Type 2 Diabetes *Mellitus* and Parkinson's Disease: What Do We Know?

Diabetes Mellitus *Tipo 2 e Doença de Parkinson: O que Sabemos?*

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Abstract

Parkinson´s disease (PD) is the second most common neurodegenerative disorder and Diabetes *Mellitus* (DM) is the most widespread metabolic disorder, both more prevalent in the older population with rising numbers appearing. Hypothesis are rising regarding benefits of antidiabetic medication use in PD patients.
This review aims to summarizes current evidence on the association between both diseases, possible benefits antidiabetic medication may carry and ongoing clinical trials on the matter.
Regarding potential higher risk of developing PD in patients with DM, systematic reviews and meta-analysis conclude that the positive association only appears in more robust studies (cohort). The underlying processes of dysregulated pathways are still heated research topics, although oxidative stress and impaired insulin signaling appear to be associated with dopaminergic nigrostriatal degeneration.
Since antidiabetic medicines were first associated with PD symptoms improvement in 1960, considerable research has been conducted and today GLP-1 mimetics are frontrunners.

Keywords: Parkinson's disease; diabetes *mellitus*; antidiabetic medication; exenatide; GLP-1 mimetics

Resumo

A Doença de Parkinson (DP) é a segunda doença neurodegenerativa mais comum e a Diabetes *Mellitus* (DM) é a doença metabólica mais difundida a nível mundial, sendo ambas mais prevalentes na população mais idosa, com números crescentes.
Esta revisão pretende sumarizar a evidência actual sobre a associação entre ambas as doenças, possíveis benefícios que a medicação antidiabética possa trazer e ensaios clínicos em curso sobre o assunto.
Em relação ao potencial risco acrescido que doentes com DM têm de desenvolver DP, revisões sistemáticas e meta-análises apontam para que a associação positiva só se verifique em estudos mais robustos (cohort). As vias disfuncionais subjacentes a ambas as doenças ainda são alvos de intensa investigação, sendo que o stress oxidativo e sinalização desregulada de insulina parecem estar associados a degeneração dopaminérgica nigro-estriada.
Desde que a medicação antidiabética foi associada a melhoria na sintomatologia da DP em 1960, bastante investigação tem sido conduzida e, nos dias de hoje, agonistas da incretina mostram-se promissores.

Palavras-chave: Doença de Parkinson; diabetes *mellitus*; medicação antidiabética; exenatido; agonistas GLP-1

> INTRODUCTION

Parkinson's disease (PD) is a common late-life neurodegenerative disorder presenting with motor and non-motor symptoms. [1] It affects 1-2 individuals per 1000 at any time and its prevalence increases with age, with a peaking prevalence at 85-89 years old. [2,3]
In 1817, James Parkinson published his "Essay on the shaking palsy" and carefully outlined the major motor signs of the disease: bradykinesia, rigidity, and tremor. [2]
Most cases of PD are idiopathic, however there are

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Recebido/Received: 22/09/2022; Aceite/Accepted: 29/09/2022.

known genetic and environmental factors that have been associated with the development of PD. [3] For instances, high prevalence of LRRK2 mutation in familial (16.1%) and sporadic (3.7%) PD patients have been reported in Portugal. [4]

Like PD, Diabetes *Mellitus* (DM) also affects mostly older people, although it has a higher prevalence being the most widespread metabolic disorder. [5] Type 2 DM is a chronic metabolic disorder in which either the pancreas produces inadequate quantity of insulin or the body resists insulin. [6] The development of new antidiabetic medication has changed treatment approach in people with diabetes. [7]

It has been hypothesized that patients with type 2 DM may have a higher risk of developing PD. This could be related to a common underlying process of dysregulated pathways, such as inflammation and oxidative stress. [8] Additionally, there is growing research studying the potential benefit of antidiabetic medication on PD progression. [9,10]

This review aims to summarize current evidence regarding the relationship between these two diseases and the potential role of antidiabetic medication.

> PARKINSON'S DISEASE AND DIABETES *MELLITUS*

A meta-analysis from 2011 concluded that DM constituted a risk factor for PD in the subgroup of cohort studies (which are more robust), but not case-controls. [11] Similarly, another recent meta-analysis also found that patients with DM were associated with a 15% higher risk of developing PD, but a subgroup analysis showed that this positive association only occurred in cohort studies, and not in case-control ones.

One of the most recent systematic reviews supports that the prevalence of DM in PD patients is similar to the general population (10.02 %, 95%C.I. 7.88 -12.16), but patients with DM have a higher risk of developing PD (OR 1.34, 95%CI 1.26-1.43), and with greater severity and faster progression compared with non-DM PD patients. [12]

Duration of DM might be relevant for the association, as an earlier onset of diabetes leads to a higher risk of PD, comparing to a later in life onset, with one possible explanation being the need for longer insulin dysregulation for it to cause effect on the dopaminergic system. [13]

Despite the certainty of this relationship being quite well established and accepted in research community, the common underlying mechanism between DM and PD is still unclear and a focus of intense research. It is not clear which of the various DM metabolic changes affects dopaminergic nigrostriatal degeneration in PD – or how –, but the impaired insulin signalling, and oxidative stress are the frontrunners. [14]

The emerging role of insulin as a neuromodulator appears a possible puzzle piece contributing to the neurodegeneration pathway of PD. [15] Animal studies have shown that insulin resistance leads to hyperglycemia, which increases the risk of PD. [6]

The insulin signalling pathway embraces two proteins, which are closely involved in PD pathogenesis - alpha-synuclein (α-syn) and Leucine-Rich Repeat Kinase 2 (LRRK2). Alpha-syn has also been identified in the pancreas and has been shown to functionally act as a brake on insulin secretion. [15]

Insulin resistance was also found to be associated with α-synuclein over-expression, generation of free radical and impaired mitochondrial membrane potential in dopaminergic neurons, leading to the hypothesis that insulin resistance is associated with both diabetes and PD progression. [15]

Glication occurs when the metabolites of the glucose metabolism, namely Methylgloxal, react with proteins. [16] Since glication endproducts were found in the substantia nigra, near Lewy bodies, an association between this chemical reaction and the pathogenics of diseases involving Lewy-body formations like PD was made. [17] Recent studies have been trying to assess a causal relationship between glycation and PD pathology, as well as the mechanisms behind it. One study reached to the conclusion that an increase in brain glycation leads to alpha-syn accumulation and potentiates motor, cognitive, olfactory, and colonic dysfunction via glutamatergic signalling. [18] Glycation was also shown to increase alpha-syn toxicity. [19] This perspective opens therapeutic possibilities, [20] specifically it brings focus to drugs that depress glycation or glutamatergic signalling. [18]

Despite neuroinflammation being involved in the neurodegeneration pathways, it is not clear the role of oxidative stress and other components of the degenerative process (eg. mitochondrial dysfunction, nitric oxide toxicity, and inflammation), since they could be the cause or the consequence of these diseases. [15]

The hypothesis that PD increases the blood sugar level and could probably increase the DM risk is less robust and still controversial. Few preclinical and clinical studies support this directional link. [6]

> PARKINSON'S DISEASE AND ANTIDIABETIC MEDICATION

Several antidiabetic medications ameliorate PD symp-

toms in animal models, [6] but currently intense research is also being done in humans (Table I).

Although new antidiabetic medications bring attention to this point, the fact is that this link was already described in 1960 when a few PD patients were treated with tolbutamide, a drug belonging to the sulfonylurea class, and markedly improved tremor and rigidity. [15]

Glitazones, DPP4 inhibitors and metformin have also been studied successfully in preclinical research to manage PD. However, pioglitazone's effect for instance was not replicated in clinical research, including clinical trials. [15,21]

Large cohort studies suggest metformin could reduce risk of PD, probably due to its action on the gut hormone glucagon-like peptide 1 (GLP-1). [15]

GLP-1 mimetics have shown neuroprotective effects, and can cross the blood brain barrier, making them encouraging possibilities for treatment of neurodegenerative conditions. [22] Exendin-4 (exenatide), for example, was shown to improve the number of neural stem cells and promote adult neurogenesis (in vitro and in vivo), normalizing dopamine imbalance in the substantia nigra in an animal model of PD [23] and even rescuing motor function. [24]

In 2013, Aviles-Olmos *et al*. conducted a proof-of-concept single-blind trial in which above-mentioned possibilities were corroborated, with both motor and cognitive improvements on the subjects to whom the drug was administered, comparing to controls. [25]

To deeply understand exenatide's role, a randomized, placebo controlled, double-blind trial in 2017 investigated the role of the drug in PD. [26] PD patients without DM were evaluated for 48 weeks and the exenatide group presented improvement in motor examination of the MDS-UPDRS scale. However, no significant difference was detected in cognitive or nonmotor symptoms. [21]

In 2020, a meta-analysis from three randomized control trials concluded that exenatide is associated with benefits on motor and cognitive scales, nonmotor problems, and even on the motor complications of therapy. [27]

Based on these results, other trials are being conducted/planned to evaluate the effect of this GLP1 receptor agonist in PD, such as the phase 3 exenatide – PD3 trial (NCT04232969). Additionally, other GLP1 receptor agonists are also being studied, such as liraglutide (NCT02953665), semaglutide (NCT03659682) or lixisenatide (NCT03439943) (21) – Table 1.

Other molecules from the incretin family also show promise, such as Glucose-dependent Insulinotropic polypeptides (GIPs), which exhibit protective effects (improved cell survival). [28] Novel dual GLP1/GIP receptor agonists, with their ability to cross the blood-brain barrier, show improved neuroprotection in animal models. [29-31]

Table I - Current clinical trials studying the effect of antidiabetic medicines on PD.

Title	Drug	Phase	Status	Location
Exenatide Once Weekly Over 2 Years as a Potential Disease Modifying Treatment for Parkinson's Disease	Exenatide (extented release 2mg [Bydureon])	III	Active, not recruiting	London, United Kingdom
Safety and Efficacy of Liraglutide in Parkinson's Disease	Liraglutide	II	Active, not recruiting	California, United States
GLP1R in Parkinson's Disease	Semaglutide	II	Not yet recruiting	Oslo, Norway
Study to Evaluate the Effect of Lixisenatide in Patients with Parkinson's Disease	Lixisenatide	II	Unknown	France
Trial of Exenatide for Parkinson's Disease	Exenatide	I	Completed	London, United Kingdom
Exendin-4 as a Treatment for Parkinson's Disease – Pilot Study	Exenatide	II	Unknown	London, United Kingdom
Exenatide Treatment in Parkinson's Disease	Exenatide	II	Active, not recruiting	Stockholm, Sweden
SR-Exenatide (PT320) to Evaluate Efficacy and Safety in Patients with Early Parkinson's Disease	Exenatide (PT320 2.0mg PT320 2.5mg)	II	Active, not recruiting	Republic of Korea (South Korea)
A Clinical Study of NLY01 in Patient's with Early Parkinson's Disease	NLY01	II	Active, not recruiting	United States
Effects of Exenatide on Motor Function and the Brain	Exenatide	I	Completed	Florida, United States

> CONCLUSION

The association between DM and PD has been subject to controversy, but increasing evidence has been coming to support that DM is a risk factor to PD. Common pathways and mechanisms are still a topic of research.
Regardless of the mechanisms behind these diseases and their shared pathways still not being fully understood, DM associated medicines seem to be beneficial in the treatment of PD. Given that, many investigators are studying this possibility and trying to better understand it - as the growing number of clinical trials dedicated to this relationship suggest. <

Conflitos de interesses/*Conflicts of interests*:
As autoras declaram a ausência de conflitos de interesses./*The authors declare that they have no conflicts of interests.*

Patrocínios/*Sponsorships*:
As autoras declaram que não tiveram patrocínios para a realização deste trabalho./*The authors declare that they had no sponsorships for this work.*

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