Review

Ocular Effects of GLP-1 Receptor Agonists: A Systematic Review of Current Evidence and Safety Concerns

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Ocular Effects of GLP-1 Receptor Agonists: A Systematic Review of Current Evidence and Safety Concerns

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Abstract

Glucagon-like peptide-1 receptor agonists (GLP-1RAs) have emerged as cornerstone therapies for type 2 diabetes mellitus and obesity, offering significant cardiovascular and renal protection. However, recent evidence has sparked interest and concern regarding their potential ocular effects. This review critically synthesizes current data on the impact of GLP-1RAs on diabetic retinopathy (DR), nonarteritic anterior ischemic optic neuropathy (NAION), age-related macular degeneration (AMD), and glaucoma or ocular hypertension. While preclinical studies suggest GLP-1RAs exert anti-inflammatory and neuroprotective effects in retinal tissues, clinical data remain mixed. Several large observational studies suggest a protective role against DR and glaucoma , while others raise safety concerns, particularly regarding semaglutide and NAION. Evidence on AMD is conflicting, with signals of both benefit and risk . We also discuss plausible pathophysiological mechanisms and the relevance of metabolic modulation on retinal perfusion. Overall, while GLP-1RAs hold promise for ocular protection in some contexts, vigilance is warranted, especially in patients with pre-existing eye disease. Further ophthalmology-focused prospective trials are essential to clarify long-term safety and guide clinical decision-making.

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1. Introduction

Glucagon-like peptide-1 receptor agonists (GLP-1RAs) have revolutionized the management of type 2 diabetes mellitus (T2DM) and obesity [1–3]. Beyond their proven glycemic and cardiometabolic benefits, these agents have gained attention for their potential pleiotropic effects, including on the central nervous system, kidneys, and increasingly, the eye. The discovery of GLP-1 receptor (GLP-1R) expression in retinal neurons and vascular tissues has raised the hypothesis that GLP-1RAs may influence the course of ocular diseases, either favorably or adversely [4–7]. The ocular safety of GLP-1RAs was first questioned following the SUSTAIN-6 trial, which reported an increased incidence of diabetic retinopathy complications with semaglutide[8]. Some studies suggest that GLP-1RAs may have a protective effect against diabetic retinopathy (DR) , while others report an increased risk of DR worsening, particularly with semaglutide[9–13]. Similarly, while certain analyses support a reduced incidence of age-related macular degeneration (AMD) among GLP-1RA users , other population-based studies have identified a higher risk of neovascular AMD[14,15]. Regarding optic nerve complications, several reports have associated semaglutide with an elevated risk of nonarteritic anterior ischemic optic neuropathy (NAION) [16–18].Finally, for glaucoma, some evidence points

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toward a risk reduction with GLP-1RA use , suggesting a potential neuroprotective role[14,19–21].Given the rapid and widespread use of GLP-1RAs in clinical practice, a clear understanding of their ocular implications is urgently needed. This review synthesizes current clinical and experimental evidence regarding the ocular effects of GLP-1RAs, focusing on diabetic retinopathy, NAION, AMD, and glaucoma/ocular hypertension. We also explore plausible biological mechanisms and propose areas for future research.

Diabetic Retinopathy: A Brief Overview

Diabetic retinopathy (DR) is one of the most common microvascular complications of diabetes mellitus and a leading cause of preventable vision loss in working-age adults[22] . It results from chronic hyperglycemia-induced damage to the retinal microvasculature, leading to increased vascular permeability, capillary nonperfusion, and pathological neovascularization. DR progresses from non-proliferative stages (NPDR), characterized by microaneurysms and hemorrhages, to proliferative diabetic retinopathy (PDR), marked by neovascularization and vision-threatening complications such as vitreous hemorrhage and tractional retinal detachment. Diabetic macular edema (DME), a consequence of fluid accumulation in the macula due to leaky capillaries, can occur at any stage of DR and represents a major cause of visual impairment. The pathogenesis of DR is multifactorial and involves oxidative stress, inflammation, neurodegeneration, and dysregulation of retinal blood flow. Strict glycemic control remains the cornerstone of DR prevention and progression delay. However, some glucose-lowering therapies may influence the course of DR beyond their systemic metabolic effects[23].

2. GLP-1 Receptor Agonists: Mechanism and Relevance in Ophthalmology

GLP-1RAs are a class of incretin-based therapies widely used in the management of type 2 diabetes and, more recently, obesity. These agents mimic the action of endogenous GLP-1 by binding to GLP-1 receptors and enhancing insulin secretion, inhibiting glucagon release, delaying gastric emptying, and reducing appetite. Agents such as semaglutide, liraglutide, exenatide, and dulaglutide have demonstrated significant cardiovascular and renal benefits, positioning GLP-1RAs as key components of modern diabetes care. In addition to their metabolic effects, GLP-1RAs have been shown in preclinical models to exert anti-inflammatory and neuroprotective effects on retinal tissue[5,24]. These include reduction of reactive oxygen species, inhibition of retinal glial activation, and preservation of the blood–retinal barrier. Consequently, GLP-1RAs have generated interest as potentially protective agents against DR progression. GLP-1RAs represent a cornerstone in the management of T2DM and obesity due to their robust glycemic efficacy and proven cardiovascular and renal benefits[11,12,25,26]. These agents, including semaglutide, liraglutide, exenatide, and dulaglutide, act by mimicking endogenous GLP-1, enhancing insulin secretion, inhibiting glucagon release, delaying gastric emptying, and promoting satiety[11,25].

3. GLP-1 Receptor Agonist and Diabetic Retinopathy

Beyond these systemic effects, increasing attention has been paid to their potential impact on the retina and optic nerve. Experimental studies have demonstrated that GLP-1RAs may confer direct retinal protection via anti-inflammatory, antioxidant, and neuroprotective mechanisms[11,27]. In diabetic models, they have been shown to reduce reactive oxygen species, inhibit glial activation, and preserve the blood-retinal barrier, supporting their theoretical utility in preventing or slowing the progression of DR. However, the translation of these findings into clinical outcomes remains controversial. The SUSTAIN-6 trial was among the first to raise concern regarding DR risk, reporting a higher incidence of diabetic retinopathy complications in patients receiving semaglutide compared to placebo (3.0% vs. 1.8%)[26]. While this finding was largely attributed to rapid glycemic improvement, a known trigger of early worsening of DR, the result prompted closer scrutiny of GLP-1RA ocular safety. Subsequent meta-analyses have yielded mixed results. Wang et al. reported no

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significant increase in DR risk across the class, although subanalyses indicated that older age and longer diabetes duration might modulate this association[10,12,13]. Real-world evidence has added nuance to this discussion. A large retrospective cohort analysis using Scandinavian registry data found no increase in retinopathy-related complications among GLP-1RA users compared to other antidiabetic agents[11]. Safety signals have also emerged from pharmacovigilance databases. Massy et al. and others observed increased reporting odds of visual impairment and retinopathy events with semaglutide, particularly when compared to metformin or DPP-4 inhibitors[10]. However, these data are hypothesis-generating and require cautious interpretation due to inherent biases in spontaneous reporting systems. Overall, while GLP-1RAs appear neutral,or potentially protective,regarding DR risk in most populations, caution may be warranted in individuals with pre-existing advanced retinopathy or poor baseline glycemic control, where rapid HbA1c reduction may trigger transient worsening. These findings echo prior experiences with intensive insulin therapy and highlight the need for gradual titration and close ophthalmologic monitoring[28,29]. As GLP-1RAs continue to expand in use, particularly in high-risk metabolic populations, prospective studies such as the ongoing FOCUS trial are essential to establish their long-term ocular safety profile. Future research should also address their role in other ocular disorders, including diabetic macular edema (DME), neovascular age-related macular degeneration, and optic neuropathies, for which preliminary data suggest potential applications [13,30].

4. Risk of NAION and Optic Nerve Complications with GLP-1 Receptor Agonists

NAION is a rare but potentially vision-threatening condition affecting the optic nerve head. A growing body of evidence suggests thatGLP-1 RAs, particularly semaglutide, may be associated with an increased risk of NAION and other optic nerve complications. A recent retrospective cohort study by Hathaway et al. (2024) evaluated over 16,800 patients referred to neuro-ophthalmology clinics and identified a significant association between semaglutide use and increased risk of NAION[16]. Specifically, among patients with type 2 diabetes, semaglutide users had a hazard ratio (HR) of 4.28 (95% CI 1.62–11.29) for NAION compared to matched controls; in obese or overweight patients, the HR rose to 7.64 (95% CI 2.21–26.36). This signal was echoed by Cai et al. (2025), who analyzed the FDA Adverse Event Reporting System (FAERS) and reported a notably higher reporting odds ratio (rOR) of NAION and other optic neuropathies in patients exposed to semaglutide compared to other GLP 1 RAs and antidiabetic medications . In over 810,000 new semaglutide users, semaglutide was associated with a modest but statistically significant increased risk of NAION in both active-comparator and self-controlled case-series designs, with hazard ratios ranging from 1.44 to 2.27, depending on the comparator and definition used[17] .

A large multinational retrospective cohort study using the TriNetX global health research network, conducted by Chien-Chih Chou and colleagues, analyzed over 297,000 individuals with type 2 diabetes, obesity, or both, to assess the potential association between semaglutide use and the development of NAION. The findings showed no significant increase in the risk of NAION among semaglutide users compared to those receiving other glucose-lowering or weight-loss medications, across all subgroups and at 1-, 2-, and 3-year follow-up intervals. These results suggest that semaglutide is not associated with an elevated risk of NAION in the general population, contrasting with previous single-center studies that lacked control for key confounders such as BMI or HbA1c levels[18].

In a recent case series, Ahmadi and Hamann (2025) described four patients who developed NAION shortly after initiating semaglutide therapy. All had a small optic disc diameter (<1.4 mm), reinforcing the hypothesis that the drug may act as a trigger in anatomically predisposed individuals [31].These findings support earlier pharmacovigilance signals from the FAERS database. In a separate study by Massy et al. (2025), semaglutide use was associated with a significantly elevated reporting odds ratio (rOR) for visual impairment and optic neuropathy compared to other antidiabetic agents, including other GLP-1 RAs (rOR 1.95; 95% CI 1.75–2.17), SGLT2 inhibitors (rOR 3.89; 95% CI 3.35–

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4.51), and metformin (rOR 2.23; 95% CI 1.90–2.62)[10]. The Massy et al. analysis of FAERS data further supports this association, showing significantly more reports of visual impairment and ischemic optic neuropathy with semaglutide than with other GLP 1 RAs or non-incretin antidiabetics . Despite some inconsistencies across study designs, this accumulating evidence highlights the need for heightened clinical vigilance when prescribing GLP-1 Ras, particularly semaglutide, to patients at elevated baseline risk of optic nerve ischemia, such as those with diabetes, hypertension, or crowded optic discs. From a pathophysiological perspective, NAION is typically caused by a sudden reduction in blood flow to the anterior portion of the optic nerve. This condition often arises in individuals with anatomical predispositions, such as a small and crowded optic disc, commonly referred to as a "disc at risk." While the exact mechanisms linking GLP 1 receptor agonists to NAION are still under investigation, several plausible explanations have been proposed. [32]One possible factor is the rapid improvement in glycemic control and weight loss frequently observed with semaglutide treatment. These abrupt metabolic changes may temporarily disrupt the autoregulation of optic nerve perfusion. A similar phenomenon has been observed in patients starting insulin therapy, where rapid declines in blood glucose were associated with retinal worsening. In addition, although the direct expression of GLP 1 receptors in the optic nerve has not been definitively demonstrated, these receptors have been identified in retinal ganglion cells and vascular endothelial tissues, suggesting a potential off-target effect on the microvasculature of the optic nerve. Another contributing element may be nocturnal hypotension, which can become more pronounced following significant weight loss or improved insulin sensitivity. In patients with a disc at risk, reduced perfusion pressure during sleep might be sufficient to trigger an ischemic insult at the optic nerve head. Taken together, these hypotheses suggest that GLP 1 receptor agonists, particularly semaglutide, could play a role in the development of NAION in vulnerable individuals. Although causality has not yet been established, these mechanisms highlight the need for careful monitoring and further investigations

5. Potential Impact of GLP-1 Receptor Agonists on Age-Related Macular Degeneration

AMD is a leading cause of irreversible visual impairment in older adults, particularly in Western populations. Its progressive nature and impact on central vision contribute significantly to the global burden of blindness. As the worldwide prevalence of AMD is expected to rise substantially in the coming decades, identifying preventive strategies beyond conventional treatments remains a critical area of research. A recent large-scale, retrospective cohort study utilizing the TriNetX health records database explored the long-term impact of GLP-1 RA use on the risk of developing chronic ocular diseases, including AMD, in an at-risk population aged over 60 with at least five years of ophthalmology follow-up. After propensity-score matching with patients on other anti-diabetic and lipid-lowering agents, GLP-1 RAs were associated with a significantly reduced hazard of both nonexudative and exudative AMD compared to metformin (HR 0.68 and 0.62, respectively), statins, insulin, and aspirin. These protective associations persisted across multiple time points (3 and 5 years) and were validated in several subgroup analyses. Mechanistically, the authors hypothesize that GLP-1 RAs may confer retinal protection either through direct neuroprotective action,given the presence of GLP-1 receptors in retinal layers, or by modulating systemic risk factors such as adiposity and dyslipidemia that contribute to drusen formation and retinal pigment epithelium dysfunction.[14]

In contrast, a recent population-based matched cohort study conducted in Ontario, Canada, using real-world health data from over 1 million individuals, reported an increased risk of neovascular AMD (nAMD) among patients with diabetes treated with GLP-1 RAs. In that study, exposure to GLP-1 RAs for six months or more was associated with more than double the risk of new nAMD diagnosis compared to unexposed diabetic individuals (HR 2.21, 95% CI 1.65–2.96), and this risk increased with longer treatment duration. The authors employed a strict operational definition of nAMD based on ICD coding and the subsequent administration of intravitreal anti-VEGF therapy. Several mechanisms were proposed, including GLP-1–induced upregulation of angiogenic factors

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such as VEGF via chemokine pathways (e.g., CXCL12), as well as potential retinal metabolic disturbances in the context of rapid systemic glucose normalization[14,15].

These seemingly discordant findings highlight the complex and potentially dual role of GLP-1 RAs in AMD pathophysiology. While some data support a protective effect,particularly for nonexudative AMD,other evidence points toward a potential increased risk of neovascular transformation under certain conditions. Several factors may explain the heterogeneity in results, including differences in study design, definitions of exposure and outcome, population characteristics, and the stage of AMD assessed. Notably, the protective associations in the TriNetX study emerged primarily in comparisons with medications such as insulin and statins, while the Shor et al. study compared GLP-1 RA users against untreated diabetic controls and focused exclusively on neovascular disease. In conclusion, the current body of evidence provides conflicting signals regarding the impact of GLP-1 RAs on AMD. Further prospective, ophthalmology-specific investigations are needed to clarify whether these agents mitigate or exacerbate AMD risk across its various stages. Until such data are available, caution is warranted in interpreting these associations, and clinicians should remain vigilant in monitoring ocular health among patients receiving long-term GLP-1 RA therapy.

6. Glaucoma and Ocular Hypertension: Evidence for a Protective Role of GLP-1 Receptor Agonists

While intraocular pressure (IOP) is the primary modifiable risk factor for glaucoma, growing evidence suggests that neuroinflammatory and metabolic mechanisms also contribute significantly to retinal ganglion cell (RGC) degeneration and optic nerve damage. This has stimulated interest in pharmacological agents with neuroprotective and anti-inflammatory properties, including GLP-1RAs, which are widely used for glycemic control in type 2 diabetes mellitus (T2DM). In a recent large-scale observational cohort study, Allan et al. used the TriNetX research network to compare chronic ocular outcomes in diabetic patients treated with GLP-1RAs versus those on metformin, insulin, statins, or aspirin. The study found a significantly reduced hazard of developing primary open-angle glaucoma (POAG) among GLP-1RA users across several timepoints (HR 0.79 at 5 years) . Similarly, ocular hypertension (OHT) incidence was lower in GLP-1RA users compared to control groups, although the absolute reduction in IOP was modest and not deemed clinically significant. The protective association was robust even after adjusting for systemic vascular risk factors and medication confounders[14].

Supporting these findings, a systematic review and meta-analysis by Dillan Cunha Amaral et al. analyzed five retrospective studies comprising over 156,000 individuals with T2DM, of whom 43.7% were GLP-1RA users. The pooled analysis showed a trend toward reduced glaucoma incidence in the GLP-1RA group (HR 0.78, 95% CI 0.59–1.04), though not statistically significant at first. However, a leave-one-out sensitivity analysis excluding the outlier study by Shao et al. yielded a significant reduction in glaucoma incidence (HR 0.71, 95% CI 0.60–0.85) with greatly reduced heterogeneity (I^2 = 29%) [33]. The biological plausibility of these protective effects is supported by a growing body of experimental and clinical literature: GLP-1 receptors are expressed in multiple retinal layers, including the ganglion cell layer, the main target in glaucoma[9,27,33–38]. Preclinical studies in diabetic and hypertensive models have demonstrated that GLP-1RAs reduce retinal inflammation, oxidative stress, and excitotoxic damage, all of which are implicated in glaucoma pathogenesis[7,9,39]. Notably, Sterling et al., included in the meta-analysis, used rigorous propensity score matching in racially diverse populations to show that GLP-1RAs may lower glaucoma risk independent of baseline demographics and metabolic control[40].

Mechanistically, GLP-1RAs have been shown to downregulate pro-inflammatory cytokines such as TNF-α and IL-1β and enhance anti-apoptotic signaling in retinal ganglion cells, as demonstrated by Zhang et al. and others [8]. One important hypothesis proposed by Muayad et al. is that GLP-1RAs may inhibit Na^+/K^+-ATPase in the ciliary epithelium, leading to reduced aqueous humor

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production and IOP lowering. Additionally, activation of nitric oxide signaling may enhance trabecular meshwork outflow, contributing to IOP reduction[35].

However, the heterogeneity observed in the pooled meta-analysis raises important concerns. The study by Shao et al., which compared GLP-1RAs to SGLT2 inhibitors rather than a neutral or untreated control, contributed disproportionally to variability and introduced confounding due to potential protective effects of SGLT2 inhibitors themselves (which have been shown to reduce oxidative stress and improve retinal perfusion in preclinical glaucoma models) . Despite these promising findings, several limitations remain: All included studies were retrospective and non-randomized, raising concerns of residual confounding and selection bias. There was limited information on functional outcomes, such as visual field progression or optic nerve head imaging. Most studies relied on diagnostic codes without confirmation by glaucoma specialists. Nevertheless, taken together, the current body of evidence supports a protective association between GLP-1RA use and glaucoma incidence, especially when excluding outlier designs. While not definitive, these findings underscore the potential repurposing of GLP-1RAs as neuroprotective agents in at-risk diabetic populations. Future prospective randomized controlled trials, ideally incorporating objective IOP measurements, imaging biomarkers, and functional outcomes, are urgently needed to confirm these results and explore class-specific or dose-dependent effects.

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