POINT OF VIEW

Glucagon Agonist Therapies and Vision Loss: Balancing Promise with Prudence in India

Abhyuday Saxena[1], Anupam Prakash[2*]

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Abstract

Glucagon-like peptide-1 receptor agonists (GLP-1 RAs) and dual incretin therapies such as tirzepatide have transformed the management of type 2 diabetes mellitus and obesity, with expanding cardiometabolic indications and rapid market growth globally and in India. However, emerging postmarketing evidence has raised concerns regarding ocular safety. Pharmacovigilance analyses, cohort studies, and case reports suggest an association between GLP-1–based therapies and ophthalmic adverse events, including early worsening of diabetic retinopathy and, more concerningly, nonarteritic anterior ischemic optic neuropathy (NAION)—a potentially irreversible cause of sudden vision loss in adults over 50 years. Although the absolute risk appears very low, regulatory agencies, including the WHO and European Medicines Agency, now recognize NAION as a very rare adverse effect of semaglutide, and similar signals are being explored for other agents, suggesting a possible class effect.

Proposed mechanisms include altered optic nerve head perfusion, sympathetic-mediated vasoconstriction, and rapid glycemic shifts affecting vascular autoregulation; however, causality remains unproven. In India, where over 100 million adults live with diabetes and obesity rates are rising, even rare adverse events may translate into substantial public health impact, particularly given limited access to ophthalmic care and increasing unsupervised drug use.

We advocate a balanced approach: baseline ophthalmic evaluation in high-risk individuals, informed consent regarding visual symptoms, early referral for visual complaints, strengthened pharmacovigilance, and coordinated endocrinology–ophthalmology surveillance systems. As newer triple agonists approach clinical use, integrating ocular safety into prescribing frameworks is imperative. Metabolic gains must not come at the cost of preventable vision loss.

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Background

The introduction of glucagon-like peptide-1 receptor agonists (GLP-1 RAs), such as semaglutide, liraglutide, dulaglutide, and dual GLP-1 and GIP receptor agonists like tirzepatide, appears to be a transformative advance in medical care. Initially introduced for type 2 diabetes mellitus (T2DM), the therapeutic role of glucagon-based therapies (GLP-1RA and dual GLP-1 and GIP agonists) has expanded to obesity management and cardiometabolic care as well.[1,2] The global market for GLP-1 receptor agonists is a rapidly growing, multibillion-dollar industry with a size of USD 53.46 billion in 2024, and about 6% of the US adult population taking GLP-1 RAs.[3,4]

India, home to an estimated 101 million people with diabetes[5] and among the fastest-growing obesity markets globally, is likely to have a similar widespread adoption. The Indian market size for GLP-1 receptor agonists was USD 110.55 million in 2024 and is projected to grow at 34.3% from 2025 to 2030.[6]

Semaglutide-based drugs currently hold a significant market share with increasing demand for newer formulations.[7,8] The tirzepatide molecule has also come on the anvil with a bang, and with a tremendous marketing push.

The key drivers include rising obesity and diabetes rates, expanding therapeutic uses, innovative drug formulations such as oral and combination therapies, and increased demand supported by social media and direct-to-consumer advertising. However, postmarketing surveillance has uncovered a rare but devastating safety issue: association between GLP-based therapies and ophthalmic side effects, including progression of diabetic retinopathy (DR) and, most seriously, nonarteritic anterior ischemic optic neuropathy (NAION), a leading cause of irreversible optic neuropathy in adults over 50 years.[9–11]

Cause of Concern

Blurred vision and visual impairment are among the most frequently reported ocular adverse events, which may occur within days of starting GLP-based therapies.[9,10] Evidence suggests a transient increase in the risk of early-stage diabetic retinopathy with GLP-1 RAs, especially when associated with rapid HbA1c reductions,[12,13] although long-term use is not uniformly associated with increased vision-threatening diabetic retinopathy.[14] A recent meta-analysis showed that albiglutide is responsible for these trends, as it is significantly associated with a higher risk of early-stage DR compared to placebo and a lower risk of late-stage DR compared to insulin. Large-scale studies, therefore, indicate that monitoring should be intensified during the initial months of treatment.[13,15] Other rare events associated with GLP-based therapies include retinal detachment, retinal tears, vitreous hemorrhage, papilledema, macular edema/holes, and acute visual field defects.[11]

Multiple studies also implicate GLP-based therapies with an elevated risk of development of NAION, which is a rare but potentially sight-threatening side effect that may result in permanent vision loss and deserves special attention. It presents with sudden, painless, monocular loss of vision, frequently noticed on waking up in the morning, and is associated with optic disk edema. Multiple matched cohort studies involving a large number of patients have demonstrated a higher risk of NAION among those treated with GLP-1 RAs compared to those using other antidiabetic or antiobesity medications.[16,17] Hathaway et al.[18] showed a positive association between semaglutide and NAION in overweight and diabetic cohorts, with a higher risk of NAION in overweight users (hazard ratio: 7.6 in the overweight cohort; 4.3 in diabetics). Case reports describe NAION developing in patients even without classic risk factors, with the temporal relationship closely following initiation of liraglutide or semaglutide therapy, further supporting the clinical suspicion of a drug-induced mechanism.[19] Although a recent meta-analysis[20] failed to detect a significant detrimental effect of GLP-1 RAs therapy on ischemic optic neuropathy, the confidence

[1]Senior Medical Officer, Department of Ophthalmology, Dr. R P Centre, All India Institute of Medical Sciences, New Delhi; [2]Director Professor and Head, Department of Medicine, Lady Hardinge Medical College and Associated Hospitals, New Delhi, India; *Corresponding Author

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interval reported was very wide, showing that the number of observed events could have been insufficient to yield a significant result.

The World Health Organization (WHO) and European regulatory authorities now recognize NAION as a very rare side effect of semaglutide, potentially affecting up to 1 in 10,000 users, and have issued alerts for healthcare professionals to monitor for visual symptoms during therapy.[21,22] This chronological sequence: epidemiological signal, regulatory acknowledgment, and international advisories, suggests that the association cannot be dismissed as anecdotal. Therefore, early opinions on the ocular safety of GLP-based therapies such as semaglutide[23] have changed with new evidence showing a potential risk of NAION linked to these drugs, warranting caution when prescribing them in India. Although rare, this serious side effect calls for careful patient monitoring and informed consent.

Emerging evidence implicates not only GLP-1 RAs such as semaglutide but also tirzepatide, which is a dual agonist of glucose-dependent insulinotropic polypeptide (GIP) and GLP-1.[17,24] Regulatory agencies and the Food and Drug Administration (FDA) Sentinel system recognize this may be a class effect.[25]

Proposed Mechanisms

The proposed mechanisms underlying the association between GLP-based therapies and NAION remain speculative, but several hypotheses have emerged. Proposed explanations include:

- Direct action on optic nerve perfusion: Stimulation of GLP-1 receptors in the optic nerve head may alter local blood flow or autoregulation, potentially predisposing to ischemic events, particularly in individuals with anatomical susceptibility (small/crowded disks).[19,26]
- Systemic and sympathetic nervous effects: GLP-based therapies may activate the sympathetic nervous system, leading to transient vasoconstriction and reduced optic nerve perfusion, serving as a "second hit" in patients predisposed to NAION.[19,27]
- Rapid glycemic modulation: Rapid improvement in glycemic control induced by GLP-based therapies may affect vascular autoregulation and tissue oxygenation, making the optic nerve more vulnerable to ischemia, though evidence supporting this is limited and indirect.[11]

Mechanistic links remain unproven, highlighting the need for prospective research to conclusively establish causation.

Indian Context

For India, these safety concerns have greater implications:

- Population vulnerability: India has one of the world's highest burdens of diabetes patients, estimated to be over 101 million adults as of 2025, accompanied by growing obesity rates resulting from urbanization and rapid lifestyle changes.[5] This large high-risk population amplifies the absolute impact of even rare drug-associated adverse events, such as NAION or sight-threatening retinopathy.
- Increased associated risk factors: The unique vulnerability of the Indian population to earlier onset of cardiovascular[28,29] and microvascular diseases,[30,31] can exacerbate the ocular adverse effects of GLP-based therapies, especially NAION.
- Limited access to healthcare: Specialist ophthalmic services remain concentrated in urban tertiary centers, with rural and semiurban populations often facing delayed diagnosis and management of ocular adverse events.[32,33] Regular ophthalmologic monitoring for patients on GLP-based therapies is thus often not feasible, increasing the risk of undetected progression of retinopathy or NAION.
- Unregulated access: GLP-based therapies are increasingly accessible through online pharmacies and informal retail outlets without adequate prescription oversight or ophthalmologic evaluation, raising concerns about unsupervised use and insufficient monitoring.[34]

Thus, even a rare adverse event can translate into a significant public health burden for India.

Clinical and Regulatory Imperatives

For Clinicians

- Baseline evaluation: While there are no preexisting ophthalmic signs that can identify those at risk of developing NAION, a comprehensive ophthalmological examination should precede GLP-based therapy initiation, especially in patients >50 years or with vascular comorbidities. A small crowded disk may be considered a relative contraindication for their use.
- These drugs may be avoided in patients with preexisting visual impairment due to other causes or with a predisposition for the development of NAION.
- Patient counseling: Informed consent must include a discussion of sudden, painless vision loss.
- Monitoring: Patients should be instructed to report any visual disturbance promptly.
- Discontinuation: Immediate cessation of therapy and shift to alternate treatment options for glycemic control, along with urgent ophthalmology referral, is essential upon suspicion of NAION.

For Policymakers and Regulators

- Label updates: The Central Drugs Standard Control Organization (CDSCO) and Drug Controller General of India (DCGI) must mandate warnings in prescribing information.
- Pharmacovigilance: The Pharmacovigilance Program of India (PvPI) should issue a targeted safety alert. Long-term surveillance of visual outcomes in patients on these drugs is essential.
- Professional guidance: The Indian Council of Medical Research (ICMR) should formulate consensus-based recommendations for safe prescribing.
- Development of risk stratification tools to identify the highest-risk patients must be done.
- Research to determine mechanisms, predictive biomarkers, and evidence-based protocols is urgently needed. Until then, clinical practice must prioritize informed caution.

Ethical and Practical Considerations

GLP-based therapies are poised to be a transformative therapy in reducing cardiovascular risk, aiding weight loss, and improving glycemic control. However, the irreversible and life-altering nature of NAION necessitates caution and shared decision-making. Patients deserve to know that, while the risk is very rare, the consequences can be catastrophic.

Recommendations for India

- National adverse event registry linking endocrinology and ophthalmology practices.
- Inclusion of ocular risk warnings in Indian prescribing guidelines and packaging.
- Cross-disciplinary education for physicians, emphasizing early recognition.
- Prioritization of high-risk groups (elderly, crowded disks, vascular comorbidities) for counseling and closer monitoring.

Conclusion

GLP-based therapies represent a breakthrough in diabetes and obesity management. However, the increased association with NAION—though rare—cannot be ignored. For India, with its vast population at risk and systemic vulnerabilities, the stakes are especially high. As physicians, regulators, and researchers, our responsibility is clear: to integrate ocular safety vigilance into routine GLP-based therapy prescribing. It is essential to ensure that metabolic health is not at the cost of vision. With triple agonist therapies, viz., retatrutide on the anvil, whose phase III trials are likely to be completed in 2026, the prescribing doctors need to monitor carefully for ocular side effects.

Orcid

Anupam Prakash https://orcid.org/0000-0001-8477-9039

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