10):1861-1869. doi: 10.1038/s41433-024-03017-0.

39. Tan TE, Wong TY. “Diabetic retinopathy: Looking forward to 2030,” Front Endocrinol (Lausanne). 2023;13:1077669. doi: 10.3389/fendo.2022.1077669.

Save Me I will Save you