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Type 2 diabetes mellitus as a determinant factor for the age of Parkinson's disease onset

*Amin Cervantes-Arriaga[1,2], Oscar Esquivel-Zapata[1], Emmanuel Escobar-Valdivia[2], David García-Romero[1], Marco Muñuzuri-Camacho[1], Ana J. Hernández-Medrano[1], Arturo Abundes-Corona[1], and Mayela Rodríguez-Violante[1,2]**

[1]Clinical Laboratory of Neurodegenerative Diseases, National Institute of Neurology and Neurosurgery, Mexico City; [2]Movement Disorder Clinic, National Institute of Neurology and Neurosurgery, Mexico City. Mexico

Abstract

Objective: *This study aims to identify whether type 2 diabetes mellitus (T2DM) impacts the age of Parkinson's disease (PD) onset.* **Methods:** *Consecutive people living with PD (PwP) with 2-4 years of disease duration were included and categorized according to the presence of T2DM. A 2:1 ratio randomization from the non-DM sample was performed. T2DM diagnosis was defined by a positive personal history of T2DM recorded in the medical files or reported by the subject, or the use of a hypoglycemic drug for glycemic control. A clinical assessment including the Movement Disorder Society Unified Parkinson's disease rating scale and the Hoehn and Yahr was performed by a movement disorders specialist.* **Results:** *One hundred and twenty-four non-T2DM PwP and 62 PwP with T2DM (PD-DM) were included in the study. No statistically significant differences between groups were found in motor and non-motor scores nor in disease duration. The mean age of the whole sample was 63.4 ± 11.9 years, with a mean PD duration of 3.4 ± 0.8 years. In the PD-DM group, the mean duration of T2DM was 12.4 ± 6.8 years, and T2DM was diagnosed 9.2 ± 6.8 years before the PD onset. The PD-DM group had an older age of PD onset (5.9 ± 1.6 year, $p < 0.001$).* **Conclusions:** *Patients with PD-DM had an older age at PD onset, suggesting a potential T2DM role in delaying the age of disease onset.*

Keywords: *Parkinson disease. Type 2 diabetes mellitus. Age of onset. Risk factors.*

Diabetes mellitus *tipo 2 como factor determinante de la edad de aparición de la enfermedad de Parkinson*

Resumen

Introducción: *Se ha demostrado previamente una relación entre la enfermedad de Parkinson (EP) y la diabetes* mellitus *tipo 2 (DM2). La DM2 en personas con EP se asocia con un curso más agresivo de la enfermedad. Este estudio tiene como objetivo identificar si la DM2 tiene un impacto en la edad de inicio de la EP.* **Métodos:** *Se incluyeron consecutivamente personas con enfermedad de EP (PCP) con una duración de entre dos y cuatro años y se clasificaron según la presencia de DM2. Se realizó una aleatorización de proporción 2:1 de la muestra No DM2. La evaluación clínica fue realizada por un especialista en trastornos del movimiento.* **Resultados:** *Se incluyeron un total de 124 PCP no diabéticas y 62 PCP con DM2 (EP-DM).*

***Correspondence:**
Rodríguez-Violante Mayela
E-mail: mrodriguez@innn.edu.mx

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No se encontraron diferencias estadísticamente significativas en las puntuaciones motoras y no motoras ni en la duración de la enfermedad entre los grupos. El grupo EP-DM tuvo una mayor edad de inicio de la EP (5.9 ± 1.6 años, p < 0.001) en comparación con el grupo No DM. **Conclusión:** *Los pacientes con EP-DM tenían una edad más avanzada al inicio de la EP, lo que sugiere un papel potencial de la DM2 en el retraso de la edad de inicio de la EP.*

Palabras clave: *Enfermedad de Parkinson. Diabetes* mellitus *tipo 2. Edad de inicio. Factores de riesgo.*

Introduction

Parkinson's disease (PD) is the second most crucial neurodegenerative disease worldwide. Globally, nearly 10 million persons live with PD, and its prevalence is expected to increase in the upcoming years[1].

Since the seventies, the relationship between impaired glucose metabolism, elevated insulin levels, and PD has been studied in cellular, animal, and human models. Thus, suggesting a link between PD and type 2 diabetes mellitus (T2DM)[2]. Clinical evidence shows that T2DM in people living with PD (PwP) is associated with a more aggressive disease course[3,4]. In addition, in such cases with T2DM diagnosed before PD, PwP had more significant impairment in consequent motor symptoms[5]. Furthermore, persons with PD-DM have an earlier presentation of motor complications[6].

Studies reporting the relationship between PD and T2DM are vast. However, evidence is scarce when addressing the effect of T2DM onset on the age of PD onset. This study aims to identify whether T2DM contributes to a different age of PD onset.

Methods

An observational, cross-sectional, and analytical study was carried out. The study protocol was approved by the Institutional Review Board and by the Local Ethics Committee (121/19). All participants gave their written Informed Consent.

Consecutive PwP attending the Movement Disorders Clinic at the National Institute of Neurology and Neurosurgery in Mexico City from 2018 to 2020 was recruited. The International Parkinson and Movement Disorders Society clinical criteria were used for diagnosing PD[7]. Only patients with a disease duration between 2 and 4 years were included. This range was selected based on the disease progression model proposed by Holford et al.,[8] allowing to study the disease when a more predictable progression was expected, and symptom overlap between the two conditions was less problematic.

T2DM diagnosis was defined by at least one of the following: a positive personal history of T2DM recorded in the medical files, a previous diagnosis reported by the subject, or the use of a hypoglycemic drug for glycemic control. The age of T2DM onset was determined as recorded in the medical files or as reported by the subject.

Patients with incomplete demographic or clinical data were excluded from the study. A 2:1 ratio randomization from the non-DM sample was performed. This randomization aimed to reduce the risk of errors resulting from comparing groups with highly unequal sample sizes, especially when parametric assumptions were violated. Unequal sample sizes can lead to unequal variances between samples which affect the assumption of equal variance in some statistical tests, thus increasing the risk for Type 1 error as well as loss of statistical power[9]. On the other hand, increasing the control-to-case ratio in unmatched case-control settings, results in a gain of statistical power until a ratio of 1:4 and then stabilizes thereafter[10]; in our study, samples were matched according to a disease duration between 2 and 4 years, thus a matching ratio higher than 2:1 may still have substantial power loss given that T2DM was rare (< 15%) in an under-lying cohort[11].

The age of PD onset represented the age when each subject perceived their first motor symptom. For clinical assessment, a movement disorders specialist evaluated motor symptoms. The Movement Disorder Society Unified Parkinson's Disease Rating Scale (MDS-UPDRS) was employed for assessing non-motor experiences of daily living (Part I), motor experiences of daily living (Part II), motor evaluation (Part III), and motor complications (Part IV)[12]. The Hoehn and Yahr (HY) stages were used to classify PD as mild (stages 1 and 2), moderate (stage 3), and severe (stages 4 and 5).

414 PwP were initially recruited. Seventy-six subjects were categorized as PD-DM, 14 of which were excluded due to T2DM diagnosis after PD onset. Consequently, a total of 62 PD-DM participants were incorporated into the analyses.

From the remaining 338 non-DM PD subjects, 124 were randomly assigned to match a 2:1 ratio, as described above. For the randomization, the function Random Sample of Cases from SPSS was used (Data

> Select Cases > Random Sample of Cases). Description of sociodemographic data was done with measures of central tendency (modes, medians, and means) and dispersion ranges (standard deviations and variances). For the inferential analyses, the tests used were as follows. The Pearson's and Spearman's coefficients were used to determine correlations. Comparisons of quantitative variables were performed using independent samples Student's t-test, Welch's t-test (unequal variances), or Mann-Whitney test, as needed. The Chi-square test and Fisher's test were used when comparing qualitative variables. $p < 0.05$ was considered for statistical significance. The statistical package SPSSv25.0 was used.

Results

Overall, 186 PwP (54.3% male) were analyzed. The mean age of the whole sample was 63.4 ± 11.9 years, with a mean PD duration of 3.4 ± 0.8 years. In the PD-DM group, the mean duration of T2DM was 12.4 ± 6.8 years, and T2DM was diagnosed 9.2 ± 6.8 years before the PD onset. No statistical differences in demographic and clinical variables between included and excluded subjects were found.

Regarding T2DM therapy, metformin was the most commonly used treatment (74%), both as monotherapy or as an add-on to glibenclamide (11%). In addition, 14% of the subjects were on a premixed insulin regimen.

Table 1 compares the main variables between the non-DM and the PD-DM groups. In summary, subjects in the PD-DM group were older (mean difference 5.7 ± 1.8, 95% CI: 2.2-9.3 years) and had an older age of onset (mean difference 5.9 ± 1.6, 95% CI: 2.7-9.0 years) in comparison to the non-DM group. No statistically significant differences between groups were found in motor and non-motor scores or disease duration. A statistically significant but weakly positive correlation was found between the T2DM course and the age of PD onset ($rs = 0.27$, $p = 0.03$).

Table 1. Comparisons of the main variables among the PD non-DM group and the PD-DM group

Variables	PD non-DM group (n = 124)	PD-DM group (n = 62)	p-value
Male, n (%)*	68 (54.8)	33 (53.2)	0.84
Age**	61.3 ± 13.5	67.5 ± 8.9	< 0.001
Body mass index	26.6 ± 4.6	27.9 ± 4.1	0.08
Age of PD onset**	58 ± 13.5	64.2 ± 8.8	< 0.001
PD duration**	3.4 ± 0.8	3.3 ± 0.7	0.25
MDS-UPDRS**			
Part I	8.7 ± 6.0	9.6 ± 5.6	0.18
Part II	10.5 ± 7.9	11.3 ± 8.1	0.46
Part III	28.7 ± 14.3	29.4 ± 13.5	0.48
Part IV	1.1 ± 2.7	1.0 ± 2.7	0.78
MDS-UPDRS total	41.6 ± 21.8	43.4 ± 20.6	0.42
Hoehn and Yahr, n (%)*			
Mild (1-2)	86 (69.4)	41 (66.1)	0.66
Moderate (3)	33 (26.6)	19 (30.6)	0.56
Severe (4-5)	5 (4)	2 (3.2)	0.78

PD non-DM, Parkinson's disease without diabetes mellitus type 2; PD-DM, Parkinson's disease and diabetes mellitus type 2; MDS-UPDRS, movement disorders society-unified Parkinson disease rating scale.
*Chi-square test.
**Mann–Whitney test.

Discussion

A link between PD and insulin resistance has been formerly described, suggesting a common neurodegenerative pathway[13]. Animal models have demonstrated that hyperglycemia inhibits dopaminergic neuron activity and lessens levels of extracellular dopamine[14].

On the other hand, T2DM drugs such as glucagon-like peptide-1 receptor (GLP-1R) agonists, thiazolidinediones, and dipeptidyl-peptidase 4 (DPP4) inhibitors have been proposed as potential neuroprotectors or disease modification therapies in PD based on epidemiological studies and *in vitro* models[15].

Epidemiological studies had reported T2DM as a risk factor or a protective factor for PD, depending on the study design. Prospective studies have shown an increased risk for PD[16], while case-control studies (retrospective) describe a protective role[17].

In this study, the age of PD onset was older in the DM-PD group, which may suggest a neuroprotective role in a certain stage of the pathogenesis of the T2DM. This finding was unexpected due to the substantial evidence suggesting hyperglycemia and insulin resistance as a catalyst of mitochondrial dysfunction, oxidative stress, and inflammation leading to neurodegeneration[18].

A recent meta-analysis on T2DM as a determinant of PD risk and progression failed to find age as a relevant factor. Interestingly, only one of the seven cohort studies included in the meta-analysis T2DM was required to be developed before PD, with the remaining studies also including incident T2DM cases. Age was not investigated in the two case-control studies analyzed[19].

A possible factor that could be responsible for the older age at the PD onset in the PD-DM group could

be the hypoglycemic treatment. In our cohort, the most used therapy was metformin. Metformin has shown a neuroprotective role in several neurodegenerative diseases, as well as in PD[20]. Metformin may have a potential role in almost every aspect of PD physiopathology, resulting in a possible protective factor for the development of PD[21].

In the present study, neither motor nor HY differences were found. The fact that our groups were controlled by a rather short PD progression may explain these findings.

Several limitations can be listed. First, subjects on the PD-DM were older. Arguably, the age difference might create a bias translating into the age of PD onset. While this cannot be ruled out, the PD duration in both groups is similar. Therefore, subjects in the PD-DM did not have a longer follow-up due to a longer PD duration leading to a bigger chance of developing diabetes. Age-matching between groups using the whole sample before randomization was attempted and was not feasible. Second, no biomarkers such as insulin or HbA1c were collected. In consequence, the relationship between insulin metabolism or glycemic control and its implication in the age of PD onset could not be appraised. Third, the fact that three-quarters of the PD-DM group were on metformin and that there were no patients on GLP-1R agonists, thiazolidinediones, or DPP4 inhibitors does not allow to address the possible effect of drug treatment on the age of PD onset. Finally, due to the study, design recall bias is expected.

Furthermore, the comorbidity burden of T2DM may include other conditions that have been associated with the risk of developing PD. For instance, it has been reported that the use of statins in the context of dyslipidemia decreases the risk of PD[22], as well as the use of beta-blockers commonly used to treat hypertension[23]. Other commonly sees metabolic disturbance seen in metabolic syndrome is in serum uric acid levels; low uric acid has been associated with morbidity, severity progression, non-motor symptoms, and motor complications of PD[24]. Due to the study design, these potential confounders or effect modifiers were not assessed and future studies must also consider them.

Likewise, considering that T2DM is one of the most common illnesses among our population, as well as the increasing prevalence of PD worldwide, additional longitudinal research should be conducted to determine if this phenomenon on age of PD onset might be attributed to T2DM metabolic pathogenesis, but also taking into account the role of T2DM treatment and glycemic control periodical measurements. In the future, these could provide valuable information that would furthermore help prevent or delay PD onset.

Conclusion

Patients with DM-PD had an older age at PD onset, suggesting a potential T2DM role in delaying the PD age of onset. Further, research should be conducted to identify if this phenomenon can be attributed to T2DM metabolic pathogenesis but also to T2DM treatment and glycemic control.

Funding

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Conflict of interests

None.

Ethical disclosures

Protection of human and animal subjects. The authors declare that the procedures followed were in accordance with the regulations of the relevant clinical research ethics committee and with those of the Code of Ethics of the World Medical Association (Declaration of Helsinki).

Confidentiality of data. The authors declare that they have followed the protocols of their work center on the publication of patient data.

Right to privacy and informed consent. The authors have obtained the written informed consent of the patients or subjects mentioned in the article. The corresponding author is in possession of this document.

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