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IMPACT OF GLP-1 RECEPTOR AGONISTS ON THE MANAGEMENT OF DIABETIC RETINOPATHY: NEUROPROTECTIVE EFFECTS AND ASSOCIATED RISKS

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Abstract: Diabetic retinopathy (DR) is one of the most common and impactful complications of type 2 diabetes (T2DM), often leading to vision loss. With the advancement of DM2 therapies, GLP-1 receptor agonists (GLP-1RAs) have been evaluated not only for glycemic control, but also for their potential effects on DR. This review investigated the therapeutic effects, mechanisms of action and risks of GLP-1RAs in the management of DR. Relevant studies published between 2018 and 2023 were analyzed, including clinical trials, animal studies and systematic reviews. The results indicate that GLP-1RAs have neuroprotective and anti-inflammatory effects on the retina, contributing to vascular integrity and reducing blood leakage. However, in some cases, such as with semaglutide, it was observed that the rapid decrease in glycemia can exacerbate DR in patients with inadequate glycemic control. It is concluded that GLP-1RAs can be effective in the management of DR, as long as treatment is carefully monitored to avoid worsening. More long-term studies are needed to define guidelines that maximize the benefits and minimize the risks for patients with DM2 and DR.
Keywords: Diabetic Retinopathy; GLP-1 Receptor Agonists; Type 2 Diabetes Neuroprotection.

INTRODUCTION

Diabetic retinopathy (DR) is one of the most prevalent and impacting microvascular complications of type 2 diabetes mellitus (DM2) and is responsible for a high rate of vision loss among adults around the world. This condition arises due to chronic hyperglycemia, which leads to progressive neurovascular degeneration of the retina and can progress to severe forms, such as proliferative retinopathy (PR), characterized by the formation of anomalous blood vessels in the retina, which significantly increase the

risk of blindness (Tang et al., 2018). In this context, with the severe impact that PR has on patients' quality of life and on healthcare systems, research into interventions that can slow down the progression or reduce the risk of developing this ocular complication has become essential (Saw et al., 2019).

With the advancement of new classes of drugs for DM2, GLP-1 receptor agonists (GLP-1RAs) have gained prominence not only for their hypoglycemic effect, but also for their potential influence on other complications of diabetes, including DR (Liu et al., 2023). Recent studies have sought to evaluate the role of GLP-1RAs in modulating DR, with some evidence suggesting that these agents may offer protection to the retina through neuroprotective and antioxidant effects, as well as contributing to the reduction of vascular leakage and retinal neurodegeneration associated with DR (Saw et al., 2019). However, the results are still controversial: while some GLP-1RAs have been associated with potential benefits for the retina, others, such as semaglutide, have revealed an increased risk of retinal complications in certain clinical contexts (Wai et al., 2023).

The meta-analysis conducted by Tang et al. (2018) compared the risk of DR events associated with different hypoglycemic agents, including GLP-1RAs. The authors found a neutral association between GLP-1RAs and the risk of DR, although they noted that sulfonylureas showed a significantly increased risk of DR progression, indicating that some agents may be more suitable for patients with DR compared to others (Tang et al., 2018). Complementarily, Saw et al. (2019) investigated the new therapeutic options for T2DM, reporting that while most non-insulin antihyperglycemic agents showed neutral or beneficial effects on DR, semaglutide showed an association with retinal complications. These findings suggest that the choice of antihyperglycemic agents may impact the development and progression of DR, especially in patients who already show signs of ocular complications.

To further evaluate the role of GLP-1RAs in DR, Liu et al. (2023) conducted a comprehensive review, suggesting that these agents may be considered a promising therapeutic option for patients with early DR, since they have neuroprotective effects and may contribute to the integrity of the blood-retinal barrier, reducing oxidative stress and inflammation (Liu et al., 2023). These data point to the potential use of GLP-1RAs as an intervention to slow down the progression of DR, especially in patients with high cardiovascular risk or associated microvascular complications (Perais et al., 2023).

This study aims to review the current scientific literature on the effects of the use of GLP-1 receptor agonists in diabetic retinopathy, in order to understand the efficacy, limitations and possibilities of these agents in the management of DR in patients with type 2 diabetes.

METHODOLOGY

This integrative review was conducted with the aim of synthesizing and analyzing the most relevant studies related to the use of GLP-1 receptor agonists in the management of DR in patients with type 2 diabetes. Initially, an extensive search was carried out in academic databases, including PubMed, EMBASE and the Cochrane Central Register of Controlled Trials, using search terms related to the use of GLP-1RAs and diabetic retinopathy.

The inclusion criteria defined for this review included studies published between 2018 and 2023, available in English or Portuguese, which addressed therapeutic effects, mechanisms of action, adverse effects or impact on the progression of diabetic retinopathy. Studies that did not present specific data on GLP-1RAs or that exclusively addressed other classes of diabetes medication were excluded.

After the initial search, 87 potentially relevant studies were identified. The titles and abstracts of these studies were then reviewed to check that they met the inclusion criteria, and those that clearly did not meet the criteria were excluded. The remaining studies were subjected to a full analysis, assessing in detail the contributions of each one to the objectives of the review.

After careful analysis, 7 studies were selected as the most relevant for this integrative review. These studies were chosen based on their relevance to the main topics of interest, such as the effects of GLP-1RAs on DR, mechanisms of action in the retinal environment, possible adverse effects and comparisons with other classes of hypoglycemic drugs.

Synthesizing the results of these studies has provided a comprehensive understanding of the role of GLP-1RAs in the treatment of diabetic retinopathy, addressing both the potential benefits and the limitations and needs for future research into this therapeutic approach.

RESULTS

The analysis of the selected studies on the impact of GLP-1 receptor agonists (GLP-1RAs) on diabetic retinopathy (DR) shows both potential benefits and limitations. The findings present a diversity of methodological approaches, including retrospective cohort studies, clinical trials, experimental analyses in animal models and systematic reviews. These studies address, from different perspectives, the efficacy of GLP-1RAs in controlling the progression of DR, as well as their molecular mechanisms of action in the diabetic retina, especially in terms of neurovascular protection.

DISCUSSION

In the retrospective study by Joo et al. (2024), the comparison between patients who used GLP-1RAs and those who used SGLT-2 inhibitors (SGLT-2I) did not show a significant association between the use of GLP-1RAs and worsening of DR, with progression rates of 2.3% and 2.8% for each group, respectively. The study showed that GLP-1RAs do not present a greater risk of worsening than SGLT-2Is, suggesting safety in the choice of GLP-1RAs for patients with DR. However, as this study did not address specific molecular mechanisms, it leaves open how GLP-1RAs may affect the retina in biochemical and structural terms (Joo et al., 2024).

In a complementary way, the work by Vilsbøll et al. (2018), when analyzing data from the SUSTAIN clinical trials, highlights a potential risk of complications in DR with the use of semaglutide, especially in patients with pre-existing DR and inadequate glycemic control. The results showed that the rapid reduction in glycated hemoglobin (HbA1c) with semaglutide can worsen DR, an effect that is also known with insulin use. These findings highlight the importance of careful monitoring and adjustments to the pace of glucose reduction, particularly for semaglutide. Although semaglutide has shown beneficial effects for diabetes control, the risk of worsening DR in certain contexts highlights the need for further studies specific to each GLP-1 agent (Vilsbøll et al., 2018).

In animal model studies, Shu et al. (2019) and Wei et al. (2022) explored the molecular mechanisms of GLP-1RAs in the retina, showing evidence of neuroprotection and protection of the blood-retinal barrier (BRB). Shu et al. (2019) demonstrated that liraglutide prevents synaptic neurodegeneration of ganglion cells in the retina by activating the GLP-1R/Akt/GSK3β signaling pathway, a mechanism that reduces toxicity associated

Study	Objective	Methods	Results	Conclusion
Joo et al. (2024)	Comparing the progression of DR in patients using GLP-1RA and SGLT-2I	Retrospective cohort of 981 patients with DM, matched by propensity score	RD worsening rate of 2.3% (GLP-1RA) and 2.8% (SGLT-2I); No significant difference in progression or time to first worsening	GLP-1RA was not associated with progression of DR compared to SGLT-2I
Vilsbøll et al. (2018)	Evaluate the risk of complications of HD with the use of semaglutide	Post hoc analysis of the SUSTAIN-6 study and subgroups in clinical trials	Semaglutide associated with higher risk of complications in pre-existing DR due to rapid reduction in HbA1c	Rapid reduction of HbA1c with semaglutide may worsen DR in some patients; monitoring recommendations are suggested
Shu et al. (2019)	Examining the neuroprotective effects of liraglutide in DR	Diabetic mouse model with topical ocular application of liraglutide	Liraglutide reversed retinal neurodegeneration via activation of GLP-1R/Akt/GSK3β signaling	Liraglutide may prevent synaptic neurodegeneration in RD; potential as topical therapy for early RD
Wei et al. (2022)	Investigating the role of GLP-1RA in protecting the blood-retinal barrier	Study with diabetic mice and analysis of BRB proteins	GLP-1RA improved BRB structure and reduced vascular leakage by inhibiting the RhoA/ROCK pathway	GLP-1RA has a protective effect on BRB, suggesting a benefit for DR control in DM2
He et al. (2024)	Evaluating the effects of GLP-1RAs on retinal endothelial protection in RD	Retrospective cohort and molecular analysis	GLP-1RA reduced the activation of STING signaling and improved vascular integrity in the retina	GLP-1RA has anti-inflammatory effects, benefiting the retinal vasculature in DR
Sivakumar et al. (2021)	Review the role of GLP-1RAs in the management of DM2 and microvascular complications	Systematic review of clinical data	GLP-1RAs show benefits in neuroprotection, weight loss and glycemic control, with the potential to prevent RD	GLP-1RAs are suitable alternatives in the long-term treatment of DM2 with a positive impact on DR
Ntentakis et al. (2024)	Reviewing the effects of new antidiabetic classes on DR	Systematic literature review with 59 studies	GLP-1RAs, especially semaglutide, show variable risk in DR; other antidiabetics had neutral effects	Long-term investigations are recommended to assess the impact of antidiabetics on DR

Table 1.0 - Summary of the main studies on the use of GLP-1 receptor agonists (GLP-1RAs) and their effects on DR.

with hyperphosphorylation of the tau protein, implicated in neuronal degeneration. This suggests a potential use of GLP-1RAs as a protective therapy in early DR, with neuroprotective effects that go beyond glycemic control. In parallel, Wei et al. (2022) showed that GLP-1RA protects the BRB, reducing vascular leakage and strengthening retinal structure via inhibition of the RhoA/ROCK pathway. These experimental findings corroborate the potential of GLP-1RAs for neuroprotection and vascular integrity in the retina, offering promising prospects for the treatment of DR.

The study by He et al. (2024) expands this understanding by identifying that GLP-1RAs also modulate retinal inflammation, specifically by suppressing STING signaling, which is activated by mitochondrial stress in retinal endothelial cells. This inhibition of STING suggests that GLP-1RAs may act as anti-inflammatory modulators, contributing to the maintenance of vascular integrity and decreasing inflammatory and oxidative stress in diabetic retinas. These effects are promising, as chronic inflammation is one of the main factors aggravating DR, and inflammatory control may help prevent more serious complications (He et al., 2024).

The systematic review conducted by Sivakumar et al. (2021) also points to the benefits of GLP-1RAs in the microvascular complications of diabetes, including DR. The review suggests that, in addition to glycemic

control, GLP-1RAs promote weight loss and have anti-inflammatory and neuroprotective activities, essential characteristics for the long-term management of DR. These data reinforce that GLP-1RAs, especially when combined with other therapies, can offer multifactorial protection to patients with DM2.

Finally, Ntentakis et al. (2024) analyzed the impact of different classes of antidiabetic drugs on DR. The review reveals that although most of the new antidiabetics have neutral effects on the progression of DR, there are important differences between GLP-1RAs. Semaglutide, in particular, was associated with a potential worsening of DR, as well as an increased risk of macular edema in patients with greater vulnerability, such as the elderly and those with advanced kidney disease. These findings reinforce that the safety profile of GLP-1RAs can vary, and that each agent should be considered individually to avoid retinal complications in patients with DR.

Taken together, these studies suggest that GLP-1RAs play an important role in DR, with potential beneficial effects for neuroprotection and the reduction of inflammation and retinal vascular leakage. However, rapid glycemic reduction, especially with agents such as semaglutide, may pose a risk for patients with advanced DR or inadequate previous glycemic control. Thus, the choice of GLP-1RAs for the management of diabetes in patients with DR requires a careful approach, balancing the potential benefits of neuroprotection and inflammatory reduction with close monitoring to prevent worsening. These findings highlight the importance of additional long-term studies with large cohorts to better define the safety profile of GLP-1RAs in DR and identify which patients can obtain the maximum benefit from this therapeutic class.

FINAL CONSIDERATIONS

GLP-1 receptor agonists are a promising alternative for the management of DR, combining efficacy in glycemic control with neuroprotective and anti-inflammatory effects on the retina. Although these drugs show benefits, especially in maintaining the blood--retinal barrier, their use requires caution, as rapid glycemic reduction, particularly with semaglutide, can worsen DR in patients with inadequate glycemic control. Individualization of treatment and regular monitoring are essential to maximize the benefits of GLP--1RAs and minimize risks. Additional studies with larger cohorts and long-term follow-up are needed to establish safety guidelines and identify profiles of patients who would benefit most from this therapeutic class in the context of DR.

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