Association between cardiometabolic comorbidities and Parkinson's disease in a Mexican population

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Abstract

Background: The prevalence of Parkinson's disease (PD) increases as the population ages. Studies have shown that some cardiometabolic comorbidities could be associated with risk or protection against developing PD. A retrospective case-control study was carried out to analyze the relationship between PD and cardiometabolic comorbidities. **Material and methods:** Subjects with PD and controls without PD were consecutively recruited. Data on type 2 diabetes mellitus, systemic arterial hypertension (SAH), dyslipidemia and body mass index were collected. Logistic regression analyses were carried out. **Results:** A total of 781 subjects with PD (56.5% males) and 1,000 controls (44.4% males) were included. After adjusting for age and gender, SAH was found as an independent risk factor (OR: 1.32; 95% CI: 1.05-1.67; $p = 0.02$), and obesity as a protective factor (OR: 0.72; 95% CI: 0.56-0.93; $p = 0.01$). **Conclusions:** Subjects with SAH had a higher risk of having PD, while obese subjects had a lower risk of having PD. The relationship between cardiometabolic disease, its treatment, and PD etiopathogenesis appears to be extremely complex given the amount of contradictory data.

KEY WORDS: Body mass index. Diabetes mellitus. Dyslipidemia. Hypertension. Parkinson's disease. Risk.

Asociación entre comorbilidades cardiometabólicas y enfermedad de Parkinson en población mexicana

Resumen

Antecedentes: La prevalencia de la enfermedad de Parkinson (EP) aumenta a medida que la población envejece. Los estudios han demostrado que algunas comorbilidades cardiometabólicas pudieran estar asociadas con el riesgo o la protección de desarrollar la EP. Se realizó un estudio retrospectivo de casos y controles para analizar la relación entre la EP y las comorbilidades cardiometabólicas. **Material y métodos:** Se reclutaron sujetos con EP y controles sin EP de forma consecutiva. Se recolectaron datos sobre diabetes mellitus tipo 2, hipertensión arterial sistémica (HTA), dislipidemia e índice de masa corporal. Se llevó a cabo análisis de regresión logística. **Resultados:** Se incluyeron un total de 781 personas con EP (56,5% hombres) y 1,000 controles (44,4% hombres). Después de ajustar por edad y sexo, la HTA se encontró como factor de riesgo independiente (OR 1.32, IC 95% 1.05-1.67, $p = 0.02$) y la obesidad como factor protector (OR 0.72, IC 95% 0.56-0.93, $p = 0.01$). **Conclusiones:** Los sujetos con HTA tienen un mayor riesgo de tener EP; mientras que los sujetos obesos tienen un menor riesgo de tener EP. La relación entre la enfermedad cardiometabólica, su tratamiento y etiopatogenia de la EP parece ser extremadamente compleja dada la cantidad de datos contradictorios.

PALABRAS CLAVE: Índice de masa corporal. Diabetes mellitus. Dislipidemia. Hipertensión. Enfermedad de Parkinson. Riesgo.

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Introduction

The prevalence of Parkinson's disease (PD) increases as the population ages. In Mexico, the incidence density reported between 2014 and 2017 was 9.48 per 100,000 person-years, which results in a public health problem¹. PD pathophysiological mechanisms are not fully understood. Overlapping pathways, including mitochondrial abnormalities, neuroinflammation and protein aggregation, have been suggested to interact in the pathogenesis and development of the disease².

Interaction between different environmental and genetic factors could significantly contribute to the development of PD³. There is current evidence that suggests that some comorbidities could be associated with risk of PD or protection against its development^{4,5}. Among these, the main cardiometabolic risk factors have awakened great interest.

Factors that favor a pro-inflammatory state and altered free radical metabolism converge on mitochondrial dysfunction, with neurodegeneration being linked to insulin resistance in a common pathway⁶.

Type 2 diabetes mellitus (T2DM) has been associated not only to the risk of developing PD, but also as a modifying factor in the progression and natural history of the disease^{7,8}. In addition, most epidemiological studies, although not all, have reported an association between T2DM and a higher risk of PD⁹⁻¹¹.

Epidemiological studies addressing the association between systemic arterial hypertension (SAH) and PD have been conflicting, with some studies identifying SAH as a risk and others as a protective factor^{12,13}. Similarly, dyslipidemia has been a controversial issue as to whether it is a risk or protective factor for PD^{13,14}. Finally, the association between body mass index (BMI) and PD has not been conclusive either. Some studies suggest that there is no significant relationship between BMI and the development of PD^{15,16}. On the other hand, other studies, including meta-analyses, have shown that both overweight and low BMI could be a relevant risk factor¹⁷⁻¹⁹.

Establishing the interaction of pathologies is a relevant starting point for identifying possible areas of intervention. With population aging, the prevalence of cardiometabolic and neurodegenerative pathologies is going to increase.

The purpose of this case-control study is to evaluate the relationship between PD and the main cardiometabolic comorbidities in a sample from Latin America in order to enrich current knowledge.

Materials and methods

Consecutive patients diagnosed with PD using the Movement Disorders Society Clinical Diagnostic Criteria for Parkinson's²⁰ disease were included for this study, which was carried out at the Movement Disorders Clinic of the National Institute of Neurology and Neurosurgery (Mexico City, Mexico) between 2016 and 2019. Subjects with secondary hypertension, pancreatic disease, hypothyroidism or hyperthyroidism, or any type of kidney disease were excluded.

The controls, aged 50 years or older, were recruited from the outpatient clinic waiting room. All subjects agreed to participate and granted signed consent. The same exclusion criteria were considered for the control group. In addition, personal or first-degree family history of neurological or neuropsychiatric disease were also considered as exclusion criteria for this group.

Cardiometabolic history evaluation was recorded using a semi-structured questionnaire that consisted of several parts. First, sociodemographic variables were collected, which included age and gender. All subjects were questioned about known T2DM diagnosis, disease duration, and any glucose-lowering treatment. The second part evaluated the presence of a SAH diagnosis, disease duration and any antihypertensive treatment. On next part, dyslipidemia diagnosis, including disease duration and use of lipid-lowering drugs was evaluated. If the subjects were taking a glucose-lowering, antihypertensive or lipid-lowering drug without a known indication, the medical history was examined in depth in order to find out the indication. Subjects taking any of these drugs for no known reason were excluded. If necessary, subjects were provided a complete list of medications to help them remember the name of the drug.

The last part evaluated anthropometric variables, including height (in meters) and weight (in kilograms) for BMI calculation. Subjects were categorized according to their BMI into underweight, normal weight, overweight and obesity according to international standards.

The study protocol was approved by the local ethics committee (121/19) and all participants granted written informed consent.

Statistical analysis

The Kolmogorov-Smirnov test was used to test for normality. All variables of interest had a

non-parametric distribution. For the comparison of quantitative variables, Mann-Whitney's U-test was used. Qualitative variables were evaluated using the chi-square test. Variables with statistically significant differences in the bivariate analysis were included in the multivariate analysis.

For the logistic regression analyses, the presence of PD was defined as a dependent variable. Simple logistic regression was used to estimate the odds ratios (OR) for each independent variable, followed by a multivariate stepwise logistic regression. The Hosmer-Lemeshow test was used to determine the goodness of fit. A p-value < 0.05 was established for statistical significance. Statistical analyses were carried out with SPSS, version 17 (SPSS Inc., Chicago, IL, USA).

Results

A total of 781 subjects with PD (56.5% males) and 1,000 controls (44.4% males) were included. Table 1 shows a thorough comparison of the main variables between both groups.

SAH and dyslipidemia were more common in the PD group in comparison with controls. No statistically significant difference was found in the prevalence of T2DM between groups, although T2DM was somewhat more common and showed a tendency towards statistical significance in the PD group. Finally, subjects with PD had lower BMI in comparison with controls. In the PD group, normal weight was more common in comparison with controls. On the other hand, obesity was more common in controls than in the PD group.

In the bivariate analysis, using simple logistic regression, SAH (OR: 1.62; 95% confidence interval [CI]: 1.31-2.01; p < 0.001) and dyslipidemia (OR: 1.31; 95% CI: 1.01-1.70; p = 0.03) were found to be risk factors for PD. On the other hand, the presence of obesity was shown to be a protective factor against PD (OR: 0.72; 95% CI: 0.56-0.93; p = 0.01). In addition, the female gender was also shown to be a protective factor (OR: 0.61; 95% CI: 0.51-0.74; p < 0.001).

After adjusting for age and gender in the multivariate analysis, only SAH persisted as an independent risk factor (OR: 1.32; 95% CI: 1.05-1.67; p = 0.02) and obesity remained a protective factor (OR: 0.72; 95% CI: 0.56-0.93; p = 0.01). Table 2 shows a full description of the model. The presence of T2DM was included in the model owing to theoretical foundations, although statistical significance was not reached in the bivariate analysis.

Table 1. Comparison of the main variables between controls and subjects with Parkinson's disease (PD)

	Controls (n = 1,000)	PD (n = 781)	p
Gender			
Males n (%)	444 (44.4)	442 (56.6)	< 0.001*
Females n (%)	556 (55.6)	339 (43.4)	< 0.001*
Age			
Mean $\pm$ SD	57.8 $\pm$ 15.4	62.9 $\pm$ 13.2	< 0.001†
Diagnoses			
Diabetes mellitus	132 (13.2%)	128 (16.4%)	0.06*
Hypertension	225 (22.5%)	250 (32%)	< 0.01-
Dyslipidemia	141 (14.1%)	139 (17.8%)	0.03-
BMI			
Mean $\pm$ SD	27.1 $\pm$ 4.8	26.5 $\pm$ 4.8	< 0.01†
Normal (%)	325 (32.5%)	292 (37.4%)	0.03*
Underweight (%)	16 (1.6%)	20 (2.6%)	0.15*
Overweight (%)	401 (40.1%)	302 (38.7%)	0.54*
Obesity (%)	258 (25.8%)	167 (21.4%)	0.03*

*Chi-square test.

†Mann-Whitney's U-test.

BMI: body mass index; SD: standard deviation.

Discussion

This is the first Mexican case-control study to evaluate the association of the main cardiometabolic comorbidities with PD. Our study did not find a different proportion of T2DM in PD patients in comparison with controls, although a tendency was observed. On the other hand, the PD group was found to have a slightly but significantly different profile in other cardiometabolic risk factors in comparison with the general population. The PD group had a higher frequency of SAH and dyslipidemia, and a lower frequency of obesity.

In this regard, our study contrasts with some published epidemiological data based on prospective studies that have reported a higher risk of PD in patients with T2DM. In this sense, a meta-analysis published by Yue et al. showed that prospective studies conducted in different populations can significantly vary⁹. For example, a retrospective study from Taiwan and prospective studies from the US and Finland reported a risk increase. On the other hand, other prospective studies from Spain and the US failed to replicate these results. In addition, a retrospective Japanese study showed a protective effect of 0.38 for T2DM¹³. In general, this evidence suggests that ethnicity may play an important role. Study design also appears to play an important role. A more recent meta-analysis showed that cohort studies provided

Table 2. Logistic regression model using Parkinson's disease as a dependent variable

Model		B	Exp (B)	95% CI		p
1	Age	0.024	1.024	1.024	1.018	< 0.001
	Female gender	-0.483	0.617	0.617	0.509	< 0.001
2	Age	0.022	1.022	1.015	1.029	< 0.001
	Female gender	-0.487	0.615	0.507	0.745	< 0.001
	SAH	0.281	1.324	1.058	1.657	0.014
3	Age	0.021	1.022	1.014	1.029	< 0.001
	Female gender	-0.486	0.615	0.508	0.745	< 0.001
	SAH	0.272	1.313	1.047	1.645	0.018
	T2DM	0.092	1.097	0.835	1.441	0.507
4	Age	0.021	1.021	1.014	1.029	< 0.001
	Female gender	-0.491	0.612	0.505	0.741	< 0.001
	SAH	0.254	1.289	1.026	1.62	0.029
	T2DM	0.088	1.092	0.831	1.435	0.529
	Dyslipidemia	0.143	1.154	0.884	1.506	0.293
5	Age	0.02	1.02	1.013	1.028	< 0.001
	Female gender	-0.491	0.612	0.505	0.742	< 0.001
	SAH	0.281	1.324	1.052	1.666	0.017
	T2DM	0.102	1.108	0.841	1.458	0.466
	Dyslipidemia	0.17	1.186	0.907	1.551	0.213
	BMI					0.033
	Underweight	0.376	1.457	0.728	2.917	0.288
	Overweight	-0.184	0.832	0.665	1.04	0.106
	Obesity	-0.329	0.72	0.555	0.933	0.013

BMI: body mass index; CI: confidence interval; SAH: systemic arterial hypertension;
T2DM: type 2 diabetes mellitus.

strong evidence (OR: 1.29) that T2DM was associated with a higher risk of PD; on the other hand, case-control studies showed an inverse association between T2DM and PD (OR: 0.51)⁸. In our study, T2DM was somewhat more common in the PD group but without statistical significance being reached despite the fact that it was a case-control study. To the best of our knowledge, this is the first report on the Latin American population and deserves further investigation.

There are few epidemiological studies addressing the association between SAH and PD, with results ranging from no association¹⁰ to being a protective factor¹³. A recent meta-analysis by Hou et al. reported

an association of preexisting SAH with a higher risk for developing PD¹². Interestingly, a sub-analysis based on ethnic characteristics showed that most part of the risk effect was attributable to Asian studies, while little or no association was more common in Caucasian population studies. In this regard, our study adds to current knowledge by including SAH as an independent risk factor in a Latin American sample.

It is possible for the relationship between SAH and PD not to be direct. The use of propranolol has been associated with a higher risk of PE^{21,22}. Strangely enough, a recent study reported a protective effect of beta-blockers against the appearance of PD in non-diabetic patients, but the opposite in diabetic patients with PD²³.

As for dyslipidemia, our study found no statistically significant risk after adjusting for other variables. Our findings are in line with the retrospective study carried out by Yang et al.¹⁰. As in the case of SAH and beta-blockers, the association with dyslipidemia could be more related to the use of statins rather than to blood lipid levels. Jeong et al. reported that statin use was associated with an increased risk of PD¹⁹. On the other hand, a recent meta-analysis showed that atorvastatin appears to reduce the risk of PD²⁴. Interactions between cardiometabolic comorbidities, glucose-lowering drugs, statins and blood-lowering agents remain a difficult-to-elucidate issue.

Finally, the association of BMI with PD was not conclusive either. Longitudinal studies do not suggest a significant relationship between BMI and the development of PD^{19,20}. Meta-analyses have been conflicting, with both overweight and low BMI being reported as risk factors^{15,16}. The most notable limitation of these studies is that normal weight and underweight individuals were grouped together, and assessing underweight as a possible independent risk factor was therefore not possible. A study on this topic that used a Korean national database found a risk for PD of 1.28 in the underweight group, in comparison with subjects with normal BMI²³. On the other hand, the same study reported a possible protective effect for the overweight group, similar to our findings.

Our study has several limitations. First, subjects in the PD group were older. Not only is age the most important risk factor for PD, but this may also be true for all cardiometabolic comorbidities. In addition, a difference was found with regard to gender, with fewer women in the PD group. Although this is in line with epidemiological studies that report a higher

prevalence of PD in men, especially in the group aged 50 to 59 years,²⁵ we cannot rule out a selection bias, with women being more prone to participate in the control group. Given the large sample size, a gender- and age-matched control study would have been difficult to achieve. However, the regression model was adjusted for these two variables and both SAH and obesity maintained statistical significance. Second, the chronological relationship between the appearance of comorbidities and the appearance of PD was not evaluated. In this regard, it can be argued that the time of diagnosis may not really be the time of onset of any of these evaluated diseases. PD prodromal phase can last up to one decade²⁶, but T2DM, SAH and dyslipidemia can also remain undiagnosed for years, in spite of oxidative stress and chronic inflammation being present. Identifying actual onset of the disease, not its diagnosis, requires the use of specific biomarkers throughout time. Third, a self-reported diagnosis and broad operational definitions were used to define the presence or absence of all comorbidities that are susceptible to recall bias. In addition, no blood tests were carried out; therefore, cardiometabolic risk control could not be assessed.

Conclusions

Subjects with SAH had a higher risk of PD, while obesity provided a lower risk of having PD. The relationship between cardiometabolic disease, its treatment and PD etiopathogenesis appears to be extremely complex given the amount of conflicting data. A prospective cohort study evaluating preclinical biomarkers for both cardiometabolic disease and PD is required for our findings to be confirmed.

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Conflict of interests

The authors declare that they have no conflicts of interest.

Ethical disclosures

Protection of human and animal subjects. The authors declare that the procedures that were

followed adhered to the ethical standards of the responsible committee for experimentation on human beings and were in agreement with the World Medical Association and the 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 informed consent from the patients and/or subjects referred to in the article. This document is in the possession of the corresponding author.

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