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IMPACT OF GLP-1 RECEPTOR AGONISTS ON RETINAL AND VISUAL OUTCOMES IN PATIENTS WITH ESTABLISHED DIABETIC MACULAR EDEMA: A COMPREHENSIVE REVIEW

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ABSTRACT

Background: GLP-1 receptor agonists (GLP-1 RAs) are widely used in the treatment of type 2 diabetes. Following the 'SUSTAIN-6' trial, concerns have been raised regarding their impact on the retina. Most of the currently available data primarily relate to general diabetic retinopathy; however, the effects on individuals who already have diabetic macular edema (DME) and require anti-VEGF injections remain not fully understood.

Methods: Study was found across PubMed, Web of Science and Google Scholar January 2000 to September 2026. We summarized evidence on diabetic retinopathy, DME, OCT findings, visual acuity and anti-VEGF treatment, with citation tracking, reported according to the SANRA criteria.

Results: Meta-analyses have not shown a consistent overall association between the use of GLP-1 RAs and the worsening of diabetic retinopathy. The signal observed with semaglutide in the SUSTAIN-6 trial has been attributed, in part, to a rapid reduction in HbA1c levels; however, this has not yet been investigated in the context of diabetic macular edema (DME). In established DME, one large registry cohort, found no statistically significant differences in injection, visual acuity or central subfield thickness trajectories over 24 months after GLP-1 RA initiation.

Conclusions: Current evidence does not establish whether GLP-1 RAs improve or worsen established DME, or whether they alter the need for anti-VEGF therapy. Prospective research incorporating baseline OCT, HbA1c levels, and standardized outcome measure is needed in the context of DME.

Keywords: GLP-1 Receptor Agonist; Diabetic Macular Edema; Anti-VEGF; Optical Coherence Tomography; Hyper-Reflective Foci; Semaglutide; Diabetic Retinopathy

1 INTRODUCTION

Type 2 diabetes mellitus (T2DM) remains a major health problem causing microvascular complications including diabetic retinopathy (DR) and diabetic macular edema (DME) which are major causes of preventable visual impairment among working-age adults [1]. The T2DM management has been dramatically changed with the introduction of glucagon-like peptide-1 receptor agonists (GLP-1 RAs) including semaglutide, liraglutide, dulaglutide and the dual glucose-dependent insulinotropic polypeptide/glucagon-like peptide-1 agonist tirzepatide. Apart from their glucose-lowering and weight-reducing effects, GLP-1 RAs offer cardiovascular and renal benefits [2]. Thus, interest in the possible effects of these new agents on retinal health is justified.

Concern for potential adverse effects of GLP-1 RAs on the eye increased after the SUSTAIN-6 trial reported that patients in the semaglutide group had a higher rate of diabetic retinopathy complications than the placebo group [3,4]. The results of interest are the "early worsening" of diabetic retinopathy, where new retinopathy lesions may develop after improvement in glycemic control. Current evidence suggests that "early worsening" of diabetic retinopathy may reflect a metabolic change rather than a direct adverse effect of GLP-1 RAs on retinal tissue [1,5]. Reduction in chronic hyperglycemia may lead to osmotic and vascular-permeability changes in the retina which may increase the vulnerability of the retina. This may be of particular concern among patients of T2DM with long-standing disease, high baseline glycated hemoglobin and retinopathy [1,5].

This concern has the most clinical relevance to individuals who have established DME. Those at risk for developing DME do not have structural retinal abnormalities; therefore, deterioration due to treatment would not be as clinically relevant. Treatment is always aimed at reducing the burden on the eye and improving vision and anatomy. The most relevant outcomes in a clinical setting include visual acuity, retinal thickness, the presence of fluid, and the burden of treatment [6]. The volume of evidence focused on the effects of GLP-1 RAs on incident DME is rapidly growing. However, previous evidence syntheses did not specifically assess patients with established, treatment-requiring DME. As a result, the impact of initiating GLP-1 RAs on visual outcomes, OCT-defined anatomy of the retina, and the burden of anti-VEGF treatment is unclear.

The evidence relevant to this population is sparse and has mostly come from observational studies. A large American Academy of Ophthalmology IRIS Registry cohort study reported no significant differences between the GLP-1 RA [6] initiators and their matched controls in terms of the anti-VEGF injection trajectory, visual acuity, and central subfield thickness (CST) during follow-up. However, due to the lack of data on possible confounders including long-term HbA1c, body mass index (BMI), and adherence to glucose-lowering medications, the authors pointed out that the findings should be interpreted with caution. The existing evidence is primarily from a few cohort studies with little to no comparative studies of individual GLP-1 RAs. The use of imaging-confirmed retinal outcomes has also been inconsistent. This limits the ability to discern the impact of the GLP-1 RA from the rapid improvement in glycemic control, the baseline severity of the retinal conditions, and other aspects of clinical management.

This narrative review examines the available evidence regarding the impact of GLP-1 RA use on retinal outcomes in adults with T2DM and established DME. It covers potential early worsening, changes in best corrected visual acuity (BCVA) and retinal thickness, and the anti-VEGF burden. Since the focus of this review is established DME rather than new retinal disease, the authors try to address the use of GLP-1 RAs for patients with DME and DR where needed as relevant information.

2 METHODS AND APPROACHES

To perform this review, electronic searches were completed in PubMed, Web of Science and Google Scholar to find peer reviewed articles from January 2000 to September 2026. The searches were performed to find studies to assess the effect of GLP-1 RA use on retinal outcomes in people with diabetes.

Search terms included the following combinations of keywords: "GLP-1 receptor agonist," "GLP-1 RAs," "semaglutide," "liraglutide," "dulaglutide," "tirzepatide," "diabetic retinopathy," "diabetic macular edema," "DME," "macular edema," "anti-VEGF," "intravitreal injection," "visual acuity," "best-corrected visual acuity," "BCVA," "OCT," and "central subfield thickness." Boolean operators (AND and OR) were used to combine the search terms. Title and abstract field restrictions were applied where appropriate.

Combination of GLP-1 RA terms with diabetic retinopathy, diabetic macular edema and relevant retinal outcomes was of the keywords of the search strategy we used. Additional searches were performed to look for evidence concerning the improvement of diabetic retinopathy and the impact of rapid glycemic improvement. Referring to established DME in the general framework of diabetic retinopathy, priority given to studies in people with established DME, and used

broader diabetic retinopathy and glycemic control studies data to give context on early to rapid worsening. We reviewed the references of published articles, published review articles and performed searches to identify additional literature.

Studies including clinical trials, cohort studies, registry studies, observational studies and relevant limited meta-analyses were considered for inclusion. Studies that reported the influence of GLP-1 RA on retinal outcomes, i.e. on progression of diabetic retinopathy, diabetic macular edema, structural changes in retina as observed on OCT, and visual acuity, as well as studies that reported the need for anti-VEGF therapy, were considered for this review. Limited preprints and literature review were considered where they directly addressed established DME or anti-VEGF treatment outcomes.

Since this was a narrative review, the authors selected studies based on relevance to the review objectives. We did not use a formal risk-of-bias tool or an evidence-grading framework, but we considered the design and limitations of each study when interpreting the findings. Quality and completeness of the review were assessed by a scale designed to assess narrative review articles, i.e., the Scale for the Assessment of Narrative Review Articles (SANRA) (Scale for the Assessment of Narrative Review Articles) [7]. SANRA consists of 6 components, i.e. justification of review, aim, literature search, reference list, scientific reasoning, and presentation of data.

3 GLP-1 RECEPTOR AGONISTS AND DIABETIC RETINOPATHY

The observation of diabetic retinopathy (DR) associated with semaglutide in SUSTAIN-6 prompted the consideration of whether the initiation of GLP-1 RAs could potentially worsen DR[8]. The new Semaglutide information associated with DR, needs to be interpreted against other sources of evidence like meta-analyses, registry cohorts, and studies that measured glucose levels directly. Such evidence evaluates varying populations and retinal outcomes, and does not establish a class-effect [9, 10, 11]. For this part of the review, differentiating between the progression of general DR and the outcomes in adults who have diabetic macular edema (DME) is important.

3.1 DR Incidence and Progression

In the SUSTAIN-6 study, diabetic retinopathy complications occurred in 3.0% of participants receiving semaglutide and in 1.8% of the placebo group (hazard ratio {HR} 1.76, 95% confidence interval 1.11 to 2.78; P=0.02) [8]. This was a safety signal from a cardiovascular study and does not prove that all GLP-1 RAs worsen DR.

A systematic review and meta-analysis of 39 studies (24 randomized controlled trials and 15 observational studies) showed the use of GLP-1 RAs and development or progression of DR was not significant (pooled risk ratio 1.00, 95% confidence interval 0.71 to 1.43), with very high heterogeneity (I2 96.8%) [10]. Randomized controlled trials (RCTs) suggest a lower risk (RR 0.91, 95% CI 0.73 to 1.14), and observational studies suggest a higher (much more uncertain) risk (RR 2.09, 95% CI 0.47 to 9.19) [10]. Because the interval encompasses both a benefit and a detriment, it should not be interpreted to suggest that they are equivalent.

Another retrospective study using the IRIS registry (preprint) followed 350,336 eyes of adults with type 2 diabetes and diabetic retinopathy's (DR) for up to 10 years. Exposure was defined as 90 days after the first prescription of a GLP-1 RA. This study also showed no significant association of GLP-1 RA exposure with progression to proliferative DR (HR 0.96, 95% CI 0.92 to 1.01) or to severe nonproliferative DR (HR 1.03, 95% CI 0.90 to 1.17) [12]. This study also found a moderate increase in risk for GLP-1 RA exposure and panretinal photocoagulation (HR 1.07, 95% CI 1.03 to 1.12) and a similar, not significant increase for vitrectomy (HR 1.07, 95% CI 1.00 to 1.15). The absolute difference in the 5-year rate of panretinal photocoagulation was 10.56% vs 9.97%, and proliferative DR was 4.78% vs 4.95% [12]

3.2 Early Worsening of Diabetic Retinopathy

Early worsening describes short-term diabetic retinopathy changes following a rapid improvement of hyperglycaemia [11]. The SURPASS-CVOT retinopathy sub study presentation identifies the context of improving hyperglycaemia as one of the scenarios for early worsening; however, it does not demonstrate GLP-1 RAs cause retinal injury [13]. The Alwafi study, reveal another real-world evidence study, points that rapid glycemic improvement may contribute to early worsening, particularly in people with pre-existing retinopathy [10].

In the case of a patient who initiates a GLP-1 RA and is found to have worsening DR, it may be necessary to consider the patient's baseline DR status and the timing of glycaemic control improvement, rather than automatically attributing the change to the drug [9,10,13]. The current evidence does not support that all patients initiating a GLP-1 RA experience early worsening, nor does it support the presence of a defining HbA1c threshold to predict early worsening [9,10].

3.3 Relationship with Rapid HbA1c Reduction

Bethel et al. performed a synthesis of six placebo-controlled GLP-1 RA CV outcome studies. Overall, their pooled analysis did not show a statistically significant association between the use of a GLP-1 RA and the development of retinopathy (odds ratio {OR} 1.10, 95% CI 0.93-1.30), but in the study-level meta-regression, a greater average reduction in HbA1c was associated with an increased risk of retinopathy (slope = 0.77, p = 0.007) and associations were seen at both 3 months and 1 year [9]. As this is a study-level meta-regression, it supports an association between the amount of glycaemic change and the observed retinopathy signal; it does not prove that rapid HbA1c reduction caused an individual patient's retinal worsening [9].

The SURPASS-CVOT retinopathy sub study offers a useful comparison. While in this high-risk population, tirzepatide caused a greater fall in HbA1c at 6 months compared to dulaglutide (-2.18% vs. -1.28%), the 36-month DR progression outcomes from the presentation did not differ between the groups, and the authors reported no association between change in HbA1c and retinal status in either group [13]. This does not rule out the findings from the meta-regression. It suggests the relationship may vary with the population, drug, duration of follow-up and the retinal outcome measure,[13] For example, a retrospective population-based nested case-control study involving patients with mild or moderate non-proliferative diabetic retinopathy (NPDR) found no significant association between rapid HbA1c reduction and early worsening of diabetic retinopathy [14].

3.4 Clinical Implications

According to the American Academy of Ophthalmology's November 2026 statement, evidence is currently insufficient to draw a causal relationship between the use of GLP-1 RA and deterioration of diabetic retinopathy. The Academy's statement outlined important limitations of the evidence, noted an initial period of increased monitoring of diabetic retinopathy for patients initiating GLP-1 RA therapy, and recommended shared decision-making to make informed choices about initiating, continuing, or discontinuing the therapy [11]. The statement did not define a specific monitoring period.

For adults with pre-existing DME, it has been suggested that in the absence of clear-cut evidence for direct drug class retinal toxicity, clinical emphasis and interpretation should remain focused on relevant ocular outcomes for the disease (i.e., retinal anatomy, fluid status, visual acuity, and response to anti-VEGF treatment) [6].The available data supports a joint decision-making approach between patient and health care provider regarding management, and does not support retinal toxicity from this drug class or making treatment decisions based on deterioration of diabetic retinopathy [6, 9].

4 GLP-1 RECEPTOR AGONISTS AND DIABETIC MACULAR EDEMA

The evidence for GLP-1 receptor agonists (GLP-1 RAs) in patients with established diabetic macular edema (DME) is still limited. Observational data are the most pertinent, and many other publications are on diabetic retinopathy (DR) or retinal thickness in people with diabetes without treatment requiring DME. One large, preprint study, analyzed people with DME who were treated with anti-VEGF injections [6].

One small retrospective cohort from Hadassah also reported OCT and visual acuity outcome of DME patients exposed to GLP-1 RAs [15]. Yet, the study did not restrict the cohort to patients with established DME, and baseline differences between the groups limited the interpretation of findings. Table (1) summarizes this cohort, along with the IRIS Registry study, and other cohort studies that include wider diabetes populations.

4.1 DME Development and Progression

The most pertinent clinical evidence is the IRIS Registry study on adults with DME who initiated GLP-1 RAs. Compared to their matched controls, the initiation of GLP-1 RAs did not mean a change in the trajectory of anti-VEGF injections. The study also showed that, during the study period, there was no change in the trajectory of visual acuity and central subfield thickness of the eyes [6]. While these findings offer reassurance for people with established DME, they do not show a therapeutic effect.

Results from other DR studies do not show a class effect of GLP-1 RAs on DME. New DME was not associated with GLP-1 RA use in a large, pre-existing DR, study population (HR 0.98) [16]. These results described DME that was newly developing. Results do not describe previously existing DME.

The SURPASS-CVOT sub-study did include participants with macular edema in at least one eye at baseline, but the presentation did not report results specific to DME [13]. Generally, worsening of DME is described in reports of poor glycemic control. We did not identify any study showing improvement of macular edema after GLP-1 RA initiation. One review describes case-level observations of transient macular edema during rapid glycemic improvement [1]. Whether GLP-1 RA therapy worsens pre-existing DME in high-risk patients are not known.

4.2 Retinal Thickness

Retinal thickness is a key structure in DME. However, there is little evidence of what GLP-1 RAs do to the central subfield in DME. In the IRIS Registry, there was no significant difference in central subfield thickness for the GLP-1 RA group compared to matched controls [6]. In the Hadassah cohort, CST fell by 13.5 μm in the GLP-1 RA group and by 30.1 μm in controls (p=0.46), and no association was found between GLP-1 RA use and change of CST [15]. However, participants of the GLP-1 RA group had a lower baseline CST compared to controls (306 vs 363 μm P=0.02) and 33 of the 35 users took liraglutide so the findings may not apply to semaglutide or tirzepatide [15].

Among the participants with type 2 diabetes not selected for treatment with DME, 32 weeks of semaglutide increased central retinal thickness by about 1% compared with placebo (3.8 μm, 95% CI 0.9 to 6.7), with no effect on empagliflozin or the combination. [17]. The authors of the study described this effect as small, and the clinical relevance was unclear. [17] . A post hoc analysis of 40 of these participants showed a mean difference of 3.76 μm (95% CI −0.32 to 7.85) with semaglutide, and a positive association between time in range and retinal thickness across all treatment groups. Micrometers are small compared to the values seen in DME; an anti-VEGF treatment cohort, for instance, had a baseline central retinal thickness of around 441 μm.[23]

There is biologic plausibility for this effect based on previously published preclinical studies. For example, the use of liraglutide in spontaneously diabetic Torii fatty rats demonstrated attenuation of retinal thickening [18]. Similarly, a number of mechanistic studies have suggested that GLP-1 RA may impact neurovascular injury and retinal inflammation and vascular permeability [5,19]. However, preclinical data and experimental studies are usually done in animals. As a result, it cannot be concluded that the use of systemic GLP-1 RA will result in a reduction in DME in humans.

4.3 OCT findings

One of the strengths of OCT is that it can evaluate aspects of DME beyond retinal thickness. Other features such as the presence of intraretinal and subretinal fluid, *hyper-reflective foci* (HRF) and the integrity of the inner retinal layers can be used to assess DME activity and predict response to anti-VEGF therapy [20,21]. Evidence associated with GLP-1 RA exposure is very limited. The IRIS cohort reported only central subfield thickness [6]. The two semaglutide trials

that reported DME outcomes measured central retinal thickness in people with type 2 diabetes who were not chosen for having DME [17, 22]. Only the Hadassah cohort, that included people with DR and not just only DME, reported the presence of fluid and HRF associated with GLP-1 RA exposure. No feature differed significantly at follow-up and IRF resolved somewhat more often (7 of 22 vs 2 of 25 patients; P = 0.106) with GLP-1 RA treatment [15]. HRF was more common at baseline in the control group (36% vs 11%). Baseline differences in HRF and vitreous hemorrhage complicated the interpretation of the injection-response comparison [15]. Disorganization of the inner retinal layers associated with GLP-1 RA exposure was not reported in the literature. Therefore, the available evidence does not point to a specific OCT feature that reflects the GLP-1 RA response in DME.

4.4 Visual acuity

Visual acuity is the most important functional outcome, but there is little evidence for DME. In the IRIS cohort, the difference in visual acuity trajectories between initiators and matched controls, ranged from -0.05 to 0.04 logMAR, and was not significant [6]. In the Hadassah cohort, logMAR dropped by 0.14 with GLP-1 RA treatment and by 0.06 in controls (p = 0.66). Both changes were less than 0.2 logMAR, and the authors considered clinically meaningful, and the change was not attributed to GLP-1 RA use [15]. These findings do not show that GLP-1 RAs improve vision, prevent visual loss or have no effect.

Variability in DME is dependent on a number of factors including duration and severity of edema, structural and functional damage to the retina, presence of cataract, and both the timing and effectiveness of anti-VEGF treatment. In a routine-care cohort of 123 eyes with DME treated over two years, the mean change in visual acuity was only + 2.1 letters [23]. Results from clinical trials of DRE progression should not be evidence about acuity in DME [3,10, 12].

Table 1: GLP-1 Receptor Agonists and Diabetic Macular Edema outcomes of different studies and their limitation

Study (ref)	Design and population	Exposure and comparator	Follow-up	Outcomes	Limitations
IRIS Registry cohort [6]	Retrospective registry cohort. T2DM with DME, all on anti-VEGF. 9,896 matched pairs	GLP-1 RA initiators (started after DME diagnosis) vs matched controls	24 months after initiation	No significant differences in visual acuity (−0.05 to 0.04 logMAR) or CST (−14.12 to 33.58 µm) trajectories	Preprint. No HbA1c, BMI or adherence data. All eyes already on anti-VEGF
Hadassah cohort [15]	Retrospective hospital cohort. DR patients with OCT, not limited to DME. 35 vs 31	GLP-1 RA (33 liraglutide, 2 semaglutide) vs no GLP-1 RA	Mean 599 vs 405 days	CST −13.5 vs −30.1 µm (P=0.464). VA −0.14 vs −0.06 logMAR (P=0.664). IRF resolution 7/22 vs 2/25 (P=0.106)	Small sample. Baseline imbalance in CST, HRF and vitreous hemorrhage
Gullaksen RCT secondary analysis [17]	Randomized trial. T2DM at high cardiovascular risk, not selected for DME. 120 participants	Semaglutide vs placebo (also empagliflozin and combination)	32 weeks	Central retinal thickness +3.8 µm (about 1%; 95% CI 0.9 to 6.7; P=0.009) with semaglutide vs placebo	Not a DME population. Small effect, uncertain clinical meaning
Gullaksen post hoc analysis [22]	Post hoc analysis of [17]. 40 participants	Semaglutide vs placebo	32 weeks	Central retinal thickness +3.76 µm (95% CI −0.32 to 7.85; P=0.065). Higher time in range linked to greater thickness in all groups	Very small. Post hoc

5 GLP-1 RECEPTOR AGONISTS AND ANTI-VEGF TREATMENT

Anti-VEGF therapy is a treatment with burden for established DME patients, this is where we can expect to see effects of GLP-1 RAs. But evidence is limited. The largest study is a preprint, which in only shown the DME patients who are already on anti-VEGF treatment [6]. The remaining sources are a small hospital cohort of DR patients [15] and a descriptive cohort of semaglutide [3,9].

5.1 Injection frequency

The IRIS Registry cohort followed 9,896 matched pairs for 24 months after the initiation of GLP-1 RA therapy. It defined injection as the probability of receiving an injection over time, and not the total number of injections. After 24 months, the difference between the two groups was not significant [6]. The GLP-1 RA group had a lower probability of an injection before starting, the two groups were not comparable at baseline [6].

In the retrospective cohort reported by Michaeli et al., intravitreal anti-VEGF treatment response was assessed in 35 GLP-1 RA users and 31 controls with DR. Good, stable, and poor responses were reported in 14/35 versus 6/31, 13/35 versus 11/31, and 8/35 versus 14/31 patients, respectively. For the binary analysis, good and stable responses were pooled (27/35 vs. 17/31). The unadjusted odds of a good/stable response were higher in the GLP-1 RA group, but the association was not statistically significant (OR 2.78, 95% CI, 0.96–8.02; P=0.058). After adjustment for baseline HRF and vitreous hemorrhage, the estimate was attenuated and remained nonsignificant (adjusted OR 1.76, 95% CI, 0.55–5.65) [15]

An 87-person cohort, describing the effect of DR treatment with semaglutide for 2.9 years, recorded an average of 12.6 injections over the course of the study [3]. Without a comparison group, it cannot demonstrate whether semaglutide effects the frequency of injections.

A routine cohort study care recorded 123 eyes, treated for DME, with an average of 4.5 injections in year one and 2.6 injections in year two [23]. Another study, by Groothoff, J.D. Elander, illustrates the use case of exogenous insulin. This

study evaluates the response to an anti-VEGF injection, functionally and anatomically, and determined the effect of chronic exogenous insulin. [24]

5.2 Treatment response

Treatment response to anti-VEGF therapy depends on several factors including change in vision, retinal thickness, presence and type of retinal fluids, and the interval between injections. The IRIS cohort indicated no difference in change in vision and central subfield thickness between groups [6]. Michaeli et al study shown GLP-1 RA use was not significantly associated with a good or stable intravitreal anti-VEGF treatment response after adjustment for baseline hyperreflective foci (HRF) and vitreous hemorrhage. [15]

This is important because OCT features can predict treatment response irrespective of the drug. A meta-analysis of 11,342 eyes reported that subretinal fluid predicted a favorable response and disorganization of retinal inner layers a poor one [21], and HRF has been studied as a predictor of outcome [20]. A GLP-1 RA group with a different baseline mix of these features could look better or worse for reasons unrelated to the drug. One review suggests treating DME with standard retinal therapies, and keeping the patient on GLP-1 RAs for metabolic control [1].

5.3 Treatment interval

Variations in treatment interval across studies makes comparison difficult. In a treatment study, the interval reflects the extent of control [23,15]. The IRIS cohort did not report any treatment intervals [6]. The Hadassah cohort used a treat-and-extend schedule. Interval was reported to be extended in 6 of 35 participants and 1 of 31 controls, and was shortened in 1 of 35 participants and 3 of 31 controls [15]. Given these small sample sizes, no sure conclusions can be made from this study. Currently, there are no studies that explore the role of GLP-1 RAs in extending the treatment interval in established DME.

5.4 Limitations of available evidence

The evidence base is small. Like there is one registry preprint [6], one mixed DR cohort hospital study [15], one descriptive cohort study [3], and the registry results have not been peer reviewed. The only randomized evidence on diabetic eye disease, the FOCUS trial of semaglutide, along with anti-VEGF treatment for DR and DME as an outcome and is still pending [25]. These populations and outcomes should not be substituted for a prospective DME trial with standardized OCT and visual acuity, as well as anti-VEGF endpoints [3, 10, 16]. Evidence from animal models and mechanistic reviews is useful in establishing hypotheses, but cannot confirm a clinical treatment interaction [1,17,11].

6 CONCLUSION

This review investigated whether GLP-1 receptor agonists modified established DME or influenced the requirement for anti-VEGF therapy. The available data does not suggest GLP-1 receptor agonists improve or worsen established DME or impact the requirement for anti-VEGF therapy.

There were no significant between-group differences over 24 months in terms of the number of anti-VEGF injections, visual acuity or central subfield thickness following initiation of GLP-1 receptor agonists in a large observational cohort of patients with established DME.[6]

The case of SUSTAIN-6 has been [8] interpreted in part in the context of rapid reduction in HbA1c, and not as proof of direct retinal toxicity. That study investigated type 2 diabetes and diabetic retinopathy, not type 2 diabetes and diabetic macular edema, and a trial-level association does not mean cause in an individual patient.[9] Different findings are reported an increase in central retinal thickness with semaglutide in patients not selected for DME, and a better injection response in a study of diabetic retinopathy. [14,15]

It is currently not clear that how GLP-1 RAs affect the number of injections, treatment intervals, and fluid recurrence in established DME. Change may occur shortly after application, and various agents may act differently. Therefore, GLP-1 RAs should be viewed as systemic metabolic therapies and not as established treatments for DME.

Limitation

The four most important limits are as follows. First, this is a narrative review, and although the search is described in the methods, study selection entailed judgement. There was no formal assessment of study-level risk of biasness, and thus relevant studies may have been missed or weighed unevenly. Relevant evidence for established DME is primarily based on one registry preprint, with additional evidence from a small retrospective cohort of patients with DR that did not restrict to DME. Lastly, direct comparisons between individual agents in established DME are missing, as well as

early-treatment and long-term effects, are poorly showed. Injection frequency and response were defined differently in the primary studies. Rapid advancements in the field may validate some of the conclusions made here.

Future Research Priorities

Early changes in established DME may be related to the magnitude or rate of HbA1c reduction, and further research is required to identify these relationships. One potential research strategy could be to follow individuals with DME who initiate treatment with a GLP-1 RA with optical coherence tomography (OCT), visual acuity assessments, and HbA1c measurements at baseline and at intervals over the first 3 to 6 months. If DME changes are related to the magnitude or rate of improvement in glycemic control, the studies described could identify these changes. Remote or home OCT could enable more frequent monitoring of DME in the first 3 to 6 months of treatment with a GLP-1 RA as compared to clinic visits, but the potential utility of OCT in this setting is still to be determined.

Better observational study design based on the desired outcomes is essential. A set of outcomes agreed upon for systemic-drug studies in DME would make results more comparable, such as the number of injections per year, the regimen interval (treat-and-extend vs. as-needed), the best-corrected visual acuity, central retinal fluid, and a defined response grade.

Future studies should a priori define relevant features of OCT and distinguish their roles as prognostic factors, confounders and effect modifiers. Automated OCT analysis, including machine-learning methods, could support standard measurement of fluid compartments and other retinal features across large cohorts. Tools should be evaluated for use in DME before to study use case, and performance efficiency should be checked across the imaging devices and patient populations.

STATEMENTS ON COMPLIANCE WITH ETHICAL STANDARDS

Disclosure of conflict of interest

The authors declare no conflicts of interest regarding this manuscript.

Artificial intelligence statement

The authors have used artificial intelligence only for literature searching and language editing to improve the clarity of the manuscript. All scientific content, interpretation and final decision checked by authors for the final manuscript.

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