Review

Repurposing Antidiabetic Medications for Parkinson's Disease: Focus on Biomarker Strategies on Disease Modification

Narayana K. Yelleswarapu * and Christos Sidiropoulos

Posted Date: 5 February 2026

doi: 10.20944/preprints202602.0422.v1

Keywords: Parkinson's disease; antidiabetic medications; biochemical biomarkers; diseasemodifying therapies

 doi:10.20944/preprints202602.0422.v1

Review

Repurposing Antidiabetic Medications for Parkinson's Disease: Focus on Biomarker Strategies on Disease Modification

Narayana K Yelleswarapu * and Christos Sidiropoulos

Michigan State University Department of Neurology and Ophthalmology/University of Michigan Health-Sparrow Lansing Hospital

* Correspondence: yelleswa@msu.edu

Abstract

Parkinson's disease (PD) is a progressive neurodegenerative disorder. It shares many pathophysiologic similarities with Type 2 diabetes mellitus (T2DM). Numerous studies have explored the repurposing of antidiabetic medications for their potential neuroprotective effects in PD. There has not been a consolidated review on the biochemical biomarkers that have been evaluated across antidiabetic medications. This review aims to assess the current landscape of biomarker research in evaluating the efficacy of these antidiabetic agents as disease-modifying therapies in PD. We examine the molecular mechanisms targeted by these drugs, the biomarkers used to assess their effects, and the outcomes of clinical trials. The review hopes to identify gaps in current research and enhance the evaluation of antidiabetic medications in PD.

Keywords: Parkinson's disease; antidiabetic medications; biochemical biomarkers; disease-modifying therapies

1. Introduction

Parkinson's disease (PD) is a progressive neurodegenerative disorder characterized by loss of dopaminergic neurons within the substantia nigra thought to be predominantly caused by accumulation of α-synuclein (αSyn) pathology. Gradual depletion of dopaminergic neurons results in impaired motor activity resulting in resting tremor, bradykinesia, rigidity, and postural instability[1]. In addition, non-motor symptoms, i.e. mood disorders, dysautonomia, sleep disturbances, cognitive impairment, and GI complications, can occur up to 20 years preceding motor manifestation of the disease[2]. Despite tremendous advances in symptomatic treatment over the last 50 years, there are currently no FDA approved disease-modifying therapies capable of slowing or halting neurodegeneration. PD continues to remain incurable despite significant progress made in its management.

Over the years, there has been a focus on advancing diagnostic testing to better diagnose PD early, accurately, and to initiate appropriate treatment. The landscape has included tests such as dopamine transporter imaging (DaTscan), olfactory tests, polysomnography, gastric emptying assay, αSyn skin biopsy, cerebrospinal fluid (CSF) αSyn seed amplification assay, and genetic testing [3,4]. In conjunction, there has been development in biochemical biomarkers that facilitate the early diagnosis of PD. Repurposing therapies that target these biochemical biomarkers may help not only in earlier diagnosis but also better outcomes for PD patients.

There has been an emerging link between type 2 diabetes mellitus (T2DM) and PD. T2DM is a metabolic disease defined by insulin resistance and hyperglycemia. While distinct in their primary clinical manifestations, increasing evidence suggests that metabolic dysfunction, impaired insulin signaling, oxidative stress, blood-brain barrier dysfunction, and mitochondrial dysregulation contribute to PD pathophysiology, linking central nervous system degeneration to systemic

 doi:10.20944/preprints202602.0422.v1

metabolic disturbances[4,5]. Accordingly, antidiabetic medications have shown neuroprotective effects in preclinical and early human studies. Therefore, there has been an increasing interest in translational research looking at how antidiabetic medication alters biomarkers of neurodegeneration in PD.

In this review, we will explore the recent advances in anti-diabetic medications (biguanides, sulfonylureas, thiazolidinediones, dipeptidyl peptidase-4 inhibitors, sodium glucose cotransporter 2 inhibitors and Glucagon-like peptide-1 receptor agonists) that have been linked with disease modification on key PD biomarkers and their proposed outcomes in preclinical and clinical models of PD.

2. Relationship Between T2DM and PD

T2DM has been shown to increase the risk of developing PD and accelerate its progression. In multiple meta-analyses, individuals with T2DM were associated with increased risk for PD with relative risk ranging from 1.19-1.27 [6–8]. Cohort studies from Korea have shown that T2DM duration was associated with higher PD risk[9]. Another large cohort study from the UK has shown that there were elevated rates of PD following T2DM (hazard ratio 1.32, 95% confidence interval 1.29-1.35; $p < 0.001$) and that the increase was greater in individuals with complicated T2DM[10]. ***Table 1*** summarizes the relationship and interplay between these two diseases.

Table 1. Relationship between Parkinson's disease and T2DM. This table focuses on the mechanistic interplay between PD and T2DM in insulin resistance, neuroinflammation, mitochondrial dysfunction and impaired protein handling.

Mechanism	Parkinson's Disease	Type 2 Diabetes Mellitus
Insulin resistance	1. Amylin may interact with αSyn and result in dopamine cell death 2. Impaired insulin metabolism can lead to decreased neuroprotective effects	Misfolding of amylin causes pancreatic β cell death and peripheral insulin resistance leading to hyperglycemia
Neuroinflammation	NF-κB and NLRP3 inflammasome axis lead to αSyn pathology	Metabolic stress from diabetes increases activation of NF-κB and NLRP3 inflammasome
Mitochondrial dysfunction	Loss of mitochondrial complex I results in dopaminergic cell death	Insulin dysfunction results in increased vulnerability to oxidative stress
Impaired protein handling	IAPP can trigger αSyn pathology	1. IAPP aggregation disrupts β cell function 2. αSyn can promote IAPP aggregation

Mechanistically, there is extensive literature that shows pathophysiological similarities between T2DM and PD. First, insulin resistance and dysregulated insulin signaling are central to both diseases. In T2DM, misfolding of amylin may contribute to pathology due to loss of pancreatic beta cells which in turn leads to peripheral insulin resistance, then leads to hyperglycemia and β-cell dysfunction[11]. Amylin has been suggested to be involved in PD by interacting with αSyn, but whether it contributes αSyn aggregation in PD has not been studied[12]. In PD, insulin resistance occurs in the central nervous system and contributes to dopaminergic neuronal degeneration[11–13]. Insulin is thought to influence nervous system development, acts as neuroprotector by controlling apoptosis and ischemia[14], and insulin metabolism impairment is thought to lead to cognitive impairment and increase risk of neurodegenerative disorders.

Secondly, chronic inflammation and activation of the nuclear factor kappa B (NF-κB)/ nod-like receptor pyrin 3 (NLRP3) inflammasome axis are implicated in both T2DM, where hyperglycemia-induced oxidative stress triggers systemic inflammation, and in PD where neuroinflammation is

 doi:10.20944/preprints202602.0422.v1

enhanced leading to increased αSyn aggregation and further driving dopamine neuron loss[15–17]. NF-κB is a DNA binding protein required for transcription of many pro-inflammatory cytokines and chemokines. NF-κB is activated by reactive oxygen species (ROS) and pro-inflammatory cytokines, thus chronic low-grade inflammatory disorders such as T2DM result in higher levels of activated NF-κB[18]. In PD, NF-κB is thought to cause pathogenesis through induction of inflammation-mediated degeneration of dopaminergic neurons, and this has been demonstrated in a mouse model when inhibiting NF-κB prevented degeneration of dopaminergic neurons[19]. αSyn can also trigger activation of NF-κB and further release pro-inflammatory cytokines which further damages dopaminergic neurons[20]. NLRP3 inflammasome is involved with activation of caspase-1 and maturation of IL-1β and IL-18, which trigger and coordinate release of cytokines. In T2DM, NLRP3 inflammasome functions as a sensor for metabolic stress[21], can reduce glucose tolerance through modulation of gut microbiota[22], and may induce pancreatic β-cell pyroptosis[23]. In PD, NLRP3 inflammasome can also cause degeneration of dopaminergic neurons by induction of pyroptosis, can cause αSyn aggregation[24] but also further inflammatory responses by being triggered by αSyn aggregation[25,26]. Connecting T2DM to PD, chronic hyperglycemia is shown to increase αSyn deposition in pancreatic β cells, and trigger degeneration of dopaminergic neurons in PD[27].

Thirdly, both T2DM and PD have shown mitochondrial dysfunction, ferroptosis, and oxidative stress especially in β-cells and dopaminergic neurons which lead to cell death and disease progression[16,17,28]. Mitochondrial dysfunction in T2DM is thought to be a result of decreased ATP levels likely secondary to insulin dysfunction and increased vulnerability to oxidative stress[29]. PD is a disease that affects the aging brain, and aging results in mitochondrial dysfunction[30]. Specifically, loss of the mitochondrial complex I causes cell death in dopaminergic neurons, and this has been observed in mouse models in T2DM[31,32].

Fourthly, both T2DM and PD show similar patterns of impaired protein handling and aggregation. T2DM is characterized by islet amyloid polypeptide (IAPP) aggregation, while PD features αSyn aggregation. IAPP is a 37-amino acid peptide produced by pancreatic β-cells in response to hyperglycemia. When IAPP aggregate and form fibrils it disrupts β-cell function. Studies have shown that αSyn promotes IAPP aggregation[33]. On the contrary, evidence in animal models, including mice and cynomolgus monkeys, shows that IAPP can act as a trigger for αSyn pathology and accelerates its accumulation and neurotoxicity in dopaminergic neurons [34–36]. Speculation is that both proteins interact with one another in the pancreas as well as within the CNS after blood-brain barrier breakdown in elderly populations.

3. Biochemical Biomarkers in PD

Vijiaratnam et al. define a biomarker as "an objectively measured and evaluated characteristic from any substance, structure or process that can be measured in the body or its products as an indicator of normal biological or pathogenic processes, or pharmacologic responses to a therapeutic intervention"[37]. Therefore, an ideal biomarker should be reliable across the population and accessible through clinical samples. Reliable biomarkers become useful when assessing disease progression and response to interventions.

In PD, the landscape of biomarker analysis is vast and includes clinical, imaging, genetic and biochemical markers. For the purpose of this review, we will focus on the biochemical biomarkers that have been involved in the pathogenesis of PD. Biochemical biomarkers are collected from body fluids or tissue biopsies. Four classes of potential biochemical biomarkers that have been studied in PD include αSyn, markers of neuroinflammation, markers of insulin resistance, and markers of synaptic degeneration.

In PD, one of the earliest biomarkers that was evaluated was αSyn, the pathological protein that has been implicated in the substantia nigra resulting in dopaminergic neurodegeneration. Tests, evaluating total, phosphorylated and oligomeric αSyn in CSF, plasma, saliva, and skin samples have been developed [38]. CSF αSyn seeding amplification assay is highly accurate in differentiating PD from healthy controls when studied in a large and well characterized cohort sample but showed

 doi:10.20944/preprints202602.0422.v1

variability in LRRK2 variant population[39]. Commonly used in neurology clinics, the skin biopsy detection assay detected cutaneous phosphorylated αSyn with high accuracy in patients with PD and PD plus syndromes making this a minimally invasive technique [40]. Moreover, phosphorylated αSyn, specifically Ser-129p-αSyn, appears to be most specific for disease presence and severity. Unfortunately, none of the αSyn samples have been able to predict disease progression [37,41,42].

Markers of neuroinflammation (GFAP, complement levels, TNF, CRP, interleukin levels), including mitochondrial markers (DJ-1, PPAR-γ), and lysosomal dysfunction (glucocerebrosidase activity, β hexosaminidase, cathepsin D) have shown mixed results and have not been consistent across differentiating from atypical PD syndromes and measuring progression of PD[37]. In addition, inflammatory cytokine levels are elevated in a wide range of conditions.

Due to the increased risk of PD in T2DM patients, markers of insulin resistance have been considered[43]. Specifically, elevated insulin-receptor substrate-1 (IRS-1) phosphorylation, representing attenuated insulin signaling, has been found in PD patients with worsening tremor [44]. Another marker of insulin resistance is increasing hemoglobin A1c levels. Elevated hemoglobin A1c levels were shown to be associated with motor and cognitive severity and axonal damage in PD [45,46]. As discussed earlier, plasma IAPP levels can be an indirect measure for IAPP deposition withing the CNS which can implicate the burden of αSyn aggregation and disease burden in PD[47].

Markers of synaptic degeneration (SNAP25, βsynuclein, GAP43, Contactin-1) and axonal damage (NfL) have shown moderate predictability of severity of motor and cognitive progression when combined with clinical and disease specific fluid biomarkers [37,48]. Specifically, NfL shows promise for discriminating between PD and PD plus syndromes[48,49].

Several of these biochemical biomarkers associated with PD are affected by antidiabetic medications[38].

4. Antidiabetic Medications and Their Interactions on PD Biomarkers

Biguanides

Metformin, a drug from the biguanide class, is a relatively low-cost medication with minimal side effects, which makes it the preferred first-line diabetic treatment worldwide. Metformin stabilizes an individual's glycemia by inhibiting hepatic gluconeogenesis, promoting peripheral glucose uptake, and increasing insulin sensitivity. Multiple studies from cellular and animal PD models have shown that metformin improves lifespan, reduces dopaminergic neuron loss, and improves motor deficit recovery[50].

Preclinically, these neuroprotective effects are thought to be predominantly produced by activation of autophagy via AMPK signaling, which promotes degradation of misfolded proteins and damaged organelles[50–52]. This in turn can inhibit αSyn phosphorylation at Ser129 and reduces accumulation by directly interacting with αSyn monomers [50,53,54]. In MPTP mouse models, metformin use has shown reductions in oxidative stress and mitochondrial dysfunction thus improving neuronal survival and function[50,55,56]. Metformin use has also been shown to upregulate neurotrophic factors such as brain derived neurotropic factor (BDNF) and glial cell-line derived neurotrophic factor (GDNF) which supports dopaminergic neuron health[53,57,58], while suppressing elevated levels of neuroinflammatory markers and glial activation in PD[56,59]. However, metformin appears to also have neuroprotective effects independent of AMPK activation as shown in a study with MPTP-induced AMPK knock out mice treated with metformin [59].

Clinical outcomes focusing on improvement in motor and cognitive impairment showed mixed benefits[60–62]. However, a recent randomized pilot study found that there was no significant difference in motor outcomes between metformin and control groups after treatment, though metformin significantly reduced neuroinflammatory and pathological biomarkers[57]. Future clinical trials will need to address different doses of metformin and its effect on αSyn detected through CSF or through skin biopsy assays in the PD population as well as motor or non-motor outcomes to draw direct correlations between disease pathology, clinical status and medication use.

 doi:10.20944/preprints202602.0422.v1

However, metformin may also negatively affect PD neuropathology. *In vivo and in vitro* studies have found that chronic metformin use can reduce microglial activation and increase dopaminergic damage in response to MPTP [63] but also worsen cognition due to decrease in neurotrophic factors [64]. Clinically, chronic metformin use has shown no neuroprotective effects [61].

Sulfonylureas

Sulfonylureas (glipizide, glimepiride, glyburide) are another widely prescribed antidiabetic medication typically prescribed after metformin. They act by primarily blocking ATP-sensitive potassium channels in the pancreatic beta cells which stimulate insulin secretion thus lowering blood glucose.

There has not been promising data to suggest that sulfonylureas are effective at disease modification in PD[65]. One study has shown that it may even risk of PD[66]. No clinical trials of sulfonylureas use in PD were found.

Thiazolidinediones (TZDs)

Thiazolidinediones (pioglitazone and rosiglitazone) are a class of peroxisome proliferator-activated receptor gamma (PPAR-γ) agonists that improve insulin sensitivity and decrease blood glucose levels and are thus used for treatment in diabetes.

Preclinical data have shown potential modification of inflammatory effects through inhibition of microglia and astrocytes as well as production of proinflammatory cytokines and nitric oxide [67]. Several *in vivo* PD models showed neuroprotective benefits of TZDs, specifically their role in facilitating hippocampal neurogenesis, improving dopamine survivability, and improving motor performance [68–70].

Clinically, retrospective cohort and meta-analysis studies have shown a potential neuroprotective effect of TZD in PD and suggest that it may even reduce the incidence and risk of PD progression[71–73]. A Taiwan based large population database analysis of diabetic patients revealed that those taking TZDs had significantly lower risk of developing PD compared to the non-TZD group in a dose dependent manner [74]. However, in a phase 2 double blind, randomized trial, Pioglitazone at 15mg/day and 45mg/day could not modify progression of disease in early PD [75]. Disappointingly, there are limited studies that address the mechanism behind the benefits of TZDs in PD risk. The discrepancy between the preclinical data, meta analyses and clinical data have not indicated yet whether this class of diabetes medication truly holds promise in the landscape of more novel diabetic therapies.

Dipeptidyl Peptidase-4 Inhibitors (DPP4i)

DPP4i (sitagliptin, linagliptin, saxagliptin, alogliptin) are hypoglycemic agents associated with a low risk of hypoglycemia and weight gain in patients with diabetes. They improve glucose metabolism by enhancing the bioavailability of active glucagon-like peptide-1 (GLP-1) and by inhibiting its degradation.

In vivo model studies show that DPP4i 1) upregulate neuroprotective pathways such as PI3K/AKT and Nrf2[76], 2) increase levels of neurotropic factors such as BDNF and C-reactive element binding protein (CREB)[77,78], 3) reduce oxidative stress through indirect measurements of glutathione and malondialdehyde[78], 4) downregulation of proinflammatory markers (TNF-α, IL6, Iba-1, and GFAP), NF-κB, and reduce dopaminergic degeneration[77,79], and 5) decreases αSyn aggregation[80].

In the clinical setting, drug naïve, de novo PD patients with diabetes that were treated with DPP4i had significantly higher baseline DAT availability in the anterior, posterior, and ventral putamen compared to diabetic PD patients not on DPP4i [81]. Furthermore, this study showed that the DDP4i group had a slower increase in levodopa-equivalent dose over time and a lower rate of levodopa-induced dyskinesia.

 doi:10.20944/preprints202602.0422.v1

While in vivo studies draw strong links between DPP4i use and αSyn aggregation, clinical studies are yet to explore whether these antidiabetic agents affect αSyn physiology.

Sodium-Glucose Cotransporter-2 Inhibitors (SGLT2i)

SGLT2i (dapagliflozin, empagliflozin, canagliflozin, ertugliflozin, ipragliflozin, tofogliflozin, remogliflozin) are a class of antidiabetic medications that inhibit the reabsorption of glucose via the SGLT2 in the proximal tubules of the nephron and therefore lower blood sugar by enhancing glycosuria. Owing to their pleiotropic effects, they have also shown great efficacy for cardiovascular health, renal diseases, weight loss, and stabilizing blood pressure[82]. One of the predominant mechanisms by which SGLT2i produces these additional benefits is through reduction of reactive oxidative species and protecting the integrity of the mitochondria[83]. Therefore, studies indicate that SGLT2i improves mitochondrial function by reducing oxidative stress, enhancing mitochondrial biogenesis, and restoring autophagic-lysosomal balance[84–86].

Interestingly, SGLT2 are also found in the hippocampus, cerebellum, and at the blood-brain barrier endothelial cells[87]. This makes the SGLT2i particularly intriguing CNS penetrating drugs. Preclinical studies have provided promising solutions for PD. In a rat model, rotenone was used to mimic PD like motor deficits and empagliflozin, SGLT2i, treated groups showed improvements in motor function, decreases in αSyn accumulation, decreased inflammation, which was suggestive of its neuroprotective effect[88]. Similarly in a rotenone induced PD zebrafish model, empagliflozin treated groups showed improved DOPA/DA ratio, improved performance on Y-maze task, increased markers related to inflammation and autophagy [89]. Another rotenone induced PD rat model study has shown attenuation of cognitive dysfunction, improvement of dopamine secretion, and decreased dopaminergic neuronal loss[90]. Multiple similar studies in toxin induced PD models have shown improvements after SGLT2i therapy through improvements in autophagy, mitochondrial function, and inflammation [90–93]. In addition, SGLT2i have shown to downregulate *Snca* gene expression in a diabetic mouse model[94].

Clinically, SGLT2i use has also shown reductions in risk of PD dementia[95] and lower risk of incidence of PD in T2DM populations[96,97]. In a large head to head comparison study between SGLT2i and metformin using 20 year dataset of almost 900,000 patients, SGLT2i was associated with a 28% lower PD risk than metformin suggestive of its superiority in neuroprotection[98]. Another study has shown that SGLT2i were superior to DPP4i in significantly lowering risk of PD after using a retrospective cohort analysis of 89,000 Medicare beneficiaries[96]. However, this meta-analysis looking at dapagliflozin found no significant association between the medication use and risk of dementia in PD[99]. Taken together, there is promising in vivo data regarding the use of SGLT2i therapy in PD models, however, there have not been any randomized controlled trials studying this medication in PD populations.

Glucagon-like Peptide-1 Receptor Agonists (GLP-1 RA)

GLP-1 RA (exenatide, liraglutide, semaglutide, dulaglutide, tirzepatide, lixisenatide) are incretin hormones that enhance glucose-induced insulin secretion and inhibit both gastric emptying and glucagon secretion[100]. Like the SGLT2i class, they have multiple pleiotropic effects including reducing obesity, improving cardiovascular health, and improving bone health. They act via both peripheral and central mechanisms, thus there has been a lot of interest in the GLP-1 RA and their role in PD.

In preclinical models, GLP-1/GIP dual agonist DH3-CH alone and liraglutide alone (GLP-1 RA) were both effective at reducing motor decline in the MPTP mouse model of PD. This study also found decreased expression of αSyn and activation of Wnt/β-catenin signaling pathway, regulatory molecule in cell proliferation, differentiation, apoptosis, neurogenesis and stem cell maintenance[101]. Similarly, another study looking at another GLP-1/GIP dual receptor agonist, DA5-CH, in a MPTP mouse model showed reversal of MPTP induced decrease of BDNF and GDNF where as it reduced αSyn, levels of inflammation, and proinflammatory markers (IL6, Il-Iβ)[102].

 doi:10.20944/preprints202602.0422.v1

Another study in the MPTP PD mouse model found that GLP-1 RA activated PGC-1α, which regulates autophagy and cell apoptosis, and induced a neuroprotective effect[103]. In MitoPark mice, GLP-1 RA was found to reduce tyrosine hydroxylase expression by lowering reactive oxidative species and thus decreasing dopaminergic denervation[104], and another GLP-1 RA, PT320, was shown to improve L-DOPA-induced dyskinesias[105].

Clinical trials with exenatide have shown modest improvements in motor and cognitive symptoms [106–108]. Lixisenatide therapy resulted in modest effects in terms of progression of motor disability in early PD[109]. Liraglutide treatment was effective at improving both motor and nonmotor symptoms in PD, with effects sustaining while off medication[110]. In a population-based study, new users of GLP-1 RA have shown to have a 23% lower risk of PD than new users of DPP4i use[111]. However, a double blind randomized, placebo-controlled trial looking at exenatide over 96 weeks did not find any evidence of it acting as a disease-modifying treatment in PD patients when using MDS-UPDRS part III scores[112]. Interestingly, a recent metanalysis of studies involving GLP-1 RA demonstrated a detrimental effect on motor outcomes compared to placebo[113]. Overall, this class of antidiabetic medication shows the most promise in PD disease modification and multiple clinical trials are under way to draw clearer conclusions on their effects in PD.

4. Conclusions

There has been extensive evidence linking T2DM and PD. Specifically, molecular mechanisms responsible for disease pathology and progression in PD are thought to further their effects through insulin resistance, chronic inflammation, mitochondrial dysfunction and impaired protein aggregation. Insulin can have significant impact on brain function. Increasing blood glucose levels can worsen motor and cognitive performance in PD, and therefore strategies for an overall control of diabetes in the PD population can be neuroprotective. Antidiabetic medications hold promise as disease-modifying therapies in Parkinson's disease. Antidiabetic medications modulate several biochemical biomarkers relevant to PD, summarized in ***Figure 1***. The GLP-1 RAs show the most consistent neuroprotective properties in experimental settings. Sulfonylureas and TZDs do not show tremendous disease modifying properties in PD.

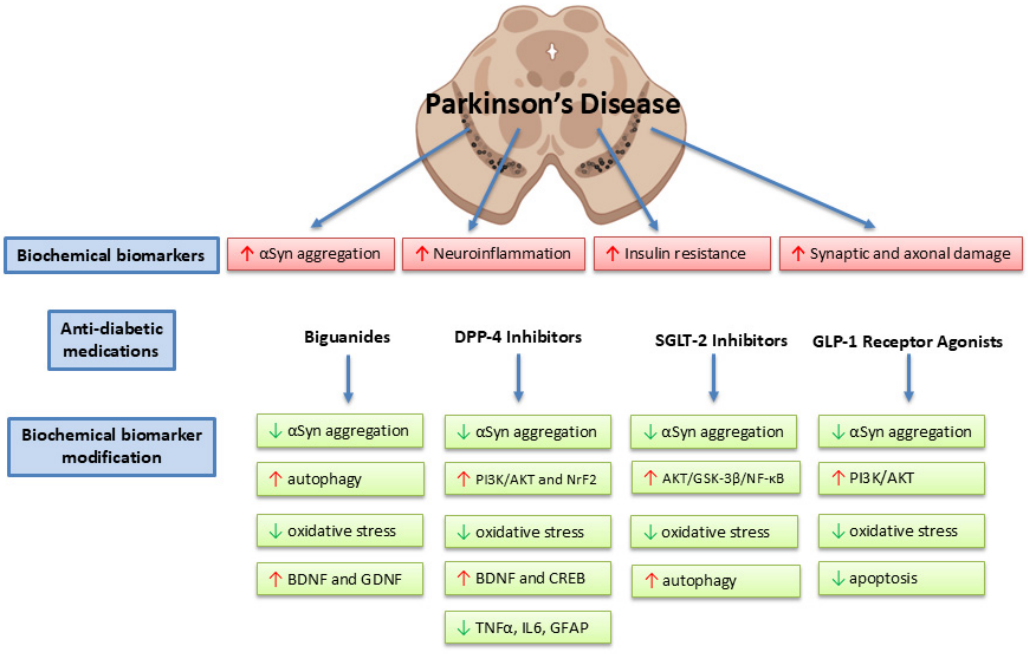

Figure 1. Antidiabetic medications modify metabolic, inflammatory, and neuroprotective biochemical biomarkers in Parkinson's disease. The four classes of antidiabetic medications (biguanides, DPP-4 inhibitors,

 doi:10.20944/preprints202602.0422.v1

SGLT-2 inhibitors and GLP-1 receptor agonists) have shown robust preclinical data in modifying biochemical biomarkers in PD.

However, there are inconsistencies in how these medications mechanistically may, if at all, modify disease progression. Several clinical trials have not been able to translate the same robust findings from preclinical models. It is possible that the effect of these medications in animal models occur as a result of poor choice of PD models. In addition, there are far too many biomarkers being assessed as a measure of neuroprotective function but very few have shown phenotypic improvement in human clinical trials. Overall, results from clinical outcomes in antidiabetic medications remain inconclusive.

Plausible explanations may be that motor scales used are not sensitive enough, non-motor outcomes should also be considered or that the effects of those medications vary across disease stages. As such, a reasonable strategy would be to focus on translating insights of disease modification from reliable preclinical PD models to controlled patient populations in clinical trials utilizing a variety of motor, non-motor and perhaps also digital outcome measures. Another strategy is to measure outcomes at appropriate phases of PD disease progression [114].

There is tremendous hope looking ahead though as more ongoing clinical trials are addressing some of these setbacks. Given the increase in focus on T2DM and weight management, the future of development and validation of biomarkers in PD is crucial for assessing the efficacy of these antidiabetic treatments with the hope of repurposing them into effective PD neuroprotective agents.

Abbreviations

The following abbreviations are used in the order of appearance in the manuscript:

PD	Parkinson's disease
T2DM	Type II Diabetes Mellitus
αsyn	α-synuclein
DaTscan	dopamine transporter imaging
CSF	Cerebrospinal fluid
NF-κB	nuclear factor kappa B
NLRP3	nod-like receptor pyrin 3
IRS-1	insulin-receptor substrate-1
AMPK	AMP-activated protein kinase
HbA1c	Hemoglobin A1c
GDNF	glial cell-line derived neurotrophic factor
BDNF	brain derived neurotropic factor
IAPP	islet amyloid polypeptide
TZD	Thiazolidinediones
PPAR-γ	peroxisome proliferator-activated receptor gamma
DDP4i	Dipeptidyl peptidase-4 inhibitors
DAT	Dopamine transporter
SGLT2i	Sodium-glucose cotransporter 2 inhibitors
GLP-1 RA	Glucagon-like peptide-1 receptor agonists

References

1. Pradeep, P.; J, K., Comprehensive review of literature on Parkinson's disease diagnosis. *Comput Biol Chem* **2024,** 113, 108228.
2. Pfeiffer, R. F., Non-motor symptoms in Parkinson's disease. *Parkinsonism Relat Disord* **2016,** 22 Suppl 1, S119-22.
3. He, R.; Yan, X.; Guo, J.; Xu, Q.; Tang, B.; Sun, Q., Recent Advances in Biomarkers for Parkinson's Disease. *Front Aging Neurosci* **2018,** 10, 305.
4. Cereda, E.; Barichella, M.; Pedrolli, C.; Klersy, C.; Cassani, E.; Caccialanza, R.; Pezzoli, G., Diabetes and risk of Parkinson's disease. *Mov Disord* **2013,** 28, (2), 257.

 doi:10.20944/preprints202602.0422.v1

5. Aguirre-Vidal, Y.; Montes, S.; Mota-Lopez, A. C.; Navarrete-Vazquez, G., Antidiabetic drugs in Parkinson's disease. *Clin Park Relat Disord* **2024,** 11, 100265.
6. Aune, D.; Schlesinger, S.; Mahamat-Saleh, Y.; Zheng, B.; Udeh-Momoh, C. T.; Middleton, L. T., Diabetes mellitus, prediabetes and the risk of Parkinson's disease: a systematic review and meta-analysis of 15 cohort studies with 29.9 million participants and 86,345 cases. *Eur J Epidemiol* **2023,** 38, (6), 591-604.
7. Chohan, H.; Senkevich, K.; Patel, R. K.; Bestwick, J. P.; Jacobs, B. M.; Bandres Ciga, S.; Gan-Or, Z.; Noyce, A. J., Type 2 Diabetes as a Determinant of Parkinson's Disease Risk and Progression. *Mov Disord* **2021,** 36, (6), 1420-1429.
8. Zhong, Q.; Wang, S., Association between diabetes mellitus, prediabetes and risk, disease progression of Parkinson's disease: A systematic review and meta-analysis. *Front Aging Neurosci* **2023,** 15, 1109914.
9. Rhee, S. Y.; Han, K. D.; Kwon, H.; Park, S. E.; Park, Y. G.; Kim, Y. H.; Yoo, S. J.; Rhee, E. J.; Lee, W. Y., Association Between Glycemic Status and the Risk of Parkinson Disease: A Nationwide Population-Based Study. *Diabetes Care* **2020,** 43, (9), 2169-2175.
10. De Pablo-Fernandez, E.; Goldacre, R.; Pakpoor, J.; Noyce, A. J.; Warner, T. T., Association between diabetes and subsequent Parkinson disease: A record-linkage cohort study. *Neurology* **2018,** 91, (2), e139-e142.
11. Cullinane, P. W.; de Pablo Fernandez, E.; Konig, A.; Outeiro, T. F.; Jaunmuktane, Z.; Warner, T. T., Type 2 Diabetes and Parkinson's Disease: A Focused Review of Current Concepts. *Mov Disord* **2023,** 38, (2), 162-177.
12. Sabari, S. S.; Balasubramani, K.; Iyer, M.; Sureshbabu, H. W.; Venkatesan, D.; Gopalakrishnan, A. V.; Narayanaswamy, A.; Senthil Kumar, N.; Vellingiri, B., Type 2 Diabetes (T2DM) and Parkinson's Disease (PD): a Mechanistic Approach. *Mol Neurobiol* **2023,** 60, (8), 4547-4573.
13. Athauda, D.; Foltynie, T., Insulin resistance and Parkinson's disease: A new target for disease modification? *Prog Neurobiol* **2016,** 145-146, 98-120.
14. Chiu, S. L.; Cline, H. T., Insulin receptor signaling in the development of neuronal structure and function. *Neural Dev* **2010,** 5, 7.
15. Alrouji, M.; Al-Kuraishy, H. M.; Al-Gareeb, A. I.; Alexiou, A.; Papadakis, M.; Jabir, M. S.; Saad, H. M.; Batiha, G. E., NF-kappaB/NLRP3 inflammasome axis and risk of Parkinson's disease in Type 2 diabetes mellitus: A narrative review and new perspective. *J Cell Mol Med* **2023,** 27, (13), 1775-1789.
16. Xxxx, S.; Ahmad, M. H.; Rani, L.; Mondal, A. C., Convergent Molecular Pathways in Type 2 Diabetes Mellitus and Parkinson's Disease: Insights into Mechanisms and Pathological Consequences. *Mol Neurobiol* **2022,** 59, (7), 4466-4487.
17. Sergi, D.; Renaud, J.; Simola, N.; Martinoli, M. G., Diabetes, a Contemporary Risk for Parkinson's Disease: Epidemiological and Cellular Evidences. *Front Aging Neurosci* **2019,** 11, 302.
18. Yaribeygi, H.; Sathyapalan, T.; Atkin, S. L.; Sahebkar, A., Molecular Mechanisms Linking Oxidative Stress and Diabetes Mellitus. *Oxid Med Cell Longev* **2020,** 2020, 8609213.
19. Ghosh, A.; Roy, A.; Liu, X.; Kordower, J. H.; Mufson, E. J.; Hartley, D. M.; Ghosh, S.; Mosley, R. L.; Gendelman, H. E.; Pahan, K., Selective inhibition of NF-kappaB activation prevents dopaminergic neuronal loss in a mouse model of Parkinson's disease. *Proc Natl Acad Sci U S A* **2007,** 104, (47), 18754-9.
20. Dolatshahi, M.; Ranjbar Hameghavandi, M. H.; Sabahi, M.; Rostamkhani, S., Nuclear factor-kappa B (NF-kappaB) in pathophysiology of Parkinson disease: Diverse patterns and mechanisms contributing to neurodegeneration. *Eur J Neurosci* **2021**.
21. Schroder, K.; Zhou, R.; Tschopp, J., The NLRP3 inflammasome: a sensor for metabolic danger? *Science* **2010,** 327, (5963), 296-300.
22. Ding, S.; Xu, S.; Ma, Y.; Liu, G.; Jang, H.; Fang, J., Modulatory Mechanisms of the NLRP3 Inflammasomes in Diabetes. *Biomolecules* **2019,** 9, (12).
23. Yu, Z. W.; Zhang, J.; Li, X.; Wang, Y.; Fu, Y. H.; Gao, X. Y., A new research hot spot: The role of NLRP3 inflammasome activation, a key step in pyroptosis, in diabetes and diabetic complications. *Life Sci* **2020,** 240, 117138.
24. Wang, S.; Yuan, Y. H.; Chen, N. H.; Wang, H. B., The mechanisms of NLRP3 inflammasome/pyroptosis activation and their role in Parkinson's disease. *Int Immunopharmacol* **2019,** 67, 458-464.

 doi:10.20944/preprints202602.0422.v1

25. Fan, Z.; Pan, Y. T.; Zhang, Z. Y.; Yang, H.; Yu, S. Y.; Zheng, Y.; Ma, J. H.; Wang, X. M., Systemic activation of NLRP3 inflammasome and plasma alpha-synuclein levels are correlated with motor severity and progression in Parkinson's disease. *J Neuroinflammation* **2020,** 17, (1), 11.
26. Codolo, G.; Plotegher, N.; Pozzobon, T.; Brucale, M.; Tessari, I.; Bubacco, L.; de Bernard, M., Triggering of inflammasome by aggregated alpha-synuclein, an inflammatory response in synucleinopathies. *PLoS One* **2013,** 8, (1), e55375.
27. Lv, Y. Q.; Yuan, L.; Sun, Y.; Dou, H. W.; Su, J. H.; Hou, Z. P.; Li, J. Y.; Li, W., Long-term hyperglycemia aggravates alpha-synuclein aggregation and dopaminergic neuronal loss in a Parkinson's disease mouse model. *Transl Neurodegener* **2022,** 11, (1), 14.
28. Duta, C.; Muscurel, C.; Dogaru, C. B.; Stoian, I., Ferroptosis-A Shared Mechanism for Parkinson's Disease and Type 2 Diabetes. *Int J Mol Sci* **2024,** 25, (16).
29. Moreira, P. I.; Rolo, A. P.; Sena, C.; Seica, R.; Oliveira, C. R.; Santos, M. S., Insulin attenuates diabetes-related mitochondrial alterations: a comparative study. *Med Chem* **2006,** 2, (3), 299-308.
30. Santos, R. X.; Correia, S. C.; Alves, M. G.; Oliveira, P. F.; Cardoso, S.; Carvalho, C.; Seica, R.; Santos, M. S.; Moreira, P. I., Mitochondrial quality control systems sustain brain mitochondrial bioenergetics in early stages of type 2 diabetes. *Mol Cell Biochem* **2014,** 394, (1-2), 13-22.
31. Khang, R.; Park, C.; Shin, J. H., Dysregulation of parkin in the substantia nigra of db/db and high-fat diet mice. *Neuroscience* **2015,** 294, 182-92.
32. Gonzalez-Rodriguez, P.; Zampese, E.; Stout, K. A.; Guzman, J. N.; Ilijic, E.; Yang, B.; Tkatch, T.; Stavarache, M. A.; Wokosin, D. L.; Gao, L.; Kaplitt, M. G.; Lopez-Barneo, J.; Schumacker, P. T.; Surmeier, D. J., Disruption of mitochondrial complex I induces progressive parkinsonism. *Nature* **2021,** 599, (7886), 650-656.
33. Mucibabic, M.; Steneberg, P.; Lidh, E.; Straseviciene, J.; Ziolkowska, A.; Dahl, U.; Lindahl, E.; Edlund, H., alpha-Synuclein promotes IAPP fibril formation in vitro and beta-cell amyloid formation in vivo in mice. *Sci Rep* **2020,** 10, (1), 20438.
34. Meng, L.; Li, Y.; Liu, C.; Zhang, G.; Chen, J.; Xiong, M.; Pan, L.; Zhang, X.; Chen, G.; Xiong, J.; Liu, C.; Xu, X.; Bu, L.; Zhang, Z.; Zhang, Z., Islet amyloid polypeptide triggers alpha-synuclein pathology in Parkinson's disease. *Prog Neurobiol* **2023,** 226, 102462.
35. Yu, H.; Sun, T.; He, X.; Wang, Z.; Zhao, K.; An, J.; Wen, L.; Li, J. Y.; Li, W.; Feng, J., Association between Parkinson's Disease and Diabetes Mellitus: From Epidemiology, Pathophysiology and Prevention to Treatment. *Aging Dis* **2022,** 13, (6), 1591-1605.
36. Sun, Y.; Guo, C.; Yuan, L.; Li, W.; Wang, Z. Y.; Yue, F.; Li, J. Y., Cynomolgus Monkeys With Spontaneous Type-2-Diabetes-Mellitus-Like Pathology Develop Alpha-Synuclein Alterations Reminiscent of Prodromal Parkinson's Disease and Related Diseases. *Front Neurosci* **2020,** 14, 63.
37. Vijiaratnam, N.; Foltynie, T., How should we be using biomarkers in trials of disease modification in Parkinson's disease? *Brain* **2023,** 146, (12), 4845-4869.
38. Arya, R.; Haque, A.; Shakya, H.; Billah, M. M.; Parvin, A.; Rahman, M. M.; Sakib, K. M.; Faruquee, H. M.; Kumar, V.; Kim, J. J., Parkinson's Disease: Biomarkers for Diagnosis and Disease Progression. *Int J Mol Sci* **2024,** 25, (22).
39. Siderowf, A.; Concha-Marambio, L.; Lafontant, D. E.; Farris, C. M.; Ma, Y.; Urenia, P. A.; Nguyen, H.; Alcalay, R. N.; Chahine, L. M.; Foroud, T.; Galasko, D.; Kieburtz, K.; Merchant, K.; Mollenhauer, B.; Poston, K. L.; Seibyl, J.; Simuni, T.; Tanner, C. M.; Weintraub, D.; Videnovic, A.; Choi, S. H.; Kurth, R.; Caspell-Garcia, C.; Coffey, C. S.; Frasier, M.; Oliveira, L. M. A.; Hutten, S. J.; Sherer, T.; Marek, K.; Soto, C.; Parkinson's Progression Markers, I., Assessment of heterogeneity among participants in the Parkinson's Progression Markers Initiative cohort using alpha-synuclein seed amplification: a cross-sectional study. *Lancet Neurol* **2023,** 22, (5), 407-417.
40. Gibbons, C. H.; Levine, T.; Adler, C.; Bellaire, B.; Wang, N.; Stohl, J.; Agarwal, P.; Aldridge, G. M.; Barboi, A.; Evidente, V. G. H.; Galasko, D.; Geschwind, M. D.; Gonzalez-Duarte, A.; Gil, R.; Gudesblatt, M.; Isaacson, S. H.; Kaufmann, H.; Khemani, P.; Kumar, R.; Lamotte, G.; Liu, A. J.; McFarland, N. R.; Miglis, M.; Reynolds, A.; Sahagian, G. A.; Saint-Hillaire, M. H.; Schwartzbard, J. B.; Singer, W.; Soileau, M. J.;

 doi:10.20944/preprints202602.0422.v1

Vernino, S.; Yerstein, O.; Freeman, R., Skin Biopsy Detection of Phosphorylated alpha-Synuclein in Patients With Synucleinopathies. *JAMA* **2024,** 331, (15), 1298-1306.

41. Vicente Miranda, H.; Cassio, R.; Correia-Guedes, L.; Gomes, M. A.; Chegao, A.; Miranda, E.; Soares, T.; Coelho, M.; Rosa, M. M.; Ferreira, J. J.; Outeiro, T. F., Posttranslational modifications of blood-derived alpha-synuclein as biochemical markers for Parkinson's disease. *Sci Rep* **2017,** 7, (1), 13713.
42. Parnetti, L.; Gaetani, L.; Eusebi, P.; Paciotti, S.; Hansson, O.; El-Agnaf, O.; Mollenhauer, B.; Blennow, K.; Calabresi, P., CSF and blood biomarkers for Parkinson's disease. *Lancet Neurol* **2019,** 18, (6), 573-586.
43. Hogg, E.; Athreya, K.; Basile, C.; Tan, E. E.; Kaminski, J.; Tagliati, M., High Prevalence of Undiagnosed Insulin Resistance in Non-Diabetic Subjects with Parkinson's Disease. *J Parkinsons Dis* **2018,** 8, (2), 259-265.
44. Chou, S. Y.; Chan, L.; Chung, C. C.; Chiu, J. Y.; Hsieh, Y. C.; Hong, C. T., Altered Insulin Receptor Substrate 1 Phosphorylation in Blood Neuron-Derived Extracellular Vesicles From Patients With Parkinson's Disease. *Front Cell Dev Biol* **2020,** 8, 564641.
45. Huxford, B.; Haque, T.; Joseph, A. B.; Simonet, C.; Gallagher, D.; Budu, C.; Dobson, R.; Noyce, A., Parkinson's Disease and Type 2 Diabetes: HbA1c Is Associated with Motor and Cognitive Severity. *Mov Disord* **2022,** 37, (2), 427-428.
46. Uyar, M.; Lezius, S.; Buhmann, C.; Potter-Nerger, M.; Schulz, R.; Meier, S.; Gerloff, C.; Kuhle, J.; Choe, C. U., Diabetes, Glycated Hemoglobin (HbA1c), and Neuroaxonal Damage in Parkinson's Disease (MARK-PD Study). *Mov Disord* **2022,** 37, (6), 1299-1304.
47. Sanchez-Gomez, A.; Alcarraz-Vizan, G.; Fernandez, M.; Fernandez-Santiago, R.; Ezquerra, M.; Camara, A.; Serrano, M.; Novials, A.; Munoz, E.; Valldeoriola, F.; Compta, Y.; Marti, M. J., Peripheral insulin and amylin levels in Parkinson's disease. *Parkinsonism Relat Disord* **2020,** 79, 91-96.
48. Lin, C. H.; Li, C. H.; Yang, K. C.; Lin, F. J.; Wu, C. C.; Chieh, J. J.; Chiu, M. J., Blood NfL: A biomarker for disease severity and progression in Parkinson disease. *Neurology* **2019,** 93, (11), e1104-e1111.
49. Tuominen, R. K.; Renko, J. M., Biomarkers of Parkinson's disease in perspective of early diagnosis and translation of neurotrophic therapies. *Basic Clin Pharmacol Toxicol* **2024,** 135, (3), 271-284.
50. Agostini, F.; Masato, A.; Bubacco, L.; Bisaglia, M., Metformin Repurposing for Parkinson Disease Therapy: Opportunities and Challenges. *Int J Mol Sci* **2021,** 23, (1).
51. Campagnoli, L. I. M.; Varesi, A.; Fahmideh, F.; Hakimizad, R.; Petkovic, P.; Barbieri, A.; Marchesi, N.; Pascale, A., From Diabetes to Degenerative Diseases: The Multifaceted Action of Metformin. *Int J Mol Sci* **2025,** 26, (19).
52. Gopar-Cuevas, Y.; Saucedo-Cardenas, O.; Loera-Arias, M. J.; Montes-de-Oca-Luna, R.; Rodriguez-Rocha, H.; Garcia-Garcia, A., Metformin and Trehalose-Modulated Autophagy Exerts a Neurotherapeutic Effect on Parkinson's Disease. *Mol Neurobiol* **2023,** 60, (12), 7253-7273.
53. Katila, N.; Bhurtel, S.; Shadfar, S.; Srivastav, S.; Neupane, S.; Ojha, U.; Jeong, G. S.; Choi, D. Y., Metformin lowers alpha-synuclein phosphorylation and upregulates neurotrophic factor in the MPTP mouse model of Parkinson's disease. *Neuropharmacology* **2017,** 125, 396-407.
54. Paudel, Y. N.; Angelopoulou, E.; Piperi, C.; Shaikh, M. F.; Othman, I., Emerging neuroprotective effect of metformin in Parkinson's disease: A molecular crosstalk. *Pharmacol Res* **2020,** 152, 104593.
55. Kang, H.; Khang, R.; Ham, S.; Jeong, G. R.; Kim, H.; Jo, M.; Lee, B. D.; Lee, Y. I.; Jo, A.; Park, C.; Kim, H.; Seo, J.; Paek, S. H.; Lee, Y. S.; Choi, J. Y.; Lee, Y.; Shin, J. H., Activation of the ATF2/CREB-PGC-1alpha pathway by metformin leads to dopaminergic neuroprotection. *Oncotarget* **2017,** 8, (30), 48603-48618.
56. Alrouji, M.; Al-Kuraishy, H. M.; Al-Gareeb, A. I.; Ashour, N. A.; Jabir, M. S.; Negm, W. A.; Batiha, G. E., Metformin role in Parkinson's disease: a double-sword effect. *Mol Cell Biochem* **2024,** 479, (4), 975-991.
57. AlRasheed, H. A.; Bahaa, M. M.; Elmasry, T. A.; Elberri, E. I.; Kotkata, F. A.; El Sabaa, R. M.; Elmorsi, Y. M.; Kamel, M. M.; Negm, W. A.; Hamouda, A. O.; Aldossary, K. M.; Salahuddin, M. M.; Yasser, M.; Eldesouqui, M.; Hamouda, M. A.; Eltantawy, N.; Elawady, M. E.; Abdallah, M. S., Randomized, double-blind, placebo-controlled pilot study of metformin as an adjunctive therapy in Parkinson's disease. *Front Pharmacol* **2025,** 16, 1497261.
58. Katila, N.; Bhurtel, S.; Park, P. H.; Hong, J. T.; Choi, D. Y., Activation of AMPK/aPKCzeta/CREB pathway by metformin is associated with upregulation of GDNF and dopamine. *Biochem Pharmacol* **2020,** 180, 114193.

 doi:10.20944/preprints202602.0422.v1

59. Bayliss, J. A.; Lemus, M. B.; Santos, V. V.; Deo, M.; Davies, J. S.; Kemp, B. E.; Elsworth, J. D.; Andrews, Z. B., Metformin Prevents Nigrostriatal Dopamine Degeneration Independent of AMPK Activation in Dopamine Neurons. *PLoS One* **2016,** 11, (7), e0159381.
60. Sobral, M. V. S.; Soares, V. G.; Moreira, J.; Rodrigues, L. K.; Rocha, P.; Bendaham, L.; Goncalves, O. R.; Pirolla, R. D. C.; Vilela, L. V.; de Abreu, V. S.; Almeida, K. J., The use of hypoglycemic drugs in Parkinson's disease: An updated meta-analysis of randomized controlled trials. *Parkinsonism Relat Disord* **2025,** 130, 107210.
61. Huang, K. H.; Chang, Y. L.; Gau, S. Y.; Tsai, T. H.; Lee, C. Y., Dose-Response Association of Metformin with Parkinson's Disease Odds in Type 2 Diabetes Mellitus. *Pharmaceutics* **2022,** 14, (5).
62. Rosell-Diaz, M.; Fernandez-Real, J. M., Metformin, Cognitive Function, and Changes in the Gut Microbiome. *Endocr Rev* **2024,** 45, (2), 210-226.
63. Ismaiel, A. A.; Espinosa-Oliva, A. M.; Santiago, M.; Garcia-Quintanilla, A.; Oliva-Martin, M. J.; Herrera, A. J.; Venero, J. L.; de Pablos, R. M., Metformin, besides exhibiting strong in vivo anti-inflammatory properties, increases mptp-induced damage to the nigrostriatal dopaminergic system. *Toxicol Appl Pharmacol* **2016,** 298, 19-30.
64. Allard, J. S.; Perez, E. J.; Fukui, K.; Carpenter, P.; Ingram, D. K.; de Cabo, R., Prolonged metformin treatment leads to reduced transcription of Nrf2 and neurotrophic factors without cognitive impairment in older C57BL/6J mice. *Behav Brain Res* **2016,** 301, 1-9.
65. Xie, Y.; Wang, J.; Jiang, J.; Liu, F.; Zhang, Y., Do oral antidiabetic medications alter the risk of Parkinson's disease? An updated systematic review and meta-analysis. *Neurol Sci* **2023,** 44, (12), 4193-4203.
66. Wahlqvist, M. L.; Lee, M. S.; Hsu, C. C.; Chuang, S. Y.; Lee, J. T.; Tsai, H. N., Metformin-inclusive sulfonylurea therapy reduces the risk of Parkinson's disease occurring with Type 2 diabetes in a Taiwanese population cohort. *Parkinsonism Relat Disord* **2012,** 18, (6), 753-8.
67. Storer, P. D.; Xu, J.; Chavis, J.; Drew, P. D., Peroxisome proliferator-activated receptor-gamma agonists inhibit the activation of microglia and astrocytes: implications for multiple sclerosis. *J Neuroimmunol* **2005,** 161, (1-2), 113-22.
68. Bonato, J. M.; Bassani, T. B.; Milani, H.; Vital, M.; de Oliveira, R. M. W., Pioglitazone reduces mortality, prevents depressive-like behavior, and impacts hippocampal neurogenesis in the 6-OHDA model of Parkinson's disease in rats. *Exp Neurol* **2018,** 300, 188-200.
69. Breidert, T.; Callebert, J.; Heneka, M. T.; Landreth, G.; Launay, J. M.; Hirsch, E. C., Protective action of the peroxisome proliferator-activated receptor-gamma agonist pioglitazone in a mouse model of Parkinson's disease. *J Neurochem* **2002,** 82, (3), 615-24.
70. Pinto, M.; Nissanka, N.; Peralta, S.; Brambilla, R.; Diaz, F.; Moraes, C. T., Pioglitazone ameliorates the phenotype of a novel Parkinson's disease mouse model by reducing neuroinflammation. *Mol Neurodegener* **2016,** 11, 25.
71. Zhu, Y.; Pu, J.; Chen, Y.; Zhang, B., Decreased risk of Parkinson's disease in diabetic patients with thiazolidinediones therapy: An exploratory meta-analysis. *PLoS One* **2019,** 14, (10), e0224236.
72. Hussain, S.; Singh, A.; Baxi, H.; Taylor, B.; Burgess, J.; Antony, B., Thiazolidinedione use is associated with reduced risk of Parkinson's disease in patients with diabetes: a meta-analysis of real-world evidence. *Neurol Sci* **2020,** 41, (12), 3697-3703.
73. Brauer, R.; Bhaskaran, K.; Chaturvedi, N.; Dexter, D. T.; Smeeth, L.; Douglas, I., Glitazone Treatment and Incidence of Parkinson's Disease among People with Diabetes: A Retrospective Cohort Study. *PLoS Med* **2015,** 12, (7), e1001854.
74. Lin, H. L.; Lin, H. C.; Tseng, Y. F.; Chao, J. C.; Hsu, C. Y., Association of thiazolidinedione with a lower risk of Parkinson's disease in a population with newly-diagnosed diabetes mellitus. *Ann Med* **2018,** 50, (5), 430-436.
75. Investigators, N. E. T. i. P. D. F.-Z., Pioglitazone in early Parkinson's disease: a phase 2, multicentre, double-blind, randomised trial. *Lancet Neurol* **2015,** 14, (8), 795-803.
76. Soni, R.; Pankaj, V.; Roy, S.; Khairnar, A.; Shah, J., Upregulation of the PI3K/AKT and Nrf2 Pathways by the DPP-4 Inhibitor Sitagliptin Renders Neuroprotection in Chemically Induced Parkinson's Disease Mouse Models. *ACS Chem Neurosci* **2025,** 16, (7), 1402-1417.

 doi:10.20944/preprints202602.0422.v1

77. Yu, S. J.; Wang, Y.; Shen, H.; Bae, E. K.; Li, Y.; Sambamurti, K.; Tones, M. A.; Zaleska, M. M.; Hoffer, B. J.; Greig, N. H., DPP-4 inhibitors sitagliptin and PF-00734,200 mitigate dopaminergic neurodegeneration, neuroinflammation and behavioral impairment in the rat 6-OHDA model of Parkinson's disease. *Geroscience* **2024,** 46, (5), 4349-4371.
78. Maanvi; Kumari, S.; Deshmukh, R., Dipeptidyl peptidase 4(DPP4) inhibitors stride up the management of Parkinson's disease. *Eur J Pharmacol* **2023,** 939, 175426.
79. Nassar, N. N.; Al-Shorbagy, M. Y.; Arab, H. H.; Abdallah, D. M., Saxagliptin: a novel antiparkinsonian approach. *Neuropharmacology* **2015,** 89, 308-17.
80. Jeong, S. H.; Kim, Y. J.; Shin, J. Y.; Oh, K. W.; Lee, J. W.; Lee, P. H., DPP-4 inhibitor alleviates gut-brain axis pathology in Parkinson's disease. *Gut* **2025**.
81. Jeong, S. H.; Chung, S. J.; Yoo, H. S.; Hong, N.; Jung, J. H.; Baik, K.; Lee, Y. H.; Sohn, Y. H.; Lee, P. H., Beneficial effects of dipeptidyl peptidase-4 inhibitors in diabetic Parkinson's disease. *Brain* **2021,** 144, (4), 1127-1137.
82. Cowie, M. R.; Fisher, M., SGLT2 inhibitors: mechanisms of cardiovascular benefit beyond glycaemic control. *Nat Rev Cardiol* **2020,** 17, (12), 761-772.
83. Yaribeygi, H.; Atkin, S. L.; Butler, A. E.; Sahebkar, A., Sodium-glucose cotransporter inhibitors and oxidative stress: An update. *J Cell Physiol* **2019,** 234, (4), 3231-3237.
84. Lin, K. J.; Wang, T. J.; Chen, S. D.; Lin, K. L.; Liou, C. W.; Lan, M. Y.; Chuang, Y. C.; Chuang, J. H.; Wang, P. W.; Lee, J. J.; Wang, F. S.; Lin, H. Y.; Lin, T. K., Two Birds One Stone: The Neuroprotective Effect of Antidiabetic Agents on Parkinson Disease-Focus on Sodium-Glucose Cotransporter 2 (SGLT2) Inhibitors. *Antioxidants (Basel)* **2021,** 10, (12).
85. Zhang, L.; Cai, L.; Lin, H.; Wu, W.; Zhu, Y.; Cai, J.; Hu, C.; Lin, X.; Sun, H.; Wei, X., Two Birds With One Stone: The Protective Role of the Antidiabetic Drug Sodium-Glucose Cotransporter-2 Inhibitor in Neurodegenerative Diseases. *Eur J Neurosci* **2025,** 62, (3), e70221.
86. Bray, J. J. H.; Foster-Davies, H.; Stephens, J. W., A systematic review examining the effects of sodium-glucose cotransporter-2 inhibitors (SGLT2is) on biomarkers of inflammation and oxidative stress. *Diabetes Res Clin Pract* **2020,** 168, 108368.
87. Esterline, R. L.; Vaag, A.; Oscarsson, J.; Vora, J., MECHANISMS IN ENDOCRINOLOGY: SGLT2 inhibitors: clinical benefits by restoration of normal diurnal metabolism? *Eur J Endocrinol* **2018,** 178, (4), R113-R125.
88. Mohammed, N. N.; Tadros, M. G.; George, M. Y., Empagliflozin repurposing in Parkinson's disease; modulation of oxidative stress, neuroinflammation, AMPK/SIRT-1/PGC-1alpha, and wnt/beta-catenin pathways. *Inflammopharmacology* **2024,** 32, (1), 777-794.
89. Unal, I.; Cansiz, D.; Beler, M.; Sezer, Z.; Guzel, E.; Emekli-Alturfan, E., Sodium-dependent glucose co-transporter-2 inhibitor empagliflozin exerts neuroprotective effects in rotenone-induced Parkinson's disease model in zebrafish; mechanism involving ketogenesis and autophagy. *Brain Res* **2023,** 1820, 148536.
90. Arab, H. H.; Safar, M. M.; Shahin, N. N., Targeting ROS-Dependent AKT/GSK-3beta/NF-kappaB and DJ-1/Nrf2 Pathways by Dapagliflozin Attenuates Neuronal Injury and Motor Dysfunction in Rotenone-Induced Parkinson's Disease Rat Model. *ACS Chem Neurosci* **2021,** 12, (4), 689-703.
91. Elkady, M. A.; Kabel, A. M.; Dawood, L. M.; Helal, A. I.; Borg, H. M.; Atia, H. A.; Sabry, N. M.; Moustafa, N. M.; Arafa, E. A.; Alsufyani, S. E.; Arab, H. H., Targeting the Sirtuin-1/PPAR-Gamma Axis, RAGE/HMGB1/NF-kappaB Signaling, and the Mitochondrial Functions by Canagliflozin Augments the Protective Effects of Levodopa/Carbidopa in Rotenone-Induced Parkinson's Disease. *Medicina (Kaunas)* **2024,** 60, (10).
92. Abdelaziz, A. M.; Rasheed, N. O. A.; Zaki, H. F.; Salem, H. A.; El-Sayed, R. M., Canagliflozin attenuates neurodegeneration and ameliorates dyskinesia through targeting the NLRP3/Nurr1/GSK-3beta/SIRT3 pathway and autophagy modulation in rotenone-lesioned rats. *Int Immunopharmacol* **2025,** 146, 113839.
93. Motawi, T. K.; Al-Kady, R. H.; Abdelraouf, S. M.; Senousy, M. A., Empagliflozin alleviates endoplasmic reticulum stress and augments autophagy in rotenone-induced Parkinson's disease in rats: Targeting the GRP78/PERK/eIF2alpha/CHOP pathway and miR-211-5p. *Chem Biol Interact* **2022,** 362, 110002.

 doi:10.20944/preprints202602.0422.v1

94. Piatkowska-Chmiel, I.; Herbet, M.; Gawronska-Grzywacz, M.; Pawlowski, K.; Ostrowska-Lesko, M.; Dudka, J., Molecular and neural roles of sodium-glucose cotransporter 2 inhibitors in alleviating neurocognitive impairment in diabetic mice. *Psychopharmacology (Berl)* **2023,** 240, (4), 983-1000.
95. Kim, H. K.; Biessels, G. J.; Yu, M. H.; Hong, N.; Lee, Y. H.; Lee, B. W.; Kang, E. S.; Cha, B. S.; Lee, E. J.; Lee, M., SGLT2 Inhibitor Use and Risk of Dementia and Parkinson Disease Among Patients With Type 2 Diabetes. *Neurology* **2024,** 103, (8), e209805.
96. Guo, J.; Tang, H.; Shao, H.; Lu, Y.; Shi, L.; Fonseca, V. A.; Cho, H.; Guo, Y.; Bian, J., Sodium-glucose cotransporter 2 inhibitors and the risk of Parkinson disease in real-world patients with type 2 diabetes. *Diabetes Obes Metab* **2024,** 26, (12), 5727-5736.
97. Yeh, J. A.; Lin, S. M.; Liu, Y. C.; Hsu, J. Z.; Huang, A. H.; Munir, K. M.; Peng, C. C.; Loh, C. H.; Huang, H. K., Association of SGLT2 inhibitors and GLP-1 receptor agonists with the risk of Parkinson's disease in patients with type 2 diabetes: A propensity score-matched cohort study with meta-analysis. *Diabetes Res Clin Pract* **2025,** 229, 112914.
98. Sun, M.; Wang, X.; Lu, Z.; Yang, Y.; Lv, S.; Miao, M.; Chen, W. M.; Wu, S. Y.; Zhang, J., SGLT2 inhibitors vs. metformin for Parkinson's disease risk reduction in type 2 diabetes. *J Parkinsons Dis* **2025,** 15, (7), 1240-1252.
99. Fernandes, J. V.; Ramos, J. V.; Holanda, M. M., Association between dapagliflozin and risk of dementia and Parkinson's disease: a subgroup analysis of a meta-analysis of randomized controlled trials. *Minerva Med* **2025,** 116, (4), 323-328.
100. Baggio, L. L.; Drucker, D. J., Glucagon-like peptide-1 receptors in the brain: controlling food intake and body weight. *J Clin Invest* **2014,** 124, (10), 4223-6.
101. Feng, P.; Liu, Z.; Lv, D.; Hao, W.; Li, D.; Xue, G.; Bai, B.; Holscher, C., The novel GLP-1 / GIP dual agonist DA3-CH is more effective than liraglutide in the MPTP mouse model of Parkinson's disease. *Eur J Pharmacol* **2025,** 1003, 177972.
102. Lv, M.; Xue, G.; Cheng, H.; Meng, P.; Lian, X.; Holscher, C.; Li, D., The GLP-1/GIP dual-receptor agonist DA5-CH inhibits the NF-kappaB inflammatory pathway in the MPTP mouse model of Parkinson's disease more effectively than the GLP-1 single-receptor agonist NLY01. *Brain Behav* **2021,** 11, (8), e2231.
103. Wu, P.; Dong, Y.; Chen, J.; Guan, T.; Cao, B.; Zhang, Y.; Qi, Y.; Guan, Z.; Wang, Y., Liraglutide Regulates Mitochondrial Quality Control System Through PGC-1alpha in a Mouse Model of Parkinson's Disease. *Neurotox Res* **2022,** 40, (1), 286-297.
104. Wang, V.; Tseng, K. Y.; Kuo, T. T.; Huang, E. Y.; Lan, K. L.; Chen, Z. R.; Ma, K. H.; Greig, N. H.; Jung, J.; Choi, H. I.; Olson, L.; Hoffer, B. J.; Chen, Y. H., Attenuating mitochondrial dysfunction and morphological disruption with PT320 delays dopamine degeneration in MitoPark mice. *J Biomed Sci* **2024,** 31, (1), 38.
105. Kuo, T. T.; Chen, Y. H.; Wang, V.; Huang, E. Y.; Ma, K. H.; Greig, N. H.; Jung, J.; Choi, H. I.; Olson, L.; Hoffer, B. J.; Tseng, K. Y., PT320, a Sustained-Release GLP-1 Receptor Agonist, Ameliorates L-DOPA-Induced Dyskinesia in a Mouse Model of Parkinson's Disease. *Int J Mol Sci* **2023,** 24, (5).
106. Aviles-Olmos, I.; Dickson, J.; Kefalopoulou, Z.; Djamshidian, A.; Ell, P.; Soderlund, T.; Whitton, P.; Wyse, R.; Isaacs, T.; Lees, A.; Limousin, P.; Foltynie, T., Exenatide and the treatment of patients with Parkinson's disease. *J Clin Invest* **2013,** 123, (6), 2730-6.
107. Mulvaney, C. A.; Duarte, G. S.; Handley, J.; Evans, D. J.; Menon, S.; Wyse, R.; Emsley, H. C., GLP-1 receptor agonists for Parkinson's disease. *Cochrane Database Syst Rev* **2020,** 7, (7), CD012990.
108. Athauda, D.; Maclagan, K.; Skene, S. S.; Bajwa-Joseph, M.; Letchford, D.; Chowdhury, K.; Hibbert, S.; Budnik, N.; Zampedri, L.; Dickson, J.; Li, Y.; Aviles-Olmos, I.; Warner, T. T.; Limousin, P.; Lees, A. J.; Greig, N. H.; Tebbs, S.; Foltynie, T., Exenatide once weekly versus placebo in Parkinson's disease: a randomised, double-blind, placebo-controlled trial. *Lancet* **2017,** 390, (10103), 1664-1675.
109. Meissner, W. G.; Remy, P.; Giordana, C.; Maltete, D.; Derkinderen, P.; Houeto, J. L.; Anheim, M.; Benatru, I.; Boraud, T.; Brefel-Courbon, C.; Carriere, N.; Catala, H.; Colin, O.; Corvol, J. C.; Damier, P.; Dellapina, E.; Devos, D.; Drapier, S.; Fabbri, M.; Ferrier, V.; Foubert-Samier, A.; Frismand-Kryloff, S.; Georget, A.; Germain, C.; Grimaldi, S.; Hardy, C.; Hopes, L.; Krystkowiak, P.; Laurens, B.; Lefaucheur, R.; Mariani, L. L.; Marques, A.; Marse, C.; Ory-Magne, F.; Rigalleau, V.; Salhi, H.; Saubion, A.; Stott, S. R. W.; Thalamas,

 doi:10.20944/preprints202602.0422.v1

C.; Thiriez, C.; Tir, M.; Wyse, R. K.; Benard, A.; Rascol, O.; Group, L. S., Trial of Lixisenatide in Early Parkinson's Disease. *N Engl J Med* **2024,** 390, (13), 1176-1185.

110. Aviles-Olmos, I.; Espinoza-Vinces, C.; Portugal, L. R.; Luquin, M. R., Targeting Metabolic Dysfunction in Parkinson's Disease: The Role of GLP-1 Agonists in Body Weight Regulation and Neuroprotection. *Curr Diab Rep* **2025,** 25, (1), 49.
111. Tang, H.; Lu, Y.; Okun, M. S.; Donahoo, W. T.; Ramirez-Zamora, A.; Wang, F.; Huang, Y.; Armstrong, M.; Svensson, M.; Virnig, B. A.; DeKosky, S. T.; Bian, J.; Guo, J., Glucagon-Like Peptide-1 Receptor Agonists and Risk of Parkinson's Disease in Patients with Type 2 Diabetes: A Population-Based Cohort Study. *Mov Disord* **2024,** 39, (11), 1960-1970.
112. Vijiaratnam, N.; Girges, C.; Auld, G.; McComish, R.; King, A.; Skene, S. S.; Hibbert, S.; Wong, A.; Melander, S.; Gibson, R.; Matthews, H.; Dickson, J.; Carroll, C.; Patrick, A.; Inches, J.; Silverdale, M.; Blackledge, B.; Whiston, J.; Hu, M.; Welch, J.; Duncan, G.; Power, K.; Gallen, S.; Kerr, J.; Chaudhuri, K. R.; Batzu, L.; Rota, S.; Jabbari, E.; Morris, H.; Limousin, P.; Greig, N.; Li, Y.; Libri, V.; Gandhi, S.; Athauda, D.; Chowdhury, K.; Foltynie, T., Exenatide once a week versus placebo as a potential disease-modifying treatment for people with Parkinson's disease in the UK: a phase 3, multicentre, double-blind, parallel-group, randomised, placebo-controlled trial. *Lancet* **2025,** 405, (10479), 627-636.
113. Ristori Costa, G.; Ferreira Cavalcante, L. F.; Massafelli Battistuta, S.; Makabe, P. F.; Silva Fanucci Bueno, I.; Yuamoto, B.; Goncalves Vilela, F. E.; Giacon Meloni, L. G.; Donizete de Faria, D.; Anghinah, R.; Haddad Santos, D., The Effect of GLP-1RA on the Motor Function of Patients With Parkinson Disease: A Systematic Review and Meta-Analysis. *Neurol Clin Pract* **2025,** 15, (6), e200548.
114. Vijiaratnam, N.; Simuni, T.; Bandmann, O.; Morris, H. R.; Foltynie, T., Progress towards therapies for disease modification in Parkinson's disease. *Lancet Neurol* **2021,** 20, (7), 559-572.