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The eye in the era of GLP-1 receptor agonists – a narrative review of current evidence

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ABSTRACT

Introduction and aim. Glucagon-like peptide-1 receptor agonists (GLP-1RAs) are widely used in the treatment of type 2 diabetes and obesity. However, their effects on the visual system remain unclear. This narrative review summarizes current evidence and aims to clarify the association between GLP-1RAs and ocular outcomes.

Literature search. A literature search was conducted using PubMed/MEDLINE, Embase, and ScienceDirect electronic databases. Findings were grouped into thematic categories: diabetic retinopathy, NAION, AMD and other ocular events, and glaucoma.

Analysis of the literature. The available evidence is heterogeneous and sometimes conflicting. GLP-1RAs may be associated with diabetic retinopathy progression, particularly in patients with pre-existing type 2 diabetes, likely related to rapid glycemic improvement rather than direct drug toxicity. Reports of NAION remain rare, and causality has not been definitively established. The reviewed studies also indicate that GLP-1RAs may reduce AMD risk. Preclinical and observational studies suggest possible neuroprotective and intraocular pressure-lowering effects in glaucoma, while clinical evidence remain limited.

Conclusion. Current evidence does not indicate a consistent increase in major ophthalmic adverse outcomes associated with GLP-1RAs use. However, evidence remains limited and largely observational. Careful ophthalmic assessment and follow-up may be considered in high-risk individuals. Further prospective studies are needed to clarify causal relationships.

Keywords. age-related macular degeneration, diabetic retinopathy, glaucoma, glucagon-like peptide-1 receptor agonists, non-arteritic ischemic optic neuropathy, type 2 diabetes mellitus

Introduction

Glucagon-like peptide-1 receptor agonists (GLP-1RAs) have become important therapeutic agents in the management of type 2 diabetes and obesity, due to their high efficacy in glycemic and weight control.[1] By mimicking the action of endogenous glucagon-like peptide-1, they stimulate insulin secretion in pancreatic β-cells, leading to a reduction in blood glucose levels, as well as influence neurons in the central appetite-regulating pathways, thus reducing appetite.[2]

Their high clinical effectiveness and proven cardiovascular, renal, and metabolic benefits have resulted in widespread use of GLP-1RAs among various patient populations.[3-6] In 2024, over 26% of US adults with diabetes reported using injectable GLP-1RAs and 1 in 8 adults in the US report having used GLP-1RAs medication.[7,8] Due to increasing use of GLP-1RAs, evaluating long-term safety, beyond known metabolic endpoints, including potential visual effects, has become an important clinical and research priority.[9,10]

Historically, exenatide was the first GLP-1RA medication approved by the FDA as adjunctive therapy to improve glycemic control in patients with type 2 diabetes mellitus in 2005. Other GLP-1RAs have since entered the market, including liraglutide, dulaglutide, lixisenatide, semaglutide, alongside the dual GIP/GLP-1RA, tirzepatide. As further research progressed, new indications for the use of incretin-based therapies have emerged. Currently, most are approved for glycemic control and to reduce the risk of major cardiovascular events in patients with type 2 diabetes mellitus. Additionally, three of them are also registered for weight loss, including liraglutide, semaglutide, and tirzepatide.

In recent years, researchers have reported various possible links between GLP-1RAs and ocular safety.[11] However, recent studies regarding GLP-1RAs use and occurrence of non-arteritic anterior ischemic optic neuropathy have substantially expanded interest in the systemic effects of incretin-based therapies. Emerging data are, however, sometimes conflicting. These opposing signals have contributed to ambiguity in ophthalmological recommendations and underscore a critical research gap.

Additionally, ocular health is a crucial area, especially in patients with metabolic disorders who are inherently predisposed to microvascular and neurovascular eye complications, including diabetic retinopathy and ischemic optic nerve disorders, and even subtle drug-related effects may carry important clinical consequences. This highlights the need to explore potential relationships between GLP-1RAs and ophthalmological aspects. Identifying clinically relevant domains may help integrate ophthalmic considerations into guidelines for GLP-1RAs use, thereby enhancing both safety and efficacy of these agents in routine clinical practice.

Although several reviews addressing ophthalmic outcomes of GLP-1RAs have been published recently, the rapidly evolving literature in this field warrants continual reassessment of the available evidence. In contrast

to earlier reviews, the present review incorporates studies published through 2026, including recently reported ophthalmic safety signals and comparative analyses involving newer incretin-based therapies such as tirzepatide. Importantly, this review provides a broad overview of ocular outcomes associated with GLP-1RAs, including retinal, neuro-ophthalmic, glaucomatous, and ocular surface disorders rather than focusing on a single complication or individual agent. The review also emphasizes the hierarchy and limitations of available evidence. Additionally, mechanistic and clinical data are discussed separately to improve evidence interpretation. Given the rapidly growing global use of GLP-1RAs and increasing number of reported ocular outcomes, an updated overview of the evidence remains clinically relevant.

Aim

This narrative review aims to critically evaluate current evidence on the association between GLP-1RAs and ocular outcomes, including diabetic retinopathy, non-arteritic anterior ischemic optic neuropathy, age-related macular degeneration and other structural or functional eye changes, along with the neuroprotective and anti-inflammatory role of GLP-1RAs, particularly in the context of glaucoma. This review strives to clarify the clinical relevance of reported associations and identify the gaps requiring further investigation.

Literature search

This article is a narrative review of the available literature concerning the influence of GLP-1RAs on the visual system. A structured literature search was conducted using PubMed/MEDLINE, Embase and ScienceDirect electronic databases for studies published up to 22 December 2025. To ensure the currency of findings and address the rapidly evolving nature of the literature in this field, an updated search was performed in May 2026. The search methodology combined Medical Subject Headings (MeSH) with relevant free-text terms, including: ("glucagon-like peptide-1" OR "glucagon-like peptide-1 receptor agonists" OR GLP-1RA OR semaglutide OR liraglutide OR dulaglutide OR exenatide OR tirzepatide) AND ("eye diseases" OR retinopathy OR "diabetic retinopathy" OR "optic neuropathy" OR NAION OR "age-related macular degeneration" OR "macular edema" OR AMD OR retina OR papilledema OR glaucoma OR "dry eye" OR "intraocular pressure" OR eye OR ocular OR ophthalmology OR vision OR "visual impairment").

The combined initial and updated searches yielded 2,409 records. After removing duplicates, 1,565 titles and abstracts were screened, resulting in 150 full-text articles assessed for eligibility. Furthermore, manual screening of reference lists and reassessment of recently published and previously overlooked relevant literature were performed to identify additional studies not captured during the initial database search. Ultimately, 80 studies were included in this review.

Studies were eligible for inclusion if they addressed visual or ocular outcomes associated with the use of GLP-1RAs in the adult human population or explored potential mechanisms of these effects using

experimental or animal models. Only articles written in English and published in peer-reviewed journals were included in the analysis. Due to the limited availability of high-quality randomized evidence, a broad range of study designs with varying levels of evidence was included, comprising randomized clinical trials, cohort studies, case-control studies, pharmacovigilance analyses, case reports, and reviews. Preclinical findings were analyzed separately from clinical data, particularly in sections addressing potential biological mechanisms.

Data extraction focused on the type of GLP-1RAs, study design, study population, reported ocular outcomes, relationships between drug exposure and visual findings, potential confounders, and key study limitations. The results were synthesized qualitatively and organized into thematic categories, including diabetic retinopathy (DR), non-arteritic anterior ischemic optic neuropathy (NAION), age-related macular degeneration (AMD) and other ocular events, as well as glaucoma. Given the narrative nature of the review, no formal risk-of-bias assessment or quantitative synthesis was performed. Differences between studies were discussed in the context of study design, evidence level and clinical context.

Analysis of the literature

Diabetic retinopathy

Diabetic retinopathy (DR) is a microvascular complication of diabetes mellitus that may lead to vision-threatening damage to the retina, eventually leading to blindness.[12] The relationship between GLP-1RAs and DR remains complex and is not fully consistent across studies.

Evidence from preclinical studies suggests a potential protective effect. Dulaglutide has been shown to improve retinal structure and vascular function in experimental mouse models with type 2 diabetes (T2D).[13] While preclinical models suggest potential benefits at the retinal level, bridging the translational gap to human clinical practice remains challenging, reflecting a multifaceted clinical reality.

Evidence from randomized clinical trials (RCTs) did not consistently support a direct association. A meta-analysis of 61 RCTs (n=188,463) found no significant difference in risk of DR between GLP-1RAs and comparator therapies.[14] In contrast, a second meta-analysis including 13 RCTs indicated possible association with DR worsening. Yoshida et al. identified a higher incidence of rapidly worsening DR in four major RCTs with CV benefits in T2D. The significant association between GLP-1RAs and DR was also observed in subgroups of RCTs with a duration exceeding 52 weeks and when compared with placebo. A similar association was observed in patients with diabetes treated for ≥10 years, however it did not reach statistical significance. The presented associations were observed for liraglutide, semaglutide and dulaglutide.[15]

Observational studies in humans provide heterogeneous findings. A Swedish cohort study of patients with incident T2D reported a lower incidence of DR among GLP-1RA-treated patients compared with the non-exposed group (5.97 vs 12.85 per 1000 person-years).[16] Similarly, a retrospective cohort study in Saudi

Arabia suggested improvement in DR status in patients treated with liraglutide. However, the subgroup represented only a minority of the total population, and most patients showed no change in retinopathy status.[17] Furthermore, recent population based study observed that tirzepatide was associated with a lower incidence of new or progressive DR and fewer complications.[18] Another retrospective observational study of adults with T2D and moderate cardiovascular risk, without history of advanced diabetic retinal complications, focused on comparing four antidiabetic medications groups in terms of the risk of DR at 2 and 5 years of follow-up. GLP-1RAs treatment was associated with a comparable risk of vision-threatening retinopathy compared with DPP-4is and sulphonylureas, whereas SGLT2is therapy was associated with lower risk.[19] Additionally, in a separate cohort study of 981 patients, GLP-1RAs were not associated with DR progression compared with SGLT2is.[20]

Conversely, other large observational analyses reported an increased incidence of DR among patients receiving GLP1-RAs.[21,22] Wai et al. also observed a higher rate of progression of proliferative diabetic retinopathy after 1 and 3 years in a GLP1-RAs cohort compared with SGLT2i-treated patients.[23] Similarly, increased risk of progression of pre-existing DR was reported in patients receiving GLP-1RAs in additional cohort study, with tractional retinal detachment identified as a major driver of this association.[24] A small cohort study, consisting of 4,500 patients with DR, observed DR progression in 3 of 19 treated with GLP-1RAs, whereas no progression was noted in the control group.[25]

An increase in the risk of DR complications compared to placebo was also observed in SUSTAIN-6, a pre-registration trial of cardiovascular outcomes. Importantly, this signal was not observed across the SUSTAIN 1 to 5 and Japanese trials. Furthermore, the SUSTAIN-6 findings were not replicated in the cardiovascular outcome trials of liraglutide (LEADER) or dulaglutide (REWIND), nor in the PIONEER 6 trial for oral semaglutide. The results of the SUSTAIN-6 study were attributed to the magnitude and rapidity of HbA1c reduction during the first 16 weeks of treatment, particularly in patients with pre-existing DR and poor glycemic control which may partially explain discrepancies in the results.[26] To address these discrepancies, the ongoing prospective FOCUS trial (NCT03811561) is specifically investigating the long-term effects of semaglutide on DR.

Consistent with this interpretation, Berkovic and Strollo, analyzing the effect of semaglutide on patients with diabetes and obesity, suggested that DR events observed with semaglutide therapy may be related with rapid glycemic improvement rather than a direct drug-related effect.[27] Additionally, comparative analyses between different GLP-1RAs representatives (liraglutide, dulaglutide, exenatide) did not demonstrate significant differences in DR risk.[28] The significance of the route of administration was also evaluated, with higher rate of retinal adverse events, including DR, reported after subcutaneous compared with oral semaglutide.[29]

Overall, the available evidence, largely derived from observational studies with inconsistent findings, suggests heterogeneous effects of GLP-1RAs on DR and may depend on baseline patient characteristics, glycemic control and study design.

Heterogeneity in DR definitions, study design, and lack of standardized ophthalmic endpoints likely contributed to the inconsistent findings across studies. Preclinical studies focused mainly on precise molecular and retinal structural changes, whereas clinical studies evaluated heterogeneous outcomes, including incident DR, DR progression, proliferative or vision-threatening DR, retinal adverse events and need for retinal interventions. These methodological differences limit direct comparison and interpretation of the available evidence.

Non-arteritic anterior ischemic optic neuropathy

Non-arteritic anterior ischemic optic neuropathy (NAION) is characterized by acute ischemic damage of the optic nerve head resulting in abrupt, painless, usually unilateral vision loss and optic disc edema.[30,31] The potential association between the use of GLP-1RAs and NAION has recently attracted attention. However, evidence remains inconsistent and methodologically limited.

Evidence from randomized clinical trials is limited and does not support a clear association between GLP-1RA use and NAION. A meta-analysis by Silverii et al. assessed available RCTs and found no significant difference in NAION risk between patients treated with GLP-1RAs and comparator groups.[32] Recent meta-analysis including >1.5 million patients, reported the association between GLP-1RAs and elevated NAION risk (OR 1.70), however the absolute risk difference remained low (0.037%).[33] Furthermore, a dedicated safety evaluation of placebo-controlled clinical trials, demonstrated comparable NAION incidence between GLP-1RAs and placebo groups.[34] However, it should be explicitly stated that NAION is a rare outcome and was not a primary endpoint in any of the analyzed RCTs, limiting their statistical power to detect such events.

Observational studies have reported signals suggesting a possible association, although their findings are heterogeneous. The issue was first brought to public attention by Hathaway et al. in a retrospective cohort study including patients with T2D or obesity treated with semaglutide, without a prior history of NAION. The study reported a higher incidence of NAION among semaglutide-treated patients compared with individuals receiving other antidiabetic or anti-obesity medications.[35] Similarly, a large Danish nationwide cohort study including all individuals with T2D in Denmark (n=424,152) observed more than a twofold increase in NAION risk after five years of semaglutide use. Moreover, the study noted that the record-high incidence of first-time NAION episodes in 2019-2023 was temporally coincident with the introduction of semaglutide on the Danish market in November 2018.[36] These outcomes were mirrored in a study comparing semaglutide with SGLT2is, which included data from national health registers in Denmark and Norway, where the final pooled hazard ratio was 2.81.[37] Similarly, a recent large cohort study among US

Veterans demonstrated an increased NAION risk among semaglutide initiators compared with SGLT2is users.[38] This trend was further reflected in a retrospective cohort study concerning patients with T2D initiated on GLP-1RA therapy compared with DPP-4is-treated patients.[39] Notably, data regarding the temporal relationship, indicates that the timing and duration of GLP-1RAs treatment may significantly influence clinical outcomes.[40] This aspect emphasizes the complexity of the association and potentially explains the discrepant findings across previous literature, as different studies varied in drug exposure definition and the specific treatment timelines. Importantly, despite hazard ratios of concern reported in several studies, the absolute incidence increase remains low.

A multi-database study, including 37.1 million individuals with T2D, found only a slight increase in NAION risk associated with semaglutide exposure in a self-controlled case series analysis. Notably, the hazard ratio for NAION was higher only when compared to empagliflozin and showed no difference to any other non-GLP-1RAs interventions when a sensitive NAION definition was applied.[41] In other retrospective cohort study including patients with T2D without a known history of any eye disorder, the incidence of NAION was higher in semaglutide and tirzepatide cohort compared with other antidiabetic drugs, however the absolute risk remained very low (35 patients [0.04%] vs 19 patients [0.02%], HR 1.76).[42] This is further illuminated by other large-scale global and multi-databases cohort studies, which reported only a modest increased risk of NAION associated with GLP-1RAs exposure.[43-45] Consistently, a real-world cohort analysis incorporating sensitivity analyses did not confirm a statistically significant increase in risk after adjustment for confounders.[46] Similarly, Ramsey et al. observed no statistically significant change in NAION risk among patients receiving GLP-1RAs therapy in their cohort study.[21] Regional real-world data from a Polish cohort did not observe an increased risk of NAION associated with GLP-1RAs therapy, suggesting that risk signals diminish after rigorous adjustment for baseline metabolic parameters.[47]

Crucially, recent retrospective cohort analysis included over 1.2 million individuals. After adjustment for comorbidities, the authors observed significantly decreased risk of NAION in patients with T2D treated with semaglutide (OR=0.36).[48]

Pharmacovigilance data from the FAERS database have suggested higher risk of NAION associated with semaglutide use compared with other antidiabetic or anti-obesity medications.[49] However, such reporting systems are inherently limited by underreporting, reporting bias and incomplete clinical information, thus restricting the ability to establish a definitive association.

Case reports provide an additional signal but represent the lowest level of clinical evidence. Several case reports describe cases of NAION associated with GLP-1RAs therapy.[50-53] These include a case of 47-year-old woman without known risk factors and with a BMI=27.92 who developed NAION after GLP-1RAs therapy, including liraglutide and semaglutide, for weight loss. The temporal relationship between drug initiation and disease onset and clinical course, suggested a potential role of GLP-1RAs therapy in the development and progression of NAION.[51] However, such reports are inherently limited by the absence of

a control group and are insufficient to confirm a direct drug-related effect. Additionally, case reports often concern patients with established risk factors, such as hypertension and hyperlipidemia[50] or anatomical predispositions like small Bruch's membrane opening diameter and crowded optic disc.[52]

Glaucoma - a neuroprotective and anti-inflammatory role of GLP-1RAs

Evidence regarding GLP-1RAs and glaucoma is derived primarily from observational studies, with limited high-quality clinical data. Current evidence may be broadly divided into observational studies evaluating glaucoma incidence, clinical studies assessing intraocular pressure (IOP) and mechanistic and preclinical studies. Available cohort analyses suggest that GLP-1RAs use may be associated with reduced risk of glaucoma development.[54-59] However, these findings should be interpreted with caution, as they are subject to residual confounding.

Clinical incidence data

Some observational studies reported a greater risk reduction with GLP-1RAs compared with other antidiabetic medications.[54-56] Importantly, a nationwide study observed that prolonged GLP-1RA treatment extending beyond 3 years further reduced the risk.[59] No significant influence of ethnicity, race, sex, education or income on the association between GLP-1RAs use and glaucoma risk was established, although greater risk reduction was observed in patients aged >60 years and in those with coexisting T2D.[57] Furthermore, more recent evidence has also evaluated tirzepatide, a dual GIP/GLP-1 receptor agonist. Retrospective cohort analyses suggested that tirzepatide treatment was associated with lower rates of primary open-angle glaucoma and ocular hypertension compared with selective GLP-1RAs.[60,61] However, these findings remain observational and require prospective confirmation.

Intraocular pressure (IOP) data

Reduction of intraocular pressure (IOP) is one of the most frequently proposed mechanisms. In observational analyses, Hallai et al. reported that GLP-1RAs were associated with greater IOP reduction compared with other antidiabetic medications, with more pronounced effect in patients with baseline IOP ≥15 mmHg and in those with pre-existing glaucoma. Additionally, no significant difference between the injectable and oral form of semaglutide was observed.[62]

Mechanistic and preclinical evidence

Beyond IOP reduction, experimental studies have suggested that GLP-1RAs exert anti-inflammatory and neuroprotective effects on retinal ganglion cells (RGCs), which are progressively lost in glaucoma. Elevated IOP was associated with increased levels of pro-inflammatory cytokines, including C1q, TNF-α, IL-1a, which may contribute to neurotoxic astrocyte activation. It was also observed that reducing IOP to

physiological ranges did not restore cytokines levels to baseline. In preclinical models, GLP-1RAs such as NLY01 were found to reduce cytokine levels by modulating microglial cells activity (responsible for C1q, TNF-α and IL-1a production).[58]

Additional in vitro and animal studies, have suggested that high glucose conditions induces mitochondrial damage and increased reactive oxygen species overproduction, driving RGCs degeneration through mitophagy, which plays a crucial role in neurodegenerative disorders, including glaucoma.[63,64,65] Experimental studies suggested that GLP-1RAs may mitigate the ultrastructural mitochondrial damage and reduce levels of glucose-induced ROS.[66] Additionally, both *in vitro* and *in vivo* diabetic rat models demonstrated that GLP-1RAs improved RGC viability by attenuating excessive mitophagy, specifically through down-regulation of LC3A/B, increased p62 levels and inhibition of the PINK1/Parkin pathway.[65] Further mechanistic evidence from experimental models suggests that semaglutide may protect RGCs against neurodegenerative injury through modulation of glucose metabolism and mitochondrial homeostasis.[67] However, these findings derive from preclinical studies and their clinical relevance remains uncertain.

Overall, while observational and preclinical evidence suggests a potential protective role of GLP-1RAs in glaucoma, clinical evidence remains limited and does not allow definitive association.

AMD and other ocular events

Reported ocular manifestations associated with GLP-1RAs may be broadly categorized into retinal and macular disorders, ocular surface disorders, and neuro-ophthalmic or inflammatory findings.

Retinal and macular disorders

Age-related macular degeneration (AMD) is a neurodegenerative disorder and one of the leading causes of vision loss in individuals over 60. It progressively damages the central retina and choroid, leading to central vision impairment and, in advanced stages, severe visual loss.[68,69]

The potential impact of GLP-1RAs on AMD has been explored, given the growing prevalence and public health impact.[70] These findings are derived exclusively from observational studies and therefore do not allow definitive conclusions. Some cohort analyses suggest a protective association. In a recent retrospective cohort study of non-diabetic adults receiving GLP-1RAs for obesity treatment, exposure to GLP-1RAs was associated with a lower risk of both nonexudative and overall AMD compared with other weight-loss pharmacotherapies.[71] McLaughlin et al. reported that in patients with T2D, GLP-1RAs therapy was associated with a relative risk reduction of 15% in nonexudative and 20% in exudative AMD, as well as lower likelihood of progression to intermediate or advanced stages compared with other glucose-lowering therapies (27-29%).[72] Similar findings were reported in other cohort studies, with stronger

associations observed with longer duration of exposure.[73,74] However, these studies are limited by their observational design and differences in baseline metabolic and vascular risk profiles.

In contrast, another population-based study identified an approximately two-fold increased risk of neovascular AMD among patients receiving GLP-1RAs in a large cohort study. Although this study accounted for several comorbidities and socioeconomic factors, the authors noted that the underlying mechanisms remain unclear, highlighting the need for further research.[75] However, this finding was not replicated in more recent large-scale cohort analyses, which did not confirm an increased risk of neovascular AMD.[76]

Additional evidence from pharmacovigilance systems, including FAERS and VigiBase, has reported signals of various vitreoretinal and ocular adverse events temporally associated with GLP-1RAs use, including retinal hemorrhage, vitreous hemorrhage, vitreous detachment, retinal detachment, papilledema and macular edema and macular hole, compared with metformin.[77]

Observational evidence regarding diabetic macular edema (DME) remains inconsistent. Wai et al. suggested an increased incidence of DME among patients receiving GLP-1RAs at multiple follow-up time points.[23] However, large database analyses including approximately two million patients with T2D did not confirm an increased risk of DME associated with GLP-1RAs therapy after adjustment for confounders, while SGLT2is were associated with a reduced risk.[22] Similar neutral findings were further reported by Phu et al. in comparative analyses of glucose-lowering therapies.[78]

Ocular surface disorders

Evidence regarding dry eye disease (DED) is also inconsistent. A large retrospective cohort study conducted by Su et al. reported a lower risk of clinically diagnosed DED in patients treated with SGLT2is compared with GLP-1 RAs, based on electronic medical records and prescription records for dry eye medications.[79] By comparison a small prospective study reported short-term improvements in tear film stability and tear production in GLP-1RA-treated patients. However, the study was limited by small sample size (n = 35) and short follow-up duration and did not assess clinically diagnosed DED incidence.[80] These discrepancies likely reflect differences in study design and outcome definitions.

Neuro-ophthalmic and inflammatory findings

Rare ocular events, including diabetic papillitis, papilledema, optic neuritis, scleritis, and reversible bilateral central scotomas, were described, sometimes coinciding with rapid glycemic improvement.[53,81,82] However, these events were more likely related to underlying diabetic eye disease, rapid metabolic changes, or detection bias rather than a direct pharmacologic effect of GLP-1RAs. Conversely, a large retrospective cohort study involving over 36 000 patients treated with various GLP-1RAs reported a low incidence of papilledema and optic neuritis, without demonstrating a clear association with GLP-1RA therapy.[47] Overall,

these findings suggest that currently available evidence regarding the above-mentioned neuro-ophthalmic adverse events associated with GLP-1RAs remains inconsistent, and no definitive association has been established.

A detailed summary of key studies evaluating ocular outcomes associated with GLP-1RAs was presented in Table 1.

Table 1. Summary of selected studies on ocular outcomes associated with GLP-1 receptor agonists*

Study	Design	Population	Exposure/comparator	Outcome	Main results
Diabetic Retinopathy					
Małyszczak et al., 2024[14]	Systematic review and meta-analysis	T2D (n=188,463)	GLP-1RA vs placebo	DR	OR 1.08 (95% CI 0.94–1.23)
Yoshida et al., 2022[15]	Systematic review and meta-analysis (13 RCTs)	T2D	GLP-1RA vs other antidiabetic drugs or placebo	Incident DR/DR complications	RCTs with CV benefits in T2D: OR 1.23 (95% CI 1.05–1.44) RCTs >52 weeks: OR 1.2 (95% CI 1.00–1.43) RCTs using placebo as a comparator: OR 1.22 (95% CI 1.05–1.42)
Zheng et al., 2023[16]	Cohort with Mendelian randomization	T2D (n=14,119)	GLP-1RAs vs metformin or sulfonylureas	DR	HR 0.42 (95% CI 0.29–0.61)
Shah et al., 2026[18]	Retrospective cohort	T2D/obesity (n=173,846)	Tirzepetide vs no exposure to weigh-loss drugs	Mild NPDR	RR 0.864 (95% CI 0.758–0.985, p=0.029)
				PDR	RR 0.705 (95% CI 0.564–0.882, p=0.002)
				Moderate/severe NPDR	No statistical significance
Barkmeier	Retrospective	T2D with	GLP-1RA vs	Treatment for	HR 1.07 (95% CI 0.85–

et al., 2024[19]	cohort	moderate CV risk (n=371,698)	DPP-4i	DR (DME/PDR)	1.35)
			GLP-1RA vs sulfonylurea		HR 0.83 (95% CI 0.67–1.03)
			SGLT2i vs GLP-1RA		HR 0.73 (95% CI 0.55–0.97)
Ramsey et al., 2025[21]	Retrospective cohort	T2D (n=185,066)	GLP-1 RA vs non-exposed	DR	HR 1.07 (95% CI 1.03-1.11; p=0.001)
Eleftheriadou et al., 2024[22]	Retrospective cohort	T2D (n=2,305,755)	GLP-1RA + insulin vs insulin	DR	HR 1.308 (95% CI 1.261–1.357)
				DME	HR 1.013 (95% CI 0.960–1.069)
			SGLT2i + insulin vs insulin	DR	HR 1.076 (95% CI 1.027–1.127)
				DME	HR 0.835 (95% CI 0.780–0.893)
			GLP-1RA + insulin vs SGLT2i + insulin	DR	HR 1.205 (95% CI 1.153–1.259)
				DME	HR 1.130 (95% CI 1.056–1.208)
Wai et al., 2024[23]	Retrospective cohort	NPDR (n=12,962)	GLP-1RAs vs SGLT2is	Progression to proliferative DR	after 1 year of therapy: RR 1.26 (95% CI 1.04–1.51, p=0.017) after 3 years: RR 1.284 (95% CI 1.1–1.499, p=0.002)
Lin et al., 2024[24]	Retrospective cohort	Pre-existing DR (n=4,551)	GLP-1RA vs SGLT2i	New-onset PDR, vitreous hemorrhage, tractional RD	HR 1.50 (95% CI 1.01–2.23; p= 0.043) (mainly increased risk of tractional RD)

		Without pre-existing DR (n=28,647)		Newly diagnosed DR, vitreous hemorrhage, tractional RD	No statistical significance
Non-arteritic anterior ischemic optic neuropathy					
Nogueira et al., 2026[33]	Meta-analysis	T2D (n>1,500,000)	GLP-1RA vs control	NAION	OR 1.70 (95% CI 1.23-2.36)
Hathaway et al., 2024[35]	Retrospective cohort	T2D (n=710)	semaglutide vs non-GLP-1RA antidiabetic medications	NAION	HR 4.28 (95% CI, 1.62–11.29)
		Obesity (n=979)	semaglutide vs non-GLP-1RA anti-obesity medications		HR 7.64 (95% CI, 2.21–26.36)
Grauslund et al., 2024[36]	Retrospective cohort	T2D (n=424,152)	Once-weekly semaglutide vs non-exposed	NAION	HR 2.19 (95% CI 1.54–3.12)
Simonsen et al., 2025[37]	Retrospective cohort	T2D (n=61,377)	Semaglutide vs SGLT2i	NAION	HR 2.81 (95% CI 1.67–4.75)
Heberer et al., 2026[38]	Retrospective cohort	T2D (n=102,361)	Semaglutide vs SGLT2i	NAION	HR 2.33 (95% CI, 1.54-3.54; p<0.001)
Cai et al., 2025[41]	Retrospective cohort (SCCS)	T2D (n=37,100,000)	GLP-1RA vs non-GLP-1RAs medications	NAION	IRR 1.32 (95% CI, 1.14–1.54; p<0.001)

Wang et al., 2025[42]	Retrospective cohort	T2D (n=1,511,637)	Semaglutide/ tirzepatide vs other antidiabetic medications	NAION	HR 1.76 (95% CI, 1.01–3.07)
				Other optic nerve disorders	HR 1.65 (95% CI 1.18–2.31)
Lieberman et al., 2026[48]	Retrospective cohort	T2D (n=973,529)	Semaglutide vs non-GLP-1RAs medications	NAION	OR 0.36 (95% CI 0.25-0.51)
		Obesity (n=239,246)			No statistical significance
Glaucoma					
Sterling et al., 2021[54]	Retrospective cohort	T2D (n=6332)	GLP-1RAs vs other antidiabetic medications	Glaucoma	HR 0.56 (95% CI. 0.36-0.89, p=0.01)
Niazi et al., 2024[59]	Nationwide cohort	T2D (n=10,422)	GLP-1RA vs other antidiabetic medication	Glaucoma	HR 0.81 (95% CI, 0.70-0.94, p=0.006)
Hong et al., 2025[60]	Retrospective cohort	T2D (n=83,698)	Tirzepatide vs selective GLP-1RA	POAG	RR 0.50 (95% CI 0.34-0.74)
				OHTN	RR 0.59 (95% CI 0.40-0.88)
				Glaucoma treatment	RR 0.54 (95% CI 0.45-0.64)
AMD and other ocular events					
Wai et al., 2024[23]	Retrospective cohort	NPDR (n=12,962)	GLP-1RAs vs SGLT2is	Development of DME	at 3 months: RR 1.192 (95% CI 1.059–1.276, p=0.002) at 6 months: RR 1.22 (95% CI 1.13–1.32, p<0.001)

					at 1 year: RR 1.24 (95% CI 1.15–1.33; p<0.001) at 3 years: RR 1.29 (95% CI 1.21–1.38; p<0.001)
Joo et al., 2025[73]	Retrospective cohort	T2D (aged ≥50) (n=30,224)	GLP-1RAs vs insulin	Nonexudative AMD	RR 0.28 (95% CI 0.15–0.46)
			GLP-1RAs vs metformin		RR 0.25 (95% CI 0.14–0.41)
			GLP-1RAs vs SGLT2i		RR 0.42 (95% CI 0.22–0.74)
Lakhani et al., 2025[77]	Pharmacovigilance	T2D and/or obesity	Semaglutide/ tirzepatide vs metformin, empagliflozin, dulaglutide, insulin or phentermine-topiramate	Retinal hemorrhage	FAERS: OR 2.75; VigiBase: OR 5.49
				Vitreous hemorrhage	FAERS: OR 5.89; VigiBase: OR 9.00
				Vitreous detachment	FAERS: OR 4.17; VigiBase: OR 20.91
				Retinal detachment	FAERS: OR 2.44; VigiBase: OR 8.60
Su et al., 2022[79]	Retrospective cohort study	T2D (n=11,115)	SGLT2i vs GLP-1RA	DED	HR 0.78 (95% CI 0.68–0.89)

* T2D – type 2 diabetes mellitus, GLP–1RA – glucagon–like peptide–1 receptor agonist, SGLT2i – sodium–glucose cotransporter 2 inhibitor, DPP–4i – dipeptidyl peptidase–4 inhibitor, DR – diabetic retinopathy, NPDR – non–proliferative diabetic retinopathy, PDR – proliferative diabetic retinopathy, POAG – primary open–angle glaucoma, OHTN – ocular hypertension, DME – diabetic macular edema, RD – retinal detachment, NAION – non–arteritic anterior ischemic optic neuropathy, AMD – age–related macular degeneration, DED – dry eye disease, HR – hazard ratio, 95% CI – 95% confidence interval, SCCS – self–controlled case series, RR – relative risk, IRR – incidence rate ratio, OR – odds ratio

Discussion

Diabetic retinopathy

DR remains a leading cause of vision loss in both working-age and older populations, and is strongly associated with longer diabetes duration, suboptimal glycemic control, and coexisting hypertension.[83]

Evidence regarding the association between GLP-1RA therapy and DR is inconsistent across study designs. While several observational studies reported a possible increased risk of DR, randomized clinical trials and meta-analyses have not confirmed a consistent signal. Interpretation of available studies is limited by heterogeneous DR definitions, incomplete ophthalmic data, variable ophthalmic endpoints, short follow-up periods, and potential confounding related to baseline metabolic control.[25,29]

Rapid and substantial HbA1c reduction, particularly in patients with poor baseline glycemic control, likely represents an important confounding factor underlying early DR worsening signals.[26] This phenomenon is well described in the context of intensive glycemic control and is generally considered transient, with risk attenuation over longer follow-up.[83]

Overall, current evidence suggests that association between GLP-1RAs and DR is more likely related to magnitude and rapidity of glycemic improvement rather than a direct drug-specific effect. However, the quality of evidence remains limited. Given the heterogeneity of study designs and patient populations, residual uncertainty remains. Large and long-term prospective studies with detailed ophthalmic evaluation are needed to define risk profiles and underlying mechanisms.

NAION

Despite numerous studies suggesting an increased risk of NAION with GLP-1RAs use,[32,35-39] these findings should be interpreted cautiously, as several limitations have been highlighted. The study by Hathaway et al. was based on a single-center neuro-ophthalmology referral population, potentially increasing susceptibility to selection bias and limits generalizability of the findings, as highlighted in a real-world evidence appraisal by Klonoff, Hui and Gombar.[46] Additionally, the observed association may be related to rapid HbA1c-lowering effect of semaglutide and tirzepatide rather than a direct drug effect.[84]

The interpretation of these findings is further complicated by the incompletely understood pathophysiology of NAION,[85] and its multifactorial etiology, thus several risk factors may contribute to its development. Patients receiving incretin-based therapies frequently present with obesity, poorly controlled diabetes, and cardiovascular diseases, all of which are independent NAION risk factors and may contribute to confounding by indication.[30,86,87] Consequently, it becomes exceedingly difficult to definitively isolate whether a newly diagnosed NAION episode is a pharmacological side effect, or simply the natural progression of the patient's baseline metabolic syndrome. This methodological impediment highlights why interpreting observational data in this specific patient population requires extreme caution. Additional risk factors remain inconsistently supported, thereby hindering the ability to obtain reliable data on the influence of GLP-1RAs and to design an accurate study addressing this issue. A crowded optic disc, small Bruch's membrane opening diameter, low cup-to-disc ratio, sleep apnea, surgery, infections and vaccinations,

vitreopapillary traction, increased intraocular pressure, optic disc edema (i.e. in cases of papilledema) have been reported in various studies as factors contributing to NAION development, however, their definitive role remains debated.[30,31,52,86]

Importantly, while several studies report concerning relative risks, these numbers must be interpreted in the context of low baseline incidence of the disease. Given the rarity of this condition with the annual incidence of NAION ranging from 2.3 to 10.2 per 100000 in the US, even a more than twofold increase in risk, translates into a small absolute incidence rate increase (from 0.093 to 0.228 per 1000 person-years).[30,35] Moreover, the low event rate limits the ability to reliably identify associations with specific patient characteristics and to exclude unidentified confounding factors that may influence the observed results in a sample of this size.

While a potential association between GLP-1RAs and NAION cannot be excluded, current evidence in the absence of prospective studies, does not allow to establish a definitive association. From a clinical perspective, given the irreversible nature of NAION, cautious monitoring may be warranted, particularly in high-risk individuals. However, well-designed prospective studies are needed to clarify this relationship.

Glaucoma

Available evidence, largely observational, suggests a possible association between GLP-1RAs use and reduced risk of glaucoma. However, these findings are subject to residual confounding and cannot establish a definitive conclusion. Differences in baseline metabolic control or co-medications may partially explain the observed associations.

Proposed biological mechanisms are primarily based on experimental and animal studies. While such findings provide mechanistic plausibility and may seem promising, their direct clinical relevance remains uncertain.

Overall, while GLP-1RAs show potential as modulators of pathways relevant to glaucoma pathogenesis, current evidence is insufficient to support a therapeutic role. Further clinical studies are needed to determine whether these findings translate into clinical outcomes.

AMD and other ocular events

The potential of GLP-1RAs in AMD is gaining increasing attention. Some observational studies suggest that these drugs may be associated with preserved retinal function and slower disease progression, potentially through anti-inflammatory and neuroprotective mechanisms.[69-73] However, the available evidence is heterogeneous, with large cohort studies reporting mixed findings, including neutral associations for neovascular AMD and a potential protective signal for non-neovascular AMD across both diabetic and non-diabetic populations, while other reports have suggested a possible increased risk of neovascular AMD. These discrepancies highlight uncertainty regarding the direction and magnitude of the

association.[70,74,75] Additionally, most current evidence derives from observational studies, which are inherently susceptible to residual confounding and cannot establish definitive association. Well-designed clinical studies are needed to clarify the role of GLP-1RAs in AMD pathogenesis and progression.

Beyond AMD, evidence regarding other ocular adverse events remains limited and heterogeneous. It is crucial to emphasize that spontaneous reporting systems are prone to bias and may over-represent high-risk populations, including patients with long-standing diabetes, suboptimal prior glycemic control, and established microvascular complications, thereby limiting definitive conclusions.

Most non-retinopathy ocular adverse events with GLP-1RAs are rare and likely attributable to diabetic eye disease rather than a direct drug effect. From a clinical perspective, these findings do not warrant changes in prescribing practices but support baseline ophthalmic evaluation and regular follow-up in high-risk patients.

Integrated clinical implications and future directions

GLP-1 receptor expression in retinal tissue provides biological plausibility for potential direct ocular effects of incretin-based therapies. Experimental models suggest that GLP-1 receptor activation may attenuate oxidative stress, inflammation, endothelial dysfunction, and apoptosis, while improving blood-retinal barrier integrity and antioxidant defense. These findings point to potential neuroprotective and vasculoprotective effects rather than direct retinal toxicity.[88-90] Nevertheless, the available evidence is derived from in vitro and animal models, and its clinical relevance in human clinical practice remains uncertain.

Given the rapidly growing clinical use of dual GIP/GLP-1 receptor agonists, evaluating the specific ophthalmic safety profile of tirzepatide has become highly relevant. Emerging evidence suggests that its dual incretin activity may enhance retinal neuronal resilience, potentially offering broader neuroprotective and anti-inflammatory benefits compared with selective GLP-1RAs. Clinically, tirzepatide demonstrated greater reductions in HbA1c and cardiometabolic risk factors.[91] As rapid glycemic improvement itself may contribute to transient DR worsening; careful ophthalmologic monitoring remains warranted. However, large-scale real-world evidence indicates that over an extended follow-up, tirzepatide leads to a long-term reduction in DR complications.[18] At present, available evidence does not allow definitive conclusions regarding superiority or inferiority of tirzepatide with respect to ocular safety outcomes.

From a clinical perspective, current evidence does not support modification of prescribing practices solely because of concerns regarding ocular adverse effect. Nevertheless, careful ophthalmic monitoring may be warranted in patients with pre-existing risk factors. Further prospective studies with standardized ophthalmologic endpoints are needed to clarify association between incretin-based therapy and ocular outcomes.

Conclusion

Current evidence does not consistently demonstrate an increased risk of major ophthalmic adverse outcomes associated with GLP-1RAs use. However, the available data are heterogeneous and predominantly observational and therefore do not allow firm definitive conclusions. Signals of DR progression have been reported in some patients treated with different GLP-1RAs. This phenomenon appears to be more likely related to rapid and substantial reductions in HbA1c, rather than a direct drug-specific toxic effect. Reports of NAION remain rare and derive mainly from observational studies. A definitive association with GLP-1RAs exposure has not been established. For AMD, the evidence is limited and inconsistent. Some studies suggest that GLP-1RAs may reduce the risk of AMD or slow its progression, while other reports suggest a potential increase in risk of neovascular AMD. The clinical relevance of these findings remains uncertain. Most other ocular adverse events are uncommon and are likely attributable to underlying disease, detection bias, or rapid metabolic changes rather than a direct effect of the medication. Evidence regarding glaucoma is derived largely from preclinical and observational studies, suggesting potential neuroprotective and intraocular pressure-lowering effects; however, clinical evidence remains limited.

From a clinical perspective, baseline ophthalmic assessment and appropriate follow-up may be considered, particularly in individuals with pre-existing retinopathy, advanced diabetes, or additional vascular risk factors. Treatment decisions should therefore be based on individualized risk-benefit assessment, taking into account the well-established metabolic and cardiovascular advantages of GLP-1RAs.

This narrative review highlights the need for further well-designed prospective studies with standardized ophthalmic endpoints, to clarify association, elucidate underlying mechanisms, and identify patient subgroups at increased risk of ocular complications.

Declarations

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Author contributions

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Conflict of interest

The authors declare no competing interests.

Data availability

All data analyzed in this study were derived from previously published studies and are included in this published article.

Ethics approval

Not applicable.

Use of AI and AI-assisted technologies in the writing process

AI-tools (ChatGPT) were used solely for language editing, text reduction, and improving the readability of the manuscript. The content was verified and edited by the authors. The authors take full responsibility for the content of the published article.

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