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Secondary Ocular Complications Associated with GLP-1 Receptor Agonist Use for Weight Loss: A Large Retrospective Cohort Study

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Abstract

Purpose

Glucagon-like peptide-1 receptor agonists (GLP-1RAs) are widely prescribed medications for weight loss and type 2 diabetes management. Emerging case reports and pharmacovigilance data have raised concerns regarding potential ocular adverse effects. This study aimed to evaluate the incidence of secondary ocular complications in patients after initiating GLP-1RA therapy compared with matched

Methods

A retrospective cohort study was conducted using electronic health records from a large single-center community hospital system (2017–2025). We identified 216,450 adult medical records for which GLP-1RAs might reasonably be prescribed, and performed random analysis sampling amongst cohorts separated by whether or not they had been prescribed the medication. Ocular complications were identified using ICD-10 codes (H16, H25, H26, H33, H35, H40, H53, and related diagnoses). Power analysis determined the required sample size of 550 patients per cohort, and control group composition. Bivariate analyses examined demographic variables. Multivariable negative binomial regression evaluated the association between GLP-1RA exposure and ocular pathology.

Results

The most prevalent diagnoses in the study were cataracts, glaucoma, and blurry vision, representing 80% and 82% of identified pathology in the control and treatment groups respectively. In analysis, GLP-1RA use was associated with a statistically significant increase in overall ophthalmic pathology. After adjustment for age and gender, and using a log offset for time in the model, patients prescribed GLP-1RAs had approximately twice the odds of developing ocular pathology compared with unexposed patients (OR 2.03, 95% CI 1.1–4.3, $P = 0.02$). Despite this finding, there was no statistically significant difference in the distribution of specific ocular pathologies between groups.

Conclusions

In this large retrospective cohort, GLP-1RA use was associated with a two-fold higher odds of recorded ocular pathology (OR 2.03, 95% CI 1.1–4.3). Although diagnoses of glaucoma, cataract, and blurred vision were more frequent, specific conditions did not differ significantly between groups. These findings suggest a potential ocular safety signal that warrants further investigation through prospective studies to better define any clinical relevance of GLP-1RA therapy on ophthalmic health.

1. Background

Glucagon-like peptide-1 (GLP-1) agonists, such as semaglutide, liraglutide, and exenatide, have gained widespread utilization in the management of obesity, diabetes, cardiovascular disease, and weight loss. The mechanism of action of these agents allows them to function by mimicking the effects of the naturally occurring GLP-1 hormone, which helps regulate appetite, satiety, glucose metabolism, and insulin secretion. GLP-1 agonists have demonstrated significant efficacy in promoting weight loss in individuals with obesity, in turn assisting with the management of diseases significantly affected by metabolic syndrome including diabetes and cardiovascular disease. While GLP-1 agonists are generally considered safe and well-tolerated, there have been isolated reports of secondary ocular complications, including varying retinopathy, progression of diagnosed diabetic retinopathy, uveitis, idiopathic blurred vision; though the frequency and mechanisms of these complications are not well understood.

1.1 Epidemiology & Clinical Importance of GLP-1 Receptor Agonists

The prevalence of obesity and diabetes has risen sharply in the United States over the past two decades, emphasizing a growing metabolic health crisis. Recent CDC data indicates that 40.3% of U.S. adults were classified as obese between 2021 and 2023, with 9.4% meeting criteria for severe obesity. Therefore, there has been a substantial increase from 30.5% and 4.7%, respectively, between 1999 and 2000.[1] Globally, the International Diabetes Federation estimates that one in nine adults currently has diabetes, and this is projected to rise to one in eight by 2050. This 46% increase is attributed to an aging population, declining physical activity, increasing obesity prevalence, and ongoing urbanization.[2]

In response to this escalating metabolic burden, glucagon-like peptide receptor agonists (GLP-1RA), initially developed for glycemic control in type 2 diabetes, have seen rapid adoption following expanded indications for chronic weight management. Semaglutide (Wegovy) became the first FDA-approved weight-loss agent since liraglutide in 2014, and newer agents such as tirzepatide have further accelerated utilization trends.[3] Prescription rates have increased from roughly 1–3% in 2010 to as high as 34% among patients with both type 2 diabetes and obesity by 2024. Even among individuals with obesity alone, historically the lowest-utilizing cohort, GLP-1RA prescriptions rose nearly 200-fold, from 0.04% to 7.1%, demonstrating expanding use among patients without diabetes.[4] Reflecting this rapid growth, the GLP-1 market is projected to exceed 100 billion dollars by 2030, with an estimated 30 million U.S. users, representing nearly 9% of the population.[5]

1.2 History of GLP-1 agonist Medications

Glucagon-like peptide-1 receptor agonist (GLP-1RA) medications were first introduced and approved by the FDA for clinical use in 2005, with exenatide as the initial agent for type 2 diabetes.[6] Their overall mechanism of action centers around their ability to mimic endogenous GLP-1, thus stimulating GLP-1 receptors to enhance glucose-dependent insulin secretion, suppress glucagon release, slow gastric emptying, and promote satiety.[7] In the context of association with ocular effects, their mechanism extends beyond glycemic control to include direct effects on ocular tissue. GLP-1 receptors are

expressed in the retina and other ocular structures, where GLP-1RAs exert several actions. These include neuroprotection of retinal ganglion cells, anti-inflammatory effects via cytokine modulation, antioxidant activity, and stabilization of blood-retinal barrier.[8] Mechanistically, GLP-RAs achieve these via inhibiting microglial activation, reducing pro-inflammatory cytokines such as IL-6, IL-1β, and TNF-α, and upregulating tight junction proteins.[8] Thereby reducing vascular leakage and neuroinflammation in the retina.[9] They can also promote mitochondrial protection and inhibit pathways involved in retinal cell apoptosis and oxidative stress.[10]

1.3 Mechanism of Action & Systemic Effects of GLP-1 Receptor Agonists

GLP-1 receptor agonists act by mimicking endogenous GLP-1 through activating GLP-1 receptors to enhance glucose-dependent insulin secretion, suppress glucagon release from pancreatic α-cells, delay gastric emptying, and promote satiety.[11] These agents have also been shown to support pancreatic β-cell survival by promoting β-cell proliferation and reducing apoptosis, thereby improving long-term insulin secretory capacity.[12] In clinical trials, GLP-1 receptor agonists reduce all-cause mortality and lower hemoglobin A1c by approximately 1% relative to standard therapy in patients with type 2 diabetes.[13] Beyond glycemic control, GLP-1RAs confer systemic benefits, including overall body weight reduction and cardiovascular risk reduction. These systemic advantages have greatly contributed to their widespread adoption.

An important physiologic consideration of GLP-1RAs is the rapid improvement in glycemic status that often occurs shortly after treatment initiation. Sudden reductions in blood glucose and hemoglobin A1c have historically been associated with transient destabilization of microvascular beds, including the retinal circulation. In one example, seven of eighteen patients showed progression of diabetic retinopathy, and four with moderate-to-severe disease developed rapid deterioration within three to six months of initiating continuous subcutaneous insulin infusion.[14] This “early worsening” phenomenon has been documented across several time frames, ranging from three months to three years. Similar patterns have been observed in some GLP-1RA trials. One cohort study showed that tirzepatide users had higher odds of developing new-onset proliferative diabetic retinopathy (1.1% vs 0.5%; OR 2.15) despite otherwise well-controlled baseline glycemia, particularly among individuals with mild to moderate retinopathy at treatment initiation.[15] Similar concerns emerged in the SUSTAIN-6 cardiovascular outcomes trial, where semaglutide-treated patients experienced a higher rate of diabetic retinopathy complications compared with placebo. Notably, these events occurred predominantly in individuals with long-standing diabetes, higher baseline HbA1c, and pre-existing moderate-to-severe retinopathy. They were also accompanied by very rapid reductions in hemoglobin A1c of 1.9–2.5% with semaglutide versus 0.9–1.3% with placebo (standard of care diabetes medications) over just 16 weeks.[16] These findings support the hypothesis that rapid glycemic improvement, rather than a direct ophthalmic toxicity, may be causing the observed worsening. Given these systemic effects and their

impact on microvascular physiology, there is growing interest in understanding how GLP-1RAs may affect ocular tissues more specifically.

1.4 GLP-1 Receptor Expression in Ocular Tissue & Its Implications

GLP-1 receptors are expressed in the retina, retinal pigment epithelium, optic nerve, and ciliary body where they exert several actions.[17] These include: neuroprotection of retinal ganglion cells, anti-inflammatory effects via cytokine modulation, antioxidant activity, and stabilization of the blood-retinal barrier.[18] Mechanistically, GLP-RAs achieve these via inhibiting microglial activation, reducing pro-inflammatory cytokines such as IL-6, IL-1β, and TNF-α, and upregulating tight junction proteins, thereby reducing vascular leakage and neuroinflammation in the retina.[17] They can also promote mitochondrial protection and inhibit pathways involved in retinal cell apoptosis and oxidative stress.[19]

Although the existing literature indicates that GLP-1R activation provides several beneficial effects on retinal health, recent studies caution for potential adverse consequences. Rapid metabolic shifts, especially fluctuations in glycemic status, may interact with retinal microvascular physiology in ways not fully understood yet. These observations highlight the importance of investigating a plausible biologic mechanism for adverse ocular outcomes in patients treated with GLP-1 receptor agonists.

1.5 Knowledge Gap & Rationale for Present Study

As GLP-1RAs are increasingly prescribed to individuals without diabetes and to populations with varied ophthalmic and systemic risk factors, the lack of evidence on their ocular safety represents an important knowledge gap. Prior studies have been limited by small sample sizes resulting in insufficient understanding of the potential ophthalmic effects on a larger scale. To address this gap, this present study utilizes a large, diverse health system to evaluate the incidence of new-onset ophthalmic pathology following GLP-1RA initiation. By analyzing randomly selected cohorts of GLP-1RA users and non-users drawn from more than 216,000 eligible patients, and by excluding individuals with any pre-existing ocular disease, this study isolates incident pathology occurring after medication initiation. The comparison of ocular adverse event rates between groups allows for the assessment of whether GLP-1RA exposure is associated with increased ocular risk. This approach provides clinically relevant data that may help inform medical management practices for patients receiving GLP-1 receptor agonists.

1.6 Study Rationale

The rationale of this retrospective review was to delineate any potential associations between the use of GLP-1RAs and subsequent ophthalmic pathology. The retrospective nature of this review provided the opportunity to identify when the first GLP-1RA was started and if any longitudinal ophthalmic complications arose. Given the rapid increase in popularity and widespread utilization of GLP-1RAs, it was imperative to better understand the potential ophthalmic impact.

2. Methods

A retrospective analysis of 216,450 patients at JPS Health Network with a diagnosis of diabetes, obesity, and/or heart disease was conducted between December 17, 2017, to October 8, 2025. Only patients over the age of 18 were included. Patients with any pre-existing ocular conditions at the start of the study date were excluded. A power analysis was conducted to determine the sample size necessary to identify a small effect size (Cohen's d = 0.2) while maintaining $\alpha = 0.05$ and $\beta = 0.05$. A sample size of 550 individuals per group was determined to be appropriate.

A random sample of 550 individuals was created for each group. The first group, control, consists of patients who did not receive GLP-1 medication and the second group, treatment, consists of patients that were treated with GLP-1 medication.

Ocular pathologies were counted for each patient in the control group. For the treatment group, a different approach was taken. Half of the patients with ocular pathologies were diagnosed after their first GLP-1 prescription, while the other half had pre-existing ocular conditions prior to initiating GLP-1 therapy.

A bivariate analysis was conducted between the demographic variables of the two groups to ensure homogeneity. Fisher's Exact test was used to assess categorical variables, gender and race/ethnicity. The continuous variable, age, was assessed using a Mann-Whitney U test.

A negative binomial generalized linear model with a log link and an offset of log(Time) was fit to the data to assess the association between GLP-1 use and the development of ocular pathologies. This model was chosen to allow for a comparison of the rates of ocular pathologies between the two groups while accounting for the varying length of time individuals participated in the study. $log(\mu_i)=\beta_0 + \beta_1(AgeAtStudyInclusion_i)+\beta_2(Genderi_i)+\beta_3(GLP1_i) + log(Time_i)$

3. Results

A total of 1,100 patients were included in the primary analysis. 550 patients were included in the control group and 550 in the GLP-1RA group. After excluding three individuals due to missing follow up data, 1097 patients were included in the regression analysis.

Baseline demographic and clinical characteristics are summarized in Table 1. The median age at the time of study inclusion was similar between both the control group and GLP-1RA group, 48 years (IQR 36–59) vs 47 years (IQR 38–56); p = 0.52). Baseline hemoglobin A1c values were also comparable between the control and treatment (p = 0.24), although a large proportion of patients had missing hemoglobin A1c data (50.5%). There was a statistically significant difference in gender distribution between the control and treatment cohort (p < 0.001), with a higher proportion of females in the treatment group (69%) compared to the control group (52%). No significant difference was observed in the race or ethnicity distribution between groups (p = 0.27).

Table 1
Composition of Sample Stratified by Group

	Control	Treatment	P-Value
	(N = 550)	(N = 550)	
	Median [IQR]		
Age At Study Inclusion	48 [36; 59]	47 [38; 56]	0.52
	Count (Percent)		
Gender:			< 0.001
Female	287 (52%)	379 (69%)	
Male	263 (48%)	171 (31%)	
Race/Ethnicity:			0.27
Caucasian	223 (41%)	247 (45%)	
African American	175 (32%)	162 (30%)	
Hispanic	100 (18%)	103 (19%)	
Other	52 (10%)	38 (7%)	

The proportion of patients who developed at least one ocular pathology was 3.6% in the control group, and 4.5% in the GLP-1RA group. The difference was not statistically significant (odds ratio [OR] = 1.3, 95% confidence interval [CI]: 0.7–2.4; p = 0.54), as calculated by Fisher's Exact Test.

Table 2 highlights the results from the negative binomial regression analysis. After controlling for both age and gender, GLP-1RA use was significantly associated with an increased rate of ocular pathology. Patients in the GLP-1RA group experienced ocular pathologies at approximately twice the rate of those in the control group (adjusted rate ratio [aRR\ = 2.03; 95% CI: 1.1–4.3; p = 0.02). Increased age was also significantly associated with a higher rate of ocular pathology ([aRR] = 1.05 per year increase; 95% CI: 1.0-1.1; p < 0.01). Gender was not statistically associated with ocular pathology incidence (aRR = 0.80, p = 0.50).

Table 2
Estimates of the Negative Binomial Generalized Linear Model

Gender (Reference=Female)	**Odds Ratio (Adjusted)**	**95% CI**	**P-Value**
	0.80	**(0.4, 1.6)**	**0.50**
Age At Study Inclusion	1.05	(1.0, 1.1)	< 0.001
Treatment (Reference=Control)	2.03	(1.1, 4.3)	0.02

Following, a secondary analysis including baseline hemoglobin A1c as a covariate was conducted on a reduced sample of 543 patients (Table 3). In this model, baseline A1c was not significantly associated with ocular pathology rates (aRR = 1.06; 95% CI: 0.9–1.3; p = 0.43). This association between GLP-1RA use and ocular pathology was not statistically significant at a 0.05 alpha level (aRR = 2.23; 95% CI: 1.0-5.4), p = 0.05). Age remained a statistically significant predictor (p < 0.01). The reduced sample size due to missing A1c data should be considered when interpreting these findings.

Table 3
Estimates of the Negative Binomial Generalized Linear Model with Baseline A1c (N = 543)

Gender (Reference=Female)	**Odds Ratio (Adjusted)**	**95% CI**	**P-Value**
	0.52	**(0.2, 1.2)**	**0.11**
Age At Study Inclusion	1.06	(1.0, 1.1)	< 0.01
Treatment (Reference=Control)	2.23	(1.0, 5.4)	0.05
Baseline A1c	1.06	(0.9, 1.3)	0.43

The distribution of ocular pathologies by diagnostic category is shown in Table 4. Age-related cataracts were the most commonly observed condition in both the control and GLP-1RA group (70% in control, 63% in GLP-1RA cohort). Other observed conditions included retinal disorders, glaucoma, and visual disturbances. There was no statistically significant difference in the distribution of types of ocular pathology between control and treatment (p = 0.86). Additionally, a focused analysis of the diagnosis of glaucoma did not demonstrate a statistically significant difference between groups (p = 0.36), although glaucoma cases were only observed in the treatment group.

Table 4
Distribution of Ocular Pathology

ICD Code	**Control**	**Treatment**
Lacrimal System Disorders (H04)	1 (5%)	3 (4%)
Age Related Cataracts (H25)	14 (70%)	45 (63%)
Other Cataracts (H26)	1 (5%)	5 (7%)
Retinal Detachment (H33)	0 (0%)	3 (4%)
Other Retinal Disorders (H35)	3 (15%)	7 (10%)
Glaucoma (H40)	0 (0%)	6 (8%)
Visual Disturbances (H53)	1 (5%)	3 (4%)

4. Discussion

This retrospective analysis evaluated the association between GLP-1 receptor agonist use and the development of ocular pathologies among patients with diabetes, obesity (BMI > 30.0), and/or known cardiovascular disease. While crude comparisons did not demonstrate a statistically significant difference in the proportion of patients that were diagnosed with ocular pathology following usage of GLP-1 agonists, adjusted modeling suggested that GLP-1 agonist use was associated with an increased rate of ocular pathology. While this association was attenuated and became borderline ($p = 0.05$) after further adjustment for baseline hemoglobin A1c, this secondary model included only approximately half the sample size of the primary adjusted model (due to available data), resulting in reduced statistical power. This leaves the relative contributions of GLP-1RA exposure versus underlying glycemic control open to interpretation and highlights the need for caution when drawing firm conclusions from these findings.

4.1 Ocular Outcomes

In this cohort, ocular pathologies were relatively uncommon in both the control and treatment groups with overall incidence in either group less than 5%. Although the treatment group did demonstrate a numerically higher occurrence of ocular diagnosis, the difference was not statistically significant in unadjusted analyses. However, the adjusted negative bimodal model suggested a two-fold increase in the rate of ocular pathology among the GLP-1 agonist cohort. This discrepancy between crude and adjusted findings may be secondary to the difference in follow-up time, age distribution, and gender - all which were accounted for in the multivariable model. Importantly, the distribution of ocular pathology types did not significantly differ between the two groups, with age-related cataracts representing the majority of cases in both cohorts. Though glaucoma (any glaucoma diagnosis) and non-age-related cataracts were noted more frequently in the GLP-1 cohort, these findings were not statistically significant.

Thus, given that no specific ocular pathology was disproportionately represented in the treatment cohort and no statistically significant difference was observed in the pathology distribution, it is suggestive that if an association exists it may be due to a generalized increase rather than a treatment-specific effect.

4.2 Biological Mechanisms

Several underlying biological factors may explain the observed association between GLP-1RA use and ocular outcomes. One hypothesis relates to the rapid improvement in glycemic control that GLP-1RA can provide.[14] It is hypothesized that sudden improvement in glycemic control and the following osmotic shifts may transiently worsen certain pathologies, specifically diabetic retinopathy.

When further adjusted for baseline hemoglobin A1c, the association between GLP-1RA use and ocular outcomes was attenuated and reached only borderline significance ($p = 0.05$). This raises the possibility that underlying glycemic status, rather than GLP-1RA use itself, may be the predominant driver of the observed ocular outcomes. However, because this adjusted model included only about half the sample size of the primary analysis, statistical power was reduced from 0.95 to approximately 0.7. The

persistence of a borderline association despite the reduced power leaves open the possibility that a direct effect of GLP-1RA may still contribute, though the current data cannot definitively distinguish between these explanations."

4.3 Epidemiological Perspective

From an epidemiological standpoint, these findings highlight the importance of identification of confounding biases and selection bias in observational analyses. Patients who were prescribed GLP-1RA may differ systematically from the control group, particularly in regard to disease severity, duration of diabetes, or prior treatment history - differences which may not be fully captured by available covariant analyses.

Additionally, the attenuation of the treatment effect after inclusion of baseline A1c underscores the potential role of confounding by indication. Patients with worse glycemic control at baseline may be more likely to receive GLP-RA and more likely at baseline for ocular complications.

4.4 Public Health Perspective

Despite the modest - and non-statistically significant - increase in ocular pathology that was seen in the GLP-RA cohort, considerations should be taken when prescribing GLP-1RA. Especially due to the rapidly increasing use of GLP-1RA in the management of multiple conditions, understanding the safety profile is of the utmost importance. Routine ophthalmologic screening and patient education may be a beneficial consideration in specific patients receiving the medication. Further large-scale prospective studies with more complete data on glycemic control and pre-treatment disease severity are needed to clarify the nature of these associations.

5. Conclusion

In this retrospective cohort study, the use of GLP-1RA was associated with an increased rate of ocular pathologies after adjustment for age and gender. This result was attenuated, though not definitively countered, by our attempts to adjust the data for baseline A1C status.

Overall, the incidence of ocular pathology was low in both the control and GLP-1RA cohort, with no statistically significant differences identified in the distribution between cohorts. Thus, these findings do not establish a causal relationship between GLP-1RA use and development of subsequent ocular disease. Instead, these results highlight the complexity of understanding medication effects from underlying disease severity.

Given the widespread and rapidly increasing use of GLP-1RA, continued investigations into their ocular safety profile is warranted. Future studies should incorporate longitudinal prospective designs, more complete glycemic data, and detailed characterization of ophthalmologic outcomes to better understand the potential risks. However, in the interim, physicians should remain attentive to ocular health in patients on GLP-1RA therapy, especially in those with pre-existing risk factors.

6. Limitations and Future Recommendations

Patients that received GLP-1 medication saw a statistically significant twofold increase in ocular pathology rates compared to those who did not receive GLP-1 medication. Additionally, patients that received GLP-1 medication also saw increased occurrences of glaucoma and non-age-related cataracts, though this difference was not found to be statistically significant. Further analysis will need to be completed to establish a better understanding of GLP-1 medication and its association with glaucoma and cataracts.

In addition, missing data complicates full interpretation. Approximately half of the cohort lacked baseline hemoglobin A1c values, resulting in a substantially reduced sample size in the secondary model. This limits the overall statistical power as a result and raises the possibility of both residual confounding variables and type II errors.

Future interpretations of the data could focus on teasing out the differences in ocular pathology incidence by risk factor type, drug exposure length, drug dosing, and disease incidence timing during course of GLP-1 treatment.

Declarations

Ethics Approval and Consent to Participate

Ethics Approval: This retrospective study involving human participant data was reviewed and approved by the North Texas Regional Institutional Review Board (IRB Approval No. 2025-059). All study procedures were conducted in accordance with the ethical standards of the institutional research committee and the Declaration of Helsinki.

Consent to Participate: Due to the retrospective nature of the study and the use of existing de-identified data, the North Texas Regional Institutional Review Board waived the requirement for informed consent (IRB Approval No 2025-059).

Consent for Publication: Not applicable

Informed Consent

Not applicable. As above, due to the retrospective nature of the review, IRB (2025-059) approval waved the need for obtaining informed consent.

Author Contributions: Conceptualization: T.J and J.R.; Methodology: T.J. and J.R.;

Software: T.J., J.R., S.N.; Formal Analysis: S.N., J.R., and T.J.; Investigation: T.J., J.R., and S.N.; Data

Curation: S.N., J.R., and T.J.; Writing—original Draft Preparation: T.J., A.S., I.Z., and J.R.;

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Availability of data and materials: The dataset generated and analyzed during the current study are not publicly available due to institutional and patient privacy restrictions but are available from the corresponding author on reasonable request and with permission of the North Texas Regional Institutional Review Board.

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