*Mini Review*

**The Risk of Non-Arteritic Anterior Ischemic Optic Neuropathy (NAION) and worsening Diabetic Retinopathy (DR) with Semaglutide**

**Abstract**

Semaglutide, a GLP-1RA (receptor agonist), is being increasingly used for type 2 diabetes mellitus (T2DM) and weight management, broadening its clinical reach. While there has been a rapidly expanding scope, market, and exposed population for semaglutide, there have also been growing voices of concern on its retinal effects. For a clinical risk benefit analysis, reviewed here is the available scientific evidence and metanalysis of semaglutide and its ophthalmic effects. GLP‐1RAs are often associated with rapid reduction in blood sugar levels, which may lead to the development of anterior ischemic optic neuropathy of the non-arteritic type (NAION), or the progression of diabetic retinopathy (DR), with semaglutide possibly being separately associated with these eye effects, as seen in clinical studies. However, there are other co-existent risks that contribute to these ophthalmic complications, and there are large studies to show greater benefit to risk ratio of semaglutide in the population. Therefore, it is immensely important to assess individual risk factors, patient history, comorbidities, disease duration, lab parameters as well as concomitant medicines, for each patient separately, along with a thorough baseline eye checkup including a detailed retina evaluation, while deciding on GLP-1RA especially semaglutide therapy for T2DM or for weight reduction. This can enable the drug to be used effectively providing the desired clinical benefit, with the right caution and minimizing of adverse retinal effects.

**Keywords:** semaglutide, GLP-1RA, weight loss, type 2 diabetes mellitus (T2DM), NAION, diabetic retinopathy (DR).

**Introduction**

“Glucagon- like peptide-1 receptor agonist (GLP-1RAs) semaglutide (marketed as *Ozempic®, Wegovy®, Rybelsus®*), have gained widespread attention for their effectiveness not only in treating type 2 diabetes mellitus (T2DM), but also in aiding weight loss. These medications work by enhancing insulin secretion, suppressing appetite, and improving blood sugar control”.1

Semaglutide binds to GLP-1 receptors on pancreatic beta cells, to release insulin, especially in response to elevated blood glucose. It also inhibits the release of glucagon, reduces hepatic glucose release, and delays gastric emptying to prevent rapid post-meal glucose spikes. Semaglutide acts on the hypothalamus to reduce appetite, and feelings of hunger and food cravings, while the delayed gastric emptying also increases the felling of early fullness and satiety.  Other potential benefits may include promoting fat metabolism, anti-inflammatory action, and reduction of cardiovascular risk. Their benefits are thus undeniable, particularly for individuals struggling with obesity and metabolic disorders.

However, emerging research suggests that this drug may come with unexpected risk of increased incidence of two important ophthalmic complications – a) anterior ischemic optic neuropathy (AION), a condition closely related to ischemic retinopathy, and b) progression, complications or worsening of diabetic retinopathy.

**Semaglutide and NAION**

“Ischemic retinopathy is a serious eye condition caused by insufficient blood flow to the retina, compromising essential oxygen and nutrient supply, leading to cell damage. It presents as blurred vision, floaters, dark spots, or even sudden vision loss and complete blindness in severe cases”.2. Anterior ischemic optic neuropathy (AION) is a condition where vision loss occurs due to reduced blood flow to the front part of the optic nerve, often resulting in sudden, painless, and sometimes permanent vision impairment. AION can be either arteritic (AAION - almost always due to Giant Cell Arteritis), or Non-arteritic AION (NAION).

NAION is caused due to vascular issues, such as arteriosclerosis, and inflammation or damage to the small blood vessels supplying the optic nerve. Presenting symptoms are sudden, painless vision loss usually in one eye, a relative afferent pupillary defect (RAPD), initial optic disc edema followed by disc pallor. NAION is particularly concerning for individuals with diabetes, hypertension, hyperlipidemia, obesity, cardiovascular disease, smoking habits, and those aged >55 years, as they are already at a heightened risk for vascular complications. The exact mechanism linking semaglutide to NAION is still under investigation, and the causality needs further research to be firmly established, but several hypotheses exist:3

* Vascular Changes: GLP-1RA drugs influence blood vessel function and may inadvertently contribute to changes in retinal microcirculation. A sudden or excessive drop in blood sugar levels can disrupt blood flow, increasing the risk of ischemic events in the eye.
* Autonomic Nervous System Effects: These medications are known to enhance sympathetic nervous system activity, which could influence optic nerve head perfusion, making the nerve more susceptible to ischemic damage.
* Rapid Glycemic Control: While lowering blood sugar is essential for diabetes management, an overly rapid improvement in glycemic levels in patients with preexisting retinal disease might accelerate vision loss due to sudden metabolic shifts.
* Direct Effects on the Optic Nerve: Some research suggests that GLP-1 receptors are present in the optic nerve, raising the possibility that these drugs may directly affect neural tissue in ways that increase vulnerability to ischemia.

***Clinical Evidence***

A retrospective matched cohort 3-year study in over sixteen thousand patients, using data from a centralized data registry of patients evaluated by neuro-ophthalmologists to assess whether prescribed semaglutide was associated with Nonarteritic Anterior Ischemic Optic Neuropathy (NAION) in patients with type 2 diabetes (T2DM) or overweight/obesity (OO), suggested an association between semaglutide and NAION.4 The cumulative incidence of NAION for the semaglutide (T2DM, OO) versus non–GLP-1RA matched cohorts over 36 months was 8.9% (T2DM), and 6.7% (OO) versus 1.8%, and 0.8% respectively [hazard ratio [HR], 4.28 (T2DM) and 7.64 (OO) respectively (95% CI, *P* < .001]. In the T2DM and OO, NAION events occurred 3 and 7 times more in the prescribed semaglutide cohort versus the non–GLP-1RA cohort.

“In a Danish 5-year longitudinal cohort study, with over 0.1 million T2DM patients on semaglutide and over 0.3 million T2DM not exposed, once-weekly semaglutide was associated with a higher NAION rate (0.23 vs. 0.09 per 1000 person-years, *p* < 0·001) and independently predicted a higher risk of upcoming NAION (HR 2.19, 95% confidence interval 1.54 − 3.12), even when multiple other factors were taken into account. Median time from first prescription to NAION was approximately 22.2 months (10.2–37.8 months)”.5

“However, findings differed in another study with patients ≥12 years old with at least one ophthalmology or neurology visit, where 0.12 million T2DM and 58,000 OO patients with a semaglutide prescription were compared to matched controls. In T2DM patients prescribed semaglutide, the risk of NAION (RR = 0.7, 95% CI: 0.523-0.937) after 5 years was not significantly increased compared to matched T2DM controls. Furthermore, no increased NAION risk was found in the OO groups prescribed semaglutide. The cumulative 5-year risk of NAION in T2DM patients on semaglutide was 0.065% respectively, and the 2-year risk in OO prescribed semaglutide was 0.038% respectively”.6

“Another retrospective study across 14 databases including adults with T2DM taking semaglutide, assessed the association between semaglutide and NAION using 2 approaches: a) an active-comparator cohort design comparing new users of semaglutide with those taking other GLP-1RAs and non–GLP-1RA drugs, and b) a self-controlled case-series (SCCS) analysis to compare individuals’ risks during exposure and non-exposure periods for each drug. The study included over 37 million individuals with T2DM, including over eighty thousand new semaglutide users. The incidence rate of NAION was 14.5 per 100 000 person-years among semaglutide users. The HR for NAION among new users of semaglutide was not different compared with that of the non–GLP-1RAs, but semaglutide exposure showed an increased risk of NAION (meta-analysis IRR, 1.32; 95% CI, 1.14-1.54; *P* < .001). Therefore here, a modest increase in the risk of NAION among individuals with T2DM associated with semaglutide use, smaller than that previously reported, was shown, warranting further investigation into the clinical implications of this association”.7,26

“A retrospective cohort study including individuals with T2DM or obesity, further categorized into T2DM-only, obesity-only, and T2DM with obesity groups was conducted with 37,314 participants with T2DM only, 129,690 participants with obesity only, and 130,216 participants with both T2DM and obesity. The results indicated that the administration of semaglutide was not associated with the development of NAION in the T2DM-only group (1,2,3 year follow-up: HR, 2.32; 2.31; and 1.51; 95% CI), the obesity-only group (1,2,3-year follow-up: HR, 0.41; 0.67; and 0.72; 95% CI), and the T2DM with obesity group (1,2,3 year follow-up: HR, 0.81; 1.2; and 1.19; 95% CI). The findings suggested that semaglutide may not be associated with an increased risk of NAION in the general population. Therefore, avoidance of semaglutide based solely on concerns regarding the risk of NAION may not be warranted because its potential benefits for blood glucose control and cardiovascular health likely outweigh its potential risks”.8

Important confounding factors can affect study results and need to be addressed. Risk factors such as smoking, duration of diabetes, and optic disc morphology along with baseline glycated hemoglobin (HbA1c) and body mass index (BMI) need to be matched in both T2D and OO cohorts respectively, which are potential confounders. The cohorts also need to be matched for background non-semaglutide antidiabetic medications, which they have been on for a much longer period compared with semaglutide being used only in the recent past, indicating potential for bias, especially since it is used in patients with T2DM and obesity, who already have a higher risk of NAION.9

Currently, NAION is not a listed adverse drug reaction for marketed formulations of semaglutide (*Ozempic®, Wegovy®, Rybelsus®*) as per the approved label. Semaglutide has been extensively studied in various formulations globally with large numbers of study participants exposed to semaglutide for durations up to 5 years in clinical trials.10-13 Considering the extensive number of participants involved in randomized clinical trials and the large global population using GLP-1RAs, any absolute risk of developing NAION due to semaglutide use is likely to be very low and not confirmed, showing the need for additional data-driven research to verify or disprove such a link.

**Semaglutide and Diabetic Retinopathy (DR)**

Rapid glycemic control by lowering blood sugar or glycosylated hemoglobin in diabetes management, have been linked to worsening of diabetic retinopathy (DR). Patients with preexisting retinal disease are to be particularly evaluated for the risk of accelerated vision loss due to sudden metabolic shifts. However, the effects of semaglutide in DR is still not completely clear.

***Clinical Evidence***

“In a study to assess the development of DR and DME (diabetic macular edema) in around 2 million T2DM patients taking insulin, data using propensity score matching suggested that those receiving GLP‐1RA had a 31% increased risk of DR, without significant change in the risk of DME, compared with those receiving neither sodium‐glucose co‐transporter 2 inhibitors (SGLT2i) nor GLP‐1RA. The protective effect of semaglutide against DME may be attributed to the ability to modulate inflammatory processes and potentially improve endothelial cell function. However, while compared with those receiving SGLT2i, those receiving GLP‐1RA had a 20% higher risk of DR and a 13% higher risk of DME”.14.

“A study from Taiwan showed that initiating either GLP‐1RA or SGLT2i with a previous diagnosis of diabetic retinopathy showed a 50% increase in risk of progression with GLP‐1RA, primarily related to tractional retinal detachment; while for those without previous history of diabetic retinopathy, ocular outcomes were similar with the two agents.15 In a Danish Registry of T2DM, among patients not taking insulin, metformin + GLP‐1RA was associated with a 1.46‐fold increased risk of diabetic retinopathy compared with metformin + dipeptidyl peptidase‐4 inhibitors (DPP‐4i), or metformin + SGLT2i, the latter trending to still lower risk”.16

Retrospective data analysis over four thousand patients with T2DM and DR in a Retina only practice showed 87 patients on semaglutide for at least 1 year. The baseline HbA1c averaged 7.6 %, while last self-reported HbA1c averaged 7.4 %. Baseline DR severity (according to DRSS or Diabetic Retinopathy Severity Scale), correlated with progression risk: 2.7 % for DRSS level ≤ 43 (mild-moderate non proliferative DR), 28 % for levels 47/53 (moderately severe non proliferative DR), and 45 % for baseline proliferative DR.17 Therefore, the presence of baseline DR, and importantly its severity is determining factors for progression of DR in patients on semaglutide.

“The Semaglutide Unabated Sustainability in Treatment of Type 2 Diabetes (SUSTAIN)‐6 of over three thousand patients with T2DM having high cardiovascular risk included 29.4% of participants with a history of retinopathy. Retinopathy developed in 9.0% and 10.0% of participants treated with semaglutide 0.5 and 1.0 mg weekly, respectively, and significantly less frequently in 7.6% of comparators”.18,19 Some important factors to consider for those with pre-existing DR at baseline are:

* The risk of DR worsening was further increased among patients treated with insulin.
* Both among those receiving semaglutide or placebo, DR worsening occurred most often among participants having HbA1c reduction > 1.5% over 16 weeks.

Therefore, the efficacy of these agents in improving glycemia may be associated with acute worsening of DR in those with pre-existing retinopathy.

***Metanalysis suggesting DR association***

“Over 60 RCTs involving almost 0.2 million patients and 2773 DR incidents, including 29, 13, and 10 studies of GLP‐1RA, DPP4i, and SGLT2i versus placebo, respectively, showed no significant difference in DR overall for any of these drug groups”.20 “However, another meta‐analysis of 20 RCTs of 24,832 persons with T2DM treated with GLP‐1RA versus placebo, showed a significant increase in DR with oral semagutide (OR = 1.43, 1.09–1.87).21 Yet in another analysis of all GLP‐1RA, worsening retinopathy only occurred with semaglutide, but was found to occur in proportion to the decrease in HbA1c, with the increase in retinopathy for semaglutide associated with therapy duration > 1 year and with HbA1c decrease > 1%.22. Finally, among six RCTs of almost fifty thousand T2DM patients randomized to GLP‐1RA versus placebo, meta‐analysis showed no significant association between GLP‐1RA and retinopathy risk (OR 1.10; 95% CI 0.93, 1.30), while showing a significant association of retinopathy with greater average reduction in HbA1c”.23

“An analysis of 93 RCTs of GLP‐1RA compared with insulin, oral agents, or placebo in over 0.1 million participants found that those randomized to GLP‐1 RA had a 31% greater risk of early‐stage DR compared to placebo, although, compared to insulin, GLP‐1 RA use was associated with a 62% lower risk of late‐stage DR”.24 “Comparing GLP‐1RA with oral antidiabetic agents, GLP‐1RA were associated with a 39% greater risk of DR complications and a 40% greater likelihood of progression to proliferative DR. A meta‐analysis of 23 RCTs of semaglutide including over twenty-two thousand patients with T2DM showed a relative risk (RR) of DR of 1.14 (95% CI 0.98–1.33); but, compared with placebo, the RR was 1.24 (1.03–1.50); with patient age ≥ 60 years the RR was 1.27 (1.02–1.59), and with diabetes duration ≥ 10 years the RR was 1.28 (1.04–1.5)”.25

Therefore, in studies assessing diabetic retinopathy progression when on semaglutide, confounding baseline factors like stage of DR, duration of T2DM, usage of insulins and HbA1c would need matching in the test and control cohort.

***Caution and Action***

For individuals using GLP-1 receptor agonists, these findings highlight the importance of regular eye exams and proactive monitoring of visual health. If a patient is currently on semaglutide or a similar GLP-1RA medication, the following steps summarize the clinical approach towards using semaglutide for maximizing both its efficacy and safety for best patient outcomes:

*Schedule Routine Eye Exams*: Baseline eye examinations to establish DR and its severity grade should be part of screening pre-initiation of treatment. Annual or biannual ophthalmic visits to be recommended to help detect worsening of DR or early signs of ischemic retinopathy, and optic neuropathy before irreversible damage occurs.

*Report Vision Changes Immediately*: Any sudden changes in vision, such as blurriness, dark spots, or loss of peripheral vision, should be addressed as soon as possible.

*Assessing risk factors*: Individuals having history of eye disease, hypertension, cardiovascular risk factors, kidney disease, obesity or other risk factors like smoking, etc. for ischemic conditions should consult their physician about alternative treatment options or additional precautions.

*Maintaining Stable Blood Sugar Levels*: Avoiding rapid fluctuations in blood glucose and drastic drop in HbA1c can help mitigate the risk of vision-threatening complications.

**Conclusion**

GLP‐1RA are associated with significant and often rapid reduction in blood sugar levels, which may lead to DR progression, or NAION, with semaglutide possibly being separately associated with these ophthalmologic complications. One should assess patients with high HbA1c, age≥60 years, obesity, cardiovascular or renal risk factors, and more than a decade of having T2DM, very carefully for the appropriateness of semaglutide or other GLP-1RA, particularly among those with DR present at start of therapy, and/or those also on insulin therapy. Large-scale, multi-center studies and clinical trials will be essential to confirm findings in different populations to refine guidelines for patients at risk. Awareness and vigilant monitoring remain our best defense against such preventable blindness.

**Conflict of Interest**: None

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