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Risk of Nonarteritic Anterior Ischemic Optic Neuropathy in Patients Prescribed Semaglutide

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IMPORTANCE Anecdotal experience raised the possibility that semaglutide, a glucagon-like peptide 1 receptor agonist (GLP-1 RA) with rapidly increasing use, is associated with nonarteritic anterior ischemic optic neuropathy (NAION).

OBJECTIVE To investigate whether there is an association between semaglutide and risk of NAION.

DESIGN, SETTING, AND PARTICIPANTS In a retrospective matched cohort study using data from a centralized data registry of patients evaluated by neuro-ophthalmologists at 1 academic institution from December 1, 2017, through November 30, 2023, a search for *International Statistical Classification of Diseases and Related Health Problems, Tenth Revision* code H47.01 (ischemic optic neuropathy) and text search yielded 16 827 patients with no history of NAION. Propensity matching was used to assess whether prescribed semaglutide was associated with NAION in patients with type 2 diabetes (T2D) or overweight/obesity, in each case accounting for covarying factors (sex, age, systemic hypertension, T2D, obstructive sleep apnea, obesity, hyperlipidemia, and coronary artery disease) and contraindications for use of semaglutide. The cumulative incidence of NAION was determined with the Kaplan-Meier method and a Cox proportional hazards regression model adjusted for potential confounding comorbidities. Data were analyzed from December 1, 2017, through November 30, 2023.

EXPOSURES Prescriptions for semaglutide vs non–GLP-1 RA medications to manage either T2D or weight.

MAIN OUTCOMES AND MEASURES Cumulative incidence and hazard ratio of NAION.

RESULTS Among 16 827 patients, 710 had T2D (194 prescribed semaglutide; 516 prescribed non–GLP-1 RA antidiabetic medications; median [IQR] age, 59 [49-68] years; 369 [52%] female) and 979 were overweight or obese (361 prescribed semaglutide; 618 prescribed non–GLP-1 RA weight-loss medications; median [IQR] age, 47 [32-59] years; 708 [72%] female). In the population with T2D, 17 NAION events occurred in patients prescribed semaglutide vs 6 in the non–GLP-1 RA antidiabetes cohort. The cumulative incidence of NAION for the semaglutide and non–GLP-1 RA cohorts over 36 months was 8.9% (95% CI, 4.5%-13.1%) and 1.8% (95% CI, 0%-3.5%), respectively. A Cox proportional hazards regression model showed higher risk of NAION for patients receiving semaglutide (hazard ratio [HR], 4.28; 95% CI, 1.62-11.29); $P < .001$). In the population of patients who were overweight or obese, 20 NAION events occurred in the prescribed semaglutide cohort vs 3 in the non–GLP-1 RA cohort. The cumulative incidence of NAION for the semaglutide vs non–GLP-1 RA cohorts over 36 months was 6.7% (95% CI, 3.6%-9.7%) and 0.8% (95% CI, 0%-1.8%), respectively. A Cox proportional hazards regression model showed a higher risk of NAION for patients prescribed semaglutide (HR, 7.64; 95% CI, 2.21-26.36; $P < .001$).

CONCLUSIONS AND RELEVANCE This study's findings suggest an association between semaglutide and NAION. As this was an observational study, future study is required to assess causality.

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Invited Commentary

Supplemental content

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Nonarteritic anterior ischemic optic neuropathy (NAION) is the second most common form of optic neuropathy and a significant cause of blindness among adults.[1-4] Our anecdotal clinical experience motivated us to study whether semaglutide is associated with an increased risk of developing NAION.

Semaglutide (Ozempic; Novo Nordisk) was approved by the US Food and Drug Administration (FDA) in December 2017 to treat type 2 diabetes (T2D) and in December 2022 to treat obesity (typically at higher doses, as Wegovy [Novo Nordisk]). Weekly new-to-brand prescriptions in the United States of these and other glucagon-like peptide receptor agonist (GLP-1 RA) drugs increased by approximately 60% from 2021 to 2023.[5]

In major medical centers, neuro-ophthalmologists are most likely to evaluate suspected cases of NAION. This study was designed to capitalize on this expertise by characterizing the risk of NAION among individuals using semaglutide within a neuro-ophthalmology practice at a single academic center.

Key Points

Question Are prescriptions for semaglutide associated with an increased risk of nonarteritic anterior ischemic optic neuropathy (NAION) in patients with type 2 diabetes or patients who are overweight or obese?

Findings This matched cohort study of 16 827 patients revealed higher risk of NAION in patients prescribed semaglutide compared with patients prescribed non–glucagon-like peptide receptor agonist medications for diabetes or obesity.

Meaning The findings suggest a potential risk of NAION associated with prescriptions for semaglutide, but future study is required to assess causality.

Methods

Following approval by the Massachusetts General Brigham (MGB) Institutional Review Board, we conducted a retrospective, matched cohort study of neuro-ophthalmic patients at Massachusetts Eye and Ear, Boston. Our methods adhered to the Declaration of Helsinki for human research, the regulations of the Health Insurance Portability and Accountability Act, and the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline.[6] Informed consent was not required as this was a retrospective study.

Study Population

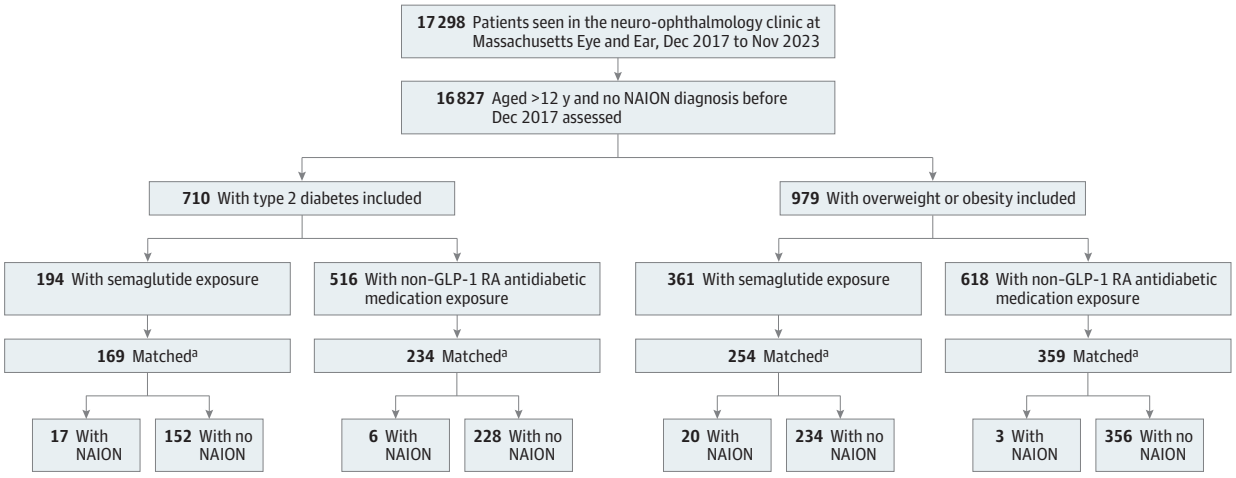
The number of unique patients who had been referred for any presumed neuro-ophthalmology indication and evaluated in our neuro-ophthalmology clinic from December 1, 2017, through November 30, 2023, was determined from the MGB centralized clinical data registry and composed our eligible cohort. Events of NAION were identified by electronic health record query for the *International Statistical Classification of Diseases and Related Health Problems, Tenth Revision* (*ICD-10*) code H47.01 (ischemic optic neuropathy) and text search (with terms "NAION" and "non-arteritic anterior ischemic optic neuropathy"). Each identified record was manually reviewed to confirm that the diagnosis of NAION had been rendered by one of our faculty members and to ascertain the time of vision loss. Our manual review confirmed that there was painless vision loss and optic nerve head edema during the acute phase, as per our prior criteria for NAION,[7] although now with more a relaxed age criterion given that our eligible cohort had a median age of 47 years. Patients with NAION prior to our start date were excluded. To mitigate risk of bias due to residual confounding effects, cohorts of T2D and overweight or obesity were analyzed separately; for each cohort, we identified comparative groups not receiving semaglutide. The categorizations of race (as American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or Other Pacific Islander, White, declined, patient does not know, race not listed, or unavailable) and sex or gender were self-reported in all cases.

To analyze the hazard ratio (HR) of NAION with respect to T2D, the study population consisted of 710 patients with T2D who were prescribed either semaglutide (n = 194) or non-GLP-1 RA antidiabetic medications (n = 516) (**Figure 1**). Non-GLP-1 RA medications that we assessed included insulin and analogues, metformin, sulfonylureas, α-glucosidase inhibitors, thiazolidinediones, dipeptidyl peptidase-4 inhibitors, and sodium-glucose transport protein 2 inhibitors.

To analyze the HR with respect to weight, we included patients who were overweight or obese (body mass index of 25-29.9 or >30, respectively [calculated as weight in kilograms divided by height in meters squared]). This study population consisted of 979 patients prescribed either semaglutide (n = 361) or non-GLP-1 RA weight-loss medications (n = 618) (Figure 1). Non-GLP-1 RA antiobesity medications that we assessed included bupropion, naltrexone, orlistat, topiramate, phentermine, and setmelanotide.

To achieve balance between cohorts (prescribed semaglutide or not) for each study population (T2D, and overweight or obese), 1:2 nearest-neighbor propensity score matching (caliper = 0.05) was used to account for demographic factors (sex, age); comorbidities related to NAION (systemic hypertension, T2D, obstructive sleep apnea); indications for use of semaglutide (T2D and obesity) and contraindications of semaglutide (personal or family history of multiple endocrine neoplasia type 2, thyroid cancer, chronic kidney disease, pancreatitis)[8]; covarying factors related to T2D or to overweight or obesity (hyperlipidemia, coronary artery disease); and use of drugs associated with NAION (phosphodiesterase type 5 inhibitors,[9] amiodarone[10]). No patient with NAION had received α-interferon.[11] After matching, all standardized mean differences (SMDs) for covariates were less than 0.1, and all SMDs and 2-way interactions among confounding factors were less than 0.15, which in the context of this study using propensity score matching indicates adequate balance between cohorts. **Table 1** and **Table 2** provide the characteristics of the T2D cohort and the obese or overweight cohort, respectively, with frequency distributions and measures of variability. The primary outcome was the first event of NAION. For all patients who experienced NAION and had been prescribed semaglutide, we confirmed by manual review that the prescribed medication had been dispensed. Although we aimed to match each

Figure 1. Cohort Selection



The flow diagram shows the cohort selection for the analysis of the risk of nonarteritic anterior ischemic optic neuropathy (NAION) in patients treated with semaglutide vs a non–glucagon-like peptide 1 receptor agonist (GLP-1 RA) either for type 2 diabetes or for overweight or obesity.

[a]Matching criteria included propensity score matching on age, sex, hypertension, type 2 diabetes, obstructive sleep apnea, obesity, hyperlipidemia, and coronary artery disease as well as lack of chronic kidney disease, personal or family history of multiple endocrine neoplasia type 2, thyroid tumors, or pancreatitis status.

treated unit with 2 control units in a 1:2 ratio, the actual matching yielded slightly lower ratios due to the relatively small sample sizes.

Patients in the eligible cohorts (T2D and overweight or obese, separately) had differing distributions of baseline characteristics (Table 1 and Table 2). To further isolate and more evenly distribute these characteristics between the eligible (ie, semaglutide vs non-GLP-1) cohorts, we performed secondary analyses with 1:1 nearest-neighbor propensity score matching plus an exact match for variables that differed by 20% or more between the cohorts for each population.

Statistical Analysis

Cumulative incidences of NAION in each cohort were determined with the Kaplan-Meier method to track first events of NAION during follow-up. Person-time was calculated from the first prescription of semaglutide vs non-GLP-1 antidiabetic or weight-control medications in the T2D and overweight or obese populations, respectively, until NAION, death (n = 42 across both populations), or end of the maximal 36-month follow-up period. The Cox proportional hazards regression model with adjustment for matching factors analyzed associations among covariates (described earlier) and the risk of NAION. The ability of our Cox model to discriminate between individuals who did and did not experience NAION was supported by the concordance correlation coefficient. Likelihood ratio testing outperformed a null model that did not incorporate predictors. The Wald test for semaglutide exposure assessed the statistical significance of individual predictors. The log-rank test assessed survival times between cohorts. Schoenfeld residuals and log-log plots for survival curves assessed the proportional hazards assumption and investigated its adequacy. All analyses were conducted with RStudio version 2024.04 statistical software (Posit). All *P* values were 2-sided and there was no adjustment for multiple analyses.

Results

Our search identified 17 298 unique patients across 6 years. Individuals younger than 12 years (the lower limit of semaglutide exposure) were excluded, which yielded 16 827 patients for analysis (Figure 1). Among the included patients, 710 had T2D (median [IQR] age, 59 [49-68] years; 369 [52%] female) and 979 were overweight or obese (median [IQR] age, 47 [32-59] years; 708 [72%] female).

Incidence of NAION in Patients With T2D

The study population with T2D included 710 patients (Figure 1). A 1:2 propensity score matching yielded adequate balance between the 2 groups (SMD < 0.1). NAION occurred in 17 patients in the semaglutide cohort vs 6 in the comparative cohort. The median (IQR) age was 57 (49-63) years for the semaglutide cohort and 58 (47-66) years for the nonsemaglutide cohort.

The Kaplan-Meier survival analysis at 36 months showed a cumulative incidence of NAION of 8.9% (95% CI, 4.5%-13.1%) for the semaglutide cohort vs 1.8% (95% CI, 0%-3.5%) for the nonsemaglutide cohort. The mean (SD) follow-up time was 33.3 (1.1) months for the semaglutide group and 34.5 (1.2) months for the nonsemaglutide group. The survival probability for the semaglutide cohort declined steepest over the initial 12 months, with a cumulative incidence of 6.5% (95% CI, 2.7%-10.2%) at year 1 (**Figure 2**A). The Cox proportional hazards regression model showed a higher NAION risk in the semaglutide cohort vs the nonsemaglutide cohort (HR, 4.28; 95%

Table 1. Demographic and Clinical Characteristics of Eligible, Propensity Score–Matched, and Exact-Matched Cohorts in Patients With Type 2 Diabetes

Characteristic	Eligible cohorts				1:2 Propensity score–matched cohorts[a]				1:1 Propensity score– and exact-matched cohorts[a]			
	No. (%)				No. (%)				No. (%)			
	Overall (n = 710)	Non-GLP-1 RA antidiabetic medication (n = 516)	Semaglutide (n = 194)	SMD	Overall (n = 403)	Non-GLP-1 RA antidiabetic medication (n = 234)	Semaglutide (n = 169)	SMD	Overall (n = 264)	Non-GLP-1 RA antidiabetic medication (n = 132)	Semaglutide (n = 132)	SMD
NAION event	37 (5)	18 (3)	19 (10)	NA	23 (6)	6 (3)	17 (10)	NA	18 (7)	4 (3)	14 (11)	NA
Age, median (IQR), y	59 (49-68)	61 (50-70)	56 (47-63)	0.37	57 (48-65)	58 (47-66)	57 (49-63)	0.03	57 (49-64)	57 (48-65)	58 (49-64)	0.01
Sex[b]												
Female	369 (52)	259 (50)	110 (57)	0.12	223 (55)	126 (54)	97 (57)	0.02	148 (56)	73 (55)	75 (57)	0.03
Male	341 (48)	257 (50)	84 (43)	0.12	180 (45)	108 (46)	72 (43)	0.02	116 (44)	59 (45)	57 (43)	0.03
Race[b]												
Asian	33 (4.6)	28 (5)	5 (3)	0.18	12 (3)	7 (3)	5 (3)	0.01	10 (3.8)	6 (5)	4 (3)	0.09
Black	72 (10)	41 (8)	31 (16)	0.22	41 (10)	23 (10)	18 (11)	0.01	18 (6.8)	9 (7)	9 (6.8)	<0.01
White	509 (72)	375 (73)	134 (69)	0.07	292 (72)	169 (72)	123 (73)	0.01	200 (76)	101 (77)	99 (75)	0.03
Other[c]	96 (14)	72 (14)	24 (12)	0.05	58 (14)	35 (15)	23 (14)	0.01	36 (14)	16 (12)	20 (15)	0.09
Systemic hypertension	529 (75)	369 (72)	160 (82)	0.28	325 (81)	187 (80)	138 (82)	0.01	226 (86)	113 (86)	113 (86)	<0.01
Obstructive sleep apnea	197 (28)	115 (22)	82 (42)	0.40	136 (34)	67 (29)	69 (41)	0.04	82 (31)	41 (31)	41 (31)	<0.01
Obesity	334 (47)	177 (34)	157 (81)	1.18	294 (73)	162 (69)	132 (78)	0.01	198 (75)	99 (75)	99 (75)	<0.01
Hyperlipidemia	429 (60)	289 (56)	140 (72)	0.35	271 (67)	152 (65)	119 (70)	0.06	184 (70)	93 (70)	91 (69)	0.03
Coronary artery disease	311 (44)	211 (41)	100 (52)	0.21	194 (48)	110 (47)	84 (50)	0.02	119 (45)	57 (43)	62 (47)	0.07
Chronic kidney disease	154 (22)	101 (20)	53 (27)	0.17	93 (23)	52 (22)	41 (24)	0.02	63 (24)	29 (22)	34 (26)	0.08
MEN type 2	0	0	0	<0.01	0	0	0	<0.01	0	0	0	<0.01
Thyroid tumors	6 (1)	5 (1)	1 (1)	0.06	2 (0.5)	1 (0.4)	1 (1)	<0.01	2 (1)	1 (1)	1 (1)	<0.01
Pancreatitis	47 (7)	31 (6)	16 (8)	0.07	30 (7)	17 (7)	13 (8)	0.03	18 (7)	9 (7)	9 (7)	<0.01
Amiodarone exposure	61 (9)	36 (7)	25 (13)	0.17	38 (9)	22 (9)	16 (9)	0.02	23 (9)	11 (8)	12 (9)	0.02
PDE5 inhibitor exposure	63 (9)	37 (7)	26 (13)	0.18	40 (10)	24 (10)	16 (9)	0.01	31 (12)	15 (11)	16 (12)	0.02

Abbreviations: GLP-1 RA, glucagon-like peptide 1 receptor agonist; MEN, multiple endocrine neoplasia; NA, not applicable; NAION, nonarteritic anterior ischemic optic neuropathy; PDE5, phosphodiesterase type 5; SMD, standardized mean difference.

[a] Propensity score matching and exact matching were performed from the same eligible cohorts.

[b] Self-reported.

[c] Includes American Indian or Alaska Native, Native Hawaiian or Other Pacific Islander, declined, patient does not know, race not listed, or unavailable.

Table 2. Demographic and Clinical Characteristics of Eligible, Propensity Score–Matched, and Exact-Matched Cohorts in Patients Who Were Overweight or Obese

Characteristic	Eligible cohorts				1:2 Propensity score-matched cohorts[a]				1:1 Propensity score- and exact-matched cohorts[a]			
	No. (%)				No. (%)				No. (%)			
	Overall (n = 979)	Non-GLP-1 RA antiobesity medication (n = 618)	Semaglutide (n = 361)	SMD	Overall (n = 613)	Non-GLP-1 RA antiobesity medication (n = 359)	Semaglutide (n = 254)	SMD	Overall (n = 442)	Non-GLP-1 RA antiobesity medication (n = 221)	Semaglutide (n = 221)	SMD
NAION event	32 (3)	5 (1)	27 (7)	NA	23 (4)	3 (1)	20 (8)	NA	18 (5)	2 (1)	16 (7)	NA
Age, median (IQR), y	47 (32-59)	44 (29-58)	50 (37-60)	0.30	46 (32-58)	44 (29-59)	46 (35-58)	0.04	46 (33-59)	45 (33-59)	46 (34-58)	0.01
Sex[b]												
Female	708 (72)	454 (73)	254 (70)	0.06	463 (76)	274 (76)	189 (74)	0.04	339 (77)	167 (76)	172 (78)	<0.01
Male	271 (28)	164 (27)	107 (30)	0.06	150 (24)	85 (24)	65 (26)	0.04	103 (23)	54 (24)	49 (22)	<0.01
Race[b]												
Asian	13 (1)	8 (1)	5 (1)	<0.01	6 (1)	4 (1)	2 (1)	0.01	3 (1)	2 (1)	1 (0.5)	0.06
Black	109 (11)	55 (9)	54 (15)	0.16	70 (11)	42 (12)	28 (11)	0.01	49 (11)	23 (10)	26 (12)	<0.01
White	742 (76)	478 (77)	264 (73)	0.09	464 (76)	273 (76)	191 (75)	0.02	337 (76)	165 (75)	172 (78)	0.05
Other[c]	115 (12)	77 (12)	38 (11)	0.06	73 (12)	40 (11)	33 (13)	0.04	53 (12)	31 (14)	22 (10)	0.03
Systemic hypertension	513 (52)	273 (44)	240 (66)	0.47	340 (55)	191 (53)	149 (59)	0.03	274 (62)	137 (62)	137 (62)	<0.01
Obstructive sleep apnea	271 (28)	125 (20)	146 (40)	0.41	193 (31)	93 (26)	100 (39)	<0.01	136 (31)	68 (31)	68 (31)	<0.01
Type 2 diabetes	269 (27)	91 (15)	178 (49)	0.69	163 (27)	86 (24)	77 (30)	0.02	130 (29)	65 (29)	65 (29)	<0.01
Hyperlipidemia	370 (38)	173 (28)	197 (55)	0.53	243 (40)	130 (36)	113 (44)	0.03	184 (42)	92 (42)	92 (42)	<0.01
Coronary artery disease	297 (30)	158 (26)	139 (39)	0.26	191 (31)	106 (30)	85 (33)	0.01	143 (32)	72 (33)	71 (32)	0.04
Chronic kidney disease	100 (10)	40 (6.5)	60 (17)	0.27	66 (11)	33 (9)	33 (13)	<0.01	37 (8)	18 (8)	19 (9)	0.02
MEN type 2	0	0	0	0.00	0	0	0	0.00	0	0	0	<0.01
Thyroid tumors	9 (1)	7 (1)	2 (1)	0.07	5 (1)	4 (1)	1 (0.4)	0.05	5 (1)	3 (1)	2 (1)	0.05
Pancreatitis	54 (6)	32 (5)	22 (6)	0.03	32 (5)	21 (6)	11 (4)	<0.01	20 (5)	7 (3)	13 (6)	0.01
Amiodarone exposure	47 (5)	20 (3)	27 (7)	0.16	25 (4)	14 (4)	11 (4)	0.01	16 (4)	8 (4)	8 (4)	0.04
PDE5 inhibitor exposure	68 (7)	29 (5)	39 (11)	0.19	46 (8)	23 (6)	23 (9)	<0.01	36 (8)	20 (9)	16 (7)	0.04

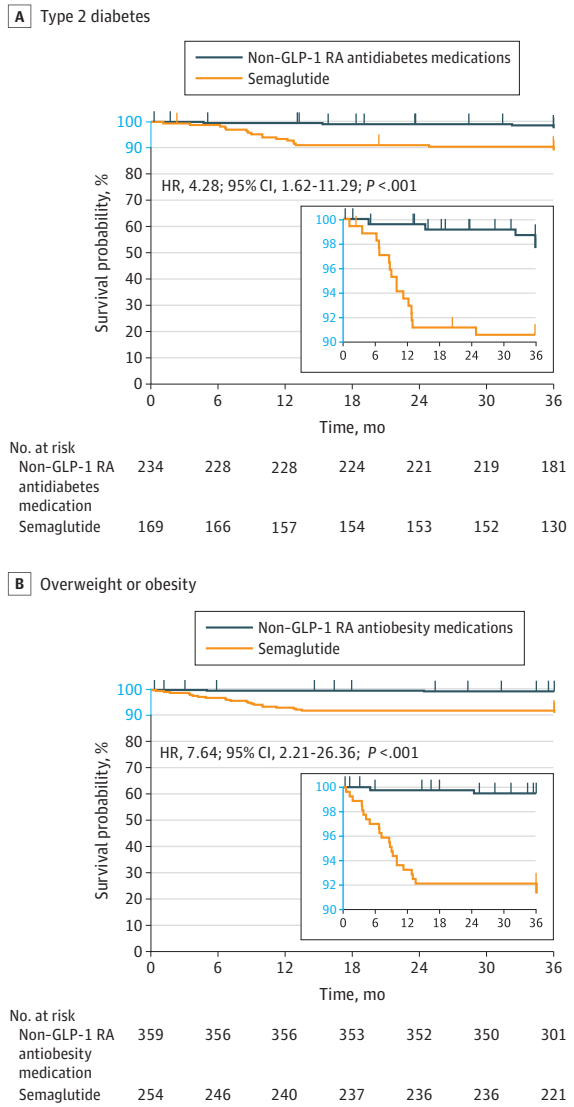
Abbreviations: GLP-1 RA, glucagon-like peptide 1 receptor agonist; MEN, multiple endocrine neoplasia; NA, not applicable; NAION, nonarteritic anterior ischemic optic neuropathy; PDE5, phosphodiesterase type 5; SMD, standardized mean difference.

[a] Propensity score matching and exact matching were performed from the same eligible cohorts.

[b] Self-reported.

[c] Includes American Indian or Alaska Native, Native Hawaiian or Other Pacific Islander, declined, patient does not know, race not listed, or unavailable.

Figure 2. Survival Analyses for Nonarteritic Anterior Ischemic Optic Neuropathy (NAION)



Survival probabilities are shown for NAION in patients with type 2 diabetes prescribed semaglutide vs a matched cohort of patients prescribed non–glucagon-like peptide 1 receptor agonist (GLP-1 RA) antidiabetic medications (A) and in patients who were overweight or obese and prescribed semaglutide vs a matched cohort of patients prescribed non–GLP-1 RA antiobesity medications (B). HR indicates hazard ratio.

CI, 1.62-11.29; $P < .001$; concordance coefficient = 0.84). The likelihood ratio test comparing the full model with a reduced model yielded a χ^2_{18} statistic of 39.10 ($P = .003$). The Wald test for the overall significance of the model produced a χ^2_{18} statistic of 25.62 ($P = .008$). The score (log-rank) test resulted in a χ^2_{18} statistic of 30.08 ($P = .009$).

Secondary analyses for baseline variables that differed by 20% or more between the 2 cohorts included an exact match for overweight or obesity and obstructive sleep apnea. The 1:1 propensity and exact matches yielded 264 patients without history of NAION. The Cox proportional hazards regression model showed a higher NAION risk in the semaglutide cohort vs the nonsemaglutide cohort (HR, 4.35; 95% CI, 1.37-13.81; $P = .01$; concordance coefficient = 0.79). The likelihood ratio test comparing the full model with a reduced model yielded a χ^2_{18} statistic of 33.88 ($P = .004$). The Wald test for the overall significance of the model produced a χ^2_{18} statistic of 23.96 ($P = .008$). The score (log-rank) test resulted in a χ^2_{18} statistic of 29.10 ($P = .01$). These results are not substantially different from those obtained with the Cox analysis based on the 1:2 propensity matching analysis. Male sex also was significant in the Cox model (HR, 2.88; 95% CI, 1.03-8.03; $P = .04$). Obesity did not significantly change the HR.

Incidence of NAION in Patients Who Were Overweight or Obese

The study population of patients who were overweight or obese included 979 patients (Figure 1). A 1:2 propensity score matching yielded adequate balance between the 2 groups (SMD < 0.1). NAION occurred in 20 patients in the semaglutide cohort vs 3 in the comparative cohort. The median (IQR) age was 46 (35-58) years for the semaglutide cohort and 44 (29-59) years for the nonsemaglutide cohort.

The Kaplan-Meier survival analysis at 36 months showed a cumulative incidence of NAION of 6.7% (95% CI, 3.6%-9.7%) for the semaglutide cohort vs 0.8% (95% CI, 0%-1.8%) for the nonsemaglutide cohort. The mean (SD) follow-up time was 34.1 (1.4) months for the semaglutide group and 35.4 (1.0) months for the nonsemaglutide group. The survival probability for the semaglutide cohort declined steepest over the initial 12 months, with a cumulative incidence of 5.5% (95% CI, 2.7%-8.3%) at year 1 (Figure 2B). The Cox proportional hazards regression model showed a higher NAION risk in the semaglutide cohort vs the nonsemaglutide cohort (HR, 7.64; 95% CI, 2.21-26.36; $P < .001$; concordance correlation coefficient = 0.86). The likelihood ratio test comparing the full model with a reduced model yielded a χ^2_{18} statistic of 56.20 ($P < .001$). The Wald test for the overall significance of the model produced a χ^2_{18} statistic of 35.05 ($P = .009$). The score (log-rank) test resulted in a χ^2_{18} statistic of 56.40 ($P < .001$).

Secondary analyses for baseline variables that differed by 20% or more between the 2 cohorts included an exact match for systemic hypertension, T2D, hyperlipidemia, and obstructive sleep apnea. The 1:1 propensity and exact matches yielded 442 patients without history of NAION. The Cox proportional hazards regression model showed a higher NAION risk in the semaglutide cohort vs the nonsemaglutide cohort (HR, 7.28; 95% CI, 1.59-33.34; $P = .01$; concordance statistic = 0.84). The likelihood ratio test comparing the full model with a reduced model yielded a χ^2_{18} statistic of 55.3 ($P < .001$). The Wald test for the overall significance of the model produced a χ^2_{18} statistic of 34.13 ($P = .04$). The score (log-rank) test resulted in a χ^2_{18} statistic of 55.11 ($P < .001$). These results are not substantially different from those obtained when the Cox analysis was performed using the 1:2 propensity matching analysis. For both primary and secondary analyses, hyperlipidemia in the Cox model increased the risk of NAION, but it was not significant when used independently as an interaction variable.

Discussion

Our main finding is that prescribed semaglutide is associated with an increased risk of NAION. Despite extensive study, the pathogenesis of NAION has not been fully eludicated.[12,13] The incidence of NAION is 2 to 10 cases per 100 000 persons,[2,14] making it the second most common cause of blindness due to optic nerve damage (with glaucoma being the most common). The relatively high HRs (4.28 and 7.64 for our T2D and overweight or obese cohorts, respectively) identified by our Cox regression analyses reveal a substantially increased risk of NAION among individuals prescribed semaglutide relative to those prescribed other medications to treat T2D and obesity or overweight. This risk appears not to be due to differences in baseline characteristics between the cohorts.

The study has several strengths. The sample size of 629 NAION cases over 6 years, which is a substantial fraction of expected cases from the Boston area, was relatively large. All diagnoses of NAION were rendered by experienced neuro-ophthalmologists. All records coded as ischemic optic neuropathy were manually reviewed to ensure the clinician had accurately diagnosed NAION. Manual review confirmed that prescribed doses of semaglutide had been dispensed for patients who experienced NAION. Propensity score matching was used to balance cohorts to address potential confounders and reduce selection bias. Also, Cox regression was used to more precisely estimate the association of semaglutide with the risk of NAION.

Nonetheless, did confounding factors influence our estimated risk of developing NAION? Given that semaglutide was first approved to treat T2D, perhaps diabetes or related comorbidities, like obesity, were culprits. Our analyses, however, suggest that plausible confounding factors were not significant contributors to the risk of NAION, although per our Cox regression model, being male might increase the risk of NAION for patients with T2D receiving semaglutide, and having hyperlipidemia might increase the risk of NAION for patients who are overweight or obese and receiving semaglutide. We also used secondary analyses (with exact matching) to further isolate potential confounding influences of baseline variables that differed substantially (≥20%) among the eligible cohorts; however, this approach yielded similar results, supporting the notion that semaglutide, not baseline characteristics, was primarily associated with the heightened risk of NAION. Our survival analyses of both cohorts (Figure 2A and B) expose the greatest risk of NAION to be within the first year following prescription of semaglutide, a temporal association that supports a potential drug-induced risk of NAION.

The first 2 injectable GLP-1 RA drugs (Ozempic and Wegovy) accounted for the highest and second highest number of weekly new-to-brand prescriptions in the United States as of April 2023, and 1.7% of all patients in the United States through much of 2023 received prescriptions for semaglutide.[15] New injectable and oral GLP-1 RA formulations are FDA approved, and even more expansive use of these drugs seems likely given their medical benefits[16-21] and widespread popularity. If true, our data anticipate increasing numbers of NAION cases related to this class of drugs.

As with any drug, however, therapeutic benefits are inseparable from adverse effects. Related to vision, patients with diabetic retinopathy who received semaglutide incurred a higher risk of exacerbation of the retinopathy, especially with rapid reduction in hemoglobin A_{1c} levels,[22] and a higher rate of progression of proliferative retinopathy and risk of new-onset macular edema.[23] There has been no prior mention, to our knowledge, of an increased risk of NAION in association with semaglutide, and our study does not inform a mechanism to link semaglutide to NAION. Despite evidence of neuroprotective properties,[24,25] expression of the GLP-1 receptor in the human optic nerve[26] and GLP-1 RA-induced enhanced sympathetic nervous system activity might influence optic nerve head perfusion and potentially increase the risk of NAION.

Limitations

There are several limitations to our study. Our tertiary care institution specializes in ophthalmology and includes a specialized neuro-ophthalmology service that evaluates a large proportion of the region's NAION cases; therefore, our findings may not be fully generalizable to other settings. Second, our retrospective study does not allow inquiry into potential biases related to decisions about which patients were prescribed semaglutide or which of those patients were referred and evaluated in our neuro-ophthalmology clinic, although notably our hospital system and our service do not exclude any patient based on insurance coverage. Third, our study could not assess whether all patients actually took the drugs as prescribed; nonadherence is a common phenomenon, even for GLP-1 RA drugs,[27] and this may have led to an inaccurate estimation of a semaglutide-associated risk. We did, however, confirm that prescribed doses of semaglutide were dispensed for all patients with NAION. Fourth, our study also is limited in that the severity of confounding factors could not be adequately assessed, as our attempt to substratify the relatively small number of NAION cases in the semaglutide-exposed cohorts (n = 17 and 20) produced wide 95% CIs and less statistical precision. Our analyses were also hindered by laboratory data that were not retrievable from outside institutions. Although we uncovered an association between prescribed semaglutide and NAION, our study did not enable definitive inquiry into relatedness. Although we showed temporal proximity between prescribed semaglutide and NAION, the highest level of confidence to assess relatedness suggested by the FDA also requires establishing risk reduction on stopping a medication and a dose-dependent association.[28] Given that our cohorts were composed of relatively small percentages of patients of races other than White (in particular, of the 16 827 patients in our eligible cohort, 5.7% were listed in the medical record as being Black or African American vs 22.5% of individuals who in 2022 self-identified similarly in the greater Boston area), our results should be considered with caution for the general population, especially given that Black individuals generally have a lower risk of NAION.[29,30]

Conclusions

This study is the first, to our knowledge, to report an association between semaglutide and NAION, although the design of our study did not enable query into a causal relationship between the two. The best approaches to confirm, refute, or refine our findings would be to conduct a much larger, retrospective, multicenter population-based cohort study; a prospective, randomized clinical study; or a postmarket analysis of all GLP-1 RA drugs. A risk inherent in larger studies, however, is the standard use of *ICD-10* diagnostic codes given that there is no *ICD-10* code for NAION. The most specific code relevant to NAION is the broader category of ischemic optic neuropathy. Our manual review of records for this study revealed that 40% of cases coded as ischemic optic neuropathy were not actually NAION but rather arteritic ischemic optic neuropathy from giant cell arteritis (which is commonly managed by neuro-ophthalmologists) or other forms of ischemic or nonischemic optic neuropathies. Manual review is not practical for extremely large databases, and the lack of a specific *ICD-10* code for NAION (as identified by Hamedani et al[31]) would be a severe hindrance for any large study. Emerging algorithms[32,33] would improve the accuracy of diagnostic coding in larger studies but would not attain the precision of a manual review and might not provide sufficient accuracy to establish a statistical association between use of a drug and occurrence of a relatively uncommon disorder like NAION.

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