Potential Eye Disorders in People With and Without Type 2 Diabetes Mellitus Exposed to GLP-1 Receptor Agonists: An Examination of the FAERS (FDA Adverse Event Reporting System) Database

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• PURPOSE: As use of glucagon-like peptide-1 receptor agonists (GLP-1RAs) for Type 2 diabetes (T2DM) and weight management increases, emerging research identifies various adverse drug reactions. This study aimed to expand this research base, focusing on eye disorders in people with and without T2DM, a novel consideration.

• DESIGN: A retrospective clinical cohort disproportionality analysis of reports made to the Food and Drug Administration Adverse Event Reporting System (FAERS).

• METHODS: FAERS was queried regarding selected GLP-1RAs. Python 3.11 was adopted to develop a program, quantifying reported cases between January 2017 - September 2025 (January 2022-September 2025 for tirzepatide) meeting the criteria for cases with and without T2DM. Main outcome measures Reporting Odds Ratios (RORs) >4.000 and 95% confidence intervals were calculated, with metformin and orlistat as controls.

• RESULTS: Compared to metformin, semaglutide showed increased reporting of optic ischemic neuropathy (ROR: 12.269 [0.915-1.967]), cataract (ROR: 31.879 [2.463-4.461]) and retinopathy (ROR: 5.185 [0.556-2.736]) in T2DM patients, and retinopathy (ROR: 9.424 [1.081-3.406]) and retinal hemorrhage (ROR: 10.253 [0.319-4.336]) in non-T2DM patients. Tirzepatide showed increased reporting of optic ischemic neuropathy (ROR: 4.619 [0.726-2.335]) and macular degeneration (ROR: 15.579 [0.554-4.938]) in T2DM patients and eye swelling (ROR: 6.475 [0.407-3.329]) in non-T2DM patients. Liraglutide showed increased reporting of cataract (ROR: 53.866 [2.945-5.028]), diabetic retinopathy (ROR: 18.162 [1.753-4.045]) and macular degeneration (ROR: 26.261 [1.076-5.460]) in T2DM patients and cataract (ROR: 9.628 [1.387-3.142]) and macular degeneration (ROR: 9.557 [0.110-4.405]) in non-T2DM patients.

• CONCLUSIONS: These results provide a signal of increased reporting of various eye disorders with GLP-1RA use compared to metformin across T2DM and non-T2DM patient cases. Further research is required to support these findings and confirm a biological causation. (Am J Ophthalmol 2026;283: 279–290.

INTRODUCTION

Glucagon-like peptide-1 receptor agonists (GLP-1RAs) are a class of incretin mimetics, drugs that stimulate insulin release, encompassing semaglutide, tirzepatide and liraglutide that lead to reduced gastric emptying, glucagon release and appetite.[1] Many of these molecules have been licensed for the treatment of Type 2 diabetes mellitus (T2DM) for over a decade, primarily for their efficacy in improving glycemic control. More recently, the therapeutic indications for certain agents in this class have been expanded to include weight management in people with or without T2DM.[2-5]

GLP-1RAs are analogues of the GLP-1 hormone which is responsible for inhibiting glucagon release, inhibiting insulin secretion and hepatic glucose production.[6] Agonizing the GLP-1 receptor stimulates its effects, each GLP-1RA acts upon it slightly differently due to their individual structure. The GLP-1 hormone has a very short half-life (1-2 minutes) after it has been synthesized from the breakdown of proglucagon[7]; therefore, the main aim of GLP-1RA structures is to increase this half-life to enable the exertion of physical effects. Liraglutide has 97% structural similarity to human GLP-1 with differences at position 34 of its molecular structure (lysine substituted for arginine) and

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a 16-carbon fatty-acid chain with a glutamic acid spacer attached to lysine at position 26.[8] These adaptations increase the half-life from 1 to 2 minutes to 13 hours, allowing daily dosing. Semaglutide, however, contains adaptations facilitating a weekly dosing regimen, namely modification at position 8 providing protection against enzymatic degradation and two amino acid substitutions and other modifications at lysine 26 with a hydrophilic spacer and C18 fatty di-acid, providing increased albumin affinity.[9] Its maximum bioavailability (89%) is reached 1-3 days postdose administration. Tirzepatide is a dual action GLP-1RA, acting additionally on the GIP receptor.[10] The action upon the GIP receptor aids in delaying gastric emptying, therefore suppressing appetite. It is the newest GLP-1RA to be brought to market, so safety and tolerability factors are still being monitored.

Common side effects of GLP-1RAs include headache, vomiting, diarrhea and fatigue.[5] With increasing use, additional ADRs have been reported, such as acute kidney injury[11] and nutritional deficiencies.[12] Recently, GLP-1RAs have been associated with increased reports of diabetic retinopathy[13] and nonarteritic anterior ischemic optic neuropathy (NAION),[14] warranting further investigation into potential associations between GLP-1 RAs and ocular disorders. Given that patients with T2DM already face an elevated risk of eye-related complications, this study compared the reporting of ocular ADRs associated with GLP-1 RAs in patients with and without T2DM. The expansion of indications to include weight management, a comparatively newer use, has contributed to a marked increase in prescribing rates.[15] Consequently, pharmacovigilance research is critical to enable the early detection and continuous monitoring of emerging ADRs.

This study aimed to evaluate the reporting of ocular ADRs associated with GLP-1 RAs in patients with and without T2DM.

METHODOLOGY

A retrospective disproportionality analysis design was adopted, using the FDA Adverse Event Reporting System. This is a publicly available, anonymized database which can be accessed at the web address listed in the data availability statement. Therefore, Institutional Review Board approval was not required. The Declaration of Helsinki was adhered to as well as all federal laws of the United Kingdom.

Of the GLP-1RAs, semaglutide, tirzepatide and liraglutide were selected for the purpose of this study due to their overlapping indications for both T2DM and weight loss, allowing for comparison between the traditional indication of hyperglycemic control in T2DM and indications which have recently been expanded to encompass weight management (Table 1).

The Food and Drug Administration Adverse Event Reporting System (FAERS)[36] was queried on 26th September 2025 for the drug and brand names of semaglutide (Wegovy, Ozempic), tirzepatide (Mounjaro), liraglutide (Saxenda, Victoza) and metformin (Glucophage) and orlistat as controls. These controls were chosen as they are the first line oral treatment option indicated for T2DM and weight loss respectively.[37,38] Data were collected between 1 January 2017 and 25 September 2025 for all drugs, except tirzepatide, for which data were collected between 1 January 2022 and 25 September 2025 due to its market availability. The FAERS database was selected as an appropriate source of reports due to its extensive collection of ADR reports (32,049,362 total as of 22nd October 2025) and suitable export functions. It was selected over European or World Health Organization equivalents as it reflected the relative rise in US based prescribing of GLP-1RAs,[39] hence the increased likelihood of ADR reporting. ADRs are organized in line with the Medical Dictionary for Regulatory Activities (MedDRA)[40] whereby "Eye Disorder" is the reaction group as per MedDRA preferred terms and is then subcategorized by reaction as per MedDRA preferred terms, enhancing consistency of language. Reactions categorized under the Eye Disorder reaction group were extracted and formed the search terms used in the analysis. Python 3.11 was adopted as an appropriate program for further analysis whereby each extracted dataset was analyzed, and the number of cases meeting all the following criteria was outputted by reaction.

For T2DM cases: categorized as "Serious"; drug of interest was the only suspect active ingredient; no concomitant products were specified; "Reason for Use" included any of: "Type 2 Diabetes Mellitus," "Diabetes Mellitus," "Diabetes Mellitus Management," "Diabetes Mellitus Inadequate Control."

For non-T2DM cases: categorized as "Serious"; drug of interest was the only suspect active ingredient; no concomitant products were specified; "Reason for Use" did *not* include any of: "Type 2 Diabetes Mellitus," "Diabetes Mellitus," "Diabetes Mellitus Management," "Diabetes Mellitus Inadequate Control."

The code written for this research was tested to ensure 100% accuracy and manual checks against the original dataset were conducted at random checkpoints. The outputted number of cases reporting each reaction for each drug were then entered into Microsoft Excel for statistical analysis. Reporting Odds Ratios (RORs) were calculated with a 95% Confidence Intervals (CI) as per Eq. (1) and Table 2.[41] ROR analysis as a form of statistical disproportionality analysis was deemed the most efficient analysis as it allows comparison between comparable groups by accounting for the number of cases absent from the group.

$$CI = LN(OR) \pm 1.96 \times \sqrt{\frac{1}{A} + \frac{1}{B} + \frac{1}{C} + \frac{1}{D}} \quad (1)$$

These calculations were carried out for each drug compared to both controls and both other drugs. For ex-

TABLE 1. Summary of GLP-1 receptor agonists detailing their target receptors, brand names, and licensed indications, illustrated by representative countries in which they were approved.

GLP-1RA by brand	Indication	Countries in which approved	References
Wegovy® (Semaglutide)	Weight management	United Kingdom	16
		European Union	17
		United States of America	18
		Canada	19
Ozempic® (Semaglutide)	Type 2 Diabetes Mellitus	United Kingdom	16
		European Union	20
		United States of America	21
		Canada	22
Ozempic® (Semaglutide)	Chronic Kidney Disease in Type 2 Diabetes	United States of America	23
Zepbound® (tirezepatide)	Weight management	United States of America	24
Mounjaro® (tirzepatide)	Weight management	United Kingdom	25
		European Union	26
		Canada	27
Mounjaro® (tirzepatide)	Type 2 Diabetes Mellitus	European Union	26
		United States of America	28
Saxenda® (liraglutide)	Weight management	United Kingdom	29
		European Union	30
		United States of America	31
		Canada	32
Victoza® (liraglutide)	Type 2 Diabetes Mellitus	United Kingdom	29
		European Union	33
		United States of America	34
		Canada	35

TABLE 2. Summary of alphabetical representations used in Eq. (1).

	Number of Reports With Event of Interest	Number of Reports Without Event of Interest
Drug of interest	a	b
Comparator drug	c	d

'a' Is the Number of Reports Associated with the Drug of Interest (e.g. semaglutide), 'b' Is the Number of Reports Not Mentioning the Event of Interest Associated with the Drug of Interest (e.g. All Reports Minus a), 'c' Is the Number of Reports Associated with the Event of Interest Relating to the Comparator Drug (e.g. metformin) and 'd' Is the Number of Reports for the Comparator Drug with No Mention of the Event of Interest (e.g. All Reports Minus c).

ample, semaglutide was compared to metformin, orlistat, tirzepatide and liraglutide. This allowed for comparison between each control as well as cross comparison between three commercially available GLP-1RAs. Although statistical significance can be determined when ROR values are > 1, it was decided to determine significance when ROR values are > 4 and exponentiated CI values > 1 to ensure a focus on the strongest possible signals.

RESULTS

The ROR analyses identified a wide range of reported ocular adverse events, as shown in Tables 3-5. It is important to recognize that these events vary substantially in their clinical severity. Some reported outcomes are potentially vision-threatening or irreversible, for example, blindness, vitreous hemorrhage and optic ischemic neuropathy; whereas others, such as cataract, photophobia and vision blurred, are generally less severe and not immediately vision threatening.

It is also important to separate ocular ADRs into two broad pragmatic groups. First, some events for which there is at least a plausible pharmacological or pathophysiological link, a mechanistic hypothesis, or an emerging regulatory or epidemiological signal linked with GLP-1RAs. These include nonarteritic anterior ischemic optic neuropathy (NAION), which has recently been identified by EMA's PRAC (European Medicines Agency's Safety Committee) as a very rare possible adverse effect of semaglutide and supported by several observational cohort studies reporting increased rates of optic nerve and visual-pathway disorders with semaglutide or tirzepatide. [42-43] Proposed mechanisms

TABLE 3. ROR Analysis (> 4.000) for Semaglutide Against Remaining GLP-1 RAs and Control Molecule.

Drug	Comparison drug	Reaction	T2DM cases			Non-T2DM cases		
			ROR unmasked	Upper 95% CI	Lower 95% CI	ROR unmasked	Upper 95% CI	Lower 95% CI
Semaglutide	Metformin	Visual Impairment	7.932	13.239	4.752	2.355	3.549	1.563
Semaglutide	Metformin	Vision Blurred	4.227	7.151	2.498	1.943	3.080	1.226
Semaglutide	Metformin	Optic Ischemic Neuropathy	12.269	22.830	6.593	N/A	N/A	N/A
Semaglutide	Metformin	Blindness	1.672	2.543	1.099	6.678	12.342	3.613
Semaglutide	Metformin	Cataract	31.879	86.609	11.734	5.829	13.440	2.528
Semaglutide	Metformin	Diabetic Retinopathy	15.955	44.140	5.767	1.665	3.680	0.753
Semaglutide	Metformin	Blindness Unilateral	24.425	182.051	3.277	N/A	N/A	N/A
Semaglutide	Metformin	Retinopathy	5.185	15.419	1.744	9.424	30.137	2.947
Semaglutide	Metformin	Glaucoma	4.063	14.769	1.118	N/A	N/A	N/A
Semaglutide	Metformin	Retinal Hemorrhage	12.192	95.270	1.560	10.253	76.415	1.376
Semaglutide	Metformin	Macular Degeneration	23.199	173.355	3.105	5.634	43.654	0.727
Semaglutide	Metformin	Papilloedema	10.971	86.621	1.389	1.170	2.846	0.481
Semaglutide	Metformin	Photophobia	4.872	43.601	0.544	N/A	N/A	N/A
Semaglutide	Metformin	Vitreous Hemorrhage	6.095	27.829	1.335	N/A	N/A	N/A
Semaglutide	Tirzepatide	Visual Impairment	2.879	5.238	1.583	1.636	2.243	1.194
Semaglutide	Tirzepatide	Vision Blurred	4.895	13.472	1.778	0.925	1.274	0.672
Semaglutide	Tirzepatide	Optic Ischemic Neuropathy	2.656	4.732	1.491	4.294	6.512	2.832
Semaglutide	Tirzepatide	Blindness	2.045	4.312	0.970	1.473	1.966	1.103
Semaglutide	Tirzepatide	Cataract	3.630	7.188	1.833	6.960	15.160	3.195
Semaglutide	Tirzepatide	Diabetic Retinopathy	1.634	3.222	0.829	3.713	9.673	1.425
Semaglutide	Tirzepatide	Retinopathy	2.667	11.554	0.616	9.843	27.173	3.566
Semaglutide	Tirzepatide	Eye Hemorrhage	5.336	40.127	0.710	3.571	8.583	1.486
Semaglutide	Liraglutide	Optic Ischemic Neuropathy	N/A	N/A	N/A	8.414	20.519	3.450
Semaglutide	Liraglutide	Retinopathy	1.055	3.604	0.309	7.405	30.377	1.805

include impaired optic nerve head perfusion, particularly in individuals with vascular comorbidities (for which systemic hypotension, particularly nocturnal hypotension, is a known risk factor), anatomically "crowded" optic disc[44-45] and drug-related modulation of endothelial function and inflammation, for which GLP-1 receptor activity in retinal vasculature provides biological plausibility.[42-43] As GLP-1 receptors are expressed in retinal endothelial and neuronal tissues, GLP-1RAs may modulate endothelial function, oxidative stress, and inflammatory activity.[46] Nevertheless, cataract, photophobia, and non-specific blurred vision are common ocular symptoms with many potential causes and, at present, lack a clear, drug-specific plausible pharmacological or pathophysiological link with GLP-1RA exposure. Where such terms appear in FAERS, they should be interpreted cautiously. In diabetics, rapidly improving hyperglycemia can temporarily worsen retinopathy / retinal oedema. This is related to changes in retinal blood vessel permeability and perhaps imbalance in growth factor (VEGF) expression.[47] It is important to note that in diabetic retinopathy or retinal oedema, some preclinical and clinical data show that GLP-1RAs, namely semaglutide, may have complex effects on retinal vasculature (including possible protective effects that enhance the functions of the retina), but rapid improvement in glycemic control can transiently worsen retinopathy in people with diabetes; thus signals involving retinopathy require careful interpretation with respect to underlying diabetes control and timing.[48]

The ROR analyses for reported semaglutide ADRs against remaining GLP-1RAs (namely liraglutide and tirzepatide) and control (namely metformin) are presented in Table 3.

The ROR analysis for semaglutide identified several strong signals, indicating an increased reporting of eye disorder ADRs compared with metformin. Optic ischemic neuropathy emerged consistently across several comparisons and in both patient groups, suggesting a higher reporting rate relative to metformin, tirzepatide and liraglutide. Cataract was also highlighted in both groups when semaglutide was compared with metformin and tirzepatide. Interestingly, retinopathy was reported more frequently in the non-T2DM group than in the T2DM group across all three comparator analyses.

The ROR analyses for reported tirzepatide ADRs against remaining GLP-1 RAs (namely liraglutide and semaglutide) and control (namely metformin) are presented in Table 4.

This analysis identified several positive signals within the T2DM group, including unilateral blindness, retinal hemorrhage and macular degeneration when compared to metformin. In the non-T2DM group, signals were observed for eye swelling and vision blurred when compared with other

TABLE 4. ROR Analysis (> 4.000) for Tirzepatide Against Remaining GLP-1 RAs and Control Molecule.

Drug	Comparison drug	Reaction	T2DM cases			Non-T2DM cases		
			ROR unmasked	Upper 95% CI	Lower 95% CI	ROR unmasked	Upper 95% CI	Lower 95% CI
Tirzepatide	Metformin	Optic Ischemic Neuropathy	4.619	10.326	2.066	N/A	N/A	N/A
Tirzepatide	Metformin	Blindness	0.818	1.755	0.381	4.534	8.575	2.398
Tirzepatide	Metformin	Cataract	8.783	28.552	2.702	0.838	2.494	0.281
Tirzepatide	Metformin	Diabetic Retinopathy	9.764	31.168	3.059	0.448	1.372	0.147
Tirzepatide	Metformin	Blindness Unilateral	11.678	112.334	1.214	N/A	N/A	N/A
Tirzepatide	Metformin	Eye Swelling	0.388	3.036	0.050	6.475	27.915	1.502
Tirzepatide	Metformin	Retinal Hemorrhage	11.678	112.334	1.214	2.873	25.713	0.321
Tirzepatide	Metformin	Macular Degeneration	15.579	139.469	1.740	6.469	51.073	0.819
Tirzepatide	Semaglutide	Eye Swelling	0.290	2.247	0.037	5.060	13.634	1.878

TABLE 5. ROR Analysis (> 4.000) for Liraglutide Against Remaining GLP-1 RAs and Control Molecule.

Drug	Comparison drug	Reaction	T2DM cases			Non-T2DM cases		
			ROR unmasked	Upper 95% CI	Lower 95% CI	ROR unmasked	Upper 95% CI	Lower 95% CI
Liraglutide	Metformin	Visual Impairment	5.444	11.076	2.676	1.641	2.836	0.950
Liraglutide	Metformin	Cataract	53.866	152.615	19.012	9.628	23.157	4.003
Liraglutide	Metformin	Diabetic Retinopathy	18.162	57.139	5.773	0.715	2.699	0.190
Liraglutide	Metformin	Blindness Unilateral	13.107	144.670	1.187	N/A	N/A	N/A
Liraglutide	Metformin	Retinopathy	4.917	22.001	1.099	1.273	7.620	0.213
Liraglutide	Metformin	Glaucoma	10.949	45.880	2.613	N/A	N/A	N/A
Liraglutide	Metformin	Retinal Hemorrhage	19.678	189.349	2.045	1.909	30.531	0.119
Liraglutide	Metformin	Macular Degeneration	26.261	235.178	2.932	9.557	81.843	1.116
Liraglutide	Tirzepatide	Cataract	6.133	12.897	2.916	11.495	26.197	5.044

GLP-1RAs. However, fewer signals were detected in the non-T2DM group relative to metformin, which is likely attributable to the limited availability of data available in this group, given metformin's role as a first-line treatment primarily for T2DM.

The ROR analyses for reported liraglutide's ADRs against remaining GLP-1 RAs (namely tirzepatide and semaglutide) and control (namely metformin) are presented in Table 5.

Liraglutide showed a significant ROR increase when the T2DM group was compared to the metformin T2DM group. Cataract ROR was 53.866 for the T2DM group and 9.628 for the non-T2DM group, indicating a higher reporting incidence with liraglutide compared to metformin. This trend was consistent in comparisons of liraglutide and Semaglutide and tirzepatide (T2DM group RORs of 1.690 and 6.133) and (non-T2DM group RORs of 1.652 and 11.495 respectively).

Orlistat failed to elicit any relevant results within the inclusion criteria as laid out in the methodology and, therefore, has been omitted from the results. This example further illustrates that adverse event reporting in FAERS may not be driven solely by a drug's pharmacological profile but can also be influenced by factors such as overall utilization and societal visibility.

DISCUSSION

As far as is currently known, this is the first study, where the reporting of ocular ADRs associated with GLP-1RAs in patients with and without T2DM was evaluated from a pharmacovigilance perspective.

Liraglutide was the first GLP-1RA approved for T2DM, marketed as Victoza in 2009 in the European Union and in 2010 by the FDA. Saxenda, the same molecule at a higher dose for weight management, received FDA approval in 2014 and EMA approval in 2015 for individuals meeting specific criteria. Liraglutide reports to the FAERS database increased between 2010 and 2012 but stabilized from 2013 onwards. These trends potentially reflect the introduction of alternative therapies and suggest that the FAERS signal may be influenced not only by prescription volume but also by external, nonpharmacological factors such as public attention, the timing of a drug's market introduction, or the emergence of competing agents. It is important to note that newly approved drugs often experience a period of heightened reporting driven by clinicians' initial anxiety or curiosity, which can temporarily inflate adverse event reporting. Semaglutide was initially approved for T2DM by the FDA in 2017 and subsequently in other regions; it has

since demonstrated efficacy for weight management and, more recently, for metabolic-associated steatohepatitis.[49] FAERS reports associated with semaglutide have increased annually from 2017 (1 case reported) to 2025 (3100 cases reported until 26th September). Tirzepatide, a dual GLP-1RA/Glucose-dependent insulinotropic polypeptide (GIP) receptor agonist, was approved for T2DM in 2022 and for weight management in 2023,[50] with its dual mechanism allowing effective glucose control with a reduced risk of hypoglycaemia.[51] Despite its shorter time on the market, it has generated more FAERS reports (99,208 total cases) than Semaglutide (59,633 total cases) and liraglutide (14,820 total cases) between 1st January 2017 and 26th September 2025, which may reflect either increased reporting trends due to heightened awareness of ADRs or emerging adverse events, although comparative research is limited.

Equally, US prescribing of tirzepatide has increased sharply to 12,203,009 prescriptions since its introduction in 2018 to September 2025.[52] Recent data also indicate it has now bypassed semaglutide as the most frequently prescribed antidiabetic medication in the US.[52] This popularity potentially contributes to the higher number of reported ADRs for tirzepatide in recent years. Publicly accessible, up-to-date prescribing data for all GLP-1RAs at the global level are limited. However, available US data show increasing prescribing volumes across the GLP-1RA class, which is consistent with the upward trend in ADR reporting observed in the present study. Research showed that there was a significant increase in public awareness of GLP-1RAs over the past 7 years, which was also coupled with a parallel rise in Google search volumes.[53] Further research integrating comprehensive prescribing and utilization data would be essential to fully quantify reporting bias across all regions. Furthermore, as the therapeutic indications for selected GLP-1 RAs have expanded beyond T2DM to include obesity, and specifically for semaglutide in the US for the treatment of metabolic-associated steatohepatitis (MASH), progressively higher-risk patient populations are being incorporated into the user cohort.[49] As a result, the observed increase in ADR reporting may arise, at least in part, from the underlying severity of these patients' baseline conditions rather than from the pharmacological effects of the drug itself. Temporal confounding should also be considered when interpreting these findings. Newer agents such as tirzepatide have been introduced during a period of rapidly expanding clinical indications and at a time when baseline cardiometabolic risk factors in the US population, such as obesity, hypertension, diabetes, and cardiovascular disease, have been steadily increasing. Consequently, more recently approved drugs may appear to have higher ADR reporting rates not only because of true drug-specific safety effects but also because they are being used in populations with progressively greater underlying health severity. Acknowledging this temporal context helps clarify that elevated ADR signals over time may partly reflect broader shifts in population risk rather than intrinsic differences in drug safety.

The ROR analyses for GLP-1RAs revealed several signals of eye-related ADRs. In the T2DM group, semaglutide and liraglutide were associated with increased reporting of optic ischemic neuropathy, unilateral blindness, retinal hemorrhage, macular degeneration, and cataract compared with metformin, with liraglutide showing particularly high cataract RORs (53.866 in T2DM vs 9.628 in non-T2DM). In the non-T2DM group, eye swelling, blurred vision, and retinopathy were more frequently reported, with retinopathy occurring more often than in the T2DM group. Comparisons with other GLP-1RAs, including tirzepatide and semaglutide, showed consistent positive trends, although fewer signals were detected in the non-T2DM group relative to metformin, likely reflecting limited data reporting and availability. Overall, these findings suggest an elevated reporting of ocular ADRs with GLP-1RAs, particularly in patients with T2DM, which highlight the need for ongoing pharmacovigilance and further investigation. Although researchers have noted the higher number of reports for tirzepatide, the data here suggest that it is less frequently associated with eye disorders than semaglutide, with fewer relevant reports and fewer statistically significant findings.

Following statistical disproportionality analysis, several conclusions can be drawn. Notably, semaglutide was associated with a higher incidence of eye disorders compared with the other GLP-1RAs examined in this study. One ADR of particular interest identified with semaglutide was retinopathy, although this finding remains contradictory. Indeed, some studies suggest semaglutide possesses a neuroprotective effect, while others report no significant impact. For example, one study[54] found no significant difference in the development of diabetic retinopathy between patients using GLP-1RA and those on Sodium Glucose Transport-2 inhibitors such as empagliflozin. Conversely, another study[13] reported a modest neuroprotective effect in their retrospective cohort study; although the incidence of diabetic retinopathy was slightly higher, the severity of the condition was reduced compared to the control group. Findings from the present study differ from both, indicating that, when examining a larger global pharmacological database, eye disorders such as retinopathy are being actively reported by healthcare professionals and patients. Diabetic retinopathy may worsen in the context of rapid glycemic changes, including hypoglycemia, which can occur with some GLP-1RAs. Tirzepatide appears to have a lower association with this effect compared with semaglutide or liraglutide. This is consistent with the higher signal for diabetic retinopathy reports observed with semaglutide and liraglutide vs tirzepatide (Tables 3 and 4), supporting the hypothesis that glycemic fluctuations may contribute to the reported worsening of retinopathy.

Overall, eye disorders were generally more frequently reported in the T2DM group; however, several outliers were observed. Notable examples include: "semaglutide and metformin" for blindness; "semaglutide and tirzepatide" for optic ischemic neuropathy, cataract and retinopathy;

"semaglutide and liraglutide" for optic ischemic neuropathy and retinopathy; "tirzepatide and metformin" for blindness and eye swelling; "tirzepatide and semaglutide" for eye swelling and "liraglutide and tirzepatide" for cataract. Overall, the data suggest that cataract reports occur more frequently with GLP-1RAs compared with control treatments and are more commonly reported in patients with indications other than T2DM. A recent cohort study[55] found no persistent impact on the risk of cataract formation in their retrospective study; however, 84.4% of their cohort had diabetes, limiting the applicability of their findings to non-T2DM populations. Given the limited research on cataracts as an ADR associated with GLP-1RAs, it remains difficult to propose a potential biological mechanism or establish causation.

Macular degeneration was identified as an ADR associated with increased reporting for all three GLP-1RAs investigated here when compared to metformin. In the T2DM group, ROR values were 23.199 (3.105-173.355) for semaglutide, 15.579 (1.740-139.469) for tirzepatide and 26.261 (2.932-235.178) for liraglutide. In the non-T2DM group, only liraglutide showed an elevated ROR of 9.557 (1.116-81.843). Although ROR values were high for semaglutide and tirzepatide, CIs were not statistically significant in the non-T2DM comparisons due to limited data for metformin. Despite these limitations, the T2DM results suggest a potential association between GLP-1RA use and macular degeneration. While diabetes is a known risk factor for macular conditions such as diabetic macular oedema, these are not categorized under the "Macular Degeneration" preferred term according to MedDRA, indicating that the cases reported here are unlikely to be directly related to a T2DM diagnosis.

Recent research investigating emerging ADRs associated with GLP-1RAs is largely supported by the findings reported here. Optic ischemic neuropathy, which encompasses conditions such as nonarteritic anterior ischemic optic neuropathy (NAION),[56] was detected in this analysis, potentially complementing the results of other retrospective studies[14] despite using different reporting databases. Significant signals of NAION were observed for semaglutide compared with metformin (T2DM ROR: 12.269, CI: 6.593-22.830), tirzepatide (Non-T2DM ROR: 4.294, CI: 2.832-6.512), liraglutide (Non-T2DM ROR: 8.414, CI: 3.450-20.519) and tirzepatide compared to metformin (T2DM ROR:4.619, CI: 2.066-10.326). The inconsistency between T2DM and non-T2DM groups in relation to NAION reflects the limited availability of data for metformin in the non-T2DM population. Nevertheless, cross-comparisons between GLP-1RAs, identified significant signals, reinforcing the conclusions of the aforementioned retrospective study[14] and aligning with recent recommendations.[42] Our findings additionally aligned previous work[43] which identified semaglutide and tirzepatide to be more likely associated with NAION in a retrospective cohort study of T2DM populations than other GLP-1RAs. However, our findings build on this, highlighting an increased reporting of NAION in the non-T2DM group with semaglutide compared to tirzepatide (ROR: 4.294 [2.832-6.512]) with respect to what was observed in the T2DM group (ROR: 2.656 [1.491-4.732]).

Similar signals were identified in the comparison between semaglutide and liraglutide in the non-T2DM group (ROR: 8.414 [3.450-20.519]). These data suggest the non-T2DM group may be more likely to report NAION than the T2DM group, warranting further investigation. Risk factors for NAION, including hypertension, hyperlipidemia and coronary heart disease,[57] are often associated with obesity in addition to T2DM; therefore, non-T2DM groups may be somewhat susceptible to the condition; again, warranting further research. A recent report[58] suggests two hypotheses of why GLP-1RAs may trigger NAION. The first involves the rapid drop in blood glucose following GLP-1RA administration due to the cluster of NAION events in the first year of Semaglutide use. However, other glucose lowering therapies, bariatric surgery, and insulin, have not shown a risk of NAION; together with the extension of NAION risk in non-T2DM groups, this weakens this hypothesis. The second hypothesis suggests changes in hemodynamic parameters leading to hypoperfusion of the optic nerve head, a mechanism already reported for the increased risk of NAION with phosphodiesterase type 5 inhibitors. Further clinical research is required to confirm these hypotheses and ensure their relevance to GLP-1RAs.

Similarly, a recent study[59] published supported the present findings in a pharmacovigilance statistical analysis of FAERS and the World Health Organization's Vigibase. This indicates that signals identified here relating to optic nerve and retinal ocular events persist, despite different methodologies; statistical analyses; and different reporting databases. However, this study investigates the difference in reports between T2DM and non-T2DM groups, allowing comparison to aid in the development of biological causation across any statistically relevant eye disorders, whereas the other focused on general reports and specific ADRs.

When considering the identified signals, it is important to note an element of selection bias does exist. The indications for the prescribing of GLP-1RAs, T2DM and weight management consequently result in individuals with an inherently higher risk of ADRs taking these medications. Adjustment for this confounding variable would be appropriate to investigate the impact of this on the study outcomes, however the FAERS database does not include required information to allow this. Future studies should aim to identify and adjust for this variable, improving the reliability of the methodology. Additionally, considering the expansion of indications for GLP-1RA prescribing to increased disease severity cohorts, ADR reporting may increase

The focus on both T2DM and non-T2DM groups and the reporting of eye disorders allows researchers and clinicians to exercise caution specific to the group of interest.

It can additionally provide further depth regarding the biological causation of these ADR reports. A retrospective case series[60] suggested that the rapid correction of hyperglycemia may be associated with the occurrence of eye disorders. However, pharmacovigilance analysis[59] suggests an alternative causation related to weight loss, vascular alterations or hemodynamic changes, although further research is needed to confirm these findings. In considering the discrepancies between different GLP-1RA ROR findings using the same controls, one could argue that the associations between GLP-1RAs and eye disorders are unlikely to be solely driven by glycaemic effects, as previously suggested. [59] This is somewhat supported by the findings of a network meta-analysis[61] which identified tirzepatide to have the greatest glucose-lowering effect across 15 GLP-1RAs, including semaglutide and liraglutide, in T2DM patients. If the biological causation was solely linked to glycemic effects, it is likely one would identify increased reporting of related eye disorders with tirzepatide in the T2DM group, which was not the case here.

CONCLUSIONS

GLP-1RAs are valuable medications that support a broad population globally in both weight management and hyperglycemic control, helping to mitigate the long-term effects of obesity and T2DM. Their use aligns well with National Health Service (NHS) strategies[62] on weight management and reducing long-term associated health risks and well as the Welsh initiative, Delivering a Healthier Wales.[63] Despite the clear benefits of GLP-1RAs within these initiatives, proactive pharmacovigilance is essential to ensure safe use across all populations. Encouraging patients and healthcare professionals to report all ADRs is crucial for identifying emerging trends and signals,[59] such as those observed in this study. Although biological plausibility remains to be established, the present findings highlight strong signals between three GLP-1RAs and eye disorders, as classified by MedDRA preferred terms, using data from the FAERS database. The results support previous reports of NAION as an ADR associated with GLP-1RA use in patients with T2DM, while also indicating the occurrence of other eye disorders including cataract and macular detachment in all patients using the medications irrespective of T2DM status, suggesting a potential association with GLP-1RAs therapy itself. While these findings indicate strong signals, they do not establish causation and highlight the need for further urgent research to confirm or refute these associations.

Ocular adverse events with GLP-1RAs can be grouped by plausibility of mechanistic link. NAION, recently identified as a very rare possible effect of semaglutide, may arise from impaired optic-nerve perfusion, vascular comorbidities, crowded optic discs, or GLP-1RA effects on endothelial, oxidative, and inflammatory pathways. Common symptoms such as cataract, photophobia, and blurred vision lack clear mechanistic links with GLP-1RAs and should be interpreted cautiously. Retinopathy signals are complex as GLP-1RAs may have protective effects, but rapid glycemic improvements can transiently worsen retinal outcomes, so underlying diabetes status and timing are important. Further research is needed to clarify biological plausibility of these events and inform clinical guidance.

It is recommended that caution be exercised when prescribing or supplying GLP-1RAs discussed here for patients with pre-existing eye disorders, with multidisciplinary care needed to ensure appropriate monitoring until further research is available. Given the substantial ethnic and biological heterogeneity in insulin metabolism, pancreatic reserve, and the propensity for developing T2DM, a simple dichotomization into "T2DM" and "non-T2DM" groups may be problematic. For example, a White American with a large pancreatic reserve may remain non-diabetic despite having a BMI > 40, whereas a lean Asian American with limited β-cell capacity may develop T2DM at a much lower BMI. In such situations, the non-T2DM individual may still carry a higher vascular risk profile and, consequently, a higher susceptibility to NAION than the diabetic patient. For this reason, the interpretation of NAION RORs based solely on diabetes status warrants caution.

Pharmacists are well positioned to educate patients on the potential risks associated with new medications and the importance of reporting ADRs, while ophthalmologists are ideally placed to support the ongoing monitoring and early identification of ocular adverse events in their patients.

STRENGTHS AND LIMITATIONS

So far as is currently known, this is the first paper analyzing the FAERS database investigating GLP1-RAs-related eye disorders whilst separating T2DM and non-T2DM groups. The FAERS database allowed extraction and analysis of thousands of cases, allowing for statistically significant conclusions to be drawn. The use of code to conduct the extraction of eye disorder cases allowed for reliable consideration of all eye disorders listed by FAERS, with each being disregarded once deemed statistically irrelevant (if ROR $<$ 4.000). This allowed for opportunistic signals to be discovered, which was not considered within similar work.[59]

Whilst confident in the signals identified, the limitations of this study are recognized. First, terms such as "blindness" mentioned here may draw concern from readers due to the seriousness of the condition. These terms have been reported in the study as they occur within the FAERS database; however, it is important to note the conditions that are a sub-class of these terms and, therefore, should be considered. For example, "blindness" classifies the following "preferred terms" within its MedDRA definition: "blind,"

"bilateral blindness," "blindness, both eyes," "blindness, one eye, low vision other eye," "loss of vision," "no light perception," "cecity," "unqualified visual loss, both eyes," blind hypotensive eye, "profound vision impairment, both eyes," "blind hypertensive eye," "vision loss," "legal blindness, as defined in USA," "blindness impairment level not further specified," "blind both eyes," "blindness NOS" and "unspecified visual loss." Therefore, throughout this paper, the researchers acknowledge the variance in severity of potential conditions mentioned. Second, the FAERS database collects reports of adverse events rather than representing a defined population and therefore does not allow estimation of the true prevalence of adverse effects associated with GLP-1 receptor agonists. It is not a reliable data source to provide causation links, underlining the need for further follow up research to confidently support these signals. Despite this, best efforts were made to eliminate other potential causes of the reaction reported through the elimination of cases with other suspect active ingredients and concomitant products. Additionally, in the non-T2DM group, cases with "Not Specified" or similar as the reason for use were included, although the patient in the case may have a diagnosis of T2DM. The implementation of a cohort study whereby medical history is assessed would reduce this unavoidable bias.

Furthermore, the age distribution of patients receiving GLP-1RAs is an important factor to consider. Younger individuals with severe obesity, who are increasingly being treated with agents such as semaglutide and tirzepatide, are less likely to have a posterior vitreous detachment (PVD) than older adults with long-standing diabetes. If proliferative diabetic retinopathy develops in these younger patients, the absence of a PVD may predispose them to more severe complications, including vitreous hemorrhage and tractional retinal detachment, both of which carry a higher risk of vision loss. Because reliable age information is not available in FAERS, this source of clinical heterogeneity cannot be accounted for, and this limitation may influence interpretation of the observed severe ocular ADRs. Future studies should incorporate accurate age at the time of reporting and age at diagnosis of type 2 diabetes or obesity to better evaluate the impact of prolonged hyperglycemia and other biomarkers on adverse ocular outcomes, well-established risk factors for diabetic retinopathy. A further limitation is that FAERS reports often lack detailed clinical information, including diabetes subtype and comorbid conditions. As a result, the specific type or cause of retinopathy in the non-T2DM group, for example, cannot be determined, and interpretation of these signals should be approached with caution.

Most significant results were identified in comparison to metformin, as orlistat elicited limited relevant data. This resulted in fewer relevant comparisons within the non-T2DM group and only in comparison to metformin. This was unavoidable due to the lack of suitable alternative comparisons for weight management. Future studies should aim to mitigate this with a potential less suitable alternative to attempt to gather further reliable signals within this group.

Finally, it is recognized that, despite a wide range of expertise and experience, none of the authors who have contributed to this research have a specific ophthalmology background. Despite best efforts to consider only recent and relevant research, and draw sound and reasonable conclusions, an individual with ophthalmology specialty could add greater insight to this research. Therefore, it is the aim of the authors to inspire follow-up studies to better understand the signals presented here.

CREDIT AUTHORSHIP CONTRIBUTION STATEMENT

Mya Murray: Writing – original draft, Methodology, Formal analysis, Data curation. **Fabrizio Schifano:** Writing – review & editing, Methodology, Conceptualization. **Stefania Chiappini:** Writing – review & editing, Methodology. **John Martin Corkery:** Writing – review & editing. **Amira Guirguis:** Writing – review & editing, Writing – original draft, Methodology, Formal analysis, Data curation, Conceptualization.

Data availability statement: The FDA Adverse Event Reporting System data are publicly available and can be found here: https://www.fda.gov/drugs/questions-and-answers-fdas-adverse-eventreporting-system-faers/fda-adverse-event-reporting-system-faers-public-dashboard (accessed on 25 September 2025). All data files can be submitted upon request.
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