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Semaglutide and non-arteritic anterior ischemic optic neuropathy: clinical evidence, pathophysiological hypotheses, and implications for practice

Semaglutida e neuropatia óptica isquêmica anterior não arterítica: evidências clínicas, hipóteses fisiopatológicas e implicações para a prática

Semaglutida y neuropatía óptica isquémica anterior no arterítica: evidencia clínica, hipótesis fisiopatológicas e implicaciones para la práctica

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Abstract:
Background: Semaglutide provides established metabolic and cardiovascular benefits in type 2 diabetes and obesity, but a possible association with non-arteritic anterior ischemic optic neuropathy (NAION) has raised safety concerns. Objective: To critically examine the clinical evidence, putative mechanisms and implications for practice. Methods: A narrative review was conducted with bibliographic searches in November 2026 of PubMed/MEDLINE-indexed studies, supplemented by reference checking and consultation of European Medicines Agency and UK Medicines and Healthcare products Regulatory Agency communications. Primary studies, meta-analyses and scientific society guidance were prioritized. Results: Several observational cohorts and meta-analyses indicated a higher relative risk, often around twofold, whereas other investigations reported no association or inverse associations. Absolute event risks remained low; residual confounding, heterogeneity and outcome misclassification limit causal interpretation. A randomized-trial meta-analysis showed a statistical association based on few events. European regulators classified NAION as a very rare adverse reaction to semaglutide and advised discontinuation when NAION is confirmed. Conclusion: NAION is a relevant safety signal associated with semaglutide exposure, although causality and a specific pathophysiological mechanism are not established. Prompt assessment of acute visual symptoms and individualized risk–benefit decisions are warranted; universal ophthalmic screening solely because of semaglutide exposure is unsupported.

Keywords: Semaglutide; Non-arteritic anterior ischemic optic neuropathy; GLP-1 receptor agonists; Drug safety; Pharmacoepidemiology.

Resumo:
Introdução: A semaglutida é utilizada no tratamento do diabetes mellitus tipo 2 e da obesidade, com benefícios metabólicos e cardiovasculares estabelecidos. Estudos recentes identificaram um possível sinal de segurança para neuropatia óptica isquêmica anterior não arterítica (NOIA-NA), causa de perda visual súbita potencialmente irreversível. Objetivo: Examinar criticamente a associação entre semaglutida e NOIA-NA, seus possíveis mecanismos e as repercussões clínicas. Métodos: Foi realizada uma revisão narrativa com buscas bibliográficas em novembro de 2026 de estudos indexados na PubMed/MEDLINE, complementadas pela verificação das referências dos trabalhos selecionados e pela consulta a comunicados da European Medicines Agency (EMA) e da Medicines and Healthcare products Regulatory Agency (MHRA). Foram priorizados estudos originais, metanálises e orientações de sociedades científicas. Resultados:

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Coortes observacionais e algumas sínteses quantitativas apontaram aumento relativo do risco, frequentemente em torno de duas vezes, mas houve estudos com resultados nulos ou inversos. As estimativas de risco absoluto foram baixas; persistiram heterogeneidade, possível confundimento residual e limitações na confirmação diagnóstica. Uma metanálise de ensaios randomizados encontrou associação estatística, mas com poucos eventos. Em 2025, a EMA classificou a NOIA-NA como reação adversa muito rara da semaglutida; em 2026, a MHRA reforçou a orientação de suspensão quando o diagnóstico for confirmado. Conclusão: Existe um sinal clínico e regulatório relevante, mas os dados ainda não estabelecem causalidade nem identificam um mecanismo específico. Recomenda-se informar pacientes sobre sinais de alerta, encaminhar imediatamente aqueles com perda visual súbita e individualizar a decisão terapêutica, sem rastreamento oftalmológico universal por essa exposição isoladamente.

Palavras-chave: Semaglutida; Neuropatia óptica isquêmica anterior não arterítica; Agonistas do receptor de GLP-1; Segurança medicamentosa; Farmacoepidemiologia.

Resumen:
Introducción: La semaglutida se utiliza para tratar la diabetes mellitus tipo 2 y la obesidad, con beneficios metabólicos y cardiovasculares establecidos. Estudios recientes identificaron una posible señal de seguridad de neuropatía óptica isquémica anterior no arterítica (NOIA-NA), causa de pérdida visual súbita potencialmente irreversible. Objetivo: Examinar críticamente la asociación entre semaglutida y NOIA-NA, sus posibles mecanismos y repercusiones clínicas. Métodos: Se realizó una revisión narrativa mediante búsquedas bibliográficas en noviembre de 2026 de estudios indexados en PubMed/MEDLINE, complementadas con la comprobación de referencias y la consulta de comunicados de la European Medicines Agency (EMA) y la Medicines and Healthcare products Regulatory Agency (MHRA). Se priorizaron estudios originales, metanálisis y orientaciones de sociedades científicas. Resultados: Cohortes observacionales y algunas síntesis cuantitativas señalaron un incremento relativo del riesgo, frecuentemente cercano al doble, aunque hubo estudios con resultados nulos o inversos. Las estimaciones de riesgo absoluto fueron bajas; persistieron heterogeneidad, posible confusión residual y limitaciones en la confirmación diagnóstica. Un metanálisis de ensayos aleatorizados encontró asociación estadística, pero con pocos acontecimientos. En 2025, la EMA clasificó la NOIA-NA como reacción adversa muy rara de semaglutida; en 2026, la MHRA reforzó la recomendación de suspensión cuando se confirme el diagnóstico. Conclusión: Existe una señal clínica y reguladora relevante, pero los datos todavía no establecen causalidad ni identifican un mecanismo específico. Se recomienda informar sobre signos de alarma, derivar inmediatamente ante pérdida visual súbita e individualizar la decisión terapéutica, sin cribado oftalmológico universal por esta exposición aislada.

Palabras clave: Semaglutida; Neuropatía óptica isquémica anterior no arterítica; Agonistas del receptor de GLP-1; Seguridad de los medicamentos; Farmacoepidemiología.

Introduction

Glucagon-like peptide-1 (GLP-1) receptor agonists have become important components of treatment for type 2 diabetes mellitus (T2DM) and obesity. Semaglutide, available in subcutaneous and oral formulations, promotes glycemic control, weight reduction, and

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cardiovascular benefits in selected populations. Its expanding use also requires attention to rare adverse events that may not have been adequately assessed in clinical trials. [1]

In ophthalmology, the main initial warning concerned early worsening of diabetic retinopathy in certain patients following a rapid, substantial reduction in glycated hemoglobin (HbA1c). This phenomenon should not be confused with non-arteritic anterior ischemic optic neuropathy (NAION): although both affect vision, their location, pathophysiology, and diagnostic criteria differ. [2,3]

In 2024, a retrospective tertiary-center study found more NAION among people prescribed semaglutide. Subsequent multicenter studies, national cohorts, and meta-analyses produced heterogeneous estimates. Meanwhile, regulators began recognizing NAION as a possible very rare adverse reaction, although individual causality remains difficult to demonstrate. [4–20]

This review discusses the available evidence, distinguishes relative from absolute risk, analyzes mechanistic hypotheses, and summarizes recommendations useful for clinical decisions.

Review methodology

A descriptive and critically analytical narrative review was conducted. Bibliographic searches included identifying scientific articles indexed in PubMed/MEDLINE and consulting the original publications located. Combinations of “semaglutide”, “GLP-1 receptor agonists”, “non-arteritic anterior ischemic optic neuropathy”, “NAION”, “ischemic optic neuropathy”, “ocular adverse events”, and “drug safety” were used with Boolean operators AND and OR. The main conceptual strategy was: (“semaglutide” OR “GLP-1 receptor agonists”) AND (“NAION” OR “non-arteritic anterior ischemic optic neuropathy” OR “ischemic optic neuropathy”).

The search was supplemented by reference-list checking and direct consultation of official EMA and MHRA communications and the joint statement of the American Academy of Ophthalmology (AAO) and North American Neuro-Ophthalmology Society (NANOS). Priority was given to cohort studies, active-comparator investigations, clinical trials, systematic reviews, meta-analyses, and regulatory documents. Studies on NAION pathophysiology and diabetic retinopathy were included for context without assuming equivalence between outcomes.

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The critical synthesis considered population, semaglutide indication, comparator type, outcome definition and validation, adjusted association measures, absolute risk, potential confounding, and overlap among cohorts included in meta-analyses.

Semaglutide and the ophthalmic context

Semaglutide is a long-acting GLP-1 receptor agonist. Its main effects include glucose-dependent enhancement of insulin secretion, inappropriate glucagon suppression, delayed gastric emptying, and greater satiety. These effects produce metabolic improvement but do not, by themselves, establish direct optic nerve injury. [1,2]

Diabetic retinopathy warrants separate discussion. In SUSTAIN-6, more retinopathy complications were observed in a patient subgroup; later analyses suggested that the magnitude and speed of HbA1c reduction, particularly with preexisting retinopathy and insulin use, probably explained part of the finding. Extrapolating this phenomenon to NAION is only a hypothesis, not a demonstrated mechanism. [1,2]

NAION: clinical foundations and risk factors

NAION is an acute optic neuropathy usually associated with impaired optic nerve head perfusion and local anatomical susceptibility. It generally presents as sudden, painless monocular visual loss, often noticed on awakening, with optic disc swelling in the acute phase, a possible relative afferent pupillary defect, and visual field defects, particularly altitudinal defects. Diagnosis is primarily clinical, supported by fundus examination, visual field testing, and optical coherence tomography (OCT). [3,21]

Associated factors include older age, T2DM, hypertension, dyslipidemia, obstructive sleep apnea, smoking, and a small optic disc or reduced physiological cup (“disc at risk”). Some pathophysiological hypotheses involve nocturnal hypotension and altered autoregulation, but their contribution varies between cases. Arteritic anterior ischemic optic neuropathy, particularly associated with giant cell arteritis, must be urgently excluded when appropriate because it requires immediate intervention. [3,21]

The overlap between NAION risk factors and characteristics of semaglutide-treated patients introduces confounding by indication and disease severity. This makes attributing an event to the drug solely from the temporal sequence between exposure and visual loss difficult.

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Epidemiological evidence

Observational studies and heterogeneity of estimates

In 2024, Hathaway and colleagues retrospectively analyzed patients at a tertiary neuro-ophthalmology service. Among individuals with T2DM, 36-month cumulative incidence was 8.9% in the semaglutide-prescribed cohort and 1.8% in the comparator group (HR 4.28; 95% CI: 1.62–11.29). In the overweight or obesity group, HR was 7.64 (95% CI: 2.21–26.36). Because this was a highly selected population, these proportions do not represent expected incidence in the general population using the drug. [4]

A Danish national registry cohort also identified a positive association in people with T2DM. In a subsequent multicenter study, Cai and colleagues pooled 14 databases covering 37.1 million people with T2DM, including 810,390 new semaglutide users. NAION incidence among users was 14.5 cases per 100,000 person-years. Comparisons with other antidiabetic drugs were predominantly nonsignificant with the more sensitive diagnostic definition, while self-controlled analysis indicated a modest relative increase (incidence rate ratio [IRR] 1.32; 95% CI: 1.14–1.54). [5,6]

In contrast, Chou and colleagues found no statistically significant increase during up to three years of follow-up in a matched multinational cohort of patients with T2DM, obesity, or both. A 2026 study among U.S. military health system beneficiaries found an inverse association in the T2DM subgroup (adjusted OR 0.36; 95% CI: 0.25–0.51). This highlights differences between databases, operational definitions, comparators, and adjustment strategies without establishing pharmacological protection. [7,11]

In a target trial emulation involving 102,361 U.S. veterans with T2DM receiving metformin, Heberer and colleagues observed HR 2.33 (95% CI: 1.54–3.54) for semaglutide initiation versus sodium-glucose cotransporter-2 inhibitors (SGLT2i). Weighted cumulative risk was 0.29% versus 0.13% after median follow-up of 2.1 years. Male predominance among veterans limits generalizability. [8]

Comparing new GLP-1 agonist users with SGLT2i users in insurance databases, Tesfaye and colleagues reported HR 1.85 (95% CI: 1.51–2.27), with an absolute difference of 0.29 cases per 1,000 person-years. This finding concerns the therapeutic class rather than semaglutide exclusively. Similarly, a Swedish cohort by Ueda and colleagues evaluated anterior ischemic optic neuropathy (AION), a broader outcome than strictly confirmed NAION: one-

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year risk was 0.04% versus 0.02% (RR 1.93; 95% CI: 1.00–3.73), with substantial attenuation in analyses restricted to metformin users. [9,10]

Clinical trials and quantitative syntheses

Natividade and colleagues pooled 78 randomized trials with 73,640 participants. They found no overall increase in ophthalmic events (OR 1.01; 95% CI: 0.91–1.12) or diabetic retinopathy (OR 1.04; 95% CI: 0.92–1.17), but observed an association with NAION (OR 3.92; 95% CI: 1.02–15.02). The specific analysis relied on few events and had a wide interval; trial sequential analysis indicated insufficient information for a definitive conclusion about this outcome. [12]

In a meta-analysis of six observational studies, Abdelaal and colleagues reported a pooled adjusted HR of 1.63 (95% CI: 0.88–2.39), without statistical significance in the primary analysis and with low certainty of evidence. Pooling studies of the GLP-1 agonist class, Nogueira and colleagues found OR 1.70 (95% CI: 1.23–2.36), with an approximate absolute difference of 0.037 percentage points in the pooled populations. These analyses address partly different questions and should not be treated as interchangeable estimates. [13,14]

In May 2026, Chrzanowski and colleagues published a meta-analysis of observational studies in T2DM: pooled HR 2.17 (95% CI: 1.73–2.74) compared with other diabetes treatments, with an estimated absolute excess of approximately one case per 7,000 patients treated for one year. The authors rated evidence certainty as low or very low. Another meta-analysis, by Khani and colleagues, found a relative estimate of 1.93 (95% CI: 1.22–3.08) across eight cohorts, with high heterogeneity ($I^2 = 91\%$). [15,16]

A Bayesian synthesis by Dhivagaran and colleagues also identified a positive association for semaglutide (RR 2.52; 95% credible interval: 1.56–4.72). Although this reinforces an epidemiological signal, several meta-analyses share primary studies; their multiplicity therefore does not provide independent evidence equivalent to the number of published articles. [17]

Table 1. Comparative synthesis of selected studies.

Study	Design	Main finding	Interpretive limitation
Hathaway et al., 2024 [4]	Tertiary-center cohort	HR 4.28 in T2DM	Marked clinical selection; limited generalizability
Cai et al., 2025 [6]	14 databases	14.5/100,000 person-years; IRR 1.32	Reliance on diagnostic codes

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Study	Design	Main finding	Interpretive limitation
Chou et al., 2025 [7]	Multinational cohort	No significant association	Few events in some subgroups
Heberer et al., 2026 [8]	Target trial emulation	HR 2.33; 0.29% vs 0.13%	Male predominance; coded outcome
Ueda et al., 2026 [10]	Swedish national cohort	RR 1.93 at 1 year	AION outcome; attenuation with metformin
Abdelaal et al., 2026 [13]	Observational meta-analysis	Adjusted HR 1.63 (CI crosses 1)	Low certainty; sensitive estimate
Chrzanowski et al., 2026 [15]	Observational meta-analysis	HR 2.17; ~1/7,000/year additional	Risk of bias; low/very low certainty

Absolute risk, causality, and bias

A roughly twofold relative association does not mean that NAION is frequent. Absolute risk remains low in population cohorts. For clinical counseling, excess events per treated people over a specified period should preferably be reported alongside population and comparator context. EMA estimates suggest approximately one additional case per 10,000 person-years of exposure; Chrzanowski and colleagues' meta-analysis estimated approximately one additional case per 7,000 patients over one year. These figures are approximations derived through different methods rather than precise individual predictions. [15,18]

Major threats to causal inference include confounding by indication and T2DM severity, pharmacological comparator selection, surveillance bias, incomplete diagnostic coding, and few events. Neuro-ophthalmologist confirmation of NAION is inconsistent across administrative databases. Tertiary-center studies may overestimate incidence because they concentrate patients with ocular disease; large studies may lose diagnostic specificity. Successive meta-analyses may also overlap in their underlying patient databases. [4,6,8,10,13,15]

Current studies therefore support an association signal and justify pharmacovigilance and risk communication, but do not demonstrate that semaglutide is a necessary or sufficient cause of NAION in every exposed patient.

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Proposed pathophysiological mechanisms

Optic nerve head perfusion

Changes in blood pressure, intravascular volume, and microvascular autoregulation could theoretically reduce optic nerve head perfusion in predisposed individuals. Weight loss, blood pressure reduction, and gastrointestinal symptoms with possible dehydration provide plausible mechanistic pathways under particular circumstances. However, sufficient clinical evidence does not exist to demonstrate that these changes mediate the epidemiological association between semaglutide and NAION. [3,21]

Metabolic changes and rapid HbA1c reduction

Early worsening of diabetic retinopathy after intensive glycemic improvement is recognized. It is possible to hypothesize that rapid metabolic changes affect optic nerve microvascular mechanisms; however, diabetic retinopathy and NAION are distinct entities. Evidence for the former does not establish the latter, and rapid HbA1c reduction should not be presented as an established mechanism of semaglutide-related NAION. [1,2]

Anatomical susceptibility and axonal edema

An optic disc with a small cup may favor a cycle of axonal edema, microcirculatory compression, and worsening ischemia. This compartmentalization hypothesis helps explain anatomical vulnerability in NAION, but semaglutide has not been shown to directly cause optic disc edema or trigger this cycle. [3,21]

Direct toxicity

There is no robust clinical evidence of direct semaglutide neurotoxicity to the optic nerve. Experimental GLP-1 signaling models even describe neuroprotective effects in different contexts. Unvalidated biological hypotheses should not be converted into confirmed causal mechanisms.

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Regulatory position and clinical implications

In June 2025, the European Medicines Agency (EMA) pharmacovigilance committee concluded that NAION should be listed as a “very rare” adverse reaction to semaglutide-containing medicines, a frequency category of up to one case per 10,000 treated people. The agency described an approximately twofold relative increase in epidemiological studies and estimated around one excess case per 10,000 person-years of treatment. It recommended immediate medical contact for sudden visual loss or rapidly worsening vision and semaglutide discontinuation if NAION is confirmed. [18]

In February 2026, the UK MHRA issued convergent guidance: specifically ask about semaglutide in patients with sudden visual loss, refer for urgent ophthalmic assessment, and discontinue the medicine when diagnosis is established. The document recommends reporting suspected adverse reactions. [19]

The 2026 consensus by AAO and NANOS experts acknowledged the possible association's small absolute magnitude and uncertain causality. Shared decisions with the treating team were recommended when starting, continuing, or discontinuing GLP-1 agonists. This principle should not be interpreted as revoking specific regulatory guidance to discontinue semaglutide after confirmed NAION. [20]

Practical management of visual symptoms

- Sudden partial or complete visual loss, especially monocular and painless, requires urgent ophthalmic assessment regardless of semaglutide use.
- At initial assessment, document visual acuity, pupillary examination, fundus examination, and, when available and indicated, OCT and visual fields; investigate differential diagnoses, particularly arteritic AION/giant cell arteritis in at-risk patients.
- When NAION is confirmed in a semaglutide user, follow regulatory guidance to discontinue the medicine and coordinate an alternative metabolic treatment with the prescriber, avoiding discontinuation without a T2DM or obesity management plan.
- In patients without NAION, explain warning signs and individualize treatment according to cardiometabolic benefit and clinical risk; universal periodic ophthalmic screening exclusively because of semaglutide exposure is unsupported.

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- Document and report suspected adverse events to the appropriate national pharmacovigilance system, recognizing that an isolated report does not demonstrate causality.

Review limitations and future directions

This is a narrative review without duplicate systematic selection or an original meta-analysis. Consequently, it cannot quantify an independent pooled effect or exclude selection bias in the publications discussed. Furthermore, the update focused on checking PubMed/MEDLINE-indexed studies and selected primary sources; no exhaustive direct search of Embase, Scopus, or the Cochrane Library was performed. Results should be interpreted as a contextualized critical synthesis rather than a systematic review.

The primary literature presents additional challenges: few confirmed NAION events, important differences in inclusion criteria, dose and therapeutic indication, heterogeneous follow-up, active comparators with different risk profiles, administrative-code diagnoses, and potential sharing of patients across databases. Prospective studies with neuro-ophthalmological adjudication, predefined outcomes, appropriate comparators, HbA1c and blood pressure measurement, optic disc anatomy assessment, and temporal exposure analysis may clarify susceptibility and causality.

Conclusion

The association between semaglutide and NAION is a clinically relevant safety signal supported by different cohorts and meta-analyses, but estimates are heterogeneous and susceptible to confounding. Although some analyses indicate approximately doubled relative risk, absolute event frequency is low and no pathophysiological hypothesis has been definitively established.

Under 2025–2026 regulatory recommendations, semaglutide users should be advised to seek immediate care for sudden visual loss; when NAION is confirmed, the drug should be discontinued and the therapeutic regimen reassessed. Without the event, prescribing semaglutide requires individual consideration of metabolic and cardiovascular benefits, without indiscriminate discontinuation or universal ophthalmic screening for this reason alone. Further studies with greater diagnostic validity are needed to clarify the nature and magnitude of the association.

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