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Comparative Effects of Glucagon-like Peptide 1 Receptor Agonists and Metformin on Glaucoma Risk in Patients with Type 2 Diabetes

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Purpose: To compare effects of glucagon-like peptide 1 (GLP-1) receptor agonists and metformin on the risk of primary open-angle glaucoma (POAG), ocular hypertension, and the need for first-line glaucoma treatments in patients with type 2 diabetes mellitus (T2DM).

Design: A retrospective cohort study was conducted using electronic medical records data from an international electronic health record network, covering a period from May 2006-2024.

Participants: Patients with a diagnosis of T2DM who were treated with either GLP-1 receptor agonists or metformin.

Methods: Data from 120 health care organizations across 17 countries were analyzed. Patient outcomes were assessed at 1, 2, and 3 years. Propensity score matching (PSM) was used to balance covariates such as demographics, comorbidities, and medication use. Risk ratios (RRs) with 95% confidence intervals (CIs) were calculated.

Main Outcome Measures: Incidence of POAG, ocular hypertension, and the need for first-line treatments including topical drops and laser trabeculoplasty.

Results: After PSM, both groups included 61 998 patients at the 1-year follow-up, 27 414 patients at the 2-year follow-up, and 14 100 patients at the 3-year follow-up. Patients treated with GLP-1 receptor agonists showed a significantly decreased risk of POAG development compared with those receiving metformin at 1 year (RR, 0.59; 95% CI, 0.39−0.88), 2 years (RR, 0.50; 95% CI, 0.32−0.78), and 3 years (RR, 0.59; 95% CI, 0.37−0.94). Similar protective effects were observed for ocular hypertension at 1 year (RR, 0.44; 95% CI, 0.31−0.62), 2 years (RR, 0.43; 95% CI, 0.30−0.62), and 3 years (RR, 0.51; 95% CI, 0.34−0.75). The risk of first-line therapy initiation also was lower in the GLP-1 receptor agonists group at 1 year (RR, 0.63; 95% CI, 0.53−0.74), 2 years (RR, 0.71; 95% CI, 0.59−0.85), and 3 years (RR, 0.75; 95% CI, 0.62−0.91).

Conclusions: Glucagon-like peptide 1 receptor agonists are associated with a significantly lower incidence of POAG, ocular hypertension, and the need for first-line glaucoma treatments compared with metformin in patients with T2DM. These findings highlight the potential ocular benefits of GLP-1 receptor agonists and their expanding role in the clinical management of patients with diabetes.

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Glaucoma, a leading cause of irreversible blindness, is projected to impact 111.8 million people by 2040.[1] Characterized by progressive optic neuropathy and often linked to elevated intraocular pressure (IOP), glaucoma's progression underscores the urgency of early diagnosis and treatment. Despite extensive research, the precise mechanisms and risk factors of glaucoma remain complex and multifaceted.[2] Type 2 diabetes mellitus (T2DM) is an established risk factor for the development of multiple glaucoma subtypes, including primary open-angle glaucoma (POAG) and neovascular glaucoma, primarily through microvascular damage, neurodegeneration, and metabolic abnormalities resulting from chronic hyperglycemia.[3−5] Poor glycemic control has been associated with an increased risk of glaucoma development, further underscoring the importance of managing blood glucose levels in patients with diabetes.[5,6] The association between oral antihyperglycemic agents and glaucoma in patients with diabetes remains poorly understood.

Recent years have witnessed a significant increase in the use of glucagon-like peptide 1 (GLP-1) receptor agonists, a

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class of medications first approved by the United States Food and Drug Administration in 2005 to improve glycemic control in T2DM and later approved in 2014 for use as a weight loss agent in patients without diabetes.[7] Data from a collective of health care systems that provide 18% of all daily clinical care in the United States show that, from January 2018 through December 2023, > 1 063 200 patients were prescribed these agents, totalling 4 213 888 prescriptions.[8] This could be explained not just by their growing therapeutic appeal for glycemic control but also for their demonstrated efficacy in other health domains, such as the prevention and treatment of chronic kidney disease and cardiovascular diseases, as supported by clinical trials.[9,10]

Exploratory studies suggest that GLP-1 receptor agonists may offer protective benefits against glaucoma development through their neuroprotective and anti-inflammatory properties.[11,12] However, although several studies have evaluated the protective effects of GLP-1 receptor agonists against glaucoma using large de-identified health care databases, our study uniquely compared the efficacy of GLP-1 receptor agonists with metformin as first-line diabetic treatments in glaucoma prevention. These agents have the potential to reduce oxidative stress and enhance cellular survival pathways, which could lower IOP and safeguard retinal ganglion cells.[12]

This study leverages the TriNetX health research network to conduct a comprehensive analysis, investigating the risk of POAG, ocular hypertension, and the need for first-line treatments (eye drops and laser trabeculoplasty) in patients treated with GLP-1 receptor agonists compared with those treated with metformin. We assessed these outcomes at 1-, 2-, and 3-year follow-up intervals. We aimed to elucidate the potential ocular advantages of GLP-1 receptor agonists within a large, clinical population.

Methods

This was a retrospective cohort study using data from TriNetX, a global federated health research network with electronic medical records from 120 health care organizations across 17 countries. TriNetX provides only aggregate counts and statistical summaries of deidentified information to protect patient health information, allowing it to comply with the Health Insurance Portability and Accountability Act and receive a waiver from the Western Institutional Review Board. Informed consent was not obtained or required for this study because we retrospectively reviewed patient data within this clinical program, which patients consented to provide to their healthcare provider when attending their appointment. This study was conducted in accordance with the principles of the Declaration of Helsinki. Diagnoses are represented in TriNetX by the *International Classification of Diseases* (ICD), *Tenth Revision, Clinical Modification* code set, which is a modification of the World Health Organization ICD, Tenth Revision, standard. Because we are using a global dataset, we incorporated Current Procedural Terminology; ICD, Tenth Revision, Procedure Coding System; Systematized Nomenclature of Medicine Clinical Terms; and Healthcare Common Procedure Coding System codes when available. Detailed coding data are provided in Table S1 (available at www.aaojournal.org).

The data for this study were collected on June 12, 2024. The current study analyzed the database for electronic medical records from May 2006 through May 2024, starting after the approval of metformin in 1994 and the introduction of the first GLP-1 receptor agonist, exenatide, in April 2005 for the treatment of T2DM. Our study period included the transition from the ICD, Ninth Revision, to the ICD, Tenth Revision, in 2015, which TriNetX accounts for by mapping ICD, Ninth Revision, codes and other modifications to the ICD, Tenth Revision, Clinical Modification.

Study Sample

Inclusionary criteria included patients with a diagnosis of T2DM, identified by ICD, Tenth Revision, code E11, who were either treated with GLP-1 receptor agonists or metformin for the first time after the diabetes diagnosis was made. GLP-1 medications included in the analysis were lixisenatide, albiglutide, dulaglutide, semaglutide, liraglutide, exenatide, and tirzepatide. We observed outcomes at 1, 2, and 3 years of follow-up. To ensure medication continuation and adequate time for exposure, patients were required to have an additional prescription of the respective medication at least 1 year before the observed outcome interval to be included. Patients also were required to be glaucoma-naïve with no history of ocular surgery or laser trabeculoplasty. Exclusion criteria included any eye injury and the use of other blood glucose-lowering drugs, such as sulfonylureas, α-glucosidase inhibitors, thiazolidinediones, dipeptidyl peptidase 4 inhibitors, sodium-glucose cotransporter 2 inhibitors, and meglitinides, either 3 months before or at any time after starting the study medications. We also conducted a sensitivity analysis exclusively on patients not using insulin to evaluate the robustness of our findings. Figure 1 illustrates the inclusion and exclusion criteria for the study cohort.

Covariates

The TriNetX platform was used to conduct a 1:1 propensity score matching (PSM) to ensure that the characteristics and comorbidities between the groups were balanced. This matching used a nearest-neighbor greedy matching algorithm with a caliper of 0.1 standard deviation, a standard and widely accepted technique in the published literature.[13–15] The covariates included for matching were demographics (age, sex, race, and ethnicity) and diagnoses such as essential hypertension, hyperlipidemia, disorders of the thyroid gland, chronic kidney disease, sleep disorders, and chronic obstructive pulmonary disease. Clinical measures like body mass index (BMI) and hemoglobin A1c levels were considered. Medication use included systemic corticosteroids, systemic β-blockers, and insulin use. Also included were factors related to engagement with health services, specifically ophthalmology services and procedures, ensuring equal engagement with ophthalmologists among the groups, because differential access could influence the diagnosis rate of conditions under study.

Statistical Analyses

The index date for each patient within a cohort was defined as the day on which the patient first was prescribed the respective medication. For our primary outcomes, we observed the risk of POAG (ICD, Tenth Revision, code H40.11), ocular hypertension (ICD, Tenth Revision, code H40.05), and first-line treatments including medications such as β-blocking agents, prostaglandin analogs, brimonidine, brinzolamide, dorzolamide, and netarsudil and procedures like trabeculoplasty by laser surgery at 1, 2, and 3 years after the index event. Risk ratios (RRs) with 95% confidence intervals (CIs) were generated using univariable analyses. Patients who demonstrated outcomes of interest before initiating the specified medications were excluded from the analysis. Baseline characteristics were presented using averages and standard deviations for continuous variables and counts and proportions for binary variables. The PSM outcomes were assessed at each time point to

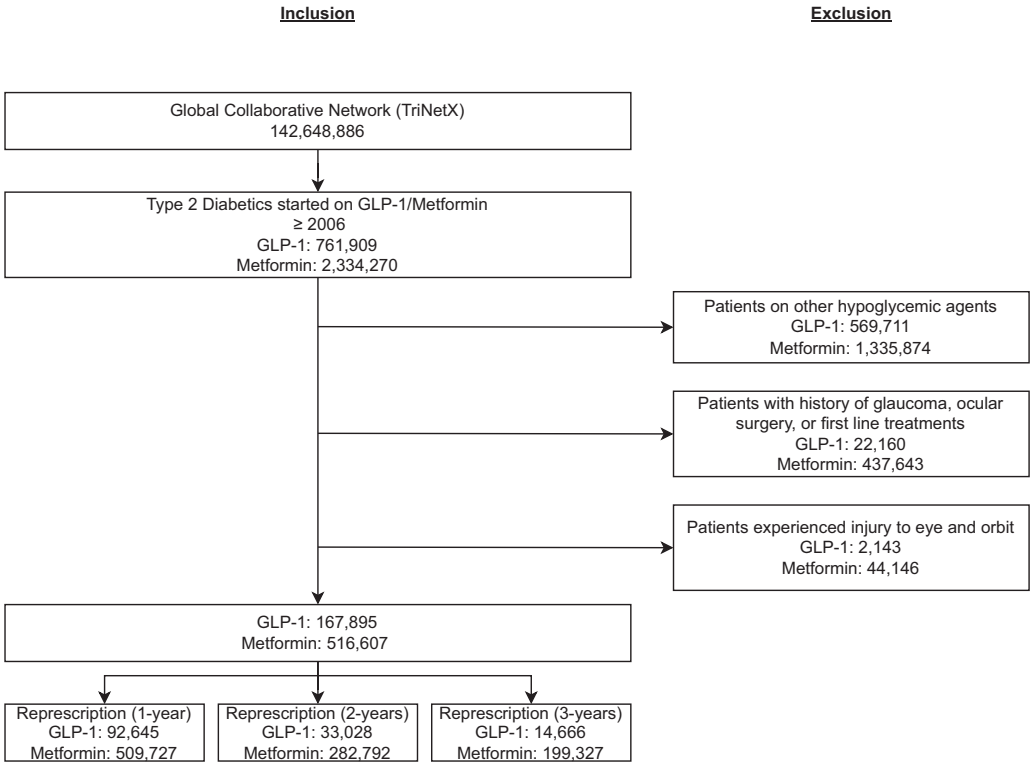

Figure 1. Flowchart illustrating the inclusion and exclusion criteria for the study cohort of patients with type 2 diabetes receiving glucagon-like peptide 1 (GLP-1) receptor agonists and metformin. From the TriNetX dataset of 142 648 886 records, we identified 3 096 179 patients with type 2 diabetes who started on GLP-1 receptor agonist or metformin therapy since 2006. Exclusion criteria were patients receiving other hypoglycemic agents; those with a history of glaucoma, ocular surgery, or first-line treatments; and those who experienced eye or orbit injuries. After exclusions, 167 895 patients remained in the GLP-1 cohort and 516 607 patients remained in the metformin cohort. Further stratification by medication adherence at 1, 2, and 3 years was applied.

evaluate the covariate balance between groups using standardized mean differences. A standardized mean difference < 0.1 between cohorts was considered well matched. The threshold for statistical significance was set at $P < 0.05$ using 2-sided tests.

Results

Baseline Characteristics

Before matching, inclusion criteria were met by 66 320 patients in the GLP-1 group and 368 503 in the metformin group at 1 year of follow-up. On matching, both groups included 61 998 patients each. The mean age after PSM was 56.1 ± 13.6 years for the GLP-1 group and 55.8 ± 15.5 years for the metformin group. The GLP-1 group consisted of 34.50% male patients and 65.50% female patients, whereas the metformin group included 34.10% male patients and 65.90% female patients. Racial distribution in the GLP-1 group was 58.15% White, 17.58% Black or African American, and 3.17% Asian. The metformin group showed a similar distribution: 59.30% White, 17.52% Black or African American, and 2.77% Asian. Regarding comorbidities, 67.25% of the GLP-1 group and 66.24% of the metformin group had essential hypertension. Hyperlipidemia was present in 48.75% of the GLP-1 group and 47.12% of the metformin group. Chronic kidney disease was observed in 14.60% of the GLP-1 group and 14.02% of the metformin group. Medication use indicated that insulin was used by 38.71% of the GLP-1 group and 37.57% of the metformin group, whereas corticosteroid use was 55.73% in the GLP-1 group and 55.11% in the metformin group. Systemic β-blocker use was present in 37.44% of the GLP-1 group and 36.56% of the metformin group. Characteristics before and after matching are shown in Table 2.

Risk of Primary Open-Angle Glaucoma, Ocular Hypertension, and Receive First-Line Treatments

Table 3 shows the risk of POAG, ocular hypertension, and the use of first-line treatments in patients receiving GLP-1 receptor agonists versus metformin over the 1-, 2-, and 3-year outcome periods. After PSM, both groups included 61 998 patients at the 1-year follow-up, 27 414 patients at the 2-year follow-up, and 14 100 patients at the 3-year follow-up.

Patients treated with GLP-1 receptor agonists showed a significantly decreased risk of POAG developing compared with those receiving metformin at 1 year (RR, 0.59; 95% CI, 0.39−0.88), 2 years (RR, 0.50; 95% CI, 0.32−0.78), and 3 years (RR, 0.59; 95% CI, 0.37−0.94). Similar associations were observed for ocular hypertension with risk reductions of

Table 2. Baseline Characteristics of Patients with Diabetes Receiving Glucagon-like Peptide 1 versus Metformin before and after Propensity Score Matching

Characteristic	Before Matching			After Matching		
	Glucagon-like Peptide 1 (n = 66 320)	*Metformin (n = 368 503)*	*Standardized Difference*	*Glucagon-like Peptide 1 (n = 61 998)*	*Metformin (n = 61 998)*	*Standardized Difference*
Age (yrs)	56.1 ± 13.6	59.4 ± 15.3		56.1 ± 13.6	55.8 ± 15.5	
Sex						
Male	22 252 (33.55)	179 042 (48.59)	0.3092	21 387 (34.50)	21 142 (34.10)	0.0083
Female	38 174 (57.56)	175 367 (47.59)	0.2007	35 450 (57.18)	35 852 (57.83)	0.0131
Unknown	5894 (8.89)	14 094 (3.83)	0.2086	5161 (8.32)	5004 (8.07)	0.0092
Race						
White	38 380 (57.87)	198 361 (53.83)	0.0815	36 054 (58.15)	37 158 (59.93)	0.0362
Black or African American	13 066 (19.70)	62 808 (17.04)	0.0687	12 102 (19.52)	12 011 (19.37)	0.0037
Asian	2002 (3.02)	26 443 (7.18)	0.1899	1965 (3.17)	1715 (2.77)	0.0238
American Indian or Alaska Native	299 (0.45)	1430 (0.39)	0.0097	271 (0.44)	274 (0.44)	0.0007
Native Hawaiian or Other Pacific Islander	629 (0.95)	2980 (0.81)	0.0150	580 (0.94)	549 (0.89)	0.0053
Other race	2584 (3.90)	16 442 (4.46)	0.0283	2444 (3.94)	2303 (3.72)	0.0119
Unknown race	9360 (14.11)	60 039 (16.29)	0.0607	8582 (13.84)	7988 (12.88)	0.0282
Ethnicity						
Hispanic or LatinX	6168 (9.30)	40 866 (11.09)	0.0592	5919 (9.55)	5539 (8.93)	0.0212
Non-Hispanic or LatinX	49 123 (74.07)	236 040 (64.05)	0.2180	45 839 (73.94)	47 229 (76.18)	0.0518
Unknown	11 029 (16.63)	91 597 (24.86)	0.2039	10 240 (16.52)	9230 (14.89)	0.0448
Comorbidities						
Essential hypertension	45 575 (68.72)	195 008 (52.92)	0.3280	41 696 (67.25)	41 066 (66.24)	0.0216
Hyperlipidemia	33 720 (50.84)	121 806 (33.05)	0.3665	30 222 (48.75)	29 212 (47.12)	0.0326
Sleep disorders	25 799 (38.90)	57 781 (15.68)	0.5400	22 491 (36.28)	22 438 (36.19)	0.0018
Disorders of thyroid gland	16 363 (24.67)	46 253 (12.55)	0.3153	14 364 (23.17)	14 008 (22.59)	0.0137
Chronic kidney disease	11 705 (17.65)	19 499 (5.29)	0.3953	9053 (14.60)	8689 (14.02)	0.0168
Chronic obstructive pulmonary disease	5232 (7.89)	23 931 (6.49)	0.0540	4766 (7.69)	4411 (7.12)	0.0219
Medication						
Insulin	27 648 (41.69)	76 555 (20.78)	0.4632	24 001 (38.71)	23 294 (37.57)	0.0235
Corticosteroid	38 499 (58.05)	109 504 (29.72)	0.5958	34 549 (55.73)	34 168 (55.11)	0.0124
Systemic β-blocker	26 299 (39.66)	84 641 (22.97)	0.3658	23,209 (37.44)	22 669 (36.56)	0.0180
Ophthalmology Visit						
CPT: ophthalmology services and procedures	6683 (10.08)	17 319 (4.70)	0.2067	5732 (9.25)	5583 (9.01)	0.0083
HCPCS: vision or hearing services	505 (0.76)	1074 (0.29)	0.0650	414 (0.67)	404 (0.65)	0.0020
SNOMED: ophthalmic examination and evaluation	500 (0.75)	1026 (0.28)	0.0664	360 (0.58)	308 (0.50)	0.0115
Hemoglobin A1c						
6.5%-10%	37 131 (55.99)	131 549 (35.70)	0.4159	33 470 (53.99)	32 867 (53.01)	0.0195
10%-15%	13 209 (19.92)	27 812 (7.55)	0.3653	10 740 (17.32)	9983 (16.10)	0.0327
≥ 15%	1047 (1.58)	2371 (0.64)	0.0893	830 (1.34)	755 (1.22)	0.0108
Body mass index, kg/m^2						
≤ 18.5	2129 (3.21)	6094 (1.65)	0.1012	1809 (2.92)	1670 (2.69)	0.0136
18.5-25	5353 (8.07)	37 626 (10.21)	0.0743	5077 (8.19)	4532 (7.31)	0.0329
25-30	15 976 (24.09)	78 619 (21.34)	0.0658	14 804 (23.88)	14 193 (22.89)	0.0233
30-35	26 600 (40.11)	83 693 (22.71)	0.3816	23 952 (38.63)	23 726 (38.27)	0.0075
≥ 35	37 118 (55.97)	80 304 (21.79)	0.7486	33 113 (53.41)	33 682 (54.33)	0.0184

CPT = Current Procedural Terminology; GLP-1 = glucagon-like peptide 1; HCPCS = Healthcare Common Procedure Coding System; SNOMED = Systematized Nomenclature of Medicine Clinical Terms.
Data are presented as No. of patients (%) or mean ± standard deviation.

Table 3. Outcomes of Glucagon-like Peptide 1 Receptor Agonists versus Metformin in Patients with Type 2 Diabetes over 1-, 2-, and 3-Year Follow-up Periods

Outcome	Follow-up Period (yrs)	Cohort after Matching (No.)	Risk Ratio	95% Confidence Interval
Primary open-angle glaucoma	1	61 998	0.59	0.39-0.88
	2	27 414	0.50	0.32-0.78
	3	14 100	0.59	0.37-0.94
Ocular hypertension	1	61 998	0.44	0.31-0.62
	2	27 414	0.43	0.30-0.62
	3	14 100	0.51	0.34-0.75
First-line treatments	1	61 998	0.63	0.53-0.74
	2	27 414	0.71	0.59-0.85
	3	14 100	0.75	0.62-0.91

56% at 1 year (RR, 0.44; 95% CI, 0.31−0.62), 57% at 2 years (RR, 0.43; 95% CI, 0.30−0.62), and 49% at 3 years (RR, 0.51; 95% CI, 0.34−0.75). The risk of first-line therapy initiation also was lower in the GLP-1 receptor agonists group at 1 year (RR, 0.63; 95% CI, 0.53−0.74), 2 years (RR, 0.71; 95% CI, 0.59−0.85), and 3 years (RR, 0.75; 95% CI, 0.62−0.91). A sensitivity analysis of patients not using insulin maintained statistical significance for all outcomes. These results are summarized in the forest plot shown in Figure 2.

Discussion

This study demonstrated that GLP-1 receptor agonists are associated with a lower risk of POAG and ocular hypertension developing compared with metformin in patients with T2DM. Specifically, patients treated with GLP-1 receptor agonists exhibited a 41% reduced risk of POAG developing at 1 year, a 50% reduced risk at 2 years, and a 41% reduced risk at 3 years ($P < 0.05$ for all). Similar protective trends were observed for ocular hypertension, with a 56% reduced risk at 1 year, a 57% reduced risk at 2 years, and a 49% reduced risk at 3 years ($P < 0.05$ for all). These findings underscore the potential of GLP-1 receptor agonists not only in glycemic control but also in mitigating the risk of glaucoma.

Multiple theoretical mechanisms explain which GLP-1 receptor agonists may provide a protective benefit against the development of glaucoma. Prior investigations provide compelling insights into the neuroprotective properties of GLP-1 receptor agonists. These agents have been shown to reduce inflammation and oxidative stress by downregulating complement component 1q, tumor necrosis factor α, and interleukin 1a, which are key contributors to neurodegenerative processes in the retina and optic nerve.[12,16] Glucagon-like peptide 1 receptor agonists improve neuronal survival and function by activating signaling pathways that enhance cellular resilience and reduce apoptotic cell death.[12,16,17] Furthermore, they mitigate inflammatory responses in the retina, decreasing the production of proinflammatory cytokines by microglia and macrophages, thus protecting retinal ganglion cells from degeneration.[11,18,19]

In addition, we found that GLP-1 receptor agonists were protective against the development of ocular hypertension, suggesting their potential IOP-lowering effect. A recent study by Hallaj et al[20] showed that GLP-1 receptor agonists such as semaglutide and liraglutide are associated significantly with a decrease in IOP, particularly in glaucomatous eyes. Furthermore, a randomized, placebo-controlled, double-blind trial demonstrated a reduced incidence of idiopathic intracranial hypertension in patients treated with GLP-1 receptor agonists.[21] This reduction in intracranial pressure was attributed to the inhibition of cerebrospinal fluid secretion by inhibiting sodium/potassium adenosine triphosphatase (Na+/K+ ATPase) activity within the choroidal plexus.[21] This finding was independent of weight loss, indicating that the protective effect on intracranial pressure was the result of direct modulation of fluid secretion.[21] Aqueous humor secretion also depends on the action of Na+/K+ ATPase, and GLP-1 receptor agonists could inhibit its activity and lower IOP by decreasing aqueous humor production.[12] Furthermore, research has shown that incubation of human umbilical vein endothelial cells with GLP-1 significantly increases the activity of endothelial nitric oxide synthase.[22] This induction of nitric oxide synthesis potentially can enhance aqueous humor outflow by relaxing the trabecular meshwork and Schlemm canal.[23] These pathways highlight the significant mechanisms by which GLP-1 receptor agonists may exert their IOP-lowering effects and protect against glaucoma.

Another potential mechanism is glycemic control. Although PSM balanced the HbA1c levels between the GLP-1 and metformin groups, thereby controlling for glycemic control, it is plausible that the improved management of diabetes itself could contribute to the reduced risk of glaucoma. This aligns with existing literature indicating that poor glycemic control is a significant risk factor for glaucoma development because of the microvascular and neurodegenerative damage resulting from chronic hyperglycemia.[5,6] One study conducted on more than 40 000 patients in the Danish registers found that patients receiving GLP-1 receptor agonists had a 1-year absolute decrease in HbA1c by −3.84 mmol/mol (95% CI, −5.36 to −2.33) compared with metformin users.[24] An article published by the American Diabetes Association advocated for GLP-1 receptor agonists as a first-line treatment for T2DM, explaining their superiority in glycemic control.[25] Glucagon-like peptide 1 receptor agonists

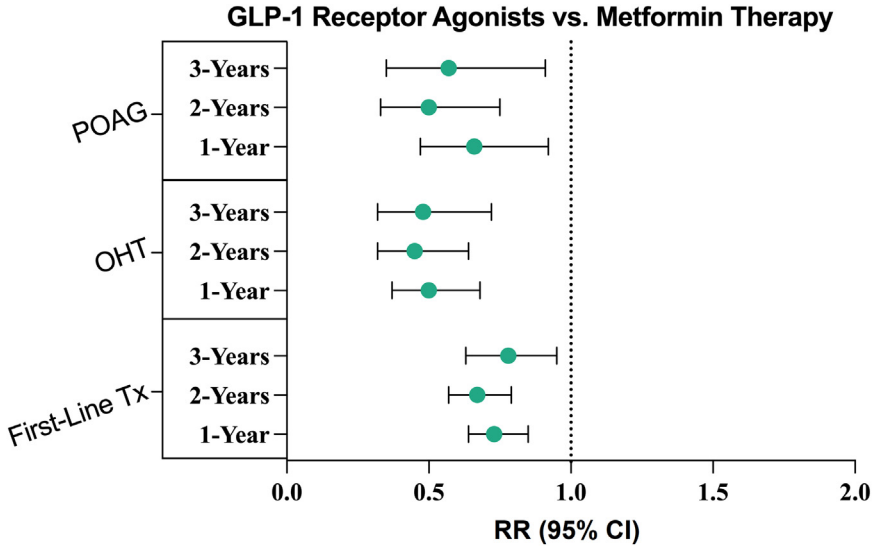

Figure 2. Graph showing risk ratios (RRs) with 95% confidence intervals (CIs) for the risk of primary open-angle glaucoma (POAG), ocular hypertension (OHT), and the need for first-line glaucoma treatments (Tx) in patients treated with GLP-1 receptor agonists compared with those treated with metformin. The figure shows outcomes at the 1-year, 2-year, and 3-year follow-ups. An RR < 1 indicates a reduced risk of these conditions and treatments in the GLP-1 receptor agonists group compared with the metformin group.

significantly improve β-cell function, enhance insulin sensitivity in muscle, and reduce hepatic glucose production through multiple pathways, unlike metformin, which primarily inhibits hepatic gluconeogenesis.[25] Although GLP-1 agonists have not been well examined as a first-line monotherapy for diabetes treatment, our study adds significant supportive evidence by uniquely comparing the efficacy of these medications in a cohort of patients with and without concurrent insulin use.

Moreover, studies have shown that weight reduction is associated with decreased IOP, which could contribute further to the reduced risk of ocular hypertension in patients treated with GLP-1 receptor agonists.[26–28] Coster et al[28] observed that individuals who experienced a reduction of 2 or more BMI units showed a corresponding decrease in IOP, with a reduction of 2.86 kg/m^2 in BMI linked to a 1-mmHg drop in IOP. Semaglutide, which was approved in 2014, was the first GLP-1 receptor agonist specifically approved for chronic weight management, with the more recent approval of tirzepatide in 2023.[29,30] Our study found a decreased risk of ocular hypertension in patients treated with GLP-1 receptor agonists after matching for BMI of patients when entering the study. The effects of potential weight loss improved glycemic control, neuroprotection, and the direct IOP-lowering mechanisms of GLP-1 receptor agonists may explain the observed protective effects against ocular hypertension and glaucoma.

Although metformin's neuroprotective effects are promising, the variability in its impact on glaucoma risk suggests that its benefits may be less consistent or potent compared with those of GLP-1 receptor agonists. According to the American Diabetes Association and the American College of Physicians, metformin is recommended as the initial pharmacologic therapy for T2DM.[31,32] Although it has demonstrated potential neuroprotective effects in various models, its specific impact on glaucoma remains less clear.[33] For example, a study published in the *Journal of the American Medical Association* in 2015 using the Clinformatics DataMart Database (OptumInsight) in the United States found that those prescribed the highest quartile of metformin hydrochloride (> 1110 g in 2 years) showed a reduced risk of open-angle glaucoma compared with those who took no metformin (HR, 0.75; 95% CI, 0.59−0.95).[34] However, other studies have reported no significant association between metformin use and OAG incidence. A study using the Korean National Health Insurance database found no statistical association between metformin use and OAG incidence (HR, 1.05; 95% CI, 0.79−1.40).[35] These conflicting findings highlight the need for further research to clarify the role of metformin in glaucoma prevention.

Our study aligns with and expands on existing research. Sterling et al,[36] in their study of data from Optum's de-identified Clinformatics Data Mart Database, explored the impact of GLP-1 receptor agonists compared with other non−GLP-1 diabetic medications and found a protective effect when GLP-1 receptor agonists were used. In contrast, Niazi et al,[37] in their study of data from the Danish Registry, demonstrated that although treatment with GLP-1 receptor agonists for more than 3 years significantly reduced the risk of glaucoma (HR, 0.71; 95% CI, 0.55−0.91; $P = 0.007$), shorter treatment durations of 0 to 1 year (HR, 0.89; 95% CI, 0.70−1.14) and 1 to 3 years (HR, 0.85; 95% CI, 0.67−1.06) did not yield significant results. These variations in hazard ratios highlight the potential for GLP-1 receptor agonists to provide benefits over different durations, contrasting with our findings in which early benefits were apparent. This could be explained by the fact that other studies included patients receiving second-line treatments, whereas our study included patients who primarily were

receiving GLP-1 receptor agonists or metformin, with the potential for concurrent insulin use. This distinction is crucial because patients receiving multiple drugs may reduce the dose of individual drugs compared with those primarily receiving GLP-1 receptor agonists who may be receiving higher doses, enhancing their neuroprotective effects. Additionally, our study included an international cohort, accounting for geographical and racial diversity, which may influence associated risks and may provide a more robust analysis. Future research should compare GLP-1 receptor agonists against a more general control group to understand better the mechanisms through which GLP-1 receptor agonists may act, including in those without diabetes and those without significant weight management needs. Such studies will help to elucidate the full potential of GLP-1 receptor agonists in glaucoma prevention and provide a deeper understanding of their neuroprotective benefits.

Our study adds significant supportive and new evidence to the literature by leveraging the substantial data available through the TriNetX network, providing a robust platform for assessing the effects of GLP-1 receptor agonists compared with metformin in reducing the risk of glaucoma among patients with T2DM. Our study leverages a global dataset, encompassing a diverse patient population from 120 health care organizations across 17 countries. This broad inclusion enhances the generalizability of our findings. Additionally, we investigated not only POAG but also ocular hypertension and the need for first-line glaucoma treatments, providing a comprehensive view of glaucoma-related conditions. The large cohort sizes contribute to the robustness of our findings. We used PSM to ensure comparability between treatment and control groups, balancing key covariates such as age, sex, race, ethnicity, hypertensive diseases, hyperlipidemia, chronic kidney disease, and medication use, including insulin and corticosteroids. One of the study's strengths is the consideration of adequate exposure time. Given the recent spike in GLP-1 use and the longer history of metformin use, a discrepancy in exposure time exists between the two medications. To address this, we ensured that patients had a represcription of the respective medication at least 1 year before the observed outcome. By observing outcomes in relationship to the represcription date, we provided fair exposure time for both groups, thereby mitigating the impact of differing exposure durations on our results.

However, our study has limitations. Propensity score matching has inherent limitations, such as reliance on the correct specification of the propensity score model and the potential inability to balance covariates fully if key variables are omitted or measured poorly. Additionally, PSM can address only observed confounders, leaving the potential for residual confounding by unmeasured factors. Despite these limitations, the use of PSM with the TriNetX platform is a standard and widely accepted technique in the published literature. Numerous studies in high-impact journals have demonstrated the robustness and reliability of using PSM with TriNetX for retrospective analyses, underscoring its credibility and strength in producing reliable and generalizable results.[13,38,39] Potential inaccuracies in the coding of medical data could impact patient selection and outcome assessment. The TriNetX data lack detailed clinical assessments such as IOP and IOP fluctuation, which are important in glaucoma management and could influence our outcomes. Although we attempted to match for access to ophthalmology care, it is inherently challenging. Differential access to ophthalmic review and care could influence the observed associations, because patients with more frequent visits may have higher glaucoma diagnosis rates because of increased screening. It is also important to acknowledge that the decision to prescribe metformin versus GLP-1 receptor agonists is influenced by patient-specific factors such as diabetes severity, comorbid conditions, and physician preference. Additionally, inequities in race, ethnicity, and socioeconomic status have been noted to play a role in GLP-1 prescribing patterns, potentially indicating a healthier population at inherently lower risk of ocular comorbidities.[40] These factors could contribute to the observed differences in glaucoma incidence and should be considered when interpreting the results.

In conclusion, our study underscores the significant protective effects of GLP-1 receptor agonists against POAG and ocular hypertension in patients with T2DM compared with those treated with metformin. Our findings reveal that the neuroprotective actions of these agents, including their anti-inflammatory effects, antioxidative properties, potentially IOP-lowering effects, may begin to confer benefits within the first 3 years of therapy. These insights highlight the importance of incorporating GLP-1 receptor agonists into the clinical management of patients with diabetes.

Footnotes and Disclosures

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HUMAN SUBJECTS: No human subjects were included in this study. TriNetX provides only aggregate counts and statistical summaries of de-identified information to protect patient health information, allowing it to comply with the Health Insurance Portability and Accountability Act and receive a waiver from the Western Institutional Review Board. Informed consent was not obtained or required for this study because we retrospectively reviewed patient data within this clinical program, which patients consented to provide to their healthcare provider when attending their appointment. This study was conducted in accordance with the principles of the Declaration of Helsinki.

No animal subjects were included in this study.

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Abbreviations and Acronyms:

BMI = body mass index; **CI** = confidence interval; **FDA** = Food and Drug Administration; **GLP-1** = glucagon-like peptide 1; **HR** = hazard ratio; **ICD** = International Classification of Diseases; **IOP** = intraocular pressure; **POAG** = primary open-angle glaucoma; **PSM** = propensity score matching; **RR** = risk ratio; **T2DM** = type 2 diabetes mellitus.

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GLP-1 receptor agonists, Primary open-angle glaucoma, Type 2 diabetes, Metformin, Ocular hypertension.

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References

1. Tham YC, Li X, Wong TY, et al. Global prevalence of glaucoma and projections of glaucoma burden through 2040: a systematic review and meta-analysis. *Ophthalmology*. 2014;121(11):2081−2090.
2. Ekici E, Moghimi S. Advances in understanding glaucoma pathogenesis: a multifaceted molecular approach for clinician scientists. *Mol Aspects Med*. 2023;94:101223.
3. Li Y, Mitchell W, Elze T, Zebardast N. Association between diabetes, diabetic retinopathy, and glaucoma. *Curr Diab Rep*. 2021;21:1−16.
4. Chopra V, Varma R, Francis BA, et al. Type 2 diabetes mellitus and the risk of open-angle glaucoma: the Los Angeles Latino Eye Study. *Ophthalmology*. 2008;115(2):227−232.e1.
5. Zhao D, Cho J, Kim MH, et al. Diabetes, fasting glucose, and the risk of glaucoma: a meta-analysis. *Ophthalmology*. 2015;122(1):72−78.
6. Song BJ, Aiello LP, Pasquale LR. Presence and risk factors for glaucoma in patients with diabetes. *Curr Diab Rep*. 2016;16:1−13.
7. Crane J, McGowan B. The GLP-1 agonist, liraglutide, as a pharmacotherapy for obesity. *Ther Adv Chronic Dis*. 2016;7(2):92−107.
8. Gratzl S, Rodriguez PJ, Cartwright BMG, et al. Monitoring report: GLP-1 RA prescribing trends-March 2024 Data, *medRxiv*. *Preprint*. 2024;2024(01):18.24301500.
9. Tuttle KR, Bain SC, Bosch-Traberg H, et al. Effects of once-weekly semaglutide on kidney disease outcomes by KDIGO risk category in the SUSTAIN 6 trial. *Kidney Int Rep*. 2024;9(7):2006−2015.
10. Kristensen SL, Rørth R, Jhund PS, et al. Cardiovascular, mortality, and kidney outcomes with GLP-1 receptor agonists in patients with type 2 diabetes: a systematic review and meta-analysis of cardiovascular outcome trials. *Lancet Diabetes Endocrinol*. 2019;7(10):776−785.
11. Cui QN, Stein LM, Fortin SM, Hayes MR. The role of glia in the physiology and pharmacology of glucagon-like peptide-1: implications for obesity, diabetes, neurodegeneration and glaucoma. *Br J Pharmacol*. 2022;179(4):715−726.
12. Lawrence ECN, Guo M, Schwartz TD, et al. Topical and systemic GLP-1R agonist administration both rescue retinal ganglion cells in hypertensive glaucoma. *Front Cell Neurosci*. 2023;17:1156829.
13. Chauhan MZ, Elhusseiny AM, Kishor KS, et al. Association of primary open-angle glaucoma with diabetic retinopathy among patients with type 1 and type 2 diabetes: a large global database study. *Ophthalmology*. 2024;131(7):827−835.
14. Wai KM, Knapp A, Ludwig CA, et al. Risk of stroke, myocardial infarction, and death after retinal artery occlusion. *JAMA Ophthalmol*. 2023;141(12):1110−1116.
15. Tran EM, Wai KM, Kossler AL, et al. Association of ocular manifestations of Marfan syndrome with cardiovascular complications. *Am J Ophthalmol*. 2024;264:85−89.
16. Reich N, Hölscher C. The neuroprotective effects of glucagon-like peptide 1 in Alzheimer's and Parkinson's disease: an in-depth review. *Front Neurosci*. 2022;16:970925.
17. Erbil D, Eren CY, Demirel C, et al. GLP-1's role in neuroprotection: a systematic review. *Brain Injury*. 2019;33(6):734−819.
18. Puddu A, Maggi D. Anti-inflammatory effects of GLP-1R activation in the retina. *Int J Mol Sci*. 2022;23(20):12428.
19. Gonçalves A, Lin C-M, Muthusamy A, et al. Protective effect of a GLP-1 analog on ischemia-reperfusion induced blood−retinal barrier breakdown and inflammation. *Invest Ophthalmol Vis Sci*. 2016;57(6):2584−2592.

20. Hallaj S, Halfpenny W, Chuter BG, et al. Association Between Glucagon-Like Peptide-1 Receptor Agonists Exposure and Intraocular Pressure Change: GLP-1 Receptor Agonists and Intraocular Pressure Change. *Am J Ophthalmol*. 2024;269:255−265.
21. Mitchell JL, Lyons HS, Walker JK, et al. The effect of GLP-1RA exenatide on idiopathic intracranial hypertension: a randomized clinical trial. *Brain*. 2023;146(5):1821−1830.
22. Ding L, Zhang J. Glucagon-like peptide-1 activates endothelial nitric oxide synthase in human umbilical vein endothelial cells. *Acta Pharmacol Sin*. 2012;33(1):75−81.
23. Wang T, Ding J, Cheng X, et al. Glucagon-like peptide-1 receptor agonists: new strategies and therapeutic targets to treat atherosclerotic cardiovascular disease. *Front Pharmacol*. 2024;15:1396656.
24. Soerensen K, Torp-Pedersen C, Pedersen-Bjerregaard U, Zareini B. GLP1-RA versus metformin as first-line therapy for achieving glycemic control and risk-factor management-a one-year nationwide cohort study. *Eur Heart J*. 2023;44(Suppl 2). ehad655. 2817.
25. Abdul-Ghani M, DeFronzo RA. Is it time to change the type 2 diabetes treatment paradigm? Yes! GLP-1 RAs should replace metformin in the type 2 diabetes algorithm. *Diabetes Care*. 2017;40(8):1121−1127.
26. Khan S, Kirubarajan A, Lee M, et al. The correlation between body weight and intraocular pressure. *Aerospace Med Hum Perform*. 2021;92(11):886−897.
27. Cohen E, Kramer M, Shochat T, et al. Relationship between body mass index and intraocular pressure in men and women: a population-based study. *J Glaucoma*. 2016;25(5):e509−e513.
28. Coster D, Rafie A, Savion-Gaiger N, et al. The effect of body mass index reduction on intraocular pressure in a large prospective cohort of apparently healthy individuals in Israel. *PloS One*. 2023;18(5):e0285759.
29. Singh G, Krauthamer M, Bjalme-Evans M. Wegovy (semaglutide): a new weight loss drug for chronic weight management. *J Invest Med*. 2022;70(1):5−13.
30. United States Food and Drug Administration. FDA approves new medication for chronic weight management. Available from: https://www.fda.gov/news-events/press-announcements/fda-approves-new-medication-chronic-weight-management; 2023. Accessed June 10, 2024.
31. Vieira IH, Barros LM, Baptista CF, et al. Recommendations for practical use of metformin, a central pharmacological therapy in type 2 diabetes. *Clin Diabetes*. 2022;40(1):97−107.
32. Qaseem A, Humphrey LL, Sweet DE, et al. Oral pharmacologic treatment of type 2 diabetes mellitus: a clinical practice guideline from the American College of Physicians. *Ann Intern Med*. 2012;156(3):218−231.
33. Daka Q, Neziri B, Lindner E, Azuara Blanco A. Metformin in glaucoma treatment. *J Glaucoma*. 2024;33(6):387−393.
34. Lin HC, Stein JD, Nan B, et al. Association of geroprotective effects of metformin and risk of open-angle glaucoma in persons with diabetes mellitus. *JAMA Ophthalmol*. 2015;133(8):915−923.
35. Kim HK, Lee W, Ryu IH, et al. Association between metformin use and the risk of developing open-angle glaucoma among patients with diabetes: a retrospective cohort study and meta-analysis. *Int Ophthalmol*. 2024;44(1):6.
36. Sterling J, Hua P, Dunaief JL, et al. Glucagon-like peptide 1 receptor agonist use is associated with reduced risk for glaucoma. *Br J Ophthalmol*. 2023;107(2):215−220.
37. Niazi S, Gnesin F, Thein AS, et al. Association between glucagon-like peptide-1 receptor agonists and the risk of glaucoma in individuals with type 2 diabetes. *Ophthalmology*. 2024;131(9):1056−1063.
38. Jeong H, Shaia JK, Markle JC, et al. Melatonin and risk of age-related macular degeneration. *JAMA Ophthalmol*. 2024;142(7):648−654.
39. Wang W, Volkow ND, Berger NA, et al. Association of semaglutide with risk of suicidal ideation in a real-world cohort. *Nat Med*. 2024;30(1):168−176.
40. Eberly LA, Yang L, Essien UR, et al. Racial, ethnic, and socioeconomic inequities in glucagon-like peptide-1 receptor agonist use among patients with diabetes in the US. *JAMA Health Forum*. 2021;2(12):e214182.