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Review Article

Ocular Adverse Events Associated with Glucagone-Like-Peptide-1 Receptor Agonists (GLP-1RA): A Systematic Review

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Abstract

Background: Glucagone-Like-Peptide-1 receptor agonists (GLP-1RA) are widely used for diabetes and obesity management, offering significant metabolic benefits. However, recent evidence links these agents to potential ocular adverse events, including vision-threatening conditions.

Objective: To evaluate the nature of ocular adverse events associated with GLP-1RA use.

Methods: We systematically searched PubMed, Cochrane Library, Web of Science, and Ovid from inception to August 2025 for randomized controlled trials, observational cohorts, and case reports examining ocular outcomes in adults treated with GLP-1RAs.

Results: Evidence for ocular outcomes were mixed. Several trials and database studies reported worsening or progression of diabetic retinopathy, particularly in patients with pre-existing disease and rapid HbA1C reduction, while rare cases of nonarteritic anterior ischemic optic neuropathy were reported. In contrast, some studies suggested protective associations with glaucoma and dry eye disease, whereas findings for age-related macular degeneration were inconsistent.

Conclusion: GLP-1RAs appear to have variable ocular effects, potentially harmful in some conditions yet protective in others. However, high-quality prospective trials are needed to confirm these associations.

***Keywords**: GLP-1 Receptor Agonists; Visual Impairment; Ocular Adverse Events; Systematic Review*

Introduction

Glucagon-like peptide-1 receptor agonists (GLP-1RA) are widely used for the management of type 2 diabetes and, more recently, chronic weight management. These agents exert their effects by activating GLP-1 receptors, leading to enhanced insulin secretion, delayed gastric emptying, and reduced postprandial glucagon release resulting in improved glycemic control and decreased caloric intake [1,2]. While effective in improving metabolic outcomes, GLP-1RA have raised concerns about potential ocular adverse effects, which remain underreported and inconsistently described despite widespread use. Reports suggest associations with retinal disorders, optic nerve damage, glaucoma, and visual disturbances, particularly in individuals with pre-existing ocular conditions. Given the potential for irreversible ocular complications, early recognition of such risks is clinically important. We conducted a systematic review to evaluate the

incidence and nature of ocular adverse events linked to GLP-1 receptor agonist use. This review synthesizes evidence from randomized controlled trials and observational studies. Findings aim to inform clinical decision-making and guide future research on the ocular safety of GLP-1 medications.

Methods

Review of the literature

This systematic review was registered in PROSPERO (CRD420251077991). Electronic databases such as PUBMED, Cochrane, Web of Science, and OVID were searched using a predefined keywords and Boolean operators: ("GLP-1 receptor agonist" OR semaglutide OR liraglutide OR dulaglutide OR exenatide OR albiglutide OR lixisenatide) AND ("eye" OR "ocular" OR "vision" OR "retinopathy" OR "diabetic retinopathy" OR "macular edema" OR "optic neuropathy" OR "glaucoma" OR "visual impairment"). The search was supplemented by hand-searching reference list of relevant studies.

Selection of studies

Studies were selected according to predefined inclusion and exclusion criteria. Inclusion criteria required studies to involve adult participants older than 18 years of age exposed to GLP-1RA; use of any GLP-1RA as the intervention; include a comparator group not using GLP-1RA (e.g. placebo, no treatment, or other glucose-lowering therapies); report ocular outcomes, including retinal disorders, optic nerve disorders, glaucoma, visual acuity changes, visual field loss, dry eye, or other ocular events; and were human-based studies with randomized controlled trials, observational studies, cohort studies, or comparative studies published in English.

Exclusion criteria included: pediatric populations younger than 18 years of age, studies lacking a comparator group, those not reporting ocular outcomes or providing insufficient ocular data and publications not available in English or not involving human participants.

Screening of studies and data extraction

Screening was conducted in two stages. All articles were screened and reviewed independently by two reviewers based on title and abstract, with disagreements resolved by discussion. Full-text articles were then assessed for eligibility by two reviewers independently, with any disagreements resolved by discussion.

Data extraction was conducted using a form capturing key information including first author, year of publication, and country, study characteristics (design, sample size, and comparator group, if present), and participant demographics (mean age, gender, and baseline ocular history). In addition, details of the intervention included the type of GLP-1RA used, indication for use, dose, duration of treatment, and concurrent antidiabetic or systemic medications. Ocular outcomes extracted included the type and severity of reported adverse events (e.g. retinopathy, glaucoma, optic neuropathy), time to onset following GLP-1RA initiation, reversibility or persistence of the event, and any reported causality assessments were also extracted. Additional variables recorded were author conclusions, study limitations, risk of bias assessment, and information on funding sources or conflicts of interest.

Results

A total of 798 studies were identified through database searching and manual reference checks. After removal of duplicates, 724 were screened by titles and abstracts. Out of 724, 109 full-text articles were assessed for eligibility.

The included studies published from inception to August 2025, consisting of randomized controlled trials, observational studies, and case reports/series. The study population included adult patients (≥18 years) exposed to GLP-1RAs, including semaglutide, liraglutide, dulaglutide, and exenatide. Sample sizes varied from case reports, large-scale retrospective cohorts to randomized controlled trials.

Studies were conducted across multiple regions, including North America, Europe, and Asia, with follow-up periods ranging from a few weeks to several years. Key ocular outcomes assessed included diabetic retinopathy, ischemic optic neuropathy, glaucoma, age-related macular degeneration, dry eye disease, and idiopathic intracranial hypertension. Most studies compared GLP-1RAs to placebo or other antidiabetic agents, and findings were mixed, with some showing potential protective effects, while others reported transient worsening especially in patients with pre-existing disease.

Diabetic retinopathy

Diabetic retinopathy (DR) is the leading cause of vision loss in patients with diabetes, with risk influenced by poor glycemic control, longer disease duration, and vascular comorbidities [3]. Rapid HbA1c lowering, a hallmark of GLP-1RAs, has also been implicated in progression [4]. In SUSTAIN-6 (Trial to Evaluate Cardiovascular and Other Long-term Outcomes with Semaglutide in Subjects with Type 2 Diabetes), a large cardiovascular outcomes trial in patients with type 2 diabetes, demonstrated that while semaglutide significantly reduced major adverse cardiovascular events, it was also associated with an increased risk of DR complications. Specifically, rates of vitreous hemorrhage, blindness, or conditions requiring intravitreal injection therapy or laser photocoagulation were significantly higher in the semaglutide group compared with placebo (HR 1.76; 95% CI, 1.11-2.78; P = 0.02) [5]. In the LEADER trial (Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results), DR events occurred slightly more often with liraglutide than with placebo (0.6 vs. 0.5 events per 100 patient-years), but this difference was not statistically significant (HR 1.15, 95% CI 0.87-1.52; P = 0.33) [6]. The FOCUS trial (Long-term effects of semaglutide on diabetic retinopathy in subjects with type 2 diabetes), a large ongoing study evaluating semaglutide in patients with type 2 diabetes, is investigating its long-term effects on diabetic eye disease and is expected to be complete in 2026 [7].

The evidence from observational studies were mixed. Several large observational studies suggest an increased risk of retinopathy progression. Wai., *et al*. reported that among individuals with non-proliferative DR, GLP-1RA use was associated with higher progression to proliferative DR at both 1 year and 3 years compared with Sodium-glucose Cotransporter-2 inhibitors (SGLT2i), as well as elevated risk of new-onset DME [8]. In contrast, Talebi., *et al*. found that GLP-1RA use was linked to reduced risks of incident DR, DME, and treatment-requiring DR/DME compared with non-user [11]. On the other hand, Tauqeer., *et al*. reported no significant differences in progression to vision-threatening DR, proliferative DR, or DME compared with other oral agents [13]. In the Angiosafe Type 2 diabetes study, with a cohort of >3,000 patients, showed that GLP-1RA use was not associated with severe DR [18]. Detailed study characteristics and outcomes are summarized in table 1.

Author	Year	Study design	Sample Size	GLP-1RA agent used	Comparator	Conclusions
Wai., *et al*. [8]	2024	Retrospective cohort study	n = 6481	GLP-1RA	SGLTI	NPDR with use of GLP-1RA
Eleftheriadou., *et al*. [9]	2024	Retrospective cohort study	n = ~2 million	GLP-1RA +insulin	SGLTI+insulin	SGLT2i+insulin use reduced the risk of DME, while GLP-1RA+insulin use increased DR risk.
Lin., *et al*. [10]	2024	Retrospective cohort study	n = 97,413	GLP-1RA	SGLT-2I	In patients with pre-existing DR, GLP-1RA was linked to higher risk of DR progression, mainly tractional RD.

Talebi., *et al*. [11]	2024	Retrospective cohort study	n = 37,258	GLP-1RA users	Nonusers	GLP-1RA use was linked to reduced risks of incident DR, DME, and treatment-requiring DR/DME.
Fadini., *et al*. [12]	2018	Retrospective pharmacovigilance analysis	n = 9, 217, 555	GLP-1RA	Other glucose lower medications	Lower retinal AE rates among GLP-1RA users versus other GLM.
Taqueer., *et al*. [13]	2025	Retrospective cohort study	n = 20,218	GLP-1RA	Other glucose lower medications	No significant differences in progression to vision-threatening DR, PDR, or DME.
Yen., *et al*. [14]	2024	Retrospective cohort study	n = 1.264,730	GLP-1RA	DDP-4I, SGLT-2I and sulfonylureas	No increased risk versus non-use, with lower risk than DPP-4I but no difference versus SGLT2i or sulfonylurea
Joo., *et al*. [15]	2024	Retrospective cohort study	n = 981	GLP-1RA (Semaglutide, dulaglutide, and exenatide)	SGLT-2I (empagliflozin, canagliflozin, and dapagliflozin)	No association between GLP-1RA use and DR worsening compared with SGLT-2I. Most events occurred in patients with pre-existing PDR, primarily vitreous hemorrhage, followed by macular edema and PDR.
Barkmeier., *et al*. [16]	2025	Retrospective observational database study	n = 371, 698	GLP-1RA	SGLT-2I, DPP-4I and sulfonylurea	GLP-1RA do not confer increased retinal risk, relative to DPP-4i and sulfonylurea.
Ueda., *et al*. [17]	2019	Retrospective multinational cohort study	n = 18,280	GLP-1RA	DPP-4I	No increased risk of DR complications with GLP-1Ras.

Table 1: *Abbreviations: GLM: Glucose Lowering Medications; GLP-1RA: Glucagon-Like Peptide-1 Receptor Agonist; SGLTI: Sodium-Glucose Co-transporter Inhibitors; DPP-4i: Dipeptidyl Peptidase-4 Inhibitors; DR: Diabetic Retinopathy; DME: Diabetic Macular Edema; PDR: Proliferative Diabetic Retinopathy; NPDR: Non-Proliferative Diabetic Retinopathy; RD: Retinal Detachment; AE: Adverse Events.*

Reports from clinical practice describe both worsening DR in some patients following semaglutide and regression of PDR and DME in others [19-20]. Additional data found that increased GLP1R expression in pancreatic tissue was linked to a decreased risk of developing DR [21].

Diabetic macular edema

Diabetic macular edema (DME), a major cause of vision loss in patients with diabetes, has also been evaluated in relation to GLP-1RA therapy. In a large comparative cohort, Su., *et al*. found that among new SGLT2i and GLP-1RA users, DME incidence was lower in the SGLTi group compared to GLP-1RA users [22]. On the other hand, Phu., *et al*. analyzed a large real-world dataset and demonstrated no increased

risk of DME with GLP-1RAs, SGLT2is, or DPP-4i after adjustment for demographic and DR duration and severity [23]. In addition, case-based reports described complete regression of DME with exenatide, maintained for six months with improved vision [24].

Glaucoma

Glaucoma is a group of optic neuropathies, characterized by progressive optic nerve damage, often associated with elevated intra-ocular pressure (IOP) [25]. Multiple large-scale cohort studies have explored the relationship between GLP-1RAs and glaucoma risk, with most suggesting a protective association [26-30]. The protective effect appears strongest with prolonged use [27], and it is particularly evident in patient younger than 60 years of age [29]. Similar benefits are also observed in non-diabetic population [30]. For comparison, Eng., *et al*. found SGLT2i to be more protective overall, with ertugliflozin showing the strongest effect compared to GLP-1Ras [31]. Key study characteristics and outcomes summarized in table 2.

Author	Year	Study design	GLP-1RA agent used	Comparator	Conclusions
Muayad., *et al*. [26]	2024	Retrospective cohort study	GLP-1RA users	Metformin	GLP-1RA use significantly reduced the risk of POAG, ocular hypertension, and initiation of glaucoma therapy compared with metformin.
Niazi., *et al*. [27]	2023	Registry-based nationwide case-control study	GLP-RA	Other GLMs	Lower glaucoma risk among GLP-1RA users
Sterling., *et al*. [28]	2023	Retrospective cohort study	GLP-1RA users	Nonusers	Lower incidence of glaucoma among GLP-1RA users compared with matched controls.
Chuang., *et al*. [29]	2023	Retrospective cohort study	GLP-1RA users	Nonusers	Lower POAG risk
Vasu., *et al*. [30]	2025	Retrospective cohort study	GLP-1RA users	Other weigh loss medications	Lower risk of POAG

Table 2: *Abbreviations: GLM: Glucose Lowering Medications; GLP-1RA: Glucagon-Like Peptide-1 Receptor Agonist; POAG: Primary Open Angle Glaucoma.*

Nonarteritic ischemic optic neuropathy

Nonarteritic anterior ischemic optic neuropathy (NAION) is the most common cause of acute optic nerve injury in adults over 50 years of age [32]. Multiple studies identified a potential association between semaglutide and increased NAION risk [33-35], However, the association between semaglutide and NAION is still unclear. Hathaway *et al*. found a significantly elevated hazard ratio for NAION in both type 2 diabetes and obesity cohorts, with 8.9% of cases occurring within the first year [33]. Case reports and small series have described patients developing NAION soon after initiating GLP-1RAs, sometimes worsening with drug switches or recurring on rechallenge, although confounding by rapid glycemic correction cannot be excluded [36-38]. In contrast, Chou., *et al*. using large real-world datasets, did not find a statistically significant association between semaglutide and NAION across diabetic, obese, and mixed cohorts [39]. Detailed key study findings and outcome are summarized in table 3.

Author	Year	Study design	GLP-1RA agent used	Comparator	Conclusions
Hathaway., *et al*. [33]	2024	Retrospective cohort study	Semaglutide	Other GLM	Observed increased risk in NAION
Grauslund., *et al*. [34]	2024	National, registry-based prospective cohort study	Semaglutide	Nonusers	Observed increased risk of NAION
Simnosen., *et al*. [35]	2025	A registry-based cohort study	Semaglutide	SGLT-2I	Observed increased risk of NAION
Chou., *et al*. [39]	2024	Retrospective cohort study	Semaglutide	Other GLM or other weigh-loss medications	Observed no association with NAION
Hsu., *et al*. [40]	2025	Retrospective cohort study	Semaglutide	Other GLM	Observed increased risk of NAION

Table 3: *Abbreviations: GLM: Glucose Lowering Medications; GLP-1RA: Glucagon-Like Peptide-1 Receptor Agonist; SGLTI: Sodium-Glucose Co-transporter Inhibitors; NAION: Non-Arteritic Anterior Ischemic Optic Neuropathy.*

A systematic review and meta-analysis of randomized controlled trials by Silverii., *et al*. identified eight cases of ION among GLP-1RA users and four cases among controls and found no significant risk increase among GLP-1RA users, though the rarity and underreporting of cases limit firm conclusions [41].

Age related macular degeneration

Age-related macular degeneration (AMD) is a degenerative retinal disease and the leading cause of blindness among those over 65 years in developed countries [42]. Insulin resistance has been implicated in its pathogenesis, particularly in neovascular AMD [43]. Since GLP-1RAs, especially semaglutide, improve insulin sensitivity primarily through weight reduction [44], they are hypothesized to lower AMD risk. However, evidence is inconsistent. In a large population-based cohort study, Shor., *et al*. analyzed 139,002 matched patients with diabetes and reported that GLP-1RA use for at least six months was associated with more than a two-fold increased risk of neovascular AMD compared to unexposed individuals [45]. Whereas, Allan., *et al*. evaluated patients with at least five years of followup and found that GLP1RA use was associated with a significantly reduced risk of nonexudative AMD compared with metformin, insulin, and statins, with benefits becoming evident after three years of treatment [46]. For comparison, other anti-hyperglycemic agents have also been evaluated in relation to AMD. Aggarwal., *et al*. found that metformin use within the two years preceding diagnosis was associated with a significantly lower risk of AMD [47]. While Hsu., *et al*. reported that in patients with newly diagnosed diabetes mellitus, use of SGLT2i for at least 90 days was linked to a reduced risk of macular degeneration [48].

The conflicting findings may reflect the inherent limitations of retrospective database studies. Differences in study populations, AMD subtypes, and follow-up durations, along with variability in comparator groups, baseline metabolic profiles, and adjustment for confounders further complicate interpretation.

Dry eye disease

Dry eye disease (DED) is a common condition characterized by defects in the production or composition of tears and ocular surface inflammation that cause conjunctival irritation [49]. In a large Chinese study, DED prevalence was reported at 17.5%, especially those with poor metabolic control, suggesting that improved glycemic management through GLP-1RAs or SGLT2i may reduce DED incidence [50]. Supporting this, a large Taiwanese cohort reported that GLP-1RA use was associated with significantly lower rates of DED and

superficial keratitis compared with non-users, with stronger effects observed in patients younger than 60 years [51]. In patients with type 2 diabetes, female sex, older age, poor glycemic control, microvascular complications, and ocular procedures were identified as significant risk factors for DED, while oral antihyperglycemic agents reduced risk compared to metformin alone, with SGLT2i most protective and GLP-1RAs second [52]. Direct comparisons indicate that SGLT2i users have a lower incidence of DED than those treated with GLP-1RAs, with consistent results across subgroups and sensitivity analyses [53].

Idiopathic intracranial hypertension

Idiopathic intracranial hypertension (IIH) is a characterized by chronically elevated intracranial pressure (ICP) of unknown cause, most often affecting obese women [54]. The most common symptoms is diffuse headaches, transient visual disturbances, and pulsatile tinnitus. Ophthalmologic examination is crucial, typically revealing bilateral papilledema that and can progress to severe vision loss or blindness in up to 24% of patients [55]. Current evidence on the use of GLP-1RA in IIH is expanding. The available studies suggest that GLP-1RA may offer meaningful outcomes in IIH, particularly in lowering ICP, reducing papilledema, and improving headache and visual outcomes, with weight loss as a key but not an exclusive factor. A randomized, placebo-controlled, double-blind trial by Mitchell and colleagues and showed that exenatide significantly and consistently reduced ICP in women with active IIH, accompanied by improvements in visual acuity and headache frequency [56]. While another study found that semaglutide given alongside standard weight management, achieved greater weight loss and reductions in monthly headache days compared with controls, though visual outcomes remained unchanged [57]. Moreover, a case report described recurrent papilledema after semaglutide discontinuation [61]. Additional studies with key findings and outcomes are summarized in table 4.

Author	Year	Study design	GLP-1RA agent used	Comparator	Conclusions
Mitchell., *et al*. [56]	2023	Prospective, randomized, parallel group, placebo- controlled trial	Exenatide	Placebo	Significantly reduced ICP with improvements in VA and headache frequency
Krajnc., *et al*. [57]	2023	Open-label, single-center, case-control pilot stud	Semaglutide, liraglutide + UCWM	UCWM only	GLP-1RA + UCWM achieved greater weight loss and reductions in monthly headache days compared with controls, though visual outcomes remained unchanged.
Kravetz., *et al*. [58]	2024	Retrospective cohort study	Acetazolamide only	Liraglutide /Semaglutide + Acetazolamide	Adding to GLP-1RA reduced BMI without worsening ocular outcomes
Azzam., *et al*. [59]	2025	Retrospective cohort study	Liraglutide	Nonusers	Significantly reduced the risk of papilledema within three months, with benefits sustained for two years
Sioutas., *et al*. [60]	2025	Retrospective cohort study	GLP-1RA users	Nonusers	Reduced medication use, fewer headaches, visual disturbances/ blindness, and papilledema, and less need for interventions.

Table 4: *Abbreviations: UCWM: Usual Care Weight Management; GLP-1RA: Glucagon-Like Peptide-1 Receptor Agonist; ICP: Intracranial Pressure; BMI: Body Mass Index.*

Other ocular manifestations

Reports of these transient but potentially serious ocular manifestations with GLP-1RA therapy have been described. Case reports have described central retinal artery occlusion [62], and reversible bilateral scotomas following semaglutide initiation [63], while a large multinational cohort suggested reduced risk of retinal vein occlusion compared with DPP-4i, with stronger effects in patients aged ≥50 years, those with HbA1c ≥7.5%, and Black patients [64]. These are largely derived from case reports or retrospective studies, which are limited by small sample sizes, reporting bias, and the inability to establish causality, with confounding from rapid glycemic improvement. These observations emphasize the importance of clinician reporting of suspected cases and the need for well-designed prospective studies to determine whether these manifestations represent true drug-related risks or coincidental findings.

Discussion

This review summarized the current evidence on ocular safety of GLP-1RAs. While evidence suggests these agents may have neuroprotective and anti-inflammatory benefits that reduce the risk of conditions such as glaucoma and dry eye disease, evidence showed potential worsening of diabetic retinopathy and rare reports of ischemic optic neuropathy.

A recently published global pharmacovigilance study by Lakhini., *et al*. analyzed over 12 million FAERS reports and 35 million VigiBase reports to evaluate ocular safety signals with GLP-1RAs. Semaglutide, in particular, showed significantly increased reporting odds for ION, DR, and several retinal complications (including vitreous detachment, hemorrhage, and tears), with additional associations for macular edema, macular hole, and papilledema identified in VigiBase. These signals were consistent across sensitivity analyses against comparators such as insulin and SGLT2 inhibitors. By contrast, tirzepatide was only associated with DR in FAERS. Because pharmacovigilance studies rely on spontaneous reporting, they cannot prove causality and are vulnerable to underreporting and reporting bias. Still, the strength of the observed safety signals highlights the importance of well-designed prospective studies [65].

As previously noted, GLP-1RA use has been linked to a modest increase in DR incidence. In SUSTAIN-6 trial, Semaglutide significantly reduced major cardiovascular outcomes but was associated with higher rate of DR complications compared to placebo, mostly in patients with pre-existing retinopathy [5]. In contrast, the LEADER trial reported a nonsignificant increase in DR events with Liraglutide compared with placebo [6]. Proposed explanation for these discrepancies include short duration of trials, absence of standardized methods of DR grading or rapid glycemic correction [66]. Multiple trials including PIONEER-6 and AWARD-11 trials did not show DR worsening [67,68], and pooled analyses from SUSTAIN 1-5 and Japanese trials showed no consistent association [5]. A consistent concept across these studies is the early worsening effect. Rapid improvement in glycemic control can trigger short-term worsening of diabetic retinopathy, despite long-term benefits. This pattern was clearly demonstrated in the Diabetes Control and Complications Trial (DCCT), where intensively treated patients with type 1 diabetes showed early progression of retinopathy but later experienced significantly better retinal outcomes compared with those receiving conventional therapy [69]. Evidence for this phenomenon in type 2 diabetes is more limited, as many major trials did not include early ophthalmic assessments. However, in SUSTAIN-6 [5], the higher rate of retinopathy complications observed with semaglutide is likely attributed to its rapid HbA1c reduction, but given the trial was relatively short, it is uncertain whether longer follow-up would have shown later benefit. Systematic review and meta-analyses showed mixed results, but collectively emphasized that baseline DR severity and the rate of glycemic improvement are central determinants of early retinal outcomes [70-75]. Preclinical evidence provides additional important context regarding the retinal effects of GLP-1RA, although human data is limited. GLP-1 receptor expression has been identified in low levels in the ganglion cell layer of the retina in healthy eyes, with loss of expression in advanced PDR [76]. Experimental studies show that GLP-1 receptors are present in the human retina and that GLP-1 based therapies can counteract early retinal damage seen in DR. In animal studies, GLP-1 RAs, whether administered systemically or topically, have been shown to protect the diabetic retina from neurodegeneration independently of glucose lowering [77], reduce inflammation and blood-retinal barrier (BRB) breakdown through suppression of proinflammatory cytokines and NF-κB signaling [78], and preserve tight-junction proteins essential

for barrier integrity [79]. Additionally, SGLT2 inhibitors may also provide retinal protection. SGLT2i are present in retinal mesangial cells and pericytes [80]. It has been demonstrated that SGLT2 in retinal pericytes regulates glucose entry and cellular tone [81,82]. High glucose leads to excessive SGLT2-mediated glucose and sodium uptake, causing pericyte swelling, loss of contractility, and microvascular dysfunction, as well as extracellular matrix overproduction and microvessel occlusion [80,83,84]. SGLT2 inhibition normalizes glucose uptake, reduces swelling, and may protect against early DR [84]. Given the potential for early worsening of diabetic retinopathy with rapid glycemic correction, particularly with short trial durations, and variability among GLP-1RA agents, future studies should assess retinopathy both prior to and following initiation of therapy using gradual glycemic control and standardized retinopathy assessments to ensure consistent and reliable outcomes.

While GLP-1RAs appears to protect the retina from neurodegeneration associated with DR, the relationship between GLP-1RA use and DME remains unclear. In SUSTAIN-6, worsening of DME was reported in patients with baseline DR in patients recieving semaglutide compared with placebo. Effects of SGLT2 inhibitors on DME is similarly limited. Experimental studies suggested that SGLT2 inhibition may help reduce retinal hypoxia and inflammation, potentially offering protective effect against DME [80,85-87]. However, the clinical relevance of these mechanisms is incompletely defined.

Regarding glaucoma, preclinical research has demonstrated that GLP-1RAs show promise as potential neuroprotective agents in neurodegenerative disorders including glaucoma [88-90], with effects observed in both the retina and the brain [91]. Ongoing clinical trials in neurodegenerative diseases such as Alzheimer's further support their neuroprotective potential [92]. While this supports a potential therapeutic role of GLP1RA in glaucoma, further studies are required to clarify whether the observed benefits are independent of glycemic control. Systematic review and meta-analyses by Amaral., *et al*. analyzed five retrospective studies (n = 156,042) and found no significant difference in glaucoma incidence between GLP-1RA users and controls; However, exclusion of one conflicting study showed a significant reduction in glaucoma risk [93]. On the other hand, Asif., *et al*. analyzed five observational studies and found no significant reduction in glaucoma incidence with GLP-1RA use versus other anti-hyperglycemics. Sensitivity analysis, however, revealed a significant protective effect [94].

Regarding NAION, the pathophysiology is incompletely understood, but it is believed to involve insufficient blood flow to the anterior optic nerve head (ONH). Relative hypoperfusion, in combination with structural or other predisposing factors, can lead to edema and infarction of optic nerve fibers [95]. Several systemic and vascular risk factors are associated with this process, including systemic hypotension, particularly nocturnal blood pressure drops, atherosclerosis, diabetes, hypertension, hyperlipidemia, obstructive sleep apnea, and cardiovascular disease [96]. However, NAION appears to be a multifactorial and complex condition. Because its underlying mechanisms are not fully defined, it remains unclear whether and how GLP-based therapies may influence the development or progression of NAION.

On the other hand, DED is influenced by inflammatory processes and damage to the lacrimal gland that can arise from diabetic neuropathy [97-99]. SGLT2i and GLP-1RA have been investigated for their potential anti-inflammatory and neuroprotective roles that could explain the reduction of DED in patients on these medications [100-104].

This variability in results emphasizes the complexity of GLP-1RA effects on the eye. This may be explained by several factors. These findings are complicated by the fact that patients receiving GLP-1RAs are more likely to have underlying chronic diseases such as diabetes, hypertension, and obesity, which themselves predispose to ocular complications, making it difficult to separate drug effects from background disease risk. The variability is further complicated by reliance on the current available data. Much of the data is derived from retrospective database studies and case reports, which are limited by coding errors, lack of standardized ophthalmic assessments, incomplete clinical details, reporting bias, and incompletely adjustment for confounders such as baseline disease severity or concurrent therapies. However, this review brings together evidence from clinical trials, real-world studies, and pharmacovigilance databases,

offering a broad perspective on how GLP-1RAs impact the eye while clearly identifying gaps in current knowledge. Its strengths include the range of data sources and the consideration of multiple ocular outcomes, from DR and ION to glaucoma, AMD, DED and IIH.

Conclusion

In conclusion, prospective randomized trials with standardized ophthalmologic outcomes are required to clarify these associations and determine whether GLP-1RAs provide meaningful ocular protection, and if so, which patient subgroups may benefit most. In the meantime, GLP-1RAs should not be withheld for ocular safety concerns alone. Formal guidelines for ocular screening specific to GLP-1 receptor agonist therapy have not yet been established. However, in patients with pre-existing eye disease or high ophthalmic risk, the potential for ocular disease worsening should be carefully balanced against the well-established cardiovascular and metabolic benefits of treatment, with closer ophthalmologic monitoring considered. Patients with preexisting DR or high-risk features such as long diabetes duration should undergo careful optic nerve evaluation, and standard DR screening should continue at least annually, or more frequently when clinically indicated. Prior to initiating semaglutide, a dilated funduscopic examination may be appropriate in diabetic or otherwise at-risk individuals to detect and manage concomitant DR, and in those with severe DR, retinopathy treatment should be initiated before or concurrently with glucose-lowering therapy due to the possibility of transient early worsening [105-106]. Management of DR in patients receiving semaglutide remains consistent with established guidelines, including the use of anti–vascular endothelial growth factor therapy when indicated. Clinicians should also discuss the rare but potentially serious risk of NAION, particularly in patients with relevant risk factors, emphasize the importance of timely screening and early detection, and ensure that any new visual symptoms, such as blurred vision, sudden or progressive vision loss, floaters, or visual field defects, warrant immediate ophthalmologic assessment.

Conflict of Interest

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