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Review

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Ophthalmological Side-Effects of Glucagon-Like Peptide Receptor Agonists

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ABSTRACT

Background: Glucagon-like peptide-1 receptor agonists (GLP-1 RAs) have become an essential component in the treatment of type 2 diabetes mellitus and obesity due to their potent glucose-lowering effects and cardiovascular benefits. However, increasing clinical use has raised concerns regarding their potential ophthalmological side effects, particularly diabetic retinopathy, diabetic macular oedema, and neuroophthalmological complications such as nonarteritic anterior ischemic optic neuropathy (NAION).

Methods: This narrative review summarizes current evidence regarding the ophthalmological safety profile of GLP-1 receptor agonists. Relevant clinical trials, meta-analyses, observational studies, and experimental data were evaluated to assess the incidence, risk factors, and potential mechanisms underlying ocular complications associated with GLP-1 RA therapy.

Main findings: Available evidence suggests that GLP-1 receptor agonists are not directly retinotoxic; however, transient worsening of diabetic retinopathy has been observed, particularly in patients with pre-existing retinal disease, high baseline HbA1c, and rapid glycaemic improvement. Most studies indicate a neutral effect on diabetic macular oedema incidence, although differences between drug classes and individual patient risk profiles have been reported. Emerging data suggest a possible association between semaglutide and NAION, although absolute risk remains low and causality has not been definitively established. Proposed mechanisms include rapid glycemic normalization, altered microvascular perfusion, endothelial dysfunction, and vascular autoregulatory changes.

Principal conclusion: GLP-1 receptor agonists remain highly effective and generally safe therapeutic agents, with ophthalmological risks primarily related to rapid metabolic improvement rather than direct drug toxicity. Careful patient selection, gradual glycemic optimization, and appropriate ophthalmological monitoring are recommended, particularly in patients with pre-existing microvascular disease.

Key words: GLP-1; diabetic retinopathy; diabetic macular oedema; semaglutide; NAION

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INTRODUCTION

Type 2 diabetes mellitus (T2DM) and obesity represent major global health challenges, with steadily increasing prevalence and substantial associated morbidity and mortality (1). Chronic hyperglycemia is the principal driver of both microvascular and macrovascular complications. Among microvascular sequelae, diabetic retinopathy remains one of the leading causes of visual impairment and preventable blindness in the working-age population worldwide. The risk and progression of retinopathy are closely related to disease duration, glycemic control, and the presence of systemic risk factors such as hypertension and dyslipidaemia. Therefore, optimal management of hyperglycemia is essential not only for metabolic stability but also for reducing the risk of long-term ocular complications (2).

Glucagon-like peptide-1 receptor agonists (GLP-1 RAs) have emerged as an important class of glucose-lowering agents in the management of T2DM and, more recently, obesity. These agents exert their effects through activation of the GLP-1 receptor, resulting in glucose-dependent stimulation of insulin secretion, suppression of glucagon release, delayed gastric emptying, and enhanced satiety. Beyond their glycaemic efficacy, GLP-1 RAs consistently promote weight reduction and have demonstrated favourable cardiovascular outcomes in large-scale clinical trials, leading to their incorporation into contemporary treatment guidelines (3). Consequently, their use has expanded rapidly across both diabetic and non-diabetic populations.

Despite their well-established metabolic and cardiovascular benefits, concerns have emerged regarding the potential ophthalmic effects of GLP-1 RAs (4). Early cardiovascular outcome trials reported an increased incidence of diabetic retinopathy complications in certain patient subgroups treated with specific GLP-1 receptor agonists. This signal prompted further investigation into the relationship between GLP-1 RA therapy and retinal outcomes. One proposed explanation is the phenomenon of early worsening of diabetic retinopathy associated with rapid improvement in glycaemic control, a process previously observed with intensive insulin therapy and other glucose-lowering strategies (5). In addition, GLP-1 receptors have been identified in retinal tissue, raising the possibility of direct pharmacological effects on retinal neurons, microvasculature, and inflammatory pathways. Beyond diabetic retinopathy progression, other ophthalmic manifestations potentially associated with GLP-1 RA therapy have been explored, including macular oedema, transient visual disturbances (6), and possible neuro-ophthalmic complications (7, 8). However, the available evidence remains heterogeneous. Distinguishing drug-specific effects from consequences of improved metabolic control is often challenging, particularly in patients with advanced baseline disease or substantial reductions in glycated haemoglobin levels. Moreover, emerging real-world data and post-marketing surveillance studies have provided additional insights while also highlighting methodological limitations and the need for cautious interpretation.

Given the expanding clinical use of GLP-1 receptor agonists and the importance of preserving visual function in patients with T2DM and obesity, a comprehensive understanding of their ophthalmological safety profile is essential. Clarifying the magnitude of risk, identifying susceptible patient subgroups, and elucidating potential underlying mechanisms are critical for informing clinical decision-making and optimizing monitoring strategies. This review aims to summarize the current evidence regarding ophthalmological adverse effects associated with GLP-1 receptor agonists, discuss proposed pathophysiological mechanisms, and evaluate their clinical relevance and implications for patient management.

PHARMACOLOGICAL BASIS OF GLP-1 AGONISTS

Mechanism of action

GLP-1 RAs are a class of incretin-based therapies that exert their pharmacological effects through selective activation of the GLP-1 receptor, a G protein–coupled receptor expressed in multiple tissues, including pancreatic islet cells, the gastrointestinal tract, the central nervous system, and cardiovascular and retinal tissues (8). These agents mimic the physiological actions of endogenous GLP-1, while demonstrating greater resistance to enzymatic degradation and prolonged duration of action, thereby enabling sustained therapeutic effects (9). The primary mechanism of action of GLP-1 RAs involves the enhancement of glucose-dependent insulin secretion from pancreatic β-cells. Upon receptor activation, intracellular signalling pathways mediated by cyclic adenosine monophosphate (cAMP) and protein kinase A are stimulated, leading to increased insulin exocytosis in the presence of elevated blood glucose levels. This glucose-dependent mechanism reduces the risk of hypoglycaemia compared with traditional insulin secretagogues (10). In parallel, GLP-1 RAs suppress glucagon secretion from pancreatic α-cells, resulting in decreased hepatic glucose production and improved overall glycaemic control.

In addition to their direct pancreatic effects, GLP-1 RAs influence glucose homeostasis through several extrapancreatic mechanisms. These include delayed gastric emptying, which slows the rate of glucose absorption and attenuates postprandial glycemic excursions. Furthermore, activation of GLP-1 receptors in the hypothalamus promotes satiety and reduces appetite, contributing to decreased caloric intake and clinically significant weight loss. This central anorectic effect represents a key therapeutic advantage, particularly in patients with obesity and metabolic syndrome (11).

GLP-1 RAs also exert important effects on β-cell function and survival. Experimental studies have demonstrated that GLP-1 receptor activation may enhance β-cell proliferation, reduce apoptosis, and improve overall β-cell function, potentially contributing to improved long-term glycemic control. Although the extent of these effects in humans remains an area of ongoing investigation, these findings suggest a possible disease-modifying role beyond symptomatic glucose lowering (12).

Beyond their metabolic actions, GLP-1 receptors are expressed in vascular endothelial cells and neural tissues, including the retina. Activation of these receptors has been associated with modulation of endothelial function, reduction of oxidative stress, and anti-inflammatory effects. These pleiotropic properties have raised interest in the potential protective as well as adverse effects of GLP-1 RAs on microvascular structures (13). In the context of ophthalmology, such mechanisms may influence retinal blood flow, vascular permeability, and neuronal survival, thereby contributing to observed changes in retinal disease progression in some patients. The pharmacokinetic profiles of GLP-1 RAs vary depending on their molecular structure and formulation, allowing for daily or once-weekly administration. Long-acting agents provide sustained receptor activation and more stable glycaemic control, which may influence both their therapeutic efficacy and safety profile (14). Understanding these pharmacological properties is essential for evaluating their systemic and ocular effects, particularly in patients at risk for microvascular complications.

GLP-1 receptor and the pancreas

The GLP-1 receptor is highly expressed in pancreatic islet cells, particularly in β-cells, where it plays a central role in the regulation of insulin secretion and glucose homeostasis. Activation of the GLP-1 receptor enhances glucose-dependent insulin release by potentiating intracellular signalling pathways

involving cAMP and calcium-dependent mechanisms. This results in increased insulin secretion during periods of hyperglycaemia, while minimizing insulin release under normoglycemic or hypoglycaemic conditions, thereby reducing the risk of hypoglycaemia (15).

In addition to stimulating insulin secretion, GLP-1 RAs suppress glucagon release from pancreatic α-cells (16). This effect contributes to reduced hepatic gluconeogenesis and decreased fasting and postprandial glucose levels. The inhibition of glucagon secretion is particularly important in patients with T2DM, in whom inappropriate glucagon secretion contributes significantly to hyperglycaemia.
GLP-1 receptor activation may also exert beneficial effects on pancreatic β-cell health. Experimental and preclinical studies have demonstrated that GLP-1 RAs can promote β-cell survival by reducing apoptosis, enhancing cellular resistance to oxidative stress, and improving functional responsiveness to glucose. Furthermore, GLP-1 receptor signaling may support β-cell preservation by modulating inflammatory pathways and improving islet microcirculation. Although the long-term clinical significance of these effects remains under investigation, these findings suggest a potential role in slowing the progressive decline in β-cell function characteristic of T2DM.

Effects on HbA1c

GLP-1 RAs have consistently demonstrated significant efficacy in reducing HbA1c levels across a wide range of clinical trials and real-world studies. The reduction in HbA1c is primarily achieved through improvements in both fasting and postprandial glycaemic control, resulting from the combined effects on insulin secretion, glucagon suppression, and delayed gastric emptying (17). The magnitude of HbA1c reduction typically ranges from approximately 0.8% to 1.8%, depending on the specific agent, baseline HbA1c level, treatment duration, and patient characteristics (18). Greater reductions are generally observed in patients with higher baseline HbA1c values and in those treated with more potent or long-acting agents. Once-weekly formulations often provide more sustained glycaemic control due to continuous receptor activation and improved treatment adherence.
Importantly, GLP-1 RAs improve glycaemic control with a low intrinsic risk of hypoglycaemia when used as monotherapy or in combination with agents that do not independently cause hypoglycaemia. This safety profile represents a significant advantage compared with insulin or sulfonylureas (19). However, rapid and substantial reductions in HbA1c, particularly in patients with long-standing poor glycaemic control, may be associated with transient worsening of microvascular complications, including diabetic retinopathy. This phenomenon highlights the importance of gradual glycaemic improvement and appropriate monitoring in high-risk patients.

Effects on the body weight

One of the distinguishing features of GLP-1 RAs compared with many traditional glucose-lowering therapies is their consistent and clinically meaningful effect on body weight reduction (20, 21). This effect is primarily mediated through central mechanisms involving activation of GLP-1 receptors in the hypothalamus and other brain regions responsible for appetite regulation. GLP-1 receptor activation promotes satiety, reduces hunger, and decreases overall caloric intake (22). In addition to central appetite suppression, delayed gastric emptying contributes to prolonged gastric distension and enhanced feelings of fullness after meals. This effect reduces postprandial food intake and contributes to sustained weight loss over time. Unlike insulin or certain oral antidiabetic agents, which are often associated with weight gain, GLP-1 RAs provide a dual benefit of improved glycaemic control and weight reduction (23).

Clinical studies have demonstrated average weight reductions ranging from approximately 3% to over 15% of baseline body weight, depending on the specific agent, dose, and treatment duration. Greater weight loss has been observed with more potent agents and higher doses used for obesity management (24). Weight reduction contributes not only to improved glycaemic control but also to improvements in blood pressure, lipid profile, and overall cardiovascular risk.

The effect on body weight is particularly relevant in patients with T2DM and obesity, as excess adiposity is a major contributor to insulin resistance and metabolic dysfunction. By addressing both hyperglycaemia and excess body weight, GLP-1 RAs provide a comprehensive therapeutic approach. Furthermore, weight loss may indirectly influence microvascular health, including retinal circulation, through improvements in systemic metabolic and inflammatory parameters.

Potential vascular effects

GLP-1 RAs have been shown to exert multiple beneficial effects on the vascular system, extending beyond their primary role in glycaemic control (25). These vascular effects involve improvements in endothelial function, modulation of inflammatory pathways, reduction of oxidative stress, and favourable influences on vascular tone and perfusion. Such actions are particularly relevant in patients with T2DM, in whom chronic hyperglycaemia contributes to endothelial dysfunction and the development of both macrovascular and microvascular complications (25).

One of the key mechanisms underlying the vascular effects of GLP-1 RAs is the improvement of endothelial function. Activation of GLP-1 receptors on endothelial cells stimulates intracellular signalling pathways that enhance nitric oxide production, promoting vasodilation and improving vascular reactivity. Improved endothelial function contributes to better tissue perfusion and may help mitigate the progression of microvascular damage (26). Additionally, GLP-1 RAs have been shown to reduce the expression of adhesion molecules and pro-inflammatory cytokines, thereby decreasing vascular inflammation, which is a critical factor in the pathogenesis of diabetic microangiopathy.

GLP-1 RAs also demonstrate antioxidant properties by reducing oxidative stress, which plays a central role in endothelial injury and vascular dysfunction in T2DM. Chronic hyperglycaemia promotes the production of reactive oxygen species, leading to cellular damage, increased vascular permeability, and impaired autoregulation of blood flow. By attenuating oxidative stress and improving mitochondrial function, GLP-1 RAs may contribute to the preservation of vascular integrity (27).

In addition to their direct vascular effects, GLP-1 RAs exert indirect vascular benefits through improvements in systemic metabolic parameters. These include reductions in HbA1c, body weight, blood pressure, and circulating lipid levels. Such changes contribute to a reduction in overall cardiovascular risk and may positively influence microvascular circulation, including retinal blood vessels (28).

GLP-1 receptors have been identified in retinal endothelial cells and neural tissues, suggesting a potential direct effect on retinal microcirculation. Experimental studies indicate that GLP-1 receptor activation may influence retinal blood flow, vascular permeability, and inflammatory responses. These effects may have both protective and potentially adverse implications, depending on the clinical context. For example, improved metabolic control may reduce long-term microvascular damage, whereas rapid improvements in glycaemic status may transiently alter retinal perfusion and vascular stability (29). Cardiovascular outcome trials have demonstrated that GLP-1 RAs reduce the risk of major adverse cardiovascular events, supporting their role in

vascular protection at the systemic level (30). However, the specific effects of GLP-1 RAs on microvascular beds, particularly in the retina, remain an area of ongoing investigation. Understanding these vascular mechanisms is essential for evaluating the potential impact of GLP-1 RAs on retinal health and the development or progression of ophthalmological complications.

Most used medications

Several GLP-1 RAs are currently widely used in clinical practice for the treatment of T2DM and obesity. These agents differ in their molecular structure, pharmacokinetic properties, dosing frequency, and overall potency in glycaemic control and weight reduction. Structural modifications that increase resistance to enzymatic degradation and prolong circulation time allow for either once-daily or once-weekly administration. These pharmacokinetic differences influence both therapeutic efficacy and patient adherence.

Semaglutide (Figure 1) is a long-acting GLP-1 RA with structural modifications that allow strong albumin binding and resistance to enzymatic degradation, resulting in a prolonged half-life of approximately 7 days. This enables once-weekly subcutaneous administration, as well as a once-daily oral formulation (31).

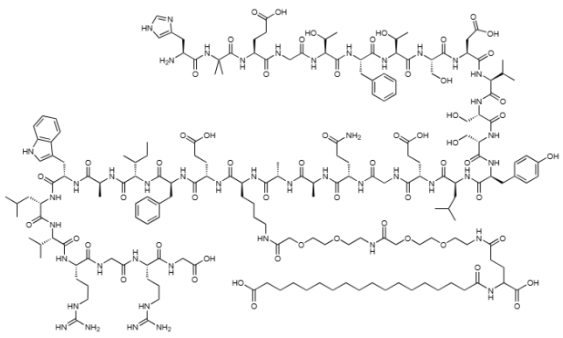

Figure 1. Semaglutide structure (32)

Semaglutide is among the most potent GLP-1 RAs in terms of glycemic control, with HbA1c reductions typically ranging from 1.0% to 1.8% (33). It also produces substantial weight loss and provides sustained receptor activation due to stable plasma concentrations. The prolonged duration of action contributes to consistent metabolic effects and improved treatment adherence.

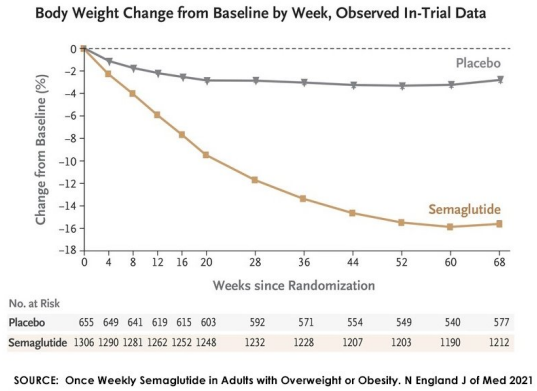

Figure 2.Semaglutide weight loss (34).

Liraglutide is a long-acting GLP-1 RA administered once daily. Its half-life of approximately 13 hours allows continuous receptor activation with daily dosing. Liraglutide reduces HbA1c by approximately 0.8% to 1.5%, depending on baseline glycaemic control and dose (35). It also produces moderate and sustained weight reduction. Compared with shorter-acting agents, liraglutide provides more stable glycaemic control and has demonstrated cardiovascular benefit in high-risk patients (36).

Dulaglutide is a once-weekly GLP-1 RA consisting of a modified GLP-1 analog fused to an immunoglobulin Fc fragment, which prolongs its half-life to approximately 5 days by reducing renal clearance and enzymatic degradation. It produces HbA1c reductions typically ranging from 1.0% to 1.5%. Dulaglutide provides continuous receptor stimulation and stable glycemic control with convenient weekly administration, contributing to improved adherence and long-term treatment persistence (37).

Exenatide was one of the first GLP-1 RAs introduced into clinical practice and is available in both twice-daily and once-weekly formulations. The twice-daily formulation has a

relatively short half-life of approximately 2 to 4 hours and primarily affects postprandial glucose levels. The once-weekly extended-release formulation provides more sustained glycemic control. HbA1c reductions typically range from 0.8% to 1.2%, which is generally slightly lower compared with newer long-acting agents. Due to shorter duration of action in its original formulation, exenatide produces more variable receptor activation compared with newer agents (38).

Tirzepatide is a dual incretin receptor agonist that activates both GLP-1 and glucose-dependent insulinotropic polypeptide (GIP) receptors. It has a prolonged half-life of approximately 5 days, allowing once-weekly administration (39). Tirzepatide demonstrates greater efficacy in reducing HbA1c compared with traditional GLP-1 RAs, with reductions ranging from approximately 1.5% to over 2.0% in clinical trials. This enhanced efficacy is attributed to its dual receptor activity, which improves insulin secretion, reduces glucagon levels, and enhances metabolic regulation. Tirzepatide also produces substantial weight reduction and sustained metabolic effects (40).

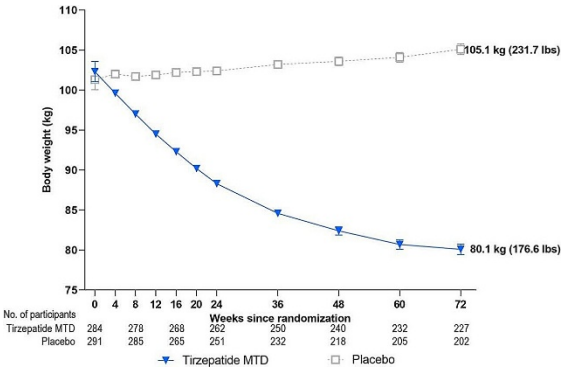

Figure 3. Tirzepatide weight loss (41).

Long-acting agents such as semaglutide, dulaglutide, and tirzepatide provide more stable plasma concentrations, greater HbA1c reduction, and improved adherence compared with shorter-acting agents. The magnitude and speed of glycemic improvement may be particularly relevant in the context of microvascular complications, including diabetic retinopathy, where rapid changes in glycemic control may influence disease progression. Understanding the pharmacokinetic and pharmacodynamic differences among these agents is essential for assessing their therapeutic effects and safety profile (42).

PATHOPHYSIOLOGICAL BASIS OF POTENTIAL OPHTALMOLOGICAL EFFECTS

The potential ophthalmological effects of GLP-1 RAs are complex and likely multifactorial, involving both indirect metabolic effects and direct actions on retinal tissues. These mechanisms include the presence of GLP-1 receptors in the retina, modulation of retinal microcirculation, the effects of rapid glycemic improvement, and possible anti-inflammatory and neuroprotective properties. Understanding these mechanisms is essential for interpreting clinical observations related to retinal changes during GLP-1 RA therapy.

GLP-1 receptors have been identified in various retinal structures, including retinal ganglion cells, inner nuclear layer neurons, and retinal endothelial cells. The presence of these receptors suggests that GLP-1 RAs may exert direct biological effects on retinal tissue. Activation of retinal GLP-1 receptors influences intracellular signaling pathways involved in cell survival, oxidative stress regulation, and inflammatory response (43).

Retinal microvascular dysfunction is a central feature in the development and progression of diabetic retinopathy. Chronic hyperglycemia leads to endothelial dysfunction, increased vascular permeability, capillary basement membrane thickening, and impaired autoregulation of retinal blood flow. GLP-1 RAs may influence these processes through both direct and indirect vascular mechanisms (44). Activation of GLP-1 receptors on endothelial cells promotes nitric oxide production, improves endothelial function, and enhances vasodilation. These effects may contribute to

improved retinal perfusion and reduced vascular injury. Furthermore, GLP-1 RAs have been shown to reduce oxidative stress and inflammatory signaling within the vascular endothelium, which may help preserve microvascular integrity (44).

One of the most important mechanisms associated with retinal changes during intensive glucose-lowering therapy is the phenomenon of early worsening of diabetic retinopathy. This phenomenon has been observed in various clinical settings, including initiation of insulin therapy and other highly effective glucose-lowering treatments. It is characterized by a transient progression of retinopathy following rapid and substantial reductions in HbA1c (45).

GLP-1 RAs, particularly more potent and long-acting agents, can produce significant and relatively rapid reductions in HbA1c. In patients with long-standing hyperglycemia and pre-existing diabetic retinopathy, this rapid improvement in glycemic control may trigger transient worsening of retinal pathology. Importantly, this effect is generally considered to be related to the magnitude and speed of glycemic improvement rather than direct retinal toxicity of the drug itself (46).

In addition to their metabolic and vascular effects, GLP-1 RAs have demonstrated anti-inflammatory and neuroprotective properties that may influence retinal health. Chronic inflammation and oxidative stress play central roles in the pathogenesis of diabetic retinopathy, contributing to endothelial dysfunction, neuronal injury, and breakdown of the blood-retinal barrier (47). GLP-1 receptor activation has been shown to reduce the production of pro-inflammatory cytokines and decrease oxidative stress in neural and vascular tissues. These effects may help protect retinal neurons from metabolic injury and reduce progressive neurodegeneration. Furthermore, GLP-1 RAs may stabilize the blood-retinal barrier and reduce vascular leakage by improving endothelial function and reducing inflammatory signaling.

OPHTAMOLOGICAL SIDE EFFECTS

Diabetic retinopathy

Diabetic retinopathy (DR) is a major microvascular complication of type 2 diabetes mellitus and remains a leading cause of visual impairment worldwide. The relationship between GLP-1 RAs and diabetic retinopathy progression has been the subject of extensive investigation, particularly following signals observed in cardiovascular outcome trials and meta-analyses. Current evidence suggests that the effects of GLP-1 RAs on retinopathy are complex and likely influenced by baseline patient characteristics, magnitude of glycemic improvement, and the presence of pre-existing retinal disease (50).

One of the most important factors associated with worsening diabetic retinopathy during GLP-1 RA therapy is the rapid and substantial reduction in HbA1c. GLP-1 RAs are highly effective glucose-lowering agents, with HbA1c reductions commonly exceeding 1%, particularly in patients with poor baseline glycemic control. Rapid improvement in glycaemia has long been recognized as a trigger for transient worsening of diabetic retinopathy, a phenomenon previously observed with intensive insulin therapy. Meta-regression analyses of cardiovascular outcome trials have demonstrated a relationship between the magnitude of HbA1c reduction and retinopathy risk, suggesting that early worsening is more closely related to the speed and extent of glycaemic improvement rather than direct retinal toxicity of GLP-1 RAs (49). This concept is further supported by safety reviews indicating that patients treated with potent GLP-1 RAs such as semaglutide require careful monitoring, particularly those with existing retinopathy or concomitant insulin therapy, due to the risk of deterioration associated with rapid glycemic improvement (51).

The proposed mechanism involves transient disruption of retinal autoregulation and microvascular stability following rapid normalization of blood glucose levels. Chronic hyperglycemia induces adaptive changes in retinal blood flow and vascular permeability; abrupt reversal of these metabolic conditions may temporarily exacerbate microvascular dysfunction, increase vascular leakage, and promote progression of retinopathy lesions.

Several large clinical trials have evaluated retinopathy outcomes in patients receiving GLP-1 RAs. The SUSTAIN-6 trial, which assessed cardiovascular outcomes with semaglutide, reported a significantly higher incidence of retinopathy complications compared with placebo (hazard ratio 1.76; 95% CI 1.11–2.78) (53). These complications included vitreous hemorrhage, need for intravitreal therapy, and photocoagulation. Importantly, affected patients had higher baseline HbA1c levels, longer diabetes duration, and a greater prevalence of pre-existing retinopathy, suggesting that patient characteristics rather than a direct toxic effect of semaglutide were responsible for the observed findings. Meta-analyses and pooled analyses of clinical trials have produced mixed results. One large meta-analysis of 93 clinical trials found that GLP-1 RA use was associated with an increased risk of early-stage diabetic retinopathy compared with placebo (risk ratio 1.31; 95% CI 1.01–1.68), while simultaneously demonstrating a protective effect against late-stage retinopathy compared with insulin (risk ratio 0.38; 95% CI 0.15–0.98) (48). These findings suggest that early worsening may represent a transient phenomenon rather than a sustained adverse effect.

Real-world data analyses have also demonstrated an increased risk of progression to proliferative diabetic retinopathy and diabetic macular oedema in patients treated with GLP-1 RAs compared with SGLT-2 inhibitors (relative risk 1.26 at 1 year and 1.29 at 3 years) (52). However, these observational findings are subject to confounding, as patients receiving GLP-1 RAs often have longer disease duration, higher HbA1c levels, and more advanced baseline disease.

The strongest predictor of retinopathy progression during GLP-1 RA therapy appears to be the presence of pre-existing diabetic retinopathy. Patients with established retinopathy, longer duration of diabetes, higher baseline HbA1c levels, and concomitant insulin use are at particularly high risk of early worsening (50-52). Safety reviews emphasize that deterioration of existing retinopathy is most likely to occur in high-risk patients undergoing rapid glycemic improvement (51). This observation is consistent with historical data from intensive glycemic control trials and suggests that the underlying mechanism is related to metabolic changes rather than direct retinal toxicity of GLP-1 receptor agonists.

Additionally, demographic and clinical characteristics such as age, diabetes duration, body mass index, and baseline glycaemic control may influence retinopathy risk during GLP-1 RA therapy (48). These findings highlight the importance of individualized risk assessment when initiating treatment.

Several mechanisms have been proposed to explain the early worsening of diabetic retinopathy associated with rapid glycemic improvement:

- Early worsening phenomenon – Rapid normalization of blood glucose levels may transiently worsen retinal microvascular pathology. Chronic hyperglycemia leads to structural and functional changes in retinal vessels, and abrupt correction may disrupt vascular autoregulation and exacerbate microvascular injury.
- Altered retinal blood flow and vascular permeability – Rapid reductions in plasma glucose may influence retinal perfusion pressure and endothelial function, resulting in increased vascular permeability and progression of retinopathy lesions.

- Osmotic and metabolic shifts – Changes in osmotic gradients and intracellular metabolism following rapid glycemic improvement may contribute to endothelial dysfunction and increased vascular leakage.
- Microvascular instability in advanced disease – Patients with established retinopathy have structurally compromised retinal vasculature that may be particularly vulnerable to sudden metabolic changes. Importantly, current evidence suggests that these effects are primarily related to rapid improvement in glycemic control rather than a direct toxic effect of GLP-1 receptor activation.

Long-term glycemic control achieved with GLP-1 RAs is expected to reduce the overall risk of diabetic retinopathy progression by improving metabolic stability and reducing microvascular damage.

Macular oedema

Diabetic macular oedema (DMO) represents one of the most significant vision-threatening complications of diabetic retinopathy and is a major cause of visual impairment in patients with type 2 diabetes mellitus. It results from disruption of the blood–retinal barrier and increased vascular permeability, leading to accumulation of extracellular fluid in the macula and subsequent retinal thickening. The incidence and progression of DMO are closely associated with the severity of diabetic retinopathy and underlying microvascular damage.

The incidence of diabetic macular oedema varies depending on the patient population, duration of diabetes, and presence of pre-existing retinopathy. Longitudinal observational studies have demonstrated that a substantial proportion of patients with diabetic retinopathy progress to vision-threatening complications, including proliferative diabetic retinopathy and DMO (54, 55). In large real-world cohort analyses involving individuals with type 2 diabetes receiving insulin therapy, the risk of developing diabetic macular oedema differed depending on the type of glucose-lowering therapy.

A large federated database study including approximately two million individuals with type 2 diabetes demonstrated that treatment with GLP-1 receptor agonists in combination with insulin was not associated with a statistically significant increase in DMO risk compared with insulin alone (hazard ratio [HR] 1.013; 95% CI 0.960–1.069) (54). However, when directly compared with sodium–glucose cotransporter 2 inhibitors (SGLT2i), GLP-1 receptor agonists were associated with a higher relative risk of developing diabetic macular oedema (HR 1.130; 95% CI 1.056–1.208) (54). These findings suggest that while GLP-1 receptor agonists may not independently increase DMO risk compared with standard therapy, differences between antihyperglycemic drug classes may exist. In contrast, treatment with SGLT2 inhibitors was associated with a reduced risk of diabetic macular oedema compared with insulin therapy alone (HR 0.835; 95% CI 0.780–0.893), suggesting potential protective effects of this drug class on retinal microvascular integrity (54). These findings support the hypothesis that antihyperglycaemic agents may exert differential effects on retinal vascular complications beyond glycemic control.

Systematic reviews evaluating multiple antihyperglycemic drug classes have generally concluded that most newer glucose-lowering therapies, including GLP-1 receptor agonists, have a neutral effect on diabetic retinopathy progression and macular oedema. However, subclass-specific differences may exist, and certain agents such as semaglutide have been associated with slight worsening of retinal outcomes in some populations, warranting careful monitoring and further investigation (56). The development of diabetic macular oedema is primarily driven by microvascular dysfunction, including endothelial injury, breakdown of the blood–retinal barrier, and increased vascular permeability. Chronic

hyperglycaemia induces structural and functional alterations in retinal capillaries, including endothelial dysfunction, basement membrane thickening, pericyte loss, and increased expression of vascular endothelial growth factor (VEGF), all of which contribute to vascular leakage and fluid accumulation within the macula (57).

Emerging evidence suggests that antihyperglycemic agents may influence retinal vascular function through mechanisms independent of glucose lowering. Experimental and clinical data indicate that GLP-1 receptor agonists and SGLT2 inhibitors may modulate oxidative stress, inflammation, and vascular remodeling within the retina (54). These effects may include reduction of endothelial cell apoptosis, attenuation of oxidative stress, and stabilization of retinal microvascular structure, potentially influencing the risk of macular oedema development.

In addition, GLP-1 receptor agonists may exert neuroprotective and vasoprotective effects in retinal tissue, including modulation of inflammatory signaling pathways and preservation of retinal neuronal integrity (54). However, rapid improvements in glycemic control associated with potent glucose-lowering therapies may transiently destabilize retinal microvasculature, potentially contributing to increased vascular permeability and fluid accumulation in susceptible individuals.

Overall, current evidence suggests that the relationship between GLP-1 receptor agonists and diabetic macular oedema is complex and likely influenced by multiple factors, including baseline retinal disease severity, magnitude and speed of glycemic improvement, and underlying vascular vulnerability. While most studies indicate a neutral effect on DMO incidence, differences between drug classes and individual patient risk profiles highlight the importance of careful retinal monitoring during initiation of intensive glucose-lowering therapy.

Neuroophtalmological aspects

Neuroophthalmological complications associated with gGLP-1 RAs, particularly semaglutide, have recently gained attention due to emerging reports of potential associations with nonarteritic anterior ischemic optic neuropathy (NAION). NAION is the most common acute ischemic optic neuropathy in adults and is characterized by sudden, painless vision loss resulting from impaired perfusion of the optic nerve head. Established risk factors include diabetes mellitus, hypertension, hyperlipidemia, obstructive sleep apnea, and structural predisposition such as a crowded optic disc (58-60).

Recent epidemiological studies have produced mixed findings regarding the association between semaglutide and NAION. A large multicenter observational study involving 37.1 million individuals with type 2 diabetes reported an incidence rate of NAION of approximately 14.5 per 100,000 person-years among semaglutide users. Although the overall risk was not significantly increased compared with most comparator medications, self-controlled case-series analysis demonstrated a modest increase in relative risk during periods of semaglutide exposure (incidence rate ratio 1.32; 95% CI 1.14–1.54), suggesting a possible temporal association (59). Similarly, retrospective cohort analyses have identified increased rates of NAION among semaglutide-treated patients in selected populations. In a matched cohort of neuro-ophthalmology patients, semaglutide exposure was associated with higher cumulative incidence of NAION compared with alternative therapies, particularly in individuals with type 2 diabetes or obesity, with hazard ratios exceeding 4.0 in some analyses (60). Registry-based population studies have also reported higher incidence rates of NAION among semaglutide users compared with patients receiving alternative glucose-lowering therapies, although findings have not been consistent across all datasets (60).

In contrast, large retrospective analyses using multinational electronic health record databases have found no significant increase in NAION risk associated with semaglutide or GLP-1 receptor agonists overall. For example, a propensity score–matched cohort study involving over 130,000 patients with type 2 diabetes found no increased risk of NAION at 1-, 3-, or 5-year follow-up in patients treated with semaglutide compared with non–GLP-1 RA therapies, with a cumulative 5-year incidence of only 0.065% (58). These findings suggest that if an association exists, the absolute risk remains very low. The heterogeneity of findings across studies may reflect differences in patient populations, baseline vascular risk factors, and study methodology. Importantly, patients prescribed GLP-1 receptor agonists often have more advanced diabetes, higher cardiovascular risk, and greater prevalence of systemic comorbidities, all of which independently increase the risk of NAION.

Several pathophysiological mechanisms have been proposed to explain a potential association between GLP-1 receptor agonists and NAION, although causality remains unproven. NAION results from impaired blood flow within the short posterior ciliary arteries supplying the optic nerve head. Rapid reductions in blood glucose associated with potent glucose-lowering therapies such as semaglutide may alter autoregulatory mechanisms and transiently compromise optic nerve perfusion. Hypoperfusion and vascular dysregulation may contribute to ischemic injury, particularly in patients with pre-existing microvascular disease (60).

Similar to the early worsening phenomenon observed in diabetic retinopathy, rapid improvements in glycemic control may destabilize microvascular circulation. Significant reductions in blood glucose may induce changes in retinal and optic nerve perfusion, potentially contributing to ischemic events in susceptible individuals (60). Structural characteristics of the optic disc, particularly a crowded optic nerve head ("disc-at-risk"), may predispose patients to ischemic events. It has been proposed that glycemic shifts may lead to venous dilation, increased vascular permeability, and venous congestion within the optic nerve head, resulting in compartment-like ischemia and subsequent optic nerve injury (60).

GLP-1 receptor agonists are frequently prescribed to patients with multiple vascular risk factors, including diabetes, hypertension, and hyperlipidaemia, all of which independently contribute to impaired optic nerve perfusion. These underlying comorbidities likely play a major role in NAION development and may confound observed associations (58,59). Interestingly, GLP-1 receptor agonists have also demonstrated anti-inflammatory and vasoprotective effects in experimental models, suggesting that they may not directly cause optic nerve injury. Some large-scale observational studies have found no increased long-term risk of NAION, supporting the hypothesis that any observed association may reflect confounding by underlying disease severity rather than a direct pharmacological effect (58).

Current evidence suggests that while a possible association between semaglutide and NAION has been reported, the absolute risk remains low and causality has not been definitively established. The available data indicate that observed events may be related to underlying vascular risk factors, rapid glycaemic improvement, and individual anatomical susceptibility rather than direct toxic effects of GLP-1 receptor agonists. Nevertheless, clinicians should remain aware of this potential risk, particularly in patients with advanced diabetes, pre-existing microvascular complications, or known structural susceptibility of the optic nerve. Careful monitoring and gradual optimization of glycaemic control may help reduce the risk of

ischemic neuroophthalmological complications.

CONCLUSION

GLP-1 RAs have emerged as a cornerstone in the management of type 2 diabetes mellitus and obesity due to their potent glucose-lowering effects, significant weight reduction, and well-established cardiovascular benefits. Their expanding clinical use has prompted increased attention toward their ophthalmological safety profile, particularly in relation to diabetic retinopathy, diabetic macular oedema, and neuroophthalmological complications such as nonarteritic anterior ischemic optic neuropathy. Current evidence suggests that GLP-1 receptor agonists do not exert direct retinal toxicity in most patients. However, transient worsening of diabetic retinopathy may occur, particularly in individuals with pre-existing retinal disease, long-standing diabetes, and high baseline HbA1c levels. This effect appears to be primarily related to the magnitude and rapidity of glycemic improvement rather than a direct pharmacological effect of GLP-1 receptor activation. Similarly, the available data indicate that GLP-1 receptor agonists generally have a neutral effect on the incidence of diabetic macular oedema, although differences between drug classes and individual patient risk profiles have been observed. Emerging evidence has also raised the possibility of an association between semaglutide and nonarthritic anterior ischemic optic neuropathy. While some observational studies suggest a modest increase in relative risk, the absolute incidence remains very low, and causality has not been definitively established. The development of such neuroophthalmological complications is likely multifactorial, involving systemic vascular risk factors, microvascular dysfunction, rapid metabolic changes, and individual anatomical susceptibility rather than a direct toxic drug effect.

Importantly, GLP-1 receptor agonists also demonstrate vasoprotective, anti-inflammatory, and neuroprotective properties, which may contribute to long-term preservation of retinal structure and function. These beneficial effects, combined with their ability to improve glycemic control and reduce cardiovascular risk, support their continued use as a highly effective therapeutic option. From a clinical perspective, careful patient selection and monitoring are essential when initiating GLP-1 receptor agonist therapy, particularly in individuals with advanced diabetic retinopathy or other microvascular complications. Gradual optimization of glycemic control and regular ophthalmological evaluation may help minimize the risk of transient disease worsening.

Future prospective studies with long-term follow-up and standardized ophthalmological endpoints are needed to further clarify the relationship between GLP-1 receptor agonists and ocular complications. Improved understanding of underlying mechanisms and identification of high-risk patient subgroups will help optimize therapeutic strategies and ensure safe and effective use of these agents in clinical practice. The available evidence indicates that the ophthalmological risks associated with GLP-1 receptor agonists are limited and largely outweighed by their substantial metabolic and cardiovascular benefits, provided that appropriate monitoring and individualized treatment approaches are implemented.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

AUTHORS' CONTRIBUTIONS

DP: acquisition of data, critical revision of the paper; IB: literature review, contribution to study conception and

design; MK: contribution to study conception and design; IĆ: literature review; BT: supervision, interpretation of data, critical revision of the paper; NG: literature review, contribution to study conception.

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