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Review

Antidiabetic drugs in Parkinson's disease

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ABSTRACT

This review explores the intricate connections between type 2 diabetes (T2D) and Parkinson's disease (PD), both prevalent chronic conditions that primarily affect the aging population. These diseases share common early biochemical pathways that contribute to tissue damage. This manuscript also systematically compiles potential shared cellular mechanisms between T2D and PD and discusses the literature on the utilization of antidiabetic drugs as potential therapeutic options for PD. This review encompasses studies investigating the experimental and clinical efficacy of antidiabetic drugs in the treatment of Parkinson's disease, along with the proposed mechanisms of action. The exploration of the benefits of antidiabetic drugs in PD presents a promising avenue for the treatment of this neurodegenerative disorder.

1. The relationship between diabetes and Parkinson's disease

PD is a progressive multisystemic disorder characterized by a diverse range of motor and nonmotor symptoms [1]. The etiology of PD remains unknown; but is primarily associated with the aging process [2]. The pathophysiology of PD is characterized by progressive degeneration of dopaminergic neurons in the *substantia nigra pars compacta* (SNpc), decrease in dopamine (DA) content, aggregation of α-synuclein, inflammation and oxidative stress [3].

Diabetes is a chronic metabolic disorder characterized by persistently elevated blood glucose levels [4,5]. The pathophysiology of T2D includes pancreatic β-cell dysfunction, resulting in impaired insulin secretion or activity, thereby disrupting glucose metabolism, promoting chronic systemic inflammation [6]. T2D is also related to disruptions in lipid and metabolism. In this sense it has shown that the higher the fasting blood glucose level in T2D patients, the higher the blood cholesterol level [7]. Also it has associate the high glycated hemoglobin levels and a dyslipidemia in adults older than 40 years [8].

Early reports documented abnormal glucose tolerance in PD patients [9–12]. Furthermore, diverse prospective cohort studies claim increased risk of PD in individuals with T2D [13–17]. Although other research did not identify a correlation between these diseases [18]. Several studies have provided evidence indicating that T2D is linked to a faster progression of motor symptoms in PD [19,20]. Network-based approaches have yielded evidence supporting a connection between diabetes and PD. Through interactome mapping, over 400 genes were implicated in both T2D and PD, highlighting the involvement of pathways such as insulin receptor and lipid signaling, immune response activation, the mitogen-activated protein kinase (MAPK) cascade, and protein serine-threonine kinase activity as convergent mechanisms [21]. Although a clear epidemiological link between T2D and PD has been established (Fig. 1), the underlying mechanisms by which T2D impacts development and severity on PD, as well as its contribution to neurodegenerative processes, remain incompletely understood. However, several studies have reported promising results from the use of antidiabetic agents (Table 1) in PD models [22,23].

2. Sulfonylureas

Sulfonylureas represent a class of hypoglycemic drugs commonly prescribed for the treatment of T2D due to their ability to stimulate insulin secretion like the glibenclamide [24]. In the brain, glibenclamide has demonstrated neuroprotective effects in *in vivo* models of PD induced by paraquat and maneb through the inhibition of NLRP3 inflammasome activation, diminishing the induced M1 proinflammatory response of microglial cells and the activation of nuclear

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factor-κB [25]. Furthermore, glibenclamide has been observed to reduce the production of proinflammatory cytokines and proteins in lipopolysaccharide (LPS)-stimulated microglial cells and to inhibit the elevation of nitric oxide (NO) levels in BV2 cells stimulated by LPS. These findings are significant, as neuroinflammation plays a crucial pathological role in PD [26]. Another example is glimepiride, which exhibits insulin-mimetic effects and activates endogenous GPI-phospholipase C, leading to the release of certain GPI-anchored proteins from the surface of adipocytes and neurons. *In vitro* studies involving pretreatment of macrophage cell lines and primary microglial cells with glimepiride have demonstrated a significant reduction in the secretion of TNF, IL-1, and IL-6, this findings suggest that glimepiride may reduce the neuroinflammation in neurodegenerative diseases like PD [27]. Other example, is the gliquidone that exhibited suppressive effects on LPS-mediated microgliosis, microglial hypertrophy, and the levels of the proinflammatory cytokines COX-2 and IL-6 in wild-type mice, with relatively smaller effects on astrogliosis [28]. Studies conducted on diabetic rats have reported that gliclazide treatment exerts antioxidant effects in the brain and sciatic nerve. These effects were demonstrated by reduction in malondialdehyde (MDA) levels, as well as, total antioxidant status, oxidative stress index, and increase the paraoxonase 1 (PON-1) activity levels [29] (Table 2).

Contrary to the preclinical results, a study conducted in patients with diabetes who were new users of metformin or sulfonylureas, there were no differences in patients treated with metformin or sulfonylureas respect to the risk of PD [30]. Nevertheless a Taiwanese population cohort study shows that incident PD risk in T2D increases 2.2-fold. Sulfonylureas further increase risk by 57 %, which is avoided by combination with metformin [31].

3. Biguanides

Biguanides have been extensively used for the treatment of T2D since the 1950s. Metformin is the most prescribed antidiabetic drug. The therapeutic effects of metformin involve the inhibition of hepatic gluconeogenesis, promotion of peripheral glucose uptake, enhanced insulin sensitivity, and mitigation of glycation processes [32]. Metformin (5 mg/ml for 5 weeks in drinking water) exhibited beneficial effects in mitigating the degeneration of substantia nigra compacta dopaminergic neurons, increased striatal dopaminergic levels, and ameliorating motor impairment in mouse model of PD 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) plus probenecid-induced [33]. It has also been postulated that metformin may exhibit a neuroprotective effect in PD through the restoration of parkin, an E3 ubiquitin ligase. This after demonstrating that expression of parkin was significantly decreased in the SN of T2D mouse models contributing subsequently PGC-1α down-regulation along with parkin-interacting substrate accumulation [34]. Additionally, a study conducted on a *C. elegans* model of PD demonstrated that mitochondrial hyperactivity is an early event in PD pathogenesis, and treatment with metformin restored mitochondrial respiration levels, resulting in significant improvement in motor function and neuronal viability [35]. Co-treatment with metformin improved L-DOPA-induced dyskinesia in a mouse model of PD induced by 6-hydroxydopamine (6-OHDA) injury by the activation of the AMPK and BDNF signaling pathways specifically in the striatum of the 6-OHDA-lesioned side [36] (Table 2).

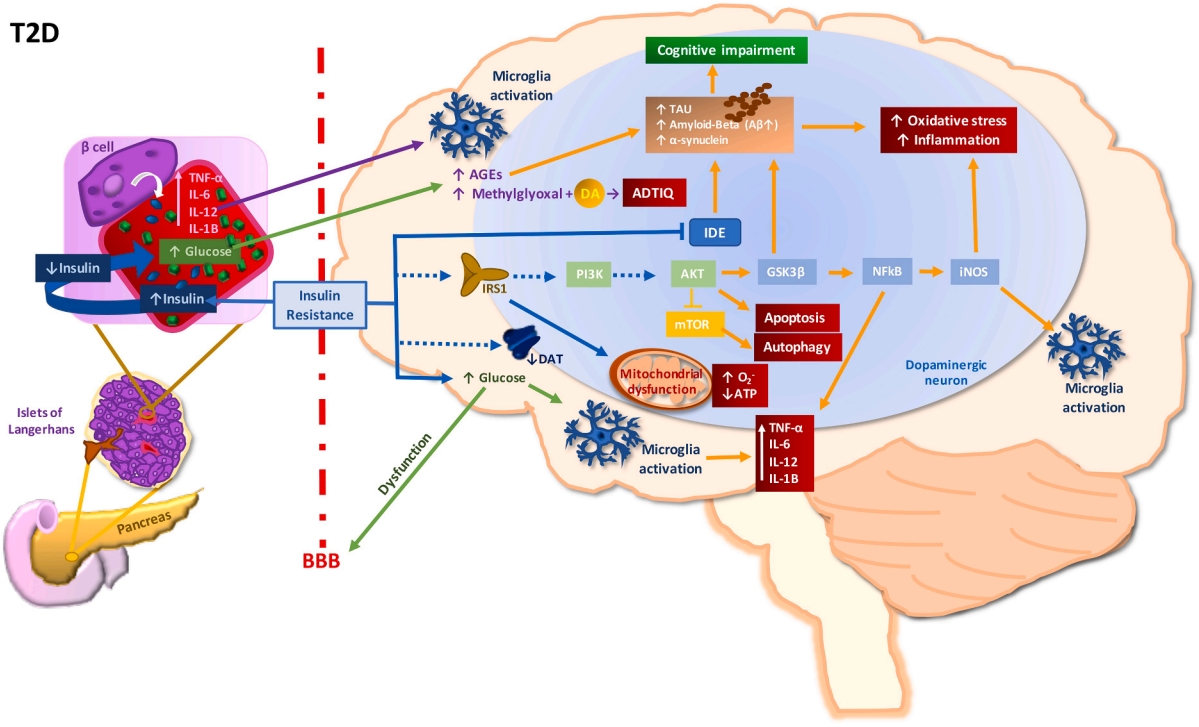

Fig. 1. Converging pathways between PD and T2D. Dashed arrows describe decreased gene expression; red boxes indicate inducers of neuronal death. In circulation, insulin resistance induced an increase in insulin levels, as a compensatory event. Subsequently, the production of insulin is decreased, promoting the blood glucose increase characteristic in diabetes. This event increases interleukins in blood, and this induces the activation of microglia in the brain. It is outlined how hyperglycemia increases the concentration of advanced glycation end-products (AGE) that induce the aggregation of proteins such as α-synucleins, Aβ and TAU. The hyperglycemia increased the levels of the glycation metabolite methylglyoxal in the brain, who react with dopamine (DA) resulting in a specific toxin for dopaminergic neurons, the 1-acetyl-6,7-dihydroxy-1,2,3,4-tetrahydroisoquinoline (ADTIQ). On the other hand, insulin resistance decreases the expression of the insulin receptor substrate 1 (IRS1) gene, generating deregulation of PI3K/AKT signaling pathways and activating GSK-3β and NFκB, triggering processes such as apoptosis, autophagy, oxidative stress and mitochondrial dysfunction that contribute to the progression of PD. Insulin resistance also reduces the expression of dopamine surface transporters (DATs) in the striatum, reducing dopamine turnover and causing the release of proinflammatory cytokines and neuroinflammation. Insulin resistance also increases protein aggregation by inhibiting insulin-degrading enzyme (IDE).

Studies in patients with T2D who receive metformin have shown contradictory results respect to the risk of developing PD. A study conducted in patients with diabetes who were new users of metformin had not influence on the risk of PD [30]. Huang and coworkers (2022) results, suggest that patients with T2D using metformin was associated with risk PD in a dose–response manner. Patients who received low dosage and intensity of metformin use (<300 cumulative defined daily dose (cDDD) by <10 DDD/month) were associated with lower odds of PD at 3 and 5 years, while in higher dosage and intensity of metformin (>300cDDD intensity >10 DDD/month) use had no neuroprotective effect [37].

3.1. 2,4-Thiazolidinediones (glitazones)

Glitazones or 2,4-thiazolidinediones (TZDs) are antidiabetic drugs that effectively improve glycemic control in patients with T2D by enhancing insulin sensitivity through binding to peroxisome proliferator-activated receptor gamma (PPAR-γ) [38]. Notably, PPAR-γ plays a key role in promoting lipogenesis and exhibits anti-inflammatory and antiproliferative properties, thereby reducing insulin resistance in adipose tissue, muscles, and liver. Additionally, expression of PPAR-γ has been detected in neurons and astrocytes [39]. Preclinical and early clinical investigations have suggested that TZDs, exhibit neuroprotective effects in PD and other neurodegenerative disorders [40].

Pioglitazone treatment has been shown to enhance the survival of dopaminergic nigral neurons and leads to the downregulation of proinflammatory cytokines and inducible nitric oxide synthase (iNOS) in macrophages and microglia thus reducing oxidative stress, and improving mitochondrial function in different models of PD [41,42,43]. Additionally, it has been reported to decrease glial activation, inhibit NFκB signaling, and provide protection to dopaminergic neurons in a mouse model of PD [44]. Lobeglitazone, a novel glitazone, effectively reversed the behavioral deficits induced by rotenone in the rearing test and reversed the alterations in tyrosine hydroxylase (TH), TNF-α, NF-κB, and PPAR-γ receptor content induced by rotenone in the SNpc and striatum in rats model of PD with T2D co-morbidity, with therapeutic effects at lower doses than rosiglitazone and pioglitazone [45]. Even novel glitazone derivatives G1 and G2 showed activity against LPS-induced inflammatory events in SH-SY5Y cells, exhibiting notable effects including the prevention of the increase in pro-inflammatory cytokines IL-1β and TNF-α, as well as a significant reduction in NO levels. This results may be attributed to the activation of central PGC-1α signaling via PPAR-γ receptor a strategy that could be an effective way to get neuroprotection in several neurodegenerative disorders like PD

Table 1
Antidiabetic and orally available small molecules described in this review.

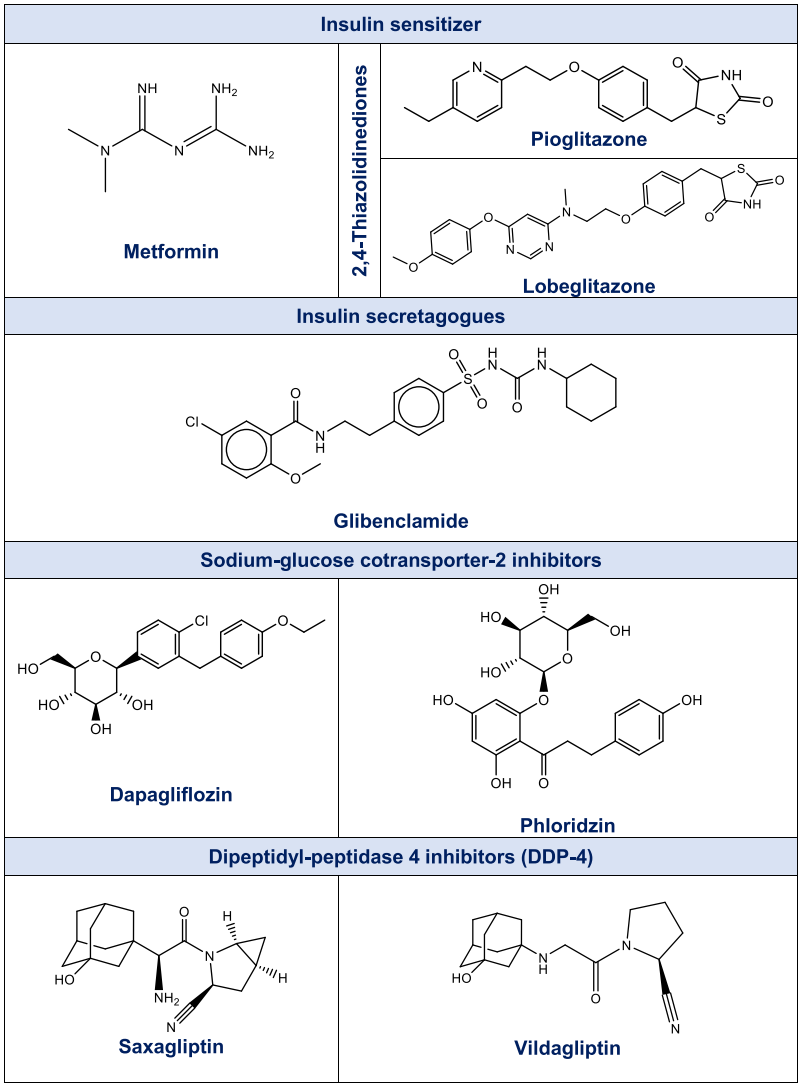

Table 2
Summary of the studies assessing antidiabetic drugs as potential treatment against Parkinson's disease.

Drug	Treatment	Parkinson's Model	Result	Ref.
Glibenclamide	1 mg/kg i.p. 8 weeks (twice per week)	Paraquat + maneb model C57BL/6 mice	– Regulation of α-synuclein dopaminergic neurodegeneration and motor impairment. – Decreases inflammation, activation of M1 – Superoxide production, lipid peroxidation, protein levels of NADPH oxidase 2 (NOX2) and inducible nitric oxide synthase (iNOS) induced were all attenuated	[80]
Glibenclamide	10 μM and 40 μM in BV2 cells 5 mg/kg p.o. per day for 8 weeks	Microglial cell line BV2 lipopolysaccharide (LPS) and 5XFAD mice	– Reduce nitric oxide (NO) induced by LPS, – reduced pro-inflammatory cytokines and proteins (IL-6 and TNF-α) in microglial cells – Reduces Aβ deposition and neuroinflammation	[26]
Metformin	400 mg/kg p.o. once daily for 2 weeks	C57BL/6J db/db mice	– restoration of parkin	[34]
Metformin	50 μM in NGM plates	C. elegans Model of PD	– restores normal mitochondrial respiration levels – reduces neurodegeneration – improves motor function	[35]
Metformin	100 mg/kg and 200 mg/kg, p.o. once daily by for 4 weeks.	6-OHDA model C57BL/6J mice	– improves motor deficits in mice – mediated increase in AMPK, AKT, GSK3b, CREB, and BDNF signaling – ameliorates astrocyte activation in the dopamine-depleted striatum.	[36]
Pioglitazone	20 mg/kg, pretreated once a day p.o., 4 days prior to injection and 3 days post injection.	LPS model Sprague-Dawley rats	– Pioglitazone prevents the LPS-induced increase in PPAR-γ, UCP2 and mitoNEET	[42]
Pioglitazone	in rodent chow at 120p.p.m., estimated to yield 20 mg/kg/day, 3 days prior to MPTP and 2–8 days after MPTP	MPTP model C57BL/6 mice	– prevented the MPTP-induced loss of TH-positive neurons inthe SN – concomitant attenuation of glial activation in the SNpc – reduction of iNOS-positive activated microglia in the SNpc	[44]
Pioglitazone	20 mg/(kg day) by 16 days	MPTP mice model	– protected TH-positive SN neurons – reduced activation of microglia, – reduced induction of iNOS-positive cells – less glial fibrillary acidic protein positive cells in striatum and SNpc.	[41]
Lobeglitazone	0.1, 0.2 or 1.0 mg/kg i.p. one hour before rotenone injections for 46 days	Rotenona Parkinson model + streptozotocin diabetes model Wistar rat	preserve normal values of tyrosine hydroxylase, TNF-α, NF-κB and PPAR-γ receptor in substantia nigra and striatum	[45]
Insulin	200 μg of insulin intranasally 24 h post 6-OHDA, once per day, for 2 weeks	6-OHDA model rat	– ameliorated motor impairments – protection of DA neurons in the SNc	[50]
Insulin	intranasal insulin administration for six weeks after 6-OHDA	6-OHDA model rat	– ameliorates cognitive impairment through Akt/GSK3β signaling pathway	[81]
Insulin	4 IU/day of IN insulin by 14 days	6-OHDA model rat	– Reduces motor dysfunction and dopaminergic cell death – Improves mitochondrial function índices – modulates mitochondria biogenesis and fission – modulates astrocytes and microglia activation	[51]
Agonist exendin-4	0.1 and 0.5 μg/kg during 7 days after intracerebral toxin injection	6-OHDA and LPS model rat	– reverse nigral lesions – protect against loss of TH+cells – restore of DA levels	[82]
Exendin-4	10 nmol/kg i.p. by 14 days	MPTP model C57Bl6 male mice	– Shows not improvement on motor behavior tests – Not enhanced the expression of antiapoptotic signaling peptide (Bcl-2) – Reduced the apoptotic signaling peptide (BAX)	[59]
Lixisenatide	10 nmol/kg i.p for 14 days	MPTP model C57Bl6 male mice	– Shows improvement on motor behavior tests – preserves TH-positive cells – enhanced the expression of antiapoptotic signaling peptide (Bcl-2) – reduced the apoptotic signaling peptide (BAX)	[59]
Liraglutide	25 nmol/kg i.p. for 14 days	MPTP model C57Bl6 male mice	– Shows improvement on motor behavior tests – preserves TH-positive cells – enhanced the expression of antiapoptotic signaling peptide (Bcl-2) – reduced the apoptotic signaling peptide (BAX)	[59]
GLP-1/GIP dual receptor agonist DA3-CH	25 nmol/kg i.p. once daily for 7 days	MPTP model C57Bl6 male mice	counteracts the detrimental effects of MPTP on motor coordination and grip strength – protect dopaminergic neurons – reduced the activation of microglia and astrocytes	[60]
Saxagliptin	1 mg/kg, p.o. for 21 days	Rotenone model male Wistar rats	– preserved SNpc TH-cells – prevent the decline in cAMP – decreased NFkB, ICAM-1, MPO, iNOS, TNF-a, Casp-3, Cyto C, Enhanced Bcl-2	[83]
Vildagliptin	2.5 mg/kg p.o. for 3 weeks	Rotenone model Wistar male rats	– preserve striatal DA content – improve the motor performance in rats – prevented the energy loss with the partial preservation of mitochondrial function – Vildagliptin succeeded to suppress the inflammatory markers MPO, TNF-α, and iNOS	[84]

[46] (Table 2).

Consistently with previous evidence, the findings reported by Brauer et al. (2015) in a large population-based cohort study, indicating a 28 % reduction in the clinical manifestation of PD among patients with T2D, who were prescribed with TZD, compared to those prescribed with other antidiabetic agents. However, it is noted that this protective association appears to be confined to the duration of TZD treatment, showing little or no longer-lasting benefit [47]. Subsequently, in a follow-up study conducted by the same research group, no evidence was found to suggest an association between the use of TZD and the incidence of PD [22]. Other retrospective cohort study has reported an association between the utilization of TZD and a reduced risk of PD incidence within a mainland Chinese population diagnosed with T2D [48].

4. Insulin

Insulin is a peptide hormone synthesized by pancreatic β-cells. Its primary functions include inhibiting glycogen breakdown, stimulating glucose uptake, and promoting glycogen synthesis [23]. Insulin pretreatment prevented cell death and attenuated the release of NO, ROS, and calcium influx in neuronal and glial cells and showed a protective role of insulin against MPP+-induced neurotoxicity in model *in vitro* of PD [49]. The neuroprotective effects of insulin were further confirmed in a rat model of PD based on 6-OHDA toxicity. In this model, intranasal insulin treatment significantly ameliorated motor impairments induced by 6-OHDA and provided robust protection of dopaminergic neurons in the SNpc [50,51]. The neuroprotective effects of insulin have been mechanistically linked to its ability to reduce ROS formation in neurons. Additionally, intranasal insulin has been shown to enhance glutathione (GSH) levels and PGC-1α protein expression and promote ATP production, thus indicating a direct involvement of insulin in promoting mitochondrial biogenesis and ATP production in the brain. Furthermore, it has been proposed that insulin's neuroprotective effects may be partly attributed to its capacity to induce anti-inflammatory phenotypes in reactive glia through activation of the PI3K/Akt pathway in a model of PD [51] (Table 2).

A preliminary pilot longitudinal study with patients who receiving 40 IU of intranasal human insulin once daily for four weeks demonstrated improved functional motor skills in PD patients. Additionally, initial findings suggested this treatment preserved cognitive performance as compared to base line and the placebo group, without risk of hypoglycemia [52].

5. Glucagon-like peptide-1 (GLP-1) receptor agonists

Glucagon-like peptide-1 (GLP-1) is an incretin hormone with growth factor-like properties that plays a crucial role in maintaining glucose homeostasis and facilitating insulin signaling. It stimulates insulin secretion and biosynthesis while inhibiting glucagon secretion, thereby regulating blood glucose levels [53]. Additionally, GLP-1 has been implicated in various cellular processes, such as cell proliferation, neuronal growth promotion, inhibition of apoptosis, and reduction of oxidative stress within the brain [54]. GLP-1 binds to G-protein coupled receptor 1 (GLP-1R). In the brain, GLP-1R mRNA has been detected in numerous regions [55]. Activation of the PI3K/Akt pathway by GLP-1R leads to various downstream effects, resulting in the inactivation of GSK3, that reduces alpha-synuclein aggregation, as well as the inactivation of FOXO1, promoting cell survival and preventing apoptosis. Additionally, GLP-1R activation leads to the inactivation of NFκB, which in turn leads to microglial cell inactivation and reduction in inflammatory mediators [56]. Emerging evidence suggests that non acylated incretin receptor agonists (IRAs) such as exendin-4 and lixisenatide are of greater interest in PD because their systemic administration allows them to access the brain [57] and exert effects that may promote neuroprotection. Preclinical studies have demonstrated that the administration of exendin-4 can reverse dopaminergic cell loss in rodent models of PD induced by 6-OHDA and LPS [58]. Comparatively, other study in MPTP mouse model of PD have suggested that liraglutide and lixisenatide may exhibit greater efficacy than exendin-4 [59]. Recently, the development of DA3-CH a new GLP-1/ Glucose-dependent insulinotropic polypeptide (GIP) dual receptor agonists, has shown increased efficacy in diabetic patients while minimizing associated side effects [60]. Others dual receptor agonists, including DA-JC1, DA-JC4, and DA-CH5, exhibiting reversal of MPTP-induced motor impairment and dopaminergic death, along with a reduction in proinflammatory cytokines which promotes their neuroprotective effects in the MPTP mouse model of PD compared to liraglutide [61,62] (Table 2).

In a clinical study with 60 Parkinson patients treated with exenatide (2 mg) once weekly for 48 weeks in addition to their usual medication, observed positive and enduring effects on off-medication motor scores as measured by MDS-UPDRS [63]. In a later analysis of the same study they achieved greater improvements in individual domains assessing mood/depression across all observer-rated outcome measures after 48 weeks including the "mood/apathy. These exploratory findings show the potential usefulness of exenatide to improve motor and non-motor symptom effects in PD patients [64]. Other clinical trials confirm that GLP-1 receptor agonists can improve clinical pathologies of PD, including prolonged benefits on cognition and motor symptoms [65]. This group of antidiabetic drugs are the ones that have shown the best results in pharmacological repositioning for PD, even reaching clinical phases. FDA-approved a novel GLP-1R agonists either are currently in progress or have completed trials. In phase 1: Effects of Exenatide on Motor Function and the Brain (clinical trial identifier NCT03456687). In phase 2: Effect of Exenatide on Disease Progression in Early Parkinson's Disease (NCT04305002), Semaglutide Effect of GLPIR Stimulation on Neuroprotection and Inflammation in Parkinson's Disease (NCT03659682), Safety and Efficacy of Liraglutide in Parkinson's Disease (NCT02953665). Trial of Exenatide for Parkinson's Disease (EXENATIDE-PD) (NCT01971242) and Exendin-4 as a Treatment for Parkinson's Disease – Pilot Study (NCT01174810). Finally in phase 3: Exenatide Once Weekly Over 2 Years as a Potential Disease Modifying Treatment for Parkinson's Disease (Exenatide-PD3) (NCT04232969) [66].

6. Dipeptidyl peptidase 4 (DPP4) inhibitors

The enzyme DPP4 plays a critical role in glucose metabolism by degrading incretins such as GLP-1 and GIP. DPP4 inhibitors are not insulin sensitizers; rather, they function by inhibiting the rapid inactivation of endogenous GLP-1, resulting in a significant increase in peripheral basal levels of GLP-1, often two- to threefold higher [67].

For example the pretreatment with linagliptin resulted in significant elevation of antioxidant enzymes, striatal DA levels and active GLP-1 in a rat model of PD [68]. In a hyperglycemic mouse model, linagliptin has been found to exhibit neuroprotective effects, mediated through the activation of the Akt/mTOR pathway, leading to anti-apoptotic and anti-inflammatory mechanisms. This is supported by the upregulation of p-Akt and p-mTOR expression, as well as the modulation of apoptosis-related factors such as Bax, Bcl-2, and caspase 9 [69]. Similarly, vildagliptin has been reported to suppress cerebral inflammation and apoptosis through two potential mechanisms: interception of the RAGE-induced NFκB signaling pathway and activation of the Nrf2-antioxidant signaling pathway [70]. Vildagliptin has also been proven to have effects against motor dysfunction by inhibiting dopaminergic neuronal apoptosis in PD model, which is associated with regulation of PI3k/Akt, ERK, and JNK signaling transduction [71] (Table 2).

Recent cohort study in diabetic patients revealed that the incidence of PD was 10 per 10 000 person-years in the control group and was significantly reduced to 5 per 10 000 person-years in the patients treated with DPP4 inhibitors [22]. Shortly after the association between PD incidence and the use of DPP4 inhibitor in diabetic patients treated with metformin plus at least one second-line oral antidiabetic (OAD) was

investigated. The findings reveled that the incidence rate was and 0.55 per 1000 person-years for the non-users of DPP4 inhibitors in contrast to 0.29 per 1000 person-years for DPP4 inhibitor users. Specifically, vildagliptin exhibited the strongest correlation with a decreased risk of developing PD. This study illustrates that the use of DPP4 inhibitors with metformin diminished the risk of PD compared to other oral antidiabetic agents combination [72]. The effects of DPP4 inhibitors on nigrostriatal dopaminergic denervation in patients with newly diagnosed PD has also been investigated. The PD patients were classified into three groups: diabetic patients with DPP4 inhibitors, diabetic patients without DPP4 inhibitors and non-diabetic. The findings suggest that DPP4 inhibitors may confer beneficial effects on the initial nigrostriatal dopamine degeneration, leading to a decrease in the rate of the longitudinal increase in levodopa-equivalent required and improving long-term motor outcomes in diabetic patients with Parkinson's disease [73]. Actually there are a phase 4 clinical study testing the beneficial neurological effects of Sitagliptin (DPP4 inhibitor) and Dapagliflozin a Sodium-Glucose Cotransporter 2 (SGLT2); named Anti-Diabetic Medications to Fight - PD and Lewy Body Dementia (ID: NCT06263673) [74].

7. Sodium-glucose cotransporter 2 (SGLT2) inhibitors

Accumulating evidence suggest that SGLT2 inhibitors, which are oral antidiabetic drugs, provide antioxidative effects and mitochondrial protection in different models with potential neuroprotective effects [75]. Dapagliflozin a SGLT2 inhibitor, has shown potential neuroprotective effects against neurodegenerative dysfunctions, as well as attenuated motor dysfunction in the context of rotenone-induced PD rat model. Furthermore, dapagliflozin administration resulted in reduced expression of α-synuclein and increased levels of DA and TH, indicating a potential positive impact on dopaminergic function [76].

On the other hand, phlorizin exhibits various neuroprotective actions that could be beneficial in PD, including antioxidant and anti-neuroinflammatory effects, as well as modulation of gene expression. Its mechanisms of action involve the suppression of apoptosis through the reduction of caspase-3, 8, and 9 levels, as well as the attenuation of α-synuclein accumulation [77]. Phlorizin also demonstrated a preventive effect on LPS-induced alterations in the hippocampus and cortex, preventing the decrease in antioxidant levels (SOD and GSH), neurotrophic factor (BDNF) levels, and cholinergic transmission. Additionally, phlorizin mitigated the increase in inflammatory/oxidative markers (TNF-α, IL-6, and MDA) [78].

In the rotenone-induced PD model, empagliflozin exhibited a restorative effect on various biochemical alterations and improved motor function in rats, as assessed by open field, grip strength, and footprint gait analysis. The administration of empagliflozin increased the intact neuron count, attenuated astrogliosis and microgliosis, and reduced immunostaining of glial fibrillary acidic protein and ionized calcium-binding adaptor protein 1. Moreover, empagliflozin moderated the GRP78/PERK/eIF2α/CHOP endoplasmic reticulum stress pathway, downregulated miR-211-5p, decreased oxidative stress, lessened astrocyte/microglial activation and neuroinflammation, and prevented autophagy [79]. These preclinical results support the study of these drugs in clinical trials. As mentioned in the previous section, Dapagliflozin is being evaluated in a clinical study (ID: NCT06263673) [74] (Table 2).

8. Conclusion

This review highlights the emerging link between diabetes and Parkinson's disease, showcasing shared pathological mechanisms including insulin resistance, mitochondrial dysfunction, oxidative stress, and increased inflammation. The paradoxical results in the relationship between the use of some antidiabetic drugs and PD could be due to the different characteristics of the studies, such the heterogeneity in the populations, drug dosages and duration, classes of drugs and follow-up lengths. The extensive literature examined in this review provides substantial evidence to support further investigations into the therapeutic potential of antidiabetic agents as alternative treatments for Parkinson's disease. Given the current lack of effective treatments to mitigate neurodegeneration, repurposing safe and proven-quality drugs, such as those used in the management of diabetes, holds promise for enhancing the lifespan of patients with neurodegenerative disorders, including Parkinson's disease.

CRediT authorship contribution statement

Yoshajandith Aguirre-Vidal: Writing – review & editing, Writing – original draft, Supervision, Conceptualization. **Sergio Montes:** Writing – original draft. **Ana Carolina Mota-López:** Writing – original draft. **Gabriel Navarrete-Vázquez:** Writing – original draft, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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