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Letter to the Editor

Beyond Glycemic Control: Can SGLT2 Inhibitors Alter the Course of Diabetic Retinopathy?

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Dear Editor,

We read with great interest the review by Babović et al. [1] published in the prestigious journal you edit, issue 81(5): 51803, identified by the DOI: https://doi.org/10.31083/pharmazie51803, which discusses the role of sodium-glucose cotransporter 2 (SGLT2) inhibitors in the management of diabetic retinopathy (DR). The authors present experimental and clinical evidence suggesting possible neuroprotective, anti-inflammatory, antioxidant, and vasculoprotective effects of these drugs. However, Webelieve it is important to delve deeper into an open question: Do the potential retinal benefits of SGLT2 inhibitors result from a direct ocular effect, or are they primarily a consequence of improved metabolic control and other systemic factors?

The biological plausibility of a direct effect on the retina is particularly interesting. The possible expression of SGLT2 in retinal endothelial cells and pericytes has been described, along with mechanisms related to the reduction of oxidative stress and inflammation, the preservation of the blood-retinal barrier, and the modulation of angiogenic factors. These experimental findings support the hypothesis of a potential retinoprotective effect, although translating this into clinical benefits still requires further evidence [1].

Recent clinical evidence shows mixed results. Xu et al. [2], in a systematic review and meta-analysis of 40 studies involving 104,586 participants, found no significant differences between SGLT2 inhibitors and placebo in the incidence of ocular events (relative risk (RR) 0.99; 95% confidence interval (CI): 0.86–1.15). These results contrast with observational studies that have found favorable associations. For example, Wai et al. [3], using electronic health records, compared patients with nonproliferative diabetic retinopathy receiving monotherapy with glucagon-like peptide-1 (GLP-1) agonists or SGLT2 inhibitors (6481 per group after matching) and observed, at three years, a lower rate of progression to proliferative retinopathy with SGLT2 (4.18% vs. 5.37%; RR with GLP-1: 1.28; 95% CI: 1.10–1.50) and a lower incidence of diabetic macular edema (18.76% vs. 24.23%). However, the comparator was a GLP-1 agonist rather than a placebo, and baseline differences in glycated hemoglobin (HbA1c) and body mass index (BMI) persisted between the groups [3]. Furthermore, a cohort study conducted in a population of more than three million patients with type 2 diabetes found a lower risk of vision-threatening retinopathy among SGLT2 users compared with users of other antidiabetic drugs [4].

These results should be interpreted with caution due to methodological differences among the studies. A recent meta-analysis, which included 16 randomized clinical trials and 19 real-world studies involving more than 2.3 million patients, found that randomized trials did not demonstrate a significant reduction in the incidence of DR, whereas real-world studies did show associations with lower incidence and progression. The authors noted that this discrepancy and the heterogeneity of the results warrant further prospective research and higher-quality clinical trials [5].

Another key aspect is the role of glycemic control. SGLT2 inhibitors lower blood glucose and HbA1c levels, in addition to modifying other metabolic and hemodynamic factors. Therefore, when a slower progression of DR is observed among users of these drugs, it is difficult to determine how much of the effect is due to direct action on the retina and how much is explained by changes in these systemic factors. This consideration is particularly relevant because, as Babović et al. [1] point out, many clinical studies have not adequately controlled for longitudinal changes in HbA1c or the concomitant use of other antidiabetic medications.

This uncertainty is particularly significant in Peru. A systematic review and meta-analysis published in 2024, involving researchers from Peruvian institutions, estimated a prevalence of DR of 37.3% among people with type 2 diabetes in Latin America and the Caribbean, although the certainty of the evidence was very low [6]. This situation highlights the need to generate regional evidence to determine whether the potential retinal effects of new antidiabetic treatments are reproducible in Latin American populations.

In this regard, future research should incorporate predefined ophthalmological outcomes, such as the progression from nonproliferative to proliferative retinopathy, the onset or progression of diabetic macular edema, and the need for anti-vascular endothelial growth factor (VEGF) treatment. It would also be advisable to include assess-

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ments using optical coherence tomography (OCT) and OCT angiography (OCT-A), and to monitor variables such as baseline and longitudinal HbA1c, duration of diabetes, blood pressure, renal function, the initial stage of diabetic retinopathy, and concomitant hypoglycemic treatments.

In conclusion, SGLT2 inhibitors represent a promising therapeutic hypothesis for diabetic retinopathy, supported by plausible experimental mechanisms and favorable associations observed in some observational studies. However, the available evidence does not yet allow us to establish that these potential retinal benefits are independent of metabolic improvement. Prospective studies with specific ophthalmic endpoints will allow us to determine more precisely whether these drugs have a true modifying effect on the progression of diabetic retinopathy.

Author Contributions

AG contributed to the conceptualization of the manuscript and the development of its content. AG and IH contributed to the literature review and the interpretation of the available information. IH provided guidance and advice on the manuscript structure. AG and IH participated in drafting and critically revising the manuscript. Both authors contributed to editorial changes in the manuscript. Both authors read and approved the final manuscript. Both authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

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Conflicts of Interest

The authors declare no conflicts of interest.

Declaration of AI and AI-Assisted Technologies in the Writing Process

During the preparation of this work, the authors used ChatGPT-3.5 in order to check spelling and grammar. After using this tool, the authors reviewed and edited the content as needed and take full responsibility for the content of the publication.

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