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Beyond Diabetes Mellitus and weight loss: the potential effect of GLP-1 agonist drugs in the treatment of Parkinson's Disease

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Abstract

Introduction

Drugs targeting insulin resistance in the brain have emerged as a potential therapeutic option for Parkinson's disease (PD). Their implication has originated from the studies indicating a link between Type 2 Diabetes Mellitus (T2DM) and PD, indicating that impairment in glucose and energy metabolism pathways contribute to the pathogenesis of PD. Owing to their potential neuroprotective properties in PD, glucagon-like peptide-1 (GLP-1) receptor agonists represent a category of antidiabetic medications that have garnered interest. The aim of this review is to evaluate the role of GLP-1 agonists as a novel treatment option for Parkinson's disease concentrating on disease modifying effects.

Methods

The search of literature was performed in databases including PubMed, Google Scholar and ScienceDirect, the timeline applied was from years 2017 to 2025. Keywords used were "Parkinson's disease", "glucagon-like peptide", "glp-1 agonists", "semaglutide". Priority was set to peer-reviewed research, preclinical studies and clinical trials. References were screened for additional studies that could support the evidence.

Results

Data from preclinical and animal studies show, that GLP-1 agonists could modify the main pathological pathways impaired in Parkinson's disease, including energy metabolism and neuroprotection. They improved the cell survival rate, autophagy stimulation, and reduced the

apoptosis of mitochondria in cytotoxic in vitro cell models of PD and reduced the levels of alpha-synuclein in the brain in the mice models. Similarly, in rat model studies, incretin mimetics reduced pro-inflammatory cytokine levels, including TNFα, NF-kB and cyclooxygenase (COX1) and were able to regulate the function of microglial cells. GLP-1 agonists could improve dopaminergic transmission - they were shown to promote dopaminergic cell viability in substantia nigra pars compacta and normalize the tyrosine hydroxylase expression. Treatment with GLP-1 agonists have a positive impact on clinical features of PD. Marked improvement of motor function was seen as a result in the clinical trials, expressed by increase in MDS-UPDRS part III scales, as well as non-motor symptoms including cognition, mood and activities of daily living.

Conclusions

GLP-1 agonists show promise to have a disease modifying effect in Parkinson's Disease by targeting factors like inflammation, insulin resistance, aiding in neuroprotection and improving motor and non-motor symptoms. As the existing knowledge gap renders making possible conclusions about the efficacy of these drugs in PD populations without insulin resistance and inflammation rather difficult, further research and clinical trials should be conducted to confirm or deny the same.

Keywords: "Parkinson's disease", "glucagon-like peptide", "glp-1 agonists", "semaglutide"

I. Introduction

Parkinson's disease (PD) is a neurodegenerative disorder which impairs motor function, and as well can lead to cognitive decline and dementia. It occurs due to loss of dopaminergic neurons in the substantia nigra pars compacta of basal ganglia. Symptoms present are resting tremors, bradykinesia, rigidity and postural instability. Non-motor symptoms can also be present, such as sleep disorders, constipation, gastrointestinal tract dysfunction, dysphagia, gastroparesis, which are more common amongst the older population.[1–3] Prevalence has increased over time, geographical regions, ethnicity, variation in time and sex of the individual where the most important risk factor is increasing age and male gender. The cause is multifactorial which involves environmental and genetic factors.[12] PD pathogenesis is due to imbalance in the dopamine system linked to disturbance in glucose metabolism and energy conversion in the body. Many studies have discovered that there is a link between brain degeneration and inflammation seen in substantia nigra pars compacta with accumulation of aggregates of a-synuclein protein known as Lewy bodies.[4]

The traditional treatment of Parkinson's disease is dopamine replacement strategy which is achieved by carbidopa/levodopa.[4] This is the current mainstay treatment for PD, which works by improving dopamine production and motor symptoms. However, prolonged use of levodopa can cause serious side effects, including dyskinesias.[5,6] Lifestyle modifications like aerobic exercises can provide benefits as well.[7] There is evidence that selegiline and rasagiline give neuroprotection in cell.[4] Dopamine agonists (DA), catechol-o-methyl-transferase (COMT) inhibitors and non-dopaminergic agents are some of the available drugs for treatment.[8] Despite advancements in symptomatic therapies,

such as dopamine replacement and deep brain stimulation, currently no disease-modifying therapies (DMTs) have been identified to slow or arrest neurodegeneration in patients with PD. [9]

Glucagon-like peptide-1 receptor agonists (GLP-1 RAs) have recently gained attention as a promising novel treatment option for Parkinson's disease due to their potential neuroprotective effects. GLP-1 receptor agonists can be used to treat neurodegenerative diseases through mitochondrial function, inflammation regulation, tau hyperphosphorylation and anti-apoptotic pathways.[10] GLP-1 plays a very important role in insulin resistance through gut-liver signalling pathway by delaying gastric emptying and it suppresses appetite.[11,12] GLP-1R is found in brain and pancreatic islets. Evidence shows that it can cross the blood-brain barrier (BBB) and affect pathways in the central nervous system (CNS).[13,14] GLP-1 receptor agonists, such as exenatide, lixisenatide, and liraglutide, semaglutide are frequently utilized in the management of type 2 diabetes mellitus and are widely known for their weight loss promoting effects, are currently undergoing trials and are being studied as a new promising agents in the treatment of PD .[9]

The aim of this article is to review the currently conducted studies on the therapeutic potential of GLP1 agonists as the novel possible treatment of Parkinson's disease, focusing on their disease modifying effects in early phases.

II. I Overlapping pathophysiology and Parkinson's disease and impairment of glucose metabolism

Concurrent presence of disorders of glucose metabolism and energy conversion in patients with Parkinson's disease may be linked to pathophysiology of the disorder.[15] Studies have shown the decreased basal metabolic rate, leading to lower energy metabolism levels and energy conversion is essentially reduced in Parkinson's disease. Furthermore, energy consumption and metabolism is impaired by reduced physical activity due to motor dysfunction.[16] Impaired energy metabolism in the brain may also be involved with cognitive impairment.[17] The complicated process of dopamine synthesis, secretion, transport and reuptake is highly related to energy metabolism, and disturbances of these mechanisms are linked to Parkinson's disease. Glucose metabolism abnormalities, insulin resistance and mitochondrial dysfunction result in energy disturbances and neuronal damage, subsequently contributing to development of PD.[15]

II.I.I Parkinson's disease and insulin resistance, relationship with Type 2 diabetes mellitus

Insulin resistance refers to absence or decrease of response to the hormone.[18] Both peripheral and brain insulin resistance are linked to cognitive decline, however, brain insulin resistance can be present independently from the peripheral resistance. Multiple studies suggest that insulin resistance could play a role in development of Parkinson's disease. Approximately 60% of PD patients have undiagnosed insulin resistance, despite the presence of diabetes, expressed by HOMA-IR ≥ 2.0 (Homeostatic Model Assessment for Insulin Resistance) and/or hemoglobin A1c (HbA1c) ≥ 5.7, which can be related to increased severity of non-motor symptoms.[19] [20] The underlying pathophysiology is that insulin resistance disrupts the uptake for glucose and oxidation, leading to chronic hyperglycemia and oxidative stress. Free radicals are capable of activating microglial cells and astrocytes, which release

pro-inflammatory cytokines, eventually leading to chronic inflammatory processes and neuronal cell damage. Brain insulin resistance has a direct role in the pathology of α-syn accumulation, the main pathological sign of PD as well as autophagy and unfolded protein response. Systemic IR causes hyperglycemia along with associated brain pathologies such us arteries veins dysfunction, chronic neuroinflammation and BBB dysfunction.[21–23]

Type 2 diabetes mellitus (T2D) has emerged as a potential risk factor of developing Parkinson's disease. Considering epidemiological studies, a meta-analysis performed by Yue et. al in 2016, included 7 cohort studies and found that a risk for T2M patients to develop PD was approximately 38%, with female patients being at the higher risk, despite PD being more prevalent among male population.[24] Additionally, the risk of developing Parkinson's disease can be associated with prolonged course of T2M. A large scale cohort study was performed in South Korea including over 15 million subjects analyzed the PD risk in four groups of participants: nondiabetic, impaired fasting glucose, diabetes less than 5 years duration, and diabetes of more than 5 years duration (Rhee et al., 2020), showed that PD risk significantly increased with the duration of diabetes.[25] Presence of Type 2 Diabetes Mellitus can be associated worsening motor symptoms and activities of daily living. In a case-control study by Pagano et al. (2018) involving 78 participants monitored over three years, type 2 diabetes mellitus (T2DM) was linked to more rapid progression and worsening of motor symptoms, reduced striatal dopamine transporter (DAT) binding, elevated tau levels in the cerebrospinal fluid, and greater cognitive decline in patients with Parkinson's disease (PD). Additionally, individuals with diabetes but without PD exhibited lower striatal DAT binding and increased cerebrospinal fluid concentrations of alpha-synuclein and tau compared to healthy controls.[26]

Insulin resistance in PD affects energy metabolism, leading to inflammatory processes and destruction of dopaminergic cells. T2D and PD contribute to neurodegeneration due to their link of shared mechanisms like chronic inflammation and insulin resistance. Therefore, novel therapeutic interventions for Parkinson's disease, which target insulin signaling defects and incretin signaling have a potential neuroprotective effect, as well as moderating of cognitive and motor symptoms.

II.II A Glp1 receptor agonists, their mechanism of action

Incretins are polypeptide hormones secreted by enteroendocrine cells that promote insulin secretion. GLP-1 and glucose-dependent insulinotropic polypeptide (GIP) are the primary members.[27] Enteroendocrine L-cells secrete GLP-1 in response to various nutrients after food intake releasing it into the bloodstream. GLP-1 binds to its specific receptor (GLP1R) causing insulin release. Moreover GLP-1 activates related intracellular signaling pathways, promoting β-cell regeneration, inhibiting β-cell apoptosis, and improving β-cell function, thereby lowering blood glucose levels, with its effects being glucose concentration-dependent.[28,29] GLP 1 and GIP (glucose dependent insulinotropic polypeptide) receptors belong to the G protein-coupled B1 class receptors (the secretin family), which can trigger the production of cAMP (cyclic adenosine monophosphate) and undergo conformational changes upon activation.[30] GLP-1 receptor agonists bind to these specific receptors distributed widely throughout the body, including pancreatic islets, renal, pulmonary, cardiovascular, gastrointestinal, immune, and brain cells.[35] They enhance insulin and amylin secretion by stimulating pancreatic β-cell

activity and inhibiting glucagon secretion from pancreatic α-cells in a glucose-dependent manner that results in regulating blood glucose level.Activation of GLP-1 receptors promotes insulin production by increasing intracellular calcium levels and ERK1/2 phosphorylation. Also they play a role in upregulation of GLUT2 transporters and glucokinase expression to enhance glucose metabolism.[31–33] They also activate peripheral and central intestinal and brain receptors, mainly those located in hypothalamus to increase feelings of satiety, regulate gastric emptying, support weight loss and regulate appetite through central mechanisms which is beneficial for managing Type 2 diabetes and obesity.[33–37] They also have cardiovascular benefits, renal protection and show a low risk of hypoglycemia.[34,38,39] These effects are particularly relevant given the increased risks of cardiovascular (including major adverse cardiovascular events) and kidney diseases in patients with diabetes.[40]

The neuroprotective potential of GLP-1 receptor agonists has been explored. Their ability to cross the blood-brain barrier (BBB) and reduce oxidative stress, inflammation, and neurodegeneration opens a new path for treating neurodegenerative diseases such as PD. Among the non-acylated, non-PEGylated incretin receptor agonists that were examined, exendin-4 and DA-JC4 were best able to cross the BBB enhancing their priority as a possible therapeutic agent in neurodegenerative diseases.[41,42] GLP-RAs show various neuroprotective effects such as restoring mitochondrial function,supporting neurogenesis and enhancing autophagy through multiple pathways.

GLP-RAs activate G protein coupled receptors in various organs promoting insulin secretion, reducing glucagon secretion, regulating appetite and supporting weight loss further showing therapeutic cardiovascular, renal (beneficial in diabetic patients) and neuroprotective effects thus showing their therapeutic potential in neurodegenerative diseases like Parkinson's disease.

III. Therapeutic potential of the GLP-1 receptor agonists in the treatment of PD

III. I Neuroprotective effect in PD

Pathogenic mechanisms involved in the development of PD are inflammation, apoptosis and oxidative stress.[43–45] GLP-1 can act on the pathogenesis of PD by activating MAPK/extracellular signal-regulated kinase 1/2 (ERK) pathway, which has an important role in synaptic plasticity. GLP-1 receptor stimulation also activates the PI3K/Akt pathway, followed by subsequent increase in cAMP and PKA and PI3K activation.[46] The Akt pathway regulates the processes that are disrupted in PD, including synaptic plasticity and autophagy, and also inhibit and pathogenic processes, including microglial activation, secretion of proinflammatory cytokines, apoptosis, tau-phosphorylation and accumulation of alpha-synuclein.

Neuroprotective effects of GLP-1 agonists have been characterized by preclinical studies. A study performed by Liu, D. X. et al. in 2022 tested the effects of liraglutide and semaglutide in vitro cell models. The results indicated that treatment with liraglutide or semaglutide after 6-OHDA induced cytotoxicity increased cell survival rate, enhanced autophagy, and reduced mitochondrial apoptosis compared with 6-OHDA alone. In addition, semaglutide was more protective than liraglutide in treating the cell model of PD.[36] Additionally, another study, performed by Holscher, C. et al 2022,

compared the efficacy of Semaglutide, versus double GLP receptor agonist DA 5 CH in animal models, discovered that DA5-CH was more potent than semaglutide in protecting the brain from 6-OHDA toxicity (n=10 in each group). This might suggest that DA5CH has better neuroprotective effects than semaglutide against 6 OHDA induced toxicity.[39] Thus, results from the preclinical studies support the promising potential of GLP-1 receptor activating agents for Parkinson's disease treatment, showing their ability to exert neuroprotective effects.

III. II Protein aggregation

The key pathological sign in PD is accumulation of alpha-synuclein protein, aggregations of which form Lewy bodies, leading to death of dopaminergic neurons in the substantia nigra.[15,47] This accumulation happens due to failure to clear aggregated proteins by proteolysis and autophagy.[48] The misfolded alpha-synuclein protein, including oligomers and fibrils, can disrupt many cellular processes, including mitochondrial dysfunction, generation of reactive oxygen species (RO), and inflammation, which contribute to neurodegeneration.[42] Treatment with GLP1 agonists are showing a great disease-modifying potential in this area, expanding the potential effect beyond symptom modification.

Preclinical studies, performed by Zhang et al., with MPTP mouse models (in which Parkinson's disease was chemically induced with neurotoxin 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine) showed that semaglutide and dual GLP1/GIP receptor agonist DA5-CH both reduce the expression of alpha-synuclein in the brain.[49] The later study, performed by the same scientists (Zhang et al, 2022), measured the effect of the same drugs on alpha - synuclein expression in 6-OHDA (6-hydroxydopamine) rat models of Parkinson's disease. The semaglutide treated models showed decreased alpha - synuclein levels compared to saline treated models ($p < 0.01$). DA5-CH showed superior results in reduction of alpha-synuclein expression than saline treated models ($p < 0.0001$) and even more significant effectiveness in comparison to semaglutide ($p < 0.05$).[39] The findings from these studies show a great potential of GLP-1 receptor agonists in modulating the key cause of the neurodegeneration, leading to Parkinson's disease.

III. III Anti-inflammatory Effect

The pathophysiology of PD is based on multiple factors like protein misfolding, aggregation, defects in the proteasome-ubiquitin system and inflammation.[50]

The effects of the DA5-CH and semaglutide on the levels of pro-inflammatory cytokines after a stereotactic injection with 6-OHDA was noted in a rat model study by Zhang et al., in 2022. Researchers found that the levels of TNFα were elevated in the 6-OHDA+saline group as compared to the sham+saline group. The group that got 6-OHDA+ semaglutide showed lower levels of TNFα and the group that received 6-OHDA+DA5-CH had the least amount of TNFα (n=5 in every group). The same was done for ILß level analyses and a similar result was noted. The same study also noted these drugs were able to protect dopaminergic neurons against the 6-OHDA induced expression of α-synuclein protein with DA5-CH producing slightly better results than semaglutide.[39] In another mice

model study conducted by Yun et al., in 2018, NLY01 (a long acting GLP1- RA) was able to inhibit the induction of mRNA for IL-1α, IL-1ß, TNFα, C1qa, IL-6 within the microglial cells of the ventral midbrain.This study was also able to conclude that NLY01 was able to prevent the conversion of astrocytes to neurotoxic A1 induced by the injection of α synuclein PFF(preformed fibrils).[51]

Exendin-4 was found to decrease levels of different mediators of inflammation like TNFα, NF-kB as well as cyclooxygenase (COX 1) in other rat model studies.[52,53] Exendin 4 was found to mediate the function of the microglial cells and exert its anti inflammatory affect through IL 10 (an anti inflammatory cytokine) expression which in turn mediates the expression of ß endorphins.[54] It has been supported by evidence that GLP1-RA's could improve signal transduction by enhancing the P13/Akt pathway, the activation of PI3/AKT pathway can inhibit the release of caspases and NK-kB, preventing the release of proinflammatory cytokines.[55]

III. IV Effect on dopaminergic neurotransmission

The dopaminergic neurotransmission in PD patients are affected by the loss of dopaminergic neurons in the brain. The apoptosis of these neurons along with a significant reduction in dopamine levels can contribute to the pathogenesis of the disease.[56] The conversion of tyrosine to L-dopa by tyrosine hydroxylase followed by decarboxylation with the help of aromatic L-amino acid decarboxylase produces dopamine in these neurons.The release of dopamine which had been transported by vesicular monoamine transporter 2 (VMAT 2) to synaptic vesicles is triggered by nerve impulses causing its release into synaptic clefts.The released dopamine binds to postsynaptic dopamine receptor and activates it. This is regulated by dopamine transporter (DAT) which maintains the balance and extracellular concentration of dopamine. Studies have shown an increased DAT results in an increased ability to reuptake dopamine into the presynaptic membrane.[57,58] Dopamine undergoes degradation by monoamine oxidase, aldehyde dehydrogenase and catechol-O-methyltransferase to finally form homovanillic acid.[59,60]

Several studies have been done to determine the effect of GLP 1 receptor agonists on dopaminergic neurotransmission. Some animal studies noted that administration of semaglutide prevented the reduction in cell viability.[36,61] An increase in cell viability would indirectly have positive effects on dopaminergic neurons as well as dopamine levels thus helping with dopaminergic neurotransmission. Another animal study by Zhang et al., in 2022 showed that semaglutide and DA-5CH protected neurons in the SNpc from the toxicity induced by 6-OHDA in PD rats along with increasing the level of striatal dopamine.[39] Dahiya, S. et al. in 2022 used indicators of dopaminergic neurotransmission(n = 128) such as measures of striatal dopamine, tyrosine hydroxylase (TH) positive neurons in the substantia nigra pars compacta (SNpc) and the TH+ optical density in the SNpc and its relation to GLP1 agonists to conduct a systematic review and meta analysis. The result was seen to be statistically significant which suggests that GLP1 agonists maybe disease modifying and slows the progression of PD.[62] SEM and liraglutide were seen to restore dopamine synthesis while SEM is more effective than liraglutide in normalizing TH expression by reducing the number of damaged dopaminergic neurons.[14,63,64] Another preclinical study stated that there was an increase in the expression of TH-containing neurons after peripheral administration of GLP 1 agonists.[65] Additionally

exenatide increased dopamine levels in PD rodent models too.[66] Thus as the studies suggest GLP 1 agonist might play a potential role in improving dopaminergic neurotransmission.

III. V Motor recovery

Motor recovery in Parkinson's disease (PD) refers to the improvement of decline in motor functions, including balance, coordination, and muscle control. The clinical trials on liraglutide, lixisenatide and exenatide, all focused on the impact of these GLP-1 receptor agonists on motor function in PD. The randomized double-blind, placebo-controlled trial of liraglutide assessed its effects for motor recovery in PD, of the once daily self-administered injections of liraglutide (1.2 or 1.8 mg, as tolerated) or placebo at the same dose levels in a 2:1 study design in patients with PD, no significant differences between active and placebo groups were detected in two other primary outcomes, including the MDS-UPDRS part III OFF medication and MDRS-2 changes from baseline. There was an improvement of 2.6 points in the liraglutide group at 54 weeks and was washed out by a 5.0 points improvement in the control group, suggesting a remarkable placebo effect on motor scores.[67] Primary motor outcome during randomized, double-blind, placebo-controlled trial of lixisenatide, MDS-UPDRS Part III showed a difference of 3.08 points (p=0.007) between the lixisenatide and placebo groups, with lixisenatide slowing the progression of motor disability. After 12 months, the lixisenatide group showed some improvement (-0.04 points), while the placebo group experienced worsening of 3.04 points. After discontinuing lixisenatide for two months, the motor scores worsened in both groups, but the lixisenatide group still had good scores (mean MDS-UPDRS Part III score of 17.7 compared to 20.6 in the placebo group). This shows a promising benefit of lixisenatide in preserving motor function even after treatment cessation. There were no significant differences in other MDS-UPDRS subscores. The need for dopaminergic medications remained unchanged, indicating that lixisenatide did not reduce the need for conventional PD treatments.[68] Exenatide was tested for its neuroprotective effects in PD in a randomized, double-blinded, placebo-control trial. After 48 weeks of taking 2mg exenatide daily, patients of moderate severity of Parkinson's disease had significant primary outcomes - 3·5 points increase of part 3 MDC-UPD ranking scale, and lower LED scores in comparison to placebo group. This effect remained significant after the 12 weeks wash-out period. They found a significant improvement in motor function in the exenatide group, with a mean improvement of 1.0 points on the MDS-UPDRS Part III after 60 weeks. However, a recent phase III clinical trial of exenatide (exenatide-PD3) indicated a lack of efficacy. Although the final results have not yet been published, they are expected to provide valuable insights for future clinical trials of other drugs, including lixisenatide.

III. VI Non-motor symptoms recovery

Clinical trials testing the efficacy of Liraglutide, Lixisenatide and Exanatide assessed the effect of these drugs on non-motor symptoms of Parkinson's disease. In liraglutide trial, there were noted improvements in non-motor symptoms, with patients having 6.6 points improvement in the NMSS (non-motor symptoms scale) , whereas the placebo patients worsened by 6.5 points, which shows evident therapeutic benefits for NMS such as mood, cognition, autonomic dysfunction, and sleep

disturbances. Subjects randomly assigned to treatment with liraglutide, and completing the protocol as designed, had a significant 13.1 points adjusted advantage in the NMSS scale over those taking placebo 52 weeks after completing drug titration (primary outcome). Sub-domain analysis showed virtually all changes favoring the liraglutide group, with five of them – including activities of daily living (ADLs) scores - reaching statistical significance. Additional neuropsychological testing showed a significant 1.3 adjusted difference in PAS Avoidance Behavior scores favoring the active treatment group ($p<0.05$). PDQ-39 scores improved by 2.5 points in the liraglutide group at 54 weeks and worsened by 11.2 points in the placebo group, a 13.7 adjusted mean difference ($p<0.001$).[68] Liraglutide also improved activities of daily living, enhancing functional independence. However motor outcomes did not show significant differences, these results suggested that liraglutide may be a promising treatment for the non-motor aspects of PD. Lixisenatide treatment did not show improvements in other NMS such as the mood, sleep, or cognitive dysfunction. The exenatide trial found no improvements in NMS, including scores on the Mattis Dementia Rating Scale, Montgomery-Asberg Depression Rating Scale, and Non-Motor Symptoms Severity Scale.[67] Taking into consideration the results of clinical trials, Liraglutide alone shows a promise in modifying the non-motor symptoms in Parkinson's disease.

III. VII Adverse effects

Glp 1 receptor agonists are known to cause a few adverse effects but most of them are mild in nature. Semaglutide displays a few gastrointestinal effects which range from mild to moderate. This includes nausea, vomiting and diarrhoea. These effects were noted to be dose dependent and subsided within 2 weeks.[69] Others included headache, nasopharyngitis, urinary tract and upper respiratory tract infections, increased level of pancreatic enzymes, increased heart and pulse rate, cholecystitis, cholelithiasis, but these were not frequently reported.[70–74] Another trial reported a 76% higher risk for retinopathy related complications in populations treated with semaglutide.[75] Similar gastrointestinal symptoms along with weight loss and injection site reaction were seen in a randomised, double-blind,placebo-controlled trial for exenatide.[76] A trial focussing on liraglutide noted that subjects randomized to liraglutide experienced injection site reactions and gastrointestinal symptoms, with nausea and loss of appetite being the most significant and higher in number. Additionally 17 lipase elevations (>3xULN in 2 cases) in 14 subjects and 28 amylase elevations were also noted.[77] Finally a trial on lixisenatide stated that gastrointestinal side effects were more common in the lixisenatide group than in the placebo group (nausea: 29% vs. 11%; vomiting: 11% vs. 4%). Moreover weight loss was also more common in the lixisenatide group (mean loss: 1.4 kg vs. 0.4 kg in the placebo group).[78] Although GLP 1 agonists do cause a few adverse effects, the drug is considered safe enough to be used in populations.

IV. Study limitations and Future Implications

Evidence from preclinical studies and clinical trials suggests the effectiveness of GLP-1 agonists as the potential disease modifying treatment for Parkinson's disease. These drugs have shown positive results in targeting the main pathological pathways of this disorder, and the improvement of motor, cognitive and non-motor symptoms. However, multiple challenges remain. GLP-1 receptor agonists

showed positive effects on motor function in PD, but they don't yet replace usual conventional PD treatment options.. Some GLP-1RAs, such as lixisenatide, show significant motor improvements while others, like liraglutide, didn't show significant results. However, liraglutide could potentially have a positive effect on non-motor symptoms, such as cognition, mood and activities of daily living. Future studies should focus on understanding the cause of these differences and effectiveness among these drugs. The studies should also consider using more objective outcome measures, in addition to clinical scoring systems to ensure more accurate assessments of treatment as some trials showed strong placebo responses. Longer and adaptive clinical trial designs should be considered, allowing for adjustments based on emerging data and enabling trials to take into consideration subtle disease progression over extended periods. Although GLP 1 agonists may promote neuroprotection through various pathways, including inflammation, autophagy and alpha-synuclein, the underlying specific mechanisms that might help with reducing Parkinson's disease symptoms are not well studied. Further research must be done focusing on the same. Similarly several studies have been conducted to see the effect of Glp 1 agonist on dopaminergic neurotransmission, and it is important that the future studies be directed towards finding the fundamental process of how these drugs have a positive effect on dopaminergic neurotransmission.

Research should also be conducted to see the effect of the drug in PD patients with comorbidities such as T2D or obesity. If the drug does prove to be effective this might help in early prevention among patients with T2D /obesity and are at a high risk of developing PD. These drugs are seen to have effects on weight loss and reducing muscle mass which might be a potential harm if used in elderly patients with PD. It may be important to prioritise high risk individuals in future trials. The main knowledge gap exists regarding the efficacy of GLP-1 agonist drugs in PD populations without insulin resistance and inflammation. Further research and clinical trials should be conducted to confirm or deny the same. Despite setbacks and need for further studies, this treatment option could contribute in changing the treatment landscape of PD and help millions of patient's worldwide suffering from this disorder.

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