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GLP-1 RECEPTOR AGONISTS IN THE TREATMENT OF NEURODEGENERATIVE DISEASES

Paulo Victor Gonçalves Secco
Cachoeiro de Itapemirim College (MULTIVIX), Espírito Santo - ES
https://orcid.org/0009-0005-5917-5846

Thais Magalhães Teixeira Lira
Metropolitan College of Manaus (FAMETRO), Manaus - Amazonas
https://orcid.org/0000-0002-5199-4768

Hagata Sabrina de Almeida Rosa
University of Cuiabá (UNIC), Cuiabá - MT
https://orcid.org/0009-0002-3680-5911

Lívia Maria Gregório Vicente Leite
Olinda Medical School (FMO), Olinda - PE
https://orcid.org/0009-0002-5706-5318

Leticia Arruda Barbosa
Federal University of Pernambuco (UFPE)
Caruaru-PE
https://orcid.org/0009-0001-7134-6493

Fernando Antonio Ferreira de Almeida Sobrinho
National University of Rosario (UNR)
Rosario-Santa Fe
https://orcid.org/0009-0009-5542-4883

Juliana Maria Xavier Nabeiro
Morgana Potrich College (FAMP)
Mineiros-GO
https://orcid.org/0009-0007-9667-3523

Nínyve Gabriela Filgueira da Silva
Maurício de Nassau University Center (UNINASSAU), Recife - PE
https://orcid.org/0009-0002-2385-3332

Jullia Rodrigues de Sousa e Silva
Federal University of Goiás (UFG)
Goiânia-GO
https://orcid.org/0000-0002-6747-6842

Muriel Terra Pizzutti dos Santos
Pontifical Catholic University of Rio Grande do Sul (PUC-RS), Porto Alegre - RS
https://orcid.org/0009-0002-1956-0123

Monique Roschel Gonçalves Castro
São Camilo University Center (CUSC)
São Paulo - SP
https://orcid.org/0009-0002-8465-9111

Abstract: Objective: To evaluate the efficacy and safety of GLP-1 receptor agonists in the management of Alzheimer's Disease (AD) and Parkinson's Disease (PD), highlighting their neuroprotective mechanisms and impact on contemporary neurology. **Methodology:** Bibliographic review of articles published between 2020 and 2025 in the PubMed-MEDLINE database, using the descriptors "GLP-1 Receptor Agonists", "Alzheimer's Disease" and "Parkinson's Disease" combined with Boolean operators "AND" and "OR". Only complete, peer-reviewed studies in English were included, excluding duplicates, abstracts and articles out of scope, resulting in the analysis of 15 studies. **Discussion:** GLP-1 agonists show neuroprotective effects in AD and PD, reducing oxidative stress, neuroinflammation and neuronal apoptosis. In AD, there is evidence of a reduction in beta-amyloid deposits and hyperphosphorylation of the tau protein, slowing disease progression. In PD, dopaminergic preservation and motor improvement are observed, suggesting a positive impact on patients' quality of life. However, the limited number of clinical trials prevents definitive conclusions, requiring further studies to confirm their long-term efficacy and safety. **Conclusion:** GLP-1 agonists show promising therapeutic potential for neurodegenerative diseases, but further studies are needed to validate their clinical application and establish safe guidelines.

Keywords: GLP-1 agonists, Alzheimer's disease, Parkinson's disease, Neuroprotection, Pharmacological treatment.

INTRODUCTION

Neurodegenerative diseases (ND), such as Alzheimer's disease (AD) and Parkinson's disease (PD), represent one of the greatest challenges in medicine today, significantly impacting the quality of life of affected individuals (Siddeeque *et al*., 2024). Although available treatments can alleviate symptoms, they are

unable to modify the progression of these diseases (Lv *et al*., 2024). Among NDs, AD is the most prevalent and leading cause of dementia, affecting more than 46 million people worldwide (Du *et al*., 2022).

In this context, glucagon-like peptide type 1 (GLP-1) receptor agonists have emerged as a promising alternative. These agents, originally developed for the treatment of type 2 diabetes, have demonstrated neuroprotective properties associated with a reduction in oxidative stress and neuroinflammation, essential factors in the pathophysiology of DN (Lv *et al*., 2024). However, there is still disagreement as to the efficacy of these drugs in the treatment of PD. While Siddeeque *et al.* (2024) indicate a limited effect, Lv *et al.* (2024) present more robust evidence of clinical improvement. Despite these disagreements, there is consensus that GLP-1 agonists represent a promising therapeutic approach for AD.

The relationship between diabetes and an increased risk of neurodegenerative diseases has been widely documented. This link is believed to be mediated by common metabolic, vascular and inflammatory pathways, including insulin resistance, mitochondrial dysfunction, formation of advanced glycation end products (AGEs) and aggregation of pathological proteins such as beta-amyloid (Aβ) and α-synuclein (Hong; Chen; Hu, 2024). These pathogenic mechanisms reinforce the hypothesis that the GLP-1 system may play a crucial role in modulating neurodegeneration.

GLP-1, an incretin hormone derived from intestinal L-cells, plays a central role in glycemic control by stimulating insulin secretion and inhibiting glucagon release (Du *et al.*, 2022). In the central nervous system, its receptors are widely distributed, including the cerebral cortex, where they can modulate neurogenesis, synaptic plasticity and the inflammatory response. The activation of these receptors by GLP-1 agonists may mimic the beneficial effects of this system on neuronal function, reinforcing the hypothesis of its therapeutic potential in DN (Hong; Chen; Hu, 2024).

Preclinical evidence supports that GLP-1 agonists cross the blood-brain barrier and activate brain receptors, promoting neuroprotection and stimulating the proliferation of neuronal progenitors (Hong; Chen; Hu, 2024). Among these drugs, long-acting formulations, such as liraglutide and lixisenatide, have shown greater stability and efficacy, being administered once a day, in contrast to short-acting ones, such as exenatide, which require multiple daily injections (Kalinderi; Papaliagkas; Fidani, 2024). Despite advances, current treatments for AD and PD are still limited, focusing mainly on symptomatic control rather than acting on the underlying degenerative processes. For AD, therapeutic strategies aim to reduce Aβ deposition, prevent tau pathology and preserve neuronal function. In PD, the main objective is to protect dopaminergic neurons, improve mitochondrial function and modulate α-synuclein aggregation, in addition to investigating gene therapies (Hong; Chen; Hu, 2024).

Given this scenario, the search for new therapeutic strategies for neurodegenerative diseases has become imperative. Therefore, this study aims to critically analyze the scientific evidence on the efficacy and safety of GLP-1 receptor agonists in the treatment of AD and PD, as well as discussing the mechanisms of action that justify their potential neuroprotective effects.

METHODOLOGY

A literature review developed according to the criteria of the PVO strategy, which stands for: population or research problem, variables and outcome. This strategy was used to develop the research question "Are GLP-1 receptor agonists effective and safe in the treatment of neurodegenerative diseases such as Alzheimer's and Parkinson's?". The searches were

carried out using the PubMed - MEDLINE (Medical Literature Analysis and Retrieval System Online) databases. The search terms were used in combination with the Boolean terms "**AND" and "OR"** using the following search strategy: (("GLP-1 Receptor Agonists") OR ("glucagon-like peptide-1 receptor agonists") OR (semaglutide) OR (exenatide) OR (liraglutide)) AND ((Neurodegenerative Diseases) OR ("Alzheimer's Disease") OR ("Parkinson's Disease")). From this search, **176** articles were found, which were then submitted to the selection criteria: articles in English; published between 2020 and 2025 and which addressed the themes proposed for this research, studies of the type (narrative review, systematic review, meta-analysis, observational studies, experimental studies. The exclusion criteria were: duplicate articles, articles available in abstract form, articles that did not directly address the proposal studied and articles that did not meet the other inclusion criteria. After applying the search strategy to the database, a total of **28** articles were found. After applying the inclusion and exclusion criteria, **15** articles were selected from the PubMed database to make up this study's collection.

DISCUSSION

Glucagon-like peptide-1 receptor agonists (GLP-1RAs), such as semaglutide (SEM), have significant potential in the treatment of neurodegenerative diseases due to their multiple actions on the central nervous system (CNS). According to Wang *et al.* (2024), semaglutide was approved by the US Food and Drug Administration (FDA) for the treatment of type 2 diabetes mellitus (DM2) in 2017 and for weight loss in 2021. Both DM2 and obesity are considered modifiable risk factors for Alzheimer's disease (AD), which reinforces interest in the role of these drugs in neuroprotection. GLP-1 receptor agonists, also known as incretin analogues, act to regulate glucose homeostasis by stimulating the release of the incretin hormone GLP-1 by intestinal L cells after meals. These agents bind to receptors widely distributed in the body, including the pancreas, kidney, lungs, cardiovascular system, gastrointestinal tract, immune system and CNS (Meca *et al.*, 2024).

MECHANISM OF ACTION OF GLP-1 RECEPTOR AGONISTS

In the CNS, GLP-1R and GIP (glucose-dependent insulinotropic polypeptide) receptors belong to the class of G protein-coupled B1 receptors and play an important role in activating intracellular pathways. Activation of these receptors induces the production of cAMP (cyclic adenosine monophosphate) and triggers a cascade of cellular reactions, including an increase in intracellular calcium levels and phosphorylation of ERK1/2 (a subfamily of proteins that regulates various cellular and physiological processes, with an essential role in the expression of inflammatory genes), processes that contribute to the regulation of insulin secretion and to neuroprotective effects (Meca *et al.*, 2024). In addition, these drugs are able to cross the blood-brain barrier (BBB), which allows them to initiate direct effects in the brain, such as modulating energy homeostasis, neurogenesis and reducing neuroinflammation (Moreira *et al.*, 2022).

Experimental studies indicate that semaglutide can reduce the severity of polymicrobial inflammation and neuroinflammation by activating GLP-1 receptors in the CNS (Wang *et al.*, 2024). In addition, GLP-1 has the ability to modulate various brain functions, including energy homeostasis, thermogenesis, water intake, neurogenesis and stress responses. The improvement in cognitive impairment observed in experimental models has led to the recommendation of GLP-1 receptor agonists for neurological deficits associated with DM2 and obesity (Meca *et al.*, 2024). Acti-

vation of these receptors is associated with a reduction in neuroinflammation by mechanisms that include inhibiting microglial activation and decreasing the release of pro-inflammatory cytokines such as TNF-α, IL-6 and IL-1β, crucial factors in the pathogenesis of AD and Parkinson's Disease (PD) (Moreira *et al*., 2022).

The neuroprotective effects of GLP-1RAs are also related to their ability to promote neurogenesis and synaptic plasticity. These drugs have been shown, in animal models, to stimulate the proliferation of neural progenitor cells and improve cognitive function by increasing the efficiency of long-term potentiation (LTP) in the hippocampus, a fundamental process for learning and memory (Moreira *et al.*, 2022). In addition, experimental evidence suggests that GLP-1 agonists can attenuate the aggregation of pathological proteins, such as amyloid plaques and neurofibrillary tangles, which are characteristic of AD. Animal models have shown that treatment with liraglutide and exendin-4 is associated with a reduction in amyloid load and tau phosphorylation, the main histopathological markers of AD (Moreira *et al*., 2022). In relation to PD, it has been observed that these agents preserve dopaminergic neurons and stimulate neurogenesis, resulting in improved motor symptoms in these experimental models (Moreira *et al*., 2022).

Despite the promising evidence obtained in pre-clinical studies, clinical trials involving GLP-1RAs for neurodegenerative diseases present heterogeneous findings. Some studies indicate improved cognitive function and cerebral glucose uptake, while others have not identified significant effects on disease progression or neurodegenerative biomarkers (Moreira *et al*., 2022). For example, a phase II clinical trial with liraglutide in patients with mild AD failed to demonstrate a significant reduction in the load of amyloid plaques, although a favorable trend was observed in the preservation of gray matter volume. A study with exenatide in PD patients showed benefits in motor function, but the evidence is still considered to be of low certainty (Moreira *et al*., 2022).

The complexity of neurodegenerative diseases suggests that a multifactorial therapeutic approach is needed, and GLP-1R signaling has emerged as a promising target due to its role in energy homeostasis and neuroinflammation. However, issues such as the optimal duration of treatment, the cerebral bioavailability of GLP-1RAs and the identification of predictive biomarkers of response still need to be clarified. Ongoing clinical trials at , including the use of semaglutide in patients with AD and PD, may provide crucial information for translating these experimental findings into clinical practice (Moreira *et al.*, 2022). Thus, although GLP-1 agonists represent a promising therapeutic approach for neurodegenerative diseases, additional well-controlled studies are needed to confirm their efficacy and establish guidelines for their clinical use.

USE OF GLP-1RAS IN ALZHEIMER'S DISEASE

Alzheimer's disease (AD) is characterized by the abnormal accumulation of beta-amyloid plaques and the hyperphosphorylation of tau protein, phenomena that result in progressive neurodegeneration. The amyloid cascade hypothesis suggests that beta-amyloid deposition triggers a neurotoxic process that culminates in synaptic dysfunction and neuronal death, contributing to the cognitive decline characteristic of the disease (Akimoto *et al.*, 2020). Within this context, GLP-1RAs have been widely studied for their neuroprotective effects, being able to modulate fundamental pathological processes in AD, including the reduction of oxidative stress, neuroinflammation and the formation of neurofibrillary tangles (Fontanella *et al*., 2024).

The relationship between type 2 diabetes mellitus (DM2) and an increased risk of developing AD has been widely documented and is explained by mechanisms such as oxidative stress, mitochondrial dysfunction and chronic inflammation. In addition, cerebral insulin resistance compromises the inhibition of the enzyme glycogen synthase kinase 3 beta (GSK3β), favoring the hyperphosphorylation of the tau protein and the formation of neurofibrillary tangles, accelerating neurodegeneration (Koychev *et al*., 2024). This correlation is due to the intersection of insulin signaling pathways in the brain, where this hormone is directly involved in memory formation and neuronal proliferation. Patients with AD, regardless of the presence of DM2, have insulin resistance in critical brain regions such as the hippocampus and cerebral cortex, which reinforces the hypothesis that GLP-1 signaling may play a therapeutic role in these conditions (Akimoto *et al.*, 2020).

Recent studies suggest that treatment with exenatide, a GLP-1 analog, is associated with significant changes in inflammatory biomarkers related to AD, such as CRP, sVCAM-1 and FCN-2 (Koychev *et al.*, 2024). CRP, for example, is elevated in the CSF of AD patients and can be detected in amyloid plaques, favoring tau protein phosphorylation. Although increased CRP levels are associated with the risk of dementia, this relationship may be modulated by the presence of the APOE4 allele, recognized as the main genetic risk factor for AD.

The reduction in sVCAM-1 observed with the use of exenatide is relevant, given that this molecule is associated with vascular inflammation, systemic endothelial dysfunction and hypertension - conditions often implicated in the cerebrovascular dysfunction of AD. FCN-2, whose expression is regulated by a gene related to susceptibility to autoimmune and infectious diseases, acts on the complement system, promoting opsonization and destruction of pathogens. The modulation of these biomarkers reinforces the anti-inflammatory and immunomodulatory potential of GLP-1 agonists in the neurodegenerative context.

A comparison between GLP-1 analogues and metformin in diabetic patients showed that the former are associated with a lower risk of AD, which can be explained by their ability to reduce insulin resistance and improve cerebral energy homeostasis. In addition, because they are injectable medications, users of these therapies require a greater understanding of how they work, which may contribute to better cognitive function and possibly reduce the risk of dementia (Akimoto *et al.*, 2020).

Another advance in the study of GLP-1 agonists is the potential of tirzepatide (TIR) for neuroprotection. According to Fontanella *et al.* (2024), treatment with TIR led to activation of the CREB/BDNF signaling pathway, known for its importance in neuronal survival and synaptic plasticity, in SHSY5Y cells exposed to both normal glucose and high levels of glucose, simulating diabetic conditions. In addition, a reduction in the expression of BAX/Bcl2, an apoptosis marker, and an increase in key proteins for neuronal support and cytoskeleton stability, including MAP-2, GAP-43 and AGBL-4, were observed. These findings reinforce the potential of tirzepatide in the prevention and treatment of neurodegenerative disorders such as AD (Fontanella *et al.*, 2024).

Given this evidence, GLP-1 receptor agonists have emerged as a promising approach for AD, acting to reduce the accumulation of beta-amyloid, modulate tau protein hyperphosphorylation and improve cognitive function. However, although pre-clinical and clinical studies show potential benefits, there are still challenges in translating these findings into clinical practice. Further research is needed to clarify the mechanisms of action, the optimal duration of treatment and the effi-

cacy of these drugs at different stages of AD. Ongoing clinical trials may provide crucial answers to consolidate the use of GLP-1RAs in the management of AD, cementing their role as a viable therapeutic alternative for neurodegenerative diseases (Fontanella *et al*., 2024).

APPLICATION OF GLP-1RAS IN PARKINSON'S DISEASE

Parkinson's disease (PD) is a progressive neurodegenerative condition characterized by the degeneration of dopaminergic neurons in the midbrain, resulting in predominantly motor manifestations such as tremor, muscle rigidity and bradykinesia. Recent studies suggest a significant correlation between type 2 diabetes mellitus (DM2) and PD, as both share common pathophysiological mechanisms, including insulin resistance, mitochondrial dysfunction and neuroinflammation. This relationship reinforces the hypothesis that drugs originally developed for the treatment of DM2, such as GLP-1RAs, may act as promising therapeutic agents in PD, offering not only symptomatic improvement, but also neuroprotective potential, impacting the progression of the disease (Greco *et al*., 2023; Kong *et al*., 2023).

Insulin plays a crucial role in neurological homeostasis, influencing synaptic plasticity and cognitive functions. Insulin resistance in the central nervous system (CNS) compromises glucose uptake by neurons and contributes to neuronal degeneration, a phenomenon observed in both DM2 and PD. This mechanism leads to dysfunction of energy homeostasis and increased production of reactive oxygen species (ROS), creating an environment favorable to the release of inflammatory mediators and triggering mitochondrial and lysosomal dysfunction. In addition, these alterations promote deficits in glucose metabolism and reduce the nutritional supply to the CNS, aggravating the progression of PD (Norgaard *et al*., 2024; Greco *et al*., 2023). Thus, therapeutic strategies that act on metabolic regulation, such as GLP-1RAs, have been explored as innovative alternatives to mitigate neurodegenerative damage in PD.

GLP-1RAs show neuroprotective effects by modulating various cellular pathways involved in neuronal survival, autophagy and cell proliferation. Activation of the GLP-1 receptor in the CNS triggers the PI3K/AKT pathway, which inhibits the GSK3-β kinase, reducing oxidative stress and promoting neuronal survival by activating different cytoprotective pathways (Greco *et al*., 2023). In addition, experimental evidence indicates that these drugs are able to reduce the aggregation of alpha-synuclein, a protein whose aberrant deposition plays a central role in the pathogenesis of PD. GLP-1RAs also promote the preservation of mitochondrial function and attenuate neuroinflammation by modulating microglia activation and the production of pro-inflammatory cytokines. These mechanisms favor the maintenance of synaptic transmission and reduce learning deficits in experimental models (Kong *et al*., 2023; Norgaard *et al*., 2024).

The main GLP-1 agonists studied in PD include exenatide, liraglutide, lixisenatide, semaglutide and NLY01, the latter being a promising experimental compound for Parkinson's disease, which binds to the GLP-1 receptor and exerts a neuroprotective function. These compounds showed significant neuroprotective effects in preclinical studies and were associated with improved motor symptoms in early clinical trials (Greco *et al*., 2023). A recent meta-analysis evaluated the impact of GLP-1RAs on cognitive and motor function in PD patients and showed that the use of exenatide was associated with a more significant improvement in motor skills and learning compared to liraglutide. However, no significant differences in cognitive function were observed between patients who used li-

raglutide and those in the placebo group. In addition, intranasal administration of exenatide, at doses between 10.47 and 104.68 μg/kg, proved to be more effective in improving cognitive function than subcutaneous administration. This difference suggests that the intranasal route may be more efficient for delivering the drug to the CNS, reducing pharmacokinetic barriers (Kong *et al*., 2023). Although the neuroprotective effects of GLP-1RAs are promising, there are still uncertainties about their definitive clinical efficacy, especially in advanced stages of PD.

In addition to GLP-1RAs, other drugs used to treat DM2 have been investigated for their neuroprotective potential in PD. Metformin, considered the first-line treatment for DM2, has been shown to reduce EROS production, promote autophagy and rescue mitochondrial dysfunction, resulting in less damage to dopaminergic neurons and improved PD motor symptoms (Greco *et al*., 2023; Kong *et al*., 2023). Similarly, inhibitors of the sodium-glucose cotransporter type 2 (SGLT2), such as empagliflozin and dapagliflozin, have shown neuroprotective effects in experimental models, reducing neuroinflammation and preserving mitochondrial function (Kong *et al.*, 2023). Another group of drugs that have been studied are the glitazones, such as pioglitazone, lobeglitazone and rosiglitazone. In addition to improving insulin sensitivity, these drugs act as agonists of the Peroxisome Proliferator-Activated Receptor (PPARs), exerting anti-inflammatory and anti-apoptotic effects. These actions contribute to reducing inflammation and cell death in neurodegenerative diseases, which can help preserve cognitive and motor function in PD patients (Greco *et al*., 2023).

Another relevant factor in the context of PD is the role of insulin in regulating neuroprotective processes. However, its low permeability to the blood-brain barrier (BBB) and the glycemic effects associated with parenteral administration limit its clinical use. To overcome these difficulties, recent studies have investigated intranasal administration of insulin via in animal models of PD. The results showed that this approach improves insulin signaling in the CNS, reduces neuroinflammation and neuronal loss, and modulates cellular processes involved in mitochondrial homeostasis. These effects are mediated by activation of the PI3K/AKT and MAPK pathways, leading to increased expression of hypoxia-inducible factor-1 (HIF-1), which is associated with angiogenesis and tissue regeneration. In addition, intranasal insulin has also been shown to restore mitochondrial activity in critical brain regions such as the hypothalamus and hippocampus, suggesting significant therapeutic potential for PD (Greco *et al.*, 2023).

Given this evidence, GLP-1 agonists have emerged as an innovative therapeutic approach for PD, acting to improve motor symptoms and modulate neurodegenerative processes. However, although pre-clinical and clinical studies indicate promising benefits, there are still gaps in understanding the mechanisms of action and the long-term efficacy of these drugs. Ongoing clinical trials could provide more robust data on the clinical applicability of GLP-1RAs in PD, helping to define guidelines for their use in medical practice (Greco *et al*., 2023; Kong *et al.*, 2023).

SAFETY AND ADVERSE EFFECTS

Although the benefits of GLP-1 agonists have been widely studied, their safety and possible adverse effects when used for indications other than DM2 need to be considered. According to Wolff *et al.* (2023), the prevalence of PD has increased globally, reinforcing the need for new therapeutic approaches that prolong survival and improve patients' quality of life. Studies analyzed by Zhang *et al.* (2023) indicate that insulin resistance may also be

present in PD, regardless of the presence of DM2, making GLP-1 agonists promising candidates for modulating this metabolic dysfunction in the CNS. However, despite the positive effects on neuroprotection, some studies suggest that these drugs may have limitations related to safety and tolerability, especially in the long term.

Clinical trials have evaluated the impact of exenatide and liraglutide on PD and have reported significant benefits, such as improved motor function and reduced disease progression. However, Zhang *et al.* (2023) points out that patients taking exenatide have reported gastrointestinal adverse effects, such as nausea, vomiting and diarrhea, which are the most common adverse events associated with GLP-1 agonists. In addition, symptoms such as involuntary weight loss and fatigue have also been observed, possibly due to the modulation of energy metabolism and the action of GLP-1 on the hypothalamus, which regulates appetite. With regard to cardiovascular safety, studies indicate that these drugs can reduce the risk of cardiovascular events, such as myocardial infarction and stroke, in patients with DM2. However, their impact on cardiovascular function in patients without diabetes is still uncertain (Zhang *et al.*, 2023).

The activation of GLP-1 and GIP receptors influences multiple physiological processes in the brain and can impact the regulation of pro-inflammatory cytokines such as TNF-α and IL-1β. According to Zhang *et al.* (2023), these inflammatory mediators are involved in insulin desensitization and in reducing the synthesis of neuronal growth factors, such as brain-derived neurotrophic factor (BDNF). The use of liraglutide and the dual agonist DA5-CH, an experimental drug with superior potential in modulating dopamine and neuroinflammation, has been shown to reduce these inflammatory markers in the substantia nigra, contributing to an improvement in the neurochemical environment in PD patients. However, despite the beneficial effects, some studies suggest that prolonged use of GLP-1 agonists may influence the modulation of the immune response, which could increase the risk of infections or other complications related to chronic inflammatory regulation (Zhang *et al.*, 2023).

In AD, the relationship between insulin resistance and neurodegeneration has been widely studied. Fontanella *et al.* (2024) point out that DM2 and AD share pathophysiological factors, including dysfunction in insulin signaling in the CNS, which compromises synaptic activity and neuronal differentiation. GLP-1 agonists, such as tirzepatide, have shown promise in modulating insulin resistance in the brain and preventing cognitive impairment. Studies have shown that tirzepatide positively regulates neuronal growth markers such as CREB and BDNF, as well as modulating apoptosis by reducing BAX levels and increasing Bcl-2.

However, adverse effects have been reported, especially in patients without DM2 or previous insulin resistance. In these cases, a rebound effect can occur with increased hepatic gluconeogenesis and the development of compensatory insulin resistance, as a form of metabolic adaptation to the modulation of the insulin-GLP-1 axis. In addition, changes in hepatic and renal metabolism have been described, such as an increase in transaminases due to the excessive mobilization of fatty acids, which can overload the liver. There is also a risk of dehydration and kidney stone formation, associated with increased urinary calcium excretion and reduced plasma volume (Fontanella *et al.*, 2024).

Although GLP-1RAs have a favorable safety profile in patients with DM2 and have shown benefits in the treatment of neurodegenerative diseases, their use for these new indications requires close monitoring of adverse

effects and potential contraindications. Additional clinical trials will be essential to determine the balance between efficacy and safety, ensuring that the benefits of these drugs outweigh the potential risks (Zhang *et al.*, 2023; Fontanella *et al.*, 2024).

FINAL CONSIDERATIONS

PD and AD are neurodegenerative pathologies that share pathophysiological mechanisms with type 2 diabetes mellitus, particularly insulin resistance and energy metabolism dysfunction. In this context, GLP-1RAs have shown significant therapeutic potential, exerting neuroprotective effects that include reducing neuroinflammation, oxidative stress, beta-amyloid plaque formation and tau protein hyperphosphorylation in AD. In addition, pre-clinical evidence indicates an improvement in neuronal plasticity and memory, while in PD patients, an attenuation of motor symptoms has been observed.

Despite the promising advances, there are still gaps that need to be clarified by future studies, such as the complete elucidation of the mechanisms of action of these drugs, the ideal duration of treatment and the dose-effect-response relationship in both diseases. Furthermore, although GLP-1RAs contribute to improving cognitive symptoms and reducing cardiovascular risks, their clinical use is still limited by relevant adverse effects, such as gastrointestinal disorders, weight loss and chronic inflammatory modulation. However, current evidence reinforces that these agents represent a significant advance in the management of neurodegenerative diseases, not only providing symptomatic relief, but also opening up new therapeutic perspectives that may modify the course of these pathologies in the future.

REFERENCES

1. AKIMOTO, Hayato *et al*. Antidiabetic drugs for the risk of Alzheimer disease in patients with type 2 DM using FAERS. **American Journal of Alzheimer's Disease & Other Dementias®**, v. 35, p. 1533317519899546, 2020.

2. DU, Haiyang *et al.* The mechanism and efficacy of GLP-1 receptor agonists in the treatment of Alzheimer's disease. **Frontiers in Endocrinology**, v. 13, p. 1033479, 2022.

3. FONTANELLA, Rosaria Anna *et al*. Tirzepatide prevents neurodegeneration through multiple molecular pathways. **Journal of Translational Medicine**, v. 22, n. 1, p. 114, 2024.

4. GRECO, Marco *et al.* Restoring autophagic function: a case for type 2 diabetes mellitus drug repurposing in Parkinson's disease. **Frontiers in Neuroscience**, v. 17, p. 1244022, 2023.

5. HONG, Chien-Tai; CHEN, Jia-Hung; HU, Chaur-Jong. Role of glucagon-like peptide-1 receptor agonists in Alzheimer's disease and Parkinson's disease. **Journal of Biomedical Science**, v. 31, n. 1, p. 102, 2024.

6. KALINDERI, Kallirhoe; PAPALIAGKAS, Vasileios; FIDANI, Liana. GLP-1 receptor agonists: a New Treatment in Parkinson's Disease.**International Journal of Molecular Sciences**, v. 25, n. 7, p. 3812, 2024.

7. KONG, Fanjing et al. Glucagon-like peptide 1 (GLP-1) receptor agonists in experimental Alzheimer's disease models: a systematic review and meta-analysis of preclinical studies. Frontiers in Pharmacology, v. 14, p. 1205207, 2023.

8. KOYCHEV, Ivan *et al.* Inflammatory proteins associated with Alzheimer's disease reduced by a GLP1 receptor agonist: a post hoc analysis of the EXSCEL randomized placebo controlled trial. **Alzheimer's Research & Therapy**, v. 16, n. 1, p. 212, 2024.

9. LV, Dongliang *et al.* Neuroprotective effects of GLP-1 class drugs in Parkinson's disease. **Frontiers in Neurology**, v. 15, p. 1462240, 2024.

10. MECA, Andreea Daniela *et al.* Unlocking the Potential: Semaglutide's Impact on Alzheimer's and Parkinson's Disease in Animal Models. **Current Issues in Molecular Biology,** v. 46, n. 6, p. 5929-5949, 2024.

11. NORGAARD, C. H. *et al.* Treatment with glucagon-like peptide-1 receptor agonists and incidence of dementia: data from pooled double-blind randomized controlled trials and nationwide disease and prescription registers. **Alzheimers Dement (NY)**, v. 8, n. 1, p. e12268, 2022.

12. SIDDEEQUE, Nabeela *et al.* Neuroprotective effects of GLP-1 receptor agonists in neurodegenerative Disorders: A Large-Scale Propensity-Matched cohort study. **International Immunopharmacology**, v. 143, p. 113537, 2024.

13. WANG, William *et al.* Associations of semaglutide with first-time diagnosis of Alzheimer's disease in patients with type 2 diabetes: Target trial emulation using nationwide real-world data in the US. **Alzheimer's & Dementia**, v. 20, n. 12, p. 8661-8672, 2024.

14. WOLFF, Andreas *et al.* Parkinson's disease therapy: what lies ahead?. **Journal of Neural Transmission**, v. 130, n. 6, p. 793-820, 2023.

15. ZHANG, Zijuan *et al.* A Dual GLP-1/GIP Receptor Agonist Is More Effective than Liraglutide in the A53T Mouse Model of Parkinson's Disease. **Parkinson's Disease**, v. 2023, n. 1, p. 7427136, 2023.