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EDITORIAL

NAION risk with semaglutide: what we know so far

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With the rising popularity of glucagon-like peptide-1 (GLP-1) receptor agonists as tools for glycaemic control and obesity interventions, an important question emerges: what are the potential ocular effects of these treatments?

Initially introduced as second- or third-line treatments for diabetes, GLP-1 receptor agonists have gained traction due to their superior efficacy, particularly in weight loss and glycaemic control. However, despite their increased popularity, there are increasing concerns about their potential ocular safety profile, particularly regarding non-arteric ischemic optic neuropathy (NAION). NAION is the second most common optic neuropathy among adults and is a multifactorial clinical condition that could lead to vision loss, colour vision impairment, and visual field defects [1]. Associations between GLP-1 receptor agonists and NAION are relatively unknown until the emergence of recent studies, though current evidence remains contradictory. This correspondence seeks to highlight some of these studies as well as raise awareness about the potential association with NAION among diabetic patients who are semaglutide users.

One of the few studies investigating the ocular risks of GLP-1 receptor agonists, conducted by Hathaway et al. also suggested an increased risk of NAION among diabetic users of semaglutide [2]. They conducted a retrospective study that used electronic diagnostic codes to recruit diabetic patients from a single institution who used semaglutide as well as recruited a control group of diabetic patients who used non-GLP-1 receptor agonist medications to assess the risk of NAION. Their study attempted to account for confounding factors by controlling for variables such as age, sex, and medical comorbidities associated with NAION. Regarding their results, Hathaway et al. reported a hazard ratio (HR) of 4.28 (95% CI: 1.62–11.29) for the risk of AION at the 36-month follow-up in their cohort of 710 diabetes patients, compared to a matched control group. However, this single institutional retrospective study had notable limitations, including a limited follow-up period, a relatively small sample size, and a lack of adjustment for potential confounders such as previous surgical history, body mass index (BMI), diabetes severity, and steroid use.

In another study, Chou et al. conducted a retrospective study to investigate the risk of NAION in diabetes patients, specifically focusing on those with a history of semaglutide use [3]. They used multi-institutional electronic diagnostic codes to recruit participants and propensity-matched them with diabetes patients who did not receive semaglutide. Their study design also incorporated propensity score matching that accounted for factors such as age, sex and various medical comorbidities. Chou et al. managed to recruit 18,657 participants with type 2 diabetes mellitus (T2DM) and interestingly, found no statistically significant increase in NAION risk associated with semaglutide use. However, similar to Hathaway et al., Chou et al.'s study was limited by a relatively short follow-up duration and failure to adjust for key confounders, such as steroid use and surgical history. Additionally, the study's lack of ethnic diversity—since only white patients were included—further limits the generalizability of the results.

In comparison, Hsu et al. retrospectively recruited 174,584 diabetic patients with semaglutide history from a multi-institutional electronic health records registry and found an increased risk for NAION from the 2 year (HR: 2.39, 95% CI: 1.37–4.18), 3 years (HR: 2.44, 95% CI: 1.44–4.12), 4 years (HR: 2.05, 95% CI: 1.26–3.34) time point from the index date of initial semaglutide use [4]. Notably, the findings of Hsu et al. did not indicate an increased risk of NAION at 1 month (HR: 2.99, 95% CI: 0.31–28.77), 3 months (HR: 1.33, 95% CI: 0.93–4.02), or 6 months (HR: 1.79, 95% CI: 0.60–5.35) time point. This contrasts with Hathaway et al., whose analysis only demonstrated an increased risk at 36 months but did not elaborate on the short-term risk of NAION. Findings from Hsu et al. also contradict those of Chou et al., which found no increased risk for NAION after semaglutide use from among their diabetic patients. However, it is important to emphasize that the findings from Hsu et al. are based on a rigorous study design, which included patients from multiple racial backgrounds (White, Black or African American, Asian, American Indian or Alaska Native, Native Hawaiian or Other Pacific Islander) and ethnic backgrounds, including Hispanic or Latino. Comparatively, another large retrospective study by Cai et al. utilized multiple electronic health registry codes and included patients from diverse ethnic and racial backgrounds [5]. Their findings also indicated an increased risk of NAION among users of semaglutide, as well as exenatide, another GLP-1 receptor agonist. This suggests that a more diverse patient population could be a contributing factor to the observed NAION risk associated with semaglutide use.

One final point to note is that Hsu et al. also employed propensity score matching and adjusted for key confounders, such as cataract surgery history, BMI, steroid use, and diabetes severity (HbA1c levels) and LDL levels. By addressing these potentially confounding variables, the findings from Hsu et al. provide high validity in demonstrating an increased risk of NAION among diabetic semaglutide users.

Nevertheless, while a select body of evidence, including studies by Hsu et al., Hathaway et al., and Cai et al., suggests a potential association between Semaglutide use and NAION, further research is still needed to confirm these findings. Furthermore, Cai et al. also suggested that other GLP-1 receptor agonists may also potentially carry risk for NAION. Therefore, a better understanding of NAION risk is crucial, as it is a potentially visually debilitating condition with a poor prognosis if not diagnosed and managed promptly. Given such emerging evidence, clinicians should be more aware of signs and symptoms of NAION such as blurred vision, impaired colour vision, and visual field defects in patients with a history of semaglutide use. Furthermore, diagnostic tools like indirect ophthalmoscopy, optical coherence tomography (OCT), and MRI of the optic nerve with gadolinium contrast could also be employed to diagnose NAION and differentiate it from other optic neuropathies, such as inflammatory optic neuropathy.

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DATA AVAILABILITY

This editorial references previously published study, and therefore no data availability statement is required

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AUTHOR CONTRIBUTIONS

AYH, YHW, CJL, NYH, YCS, CCC, HSC, YYT, JCCW wrote and edited the main text of the paper. AYH, YHW, CJL, NYH, YCS, CCC, HSC, YYT, JCCW designed, discussed, edited and guided the overall process of the paper. AYH, YHW, CJL, NYH, YCS, CCC, HSC, YYT, JCCW contributed to the drafting of the paper. All authors (AYH, YHW, CJL, NYH, YCS, CCC, HSC, YYT, JCCW) approved the final version of the manuscript and agree to be held accountable for the content therein.

COMPETING INTERESTS

The authors declare no competing interests.