GLP-1 RECEPTOR AGONISTS AND THE EYE

Researchers are working to understand the effects of these popular new therapies on ocular structures.

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Glucagon-like peptide-1 receptor agonists (GLP-1 RAs) promote physiologic glucose-dependent insulin release.[1] Originally FDA-approved for type 2 diabetes, GLP-1 RAs also lead to sustained weight loss and have revolutionized diabetes and obesity management.[2,3] Furthermore, several cardiovascular outcome trials (CVOT) suggest GLP-1 RAs confer a mortality benefit, with significant reductions in major adverse cardiovascular events, all-cause mortality, heart failure severity, and worsening kidney function.[4]

GLP-1 RAs also exert antiinflammatory and neuroprotective benefits on the central nervous system, retina, and other ocular structures,[5-8] and research shows reduced risk of neurodegenerative diseases such as Alzheimer and Parkinson dementia.[9-12] Many studies have investigated the role of GLP-1 RAs on the risk of ophthalmic diseases, including diabetic retinopathy (DR), glaucoma, AMD, idiopathic intracranial hypertension (IIH), and nonarteritic anterior ischemic optic neuropathy (NAION). Here, we provide an overview of the effect of GLP-1 RAs on ophthalmic diseases.

DIABETIC RETINOPATHY

The relationship between DR and GLP-1 RAs remains controversial. Concern was initially raised by the findings of the SUSTAIN-6 CVOT that suggested the risk of DR complications was elevated in patients using semaglutide compared with placebo (3.0% vs 1.8%, $P = .02$).[13] Two meta-analyses of other GLP-1 RA CVOTs found that GLP-1 RAs

AT A GLANCE

- Originally FDA-approved for type 2 diabetes, glucagon-like peptide-1 receptor agonists (GLP-1 RAs) also lead to sustained weight loss and have revolutionized diabetes and obesity management.
- Many studies have investigated the relationship between GLP-1 RAs and ophthalmic diseases, including diabetic retinopathy, glaucoma, AMD, idiopathic intracranial hypertension, and nonarteritic anterior ischemic optic neuropathy.

were associated with greater rates of DR progression, but both studies found that the effect was driven by the extent of hemoglobin A1c reduction, rather than the medications themselves.[14,15] Another meta-analysis of 93 clinical trials showed that GLP-1 RAs increased the risk of early-stage DR compared with placebo, with this effect being driven by albiglutide in particular.[16]

A challenge of comparing data between CVOTs is the inconsistency in the protocols for accurately detecting retinal changes. Not all studies required dilated fundus examinations or retinal imaging, and they differed in inclusion criteria that would affect risk for disease progression. For example, while the SUSTAIN-6 study included patients with proliferative DR (PDR) and diabetic macular edema (DME), other CVOTs, such as PIONEER 6, did not.[17]

Moreover, the effects of GLP-1 RAs on DR have been explored in many retrospective large database studies, which have also yielded conflicting results. Some national electronic health record (EHR) database studies showed an elevated risk of DR development or progression.[18,19] Two such studies received letters to the editor with concerns that either the study design was not rigorous enough or the dataset used was not appropriate for ophthalmic questions.[20,21]

Others showed a protective effect of GLP-1 RAs on DR progression. Zheng et al showed that GLP-1 RA use was associated with a lower risk of DR in 2,390 patients in a national Swedish registry using both observational and genetic data.[22] Several other studies showed that there was no significant relationship between GLP-1 RAs and DR worsening, including one study by Joo et al in which manual review of the data was conducted to ensure accuracy in the ICD coding used to determine outcomes.[23-25]

To resolve this confusion, the prospective FOCUS trial was initiated in 2019. The trial is studying the effects of semaglutide on DR complications in 1,500 patients with type 2 diabetes and is estimated to be completed in 2027.[26]

GLAUCOMA

Numerous studies have assessed the relationship between GLP-1 RAs and glaucoma, and most have shown that GLP-1 RAs confer a protective effect. For example, Muayad et al compared 61,998 patients with diabetes using GLP-1 RAs with metformin users in the US Collaborative Network of the TriNetX EHR database to calculate the risk of developing ocular hypertension or primary open-angle glaucoma, requiring topical glaucoma medication, or requiring laser trabeculoplasty.[27] At the 1-, 2-, and 3-year timepoints, they found that the GLP-1 RA cohort had a significantly lower risk of all three outcomes compared with metformin users.[27]

In a case-control study, Niazi et al compared 1,737 patients with glaucoma with 8,685 controls without glaucoma.[28] They found that GLP-1 RA use was associated with a lower risk of incident glaucoma (hazard ratio [HR] = .81), with the risk decreasing even further when GLP-1 RAs were used for longer than 3 years (HR = .71). However, a cohort study using TriNetX found that sodium-glucose co-transporter 2 inhibitors also significantly decreased the risk of new glaucoma diagnosis compared with GLP-1 RAs (HR = .932).[29]

In a systematic review and meta-analysis pooling these and other studies, Amaral et al found that the risk of glaucoma development was lower in patients taking GLP-1 RAs (HR = .71) compared with controls.[30] These clinical findings are supported by similar findings in basic science studies.[31]

AMD

Only two studies thus far have reported on the association between GLP-1 RAs and AMD. Allan et al used the TriNetX EHR platform to evaluate the risk of developing dry and wet AMD compared with controls in 9,669 patients taking GLP-1 RA medications.[32] Included patients were matched for age, sex, race and ethnicity, cardiovascular diseases, DR severity (including PDR and DME status), history of tobacco use, body mass index, and hemoglobin A1c percentage. The authors found that GLP-1 RA use was associated with a significantly decreased risk of developing dry AMD compared with patients taking metformin (HR = .68), insulin (HR = .72), and statins (HR = .70). Additionally, GLP-1 RA use was protective against wet AMD but only when comparing patients taking insulin (HR = .62) and statins (HR = .69).[32]

Shor et al used a nationwide Canadian EHR database to compare 46,334 patients taking GLP-1 RAs with 92,668 controls over a follow-up period of 6 months to 3 years.[33] They found that the HR for developing wet AMD was 2.21 in GLP-1 RA users compared with controls. However, this study had limited duration of drug use and a lack of controls in the regression model for wet AMD risk factors, such as baseline PDR and DME status, smoking history, hemoglobin A1c, and history of dry AMD. Additional research with rigorous study design is needed to clarify these relationships.

IIH

Several studies have explored the effect of GLP-1 RA use on IIH. A phase 2 trial studied exenatide usage on intracranial pressure (ICP) in patients with IIH over 12 weeks.[34] In the double-blind study, seven patients received subcutaneous exenatide twice daily and eight patients received placebo. By the end of the study, the ICP in exenatide users decreased by 5.6 ± 3.0 cmCSF compared with controls (P = .058).

Another study investigated the effect of GLP-1 RAs on IIH symptoms, such as monthly headache days and visual outcomes.[35] While visual parameters such as field defects and visual acuity were not significantly different between groups, GLP-1 RA users (n = 7) reported fewer daily headaches (P = .02) compared with controls (n = 8). While these results are promising, the sample sizes are very small, and further studies are warranted to support these findings.

NAION

The effect of GLP-1 RAs on NAION is inconsistent across studies. In a retrospective cohort study of 16,827 patients in a single-center neuroophthalmology clinic, Hathaway et al found that semaglutide use was significantly associated with an increased incidence of NAION among patients with diabetes (HR = 4.28).[36] The risk was further elevated in patients without diabetes taking semaglutide for weight loss (HR = 7.64, $P < .001$). These results may have limited generalizability due to bias introduced by the study's design, including the treatment setting (ie, a neuroophthalmology clinic) and potential worse baseline health in patients taking semaglutide compared with matched controls.[37]

Several studies using large databases have attempted to replicate these results. Simonsen et al used the Norwegian and Danish national health registries and found an increased risk of NAION development with semaglutide initiation (HR = 2.81).[38] Grauslund et al identified all patients with diabetes in Denmark's national health registry and found that semaglutide was an independent predictor of incident NAION (HR = 2.19).[39] However, this study did not control for relevant risk factors such as smoking, blood pressure, and body mass index. Hsu et al used the TriNetX platform to study the association between semaglutide use and the incidence of NAION and found that it was associated with an increased risk in patients with diabetes at the 2-, 3-, and 4-year timepoints but not within 1 year of GLP-1 RA initiation.[40] Due to the deidentified nature of these databases, however, none of these large-scale cohort studies could account for treatment adherence and duration of exposure, and they lacked access to ophthalmic examination data.[41]

Additionally, in retrospective cohort analyses also using the TriNetX database, both Chou et al and Abbass et al found no association between semaglutide use and risk of NAION.[42,43] Of note, Abbass et al did not control for hemoglobin A1c, lipid levels, or history of cataract surgery, which could introduce bias.[44,45] Using the FDA Sentinel System, Maro et al found that the incidence of NAION was not increased within 6 months of semaglutide initiation.[46] Finally, Klonoff et al, using the Arcadia patient registry, also found no significant increase in NAION risk in patients taking semaglutide.[47] In June 2025, the European Medicines Agency recommended cessation of semaglutide use if a patient is newly diagnosed with NAION. However, the AAO and the North American Neuro-Ophthalmology Society do not support this blanket recommendation. Instead, they advise patients who develop NAION to engage in shared decision making with their providers about whether to discontinue the drug based on individual risks. Their reasoning includes the potentially significant systemic side effects of stopping semaglutide and the lack of evidence for a causative link between GLP-1 RAs and NAION.[48]

MORE INFORMATION IS NEEDED

The newfound potential effects of GLP-1 RAs across numerous ophthalmic diseases have sparked excitement, concern, and confusion among ophthalmologists and patients alike. Many of these studies are from large databases, which are powerful tools in elucidating patterns on a population level, but can also be misleading due to their immense statistical power. They could produce findings that may be due to the bias inherent in retrospective studies. For example, ICD diagnosis codes for ophthalmic diseases can be unreliable and inaccurate,[49,50] particularly in national datasets in which manual validation of data is not possible.

Consequently, caution should be exercised when interpreting findings from large EHR studies. Future large database studies should provide increased methodologic transparency to support reproducible results.[51] Additionally, studies incorporating imaging data, visual function data, and prospective trials are warranted to further characterize the true effect of GLP-1 RA use on ocular diseases. ■

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