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Detrimental effect of type 2 diabetes mellitus in a large case series of Parkinson's disease

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ABSTRACT

Introduction: To investigate the effect of diabetes mellitus (DM) on the clinicoradiological features in patients with Parkinson's disease (PD).
Methods: 671 patients with de novo PD were classified into two groups according to the presence of DM (106 with DM and 565 without). We performed inter-group comparative analyses of the striatal dopamine transporter (DAT) availability in all patients and level of cognitive performances in 312 patients (58 with DM and 254 without). Neuroimaging analyses of cortical thickness were performed in 42 patients with DM and 42 matched patients without DM. We assessed the longitudinal changes in the levodopa-equivalent dose (LED) across time in 549 patients who were treated for at least two years (86 with DM and 463 without) using a linear mixed model.
Results: The PD patients with DM were older at the onset of parkinsonism and had more severely decreased baseline DAT availability in the caudate and ventral striatum than those without DM. The PD group with DM showed poorer performances in attention/working memory and frontal/executive function than the group without DM. Cortical thinning in the right inferomedial temporal lobe was observed in PD with DM group relative to PD without DM group. During follow-up, the PD patients with DM showed a more rapid longitudinal increase in LED than those without DM.
Conclusion: Our results suggest that coexistent DM may have a detrimental effect on disease progression as well as baseline striatal dopamine loss, brain structural alterations, and cognitive performances in patients with PD.

1. Introduction

Type 2 diabetes mellitus (DM) is a prevalent metabolic disorder characterized by obesity and chronic insulin resistance. Ample evidence has suggested that DM is a protein misfolding disease [1]: insulin resistance and progressive loss of beta cell function in DM could result from the toxic aggregates of the islet amyloid polypeptide or amylin via an increased membrane permeabilization, mitochondrial damage, endoplasmic reticulum (ER) stress, and inflammation [2,3]. This misfolded protein formation is closely linked to defects in several protein-removing pathways, including the ubiquitin proteasome system and autophagy [4].

Similarly, the accumulation of protein aggregates via the dysregulation of cellular clearing system is a key pathogenesis of neurodegenerative disorders such as Alzheimer's disease (AD) and Parkinson's disease (PD) [2]. Given that DM and neurodegenerative disorders might share common mechanisms leading to protein misfolding [3], it is not surprising that patients with DM have a 65% increased risk of developing AD [5] and 35% increased risk of developing PD [6]. In particular, several studies have demonstrated that DM has a deteriorating impact on the neurodegenerative pathologies [7] as well as the clinical course [8] of AD. In patients with PD, few studies have reported a detrimental effect of DM on motor and cognitive performance [9–11]; however, the lacking of longitudinal information on the clinical course and comprehensive neuroimaging data with a large sample size may limit its clinical significance. In the present study, we hypothesized that coexistent DM would have a detrimental effect on the current state and disease course of PD. We, therefore, assessed the

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dopamine transporter (DAT) availability of the striatum, cognitive performance, cortical thickness, and longitudinal disease progression in a large number of PD patients with and without DM.

2. Methods

2.1. Subjects

We retrospectively reviewed the database of the Yonsei Parkinson Center (671 consecutive patients with drug-naïve PD who visited the Movement Disorders outpatient clinic at Severance Hospital from April 2009 to September 2015) (Fig. S1). PD was diagnosed according to the clinical diagnostic criteria of the UK PD Society Brain Bank. ^{18}F-FP-CIT PET scans revealed decreased DAT availability in the posterior putamen on all subjects. The exclusion criteria included drug-induced parkinsonism; evidence of atypical parkinsonism; and focal brain lesions, diffuse white matter hyperintensities, or multiple lacunes in the basal ganglia on MRI. Parkinsonian motor symptoms were assessed using the Unified PD Rating Scale Part III (UPDRS- III), and olfactory function was measured using the cross-cultural smell identification test (CCSIT). Depression was evaluated using the Beck Depression Inventory (BDI), and the Korean version of the Mini-Mental State Examination (K-MMSE) [12] was used to assess general cognition. Patients with PD were classified into two groups according to the prior diagnosis of type 2 DM [13]: the PD group with DM (PD-DM+, n = 106) and the PD group without DM (PD-DM-, n = 565. This study was approved by the Yonsei University Severance Hospital institutional review board, and the need for informed consent was waived because of the retrospective nature of the study.

2.2. Quantitative analysis of ^{18}F-FP-CIT PET images

We used the same methodology to acquire and analyze the ^{18}F-FP-CIT PET images to obtain DAT availability as previously described (supplementary methods) [14].

2.3. Neuropsychological assessment

A total of 312 patients (58 with DM and 254 without) underwent a baseline comprehensive neuropsychological assessment (Seoul Neuropsychological Screening Battery [SNSB]) in the Korean language, which covers five cognitive domains (attention and working memory, frontal/executive, language, verbal and visual memory, and visuospatial functions; supplementary methods). We compared the levels of cognitive performances between the PD groups using the composite scores calculated by dividing the sum of the z-scores by the number of tests in each cognitive domain. A z-score was defined as where the score was positioned in the distribution of scores for age- and education-matched normal subjects (i.e., higher z-scores indicate better cognitive function). Additionally, 43 patients in the PD-DM+ and 173 patients in the PD-DM- underwent a serial K-MMSE twice to eight times with an interval of one year.

2.4. Cortical thickness analyses

A total of 233 patients (42 with DM and 191 without) underwent a baseline brain MRI scan which was available for the neuroimaging analyses. PD patients with DM (n = 42) were matched to those without DM (n = 42; supplementary methods). We used the CIVET pipeline (http://mcin.ca/civet/) to measure cortical thickness as previously described (supplementary methods) [15]. Then, we compared cortical thickness between the PD groups with the SurfStat toolbox [16]. The multiple comparisons were corrected using random field theory. We mapped t-scores, effect size (Cohen's d), uncorrected p, and corrected cluster-p on the standard template. In addition, we performed the correlation analysis between DM duration and cortical thickness within the PD-DM + group controlling for age, sex, years of education, PD duration, and intracranial volume (see details in supplementary methods).

2.5. Longitudinal assessment of the changes in LED over time

Of a total of 671 patients with PD, 557 were treated with PD medications for at least two years (range: 28–93 months). Among them, eight patients who were diagnosed with DM during the follow-up period were excluded because the effect of DM might not be active throughout their clinical course, but only in part. Therefore, 549 patients (86 PD-DM+ and 463 PD-DM-) were included in the assessment of the longitudinal changes in LED. The patients visited the outpatient clinic with three-to-six-month intervals between visits, and their PD medications were adjusted for effective symptom control by L.P.H and S.Y.H. according to the patients' response. The medication doses were calculated as levodopa-equivalent doses (LEDs) [17]. Additionally, we compared the longitudinal changes in LED between the 86 PD patients with DM and matched 86 without.

2.6. Statistical analyses

To compare the baseline demographic characteristics between the PD groups, Student's *t*-tests and Pearson's χ^2 tests were used for continuous and categorical variables, respectively. In order to compare the DAT availability of each striatal sub-region and cognitive performances between the PD groups, Student's *t*-tests with the false discovery rate (FDR) controlling method for multiple comparisons correction were used. A linear mixed model was used to compare the longitudinal changes in K-MMSE between the PD groups, including age, sex, and education as fixed effects. Estimated propensity scores were used to match the PD patients with DM to those without DM using age at onset, sex, PD duration, and baseline DAT availability in the posterior putamen as predictors in a logistic regression with DM status as the outcome. To compare the changes in LED over time between the PD groups, a linear mixed model was used including age at PD onset and mean DAT availability in the posterior putamen as fixed effects (supplementary methods). We also assessed the effect of duration of DM on the longitudinal changes in LED in the PD-DM + group using the DM duration × time interaction term in a linear mixed model. The statistical analyses were performed with SPSS (version 23.0; IBM Corporation, Armonk, NY, USA), and results with a two-tailed $P < 0.05$ were considered statistically significant.

3. Results

3.1. Baseline clinical characteristics of PD patients with and without DM

Duration of DM at the time when the patients in the PD-DM + group were diagnosed with PD was 10.93 ± 7.65 years. The average age and age at parkinsonian symptom onset were both higher in the PD-DM + group than in the PD-DM- group. The sex, PD duration, UPDRS-III, and CCSIT scores did not differ between the groups. There were also no significant differences in the BDI and K-MMSE scores. The PD-DM + group had a higher prevalence of hypertension and cardiac disease than the PD-DM- group (Table 1).

Compared to the PD-DM- group, the PD-DM + group showed more severely decreased DAT availability in the caudate (PD-DM+, 1.74; PD-DM-, 1.94; p = 0.006) and ventral striatum (PD-DM+, 1.94; PD-DM-, 2.13; p = 0.006) with comparable DAT availability in the anterior putamen (p = 0.536) and posterior putamen (p = 0.779; Table 1).

3.2. Neuropsychological assessment

The 312 patients with PD who underwent a detailed neuropsychological test had similar demographic characteristics and striatal DAT

Table 1
Demographic characteristics, DAT availability, and neuropsychological data of patients with PD who underwent a baseline neuropsychological test.

	PD-DM+ (n = 106)	PD-DM- (n = 565)	*p*-value
Demographic characteristics			
Age (years)	69.94 ± 8.14 (39, 85)	65.18 ± 10.34 (35, 88)	< 0.001[a]
Female, No. (%)	53 (50%)	292 (52%)	0.751[b]
Age at PD onset (years)	68.36 ± 8.18 (36, 84)	63.64 ± 10.45 (33, 85)	< 0.001[a]
PD duration (months)	18.09 ± 17.65 (1, 67)	18.27 ± 17.91 (1, 69)	0.927[a]
UPDRS-III	23.99 ± 10.72	22.51 ± 10.01	0.200[a]
CCSIT	6.43 ± 2.73	6.73 ± 2.39	0.266[a]
BDI	12.87 ± 9.25	12.66 ± 8.50	0.821[a]
K-MMSE	26.17 ± 2.87	26.61 ± 3.07	0.173[a]
Vascular risk factors			
Hypertension	64 (60%)	217 (38%)	< 0.001[b,c]
Dyslipidemia	17 (16%)	62 (11%)	0.138[b,c]
Cardiac disease	18 (17%)	51 (9%)	0.027[b,c]
Body mass index	23.94 ± 2.95	23.41 ± 2.95	0.121[a,c]
DAT availability			
Caudate	1.74 ± 0.59	1.94 ± 0.66	0.006[a,c]
Anterior putamen	2.23 ± 0.59	2.29 ± 0.67	0.536[a,c]
Posterior putamen	1.44 ± 0.54	1.43 ± 0.50	0.779[a,c]
Ventral striatum	1.94 ± 0.52	2.13 ± 0.61	0.006[a,c]
Neuropsychological data [d]			
Attention/working memory	−0.37 ± 0.80	−0.04 ± 0.82	0.016[a,c]
Frontal executive	−0.60 ± 0.86	−0.20 ± 0.86	0.009[a,c]
Language	−0.65 ± 1.16	−0.33 ± 1.12	0.069[a,c]
Memory	−0.50 ± 0.72	−0.16 ± 1.28	0.069[a,c]
Visuospatial	−0.37 ± 1.45	−0.07 ± 1.27	0.115[a,c]

The values are expressed as mean ± standard deviation, range (minimum, maximum), or number (percentage). To compare the level of cognitive performance between the groups, we used the composite z-scores for each cognitive domain. Abbreviations: DAT, dopamine transporter; PD, Parkinson's disease; PD-DM+, PD with diabetes mellitus; PD-DM-, PD without diabetes mellitus; UPDRS-III, Unified PD Rating Scale Part III; BDI, Beck Depression Inventory; K-MMSE, the Korean version of the Mini-Mental State Examination.

[a] Student's *t*-tests.

[b] Pearson's χ^2 tests.

[c] False discovery rate (FDR) controlling method for multiple comparisons correction.

[d] 312 patients with PD (58 with DM and 254 without DM) underwent a baseline neuropsychological test.

availability as the whole 671 patient sample (Table S1): the PD-DM + group (n = 58) was older in age and had a higher frequency of hypertension than the PD-DM- group (n = 254). The PD-DM + group tended to exhibit more severely decreased DAT availability in the caudate and ventral striatum. The PD-DM + group showed a poorer cognitive performance in the attention/working memory and frontal executive function domain compared to the PD-DM- group. The PD-DM + group also had a tendency for poor performances in the language and memory function domain (p = 0.069). The two groups showed comparable levels of performances in the visuospatial function domains (Table 1). In addition, the PD-DM + group tended to have a more rapid decline in the K-MMSE scores relative to the PD-DM- group (estimated changes in K-MMSE score per year: PD-DM+, −0.61 [standard error (SE) 0.17]; PD-DM-, −0.29 [0.09]; group difference, 0.33 [1.96], p = 0.091).

3.3. Cortical thickness analyses

There were no significant differences in the demographic characteristics and the striatal DAT availability between 42 patients with DM and 42 matched patients without DM (Table S2). Fig. 1 shows cortical thickness difference between the PD groups. In the t-map, blue and red indicate greater and lesser cortical thickness, respectively, in the PD-DM + group compared with the PD-DM- group (Fig. 1A). The PD-DM + group exhibited significant cortical thinning in the right inferior temporal cortex compared with the PD-DM- group (Fig. 1B–D and Table 3). No areas were found in which the PD-DM- group exhibited statistically significant cortical thinning compared to the PD-DM + group. In addition, the correlation analysis showed that the duration of DM was not significantly associated with the cortical thinning in the PD-DM + group (mean duration of DM, 10.97 ± 8.61 years; Fig. S2).

3.4. Longitudinal assessment of the changes in LED over time

The 549 patients with PD who were treated with PD medications for at least two years had similar demographic characteristics and striatal DAT availability as those of the whole 671-patient population: the PD-DM + group (n = 86) had older age and age at PD onset and decreased DAT availability in the ventral striatum compared to the PD-DM- group (n = 463). Propensity score sub-sample (86 with DM and 86 without DM) showed that there were no significant differences in the demographic characteristics and striatal DAT availability between the groups (Table S3).

The estimated monthly LED changes were 9.54 in the PD-DM + group (n = 86) and 7.09 in the PD-DM- group (n = 463; difference in LED changes between the PD groups = 2.45, p < 0.001; Table 2). We also obtained a consistent result when comparing the matched PD groups (9.44 in 86 PD-DM+; 7.90 in 86 PD-DM-; p = 0.016; Table 2). In addition, long duration of DM was not associated with the more rapid increase in LED over time in 86 patients in the PD-DM + group (mean duration of DM, 11.26 ± 7.62 years; DM duration × time, β (SE) = −0.1588 (0.0975), p = 0.105; Table S4).

4. Discussion

The present study investigated the effect of DM on the DAT availability of the striatum, cognitive performance, brain structural changes, and longitudinal disease progression in patients with de novo PD. The major findings were as follows: (1) The PD group with DM had more severely decreased DAT availability in the caudate and ventral striatum compared to that in the group without DM, while the DAT availability in the putamen was comparable between the groups. (2) PD patients with DM showed a poorer performance on attention/working memory and frontal executive function than those without DM. (3) Cortical thinning in the right inferomedial temporal lobe was observed in the PD patients with DM relative to those without DM. (4) The patients with DM at the time of PD diagnosis showed more rapid longitudinal changes in LED than those without DM. These findings suggest that the presence of DM has a detrimental effect on the clinical course as well as the baseline striatal dopamine depletion, structural integrity, and cognitive function in patients with PD.

The present study demonstrated that PD patients with DM exhibit a severe dopaminergic depletion, especially in the caudate and ventral striatum, compared to those without DM. Several studies showed that insulin resistance in DM leads to altered iron metabolism, accumulation of α-synuclein, or enhanced ER stress and inflammatory response in the midbrain, thus impairing nigrostriatal dopamine function [18–20]. In addition, vascular insufficiency, increased oxidative stress, and altered axonal transport underpinning diabetic neuropathy [21] would impair the axonal integrity of nigrostriatal fibers. However, it remains unknown whether the dopaminergic neurons in the medial part of the substantia nigra (SN) projecting to the caudate and ventral striatum are more susceptible to the DM-related process than those in the ventrolateral SN projecting to the posterior putamen. Regarding the selective vulnerability of striatal subregions, it has been reported that patients with DM had impaired integrity of the fronto-striatao-thalamic circuit arising from the caudate nucleus, but not from the putamen

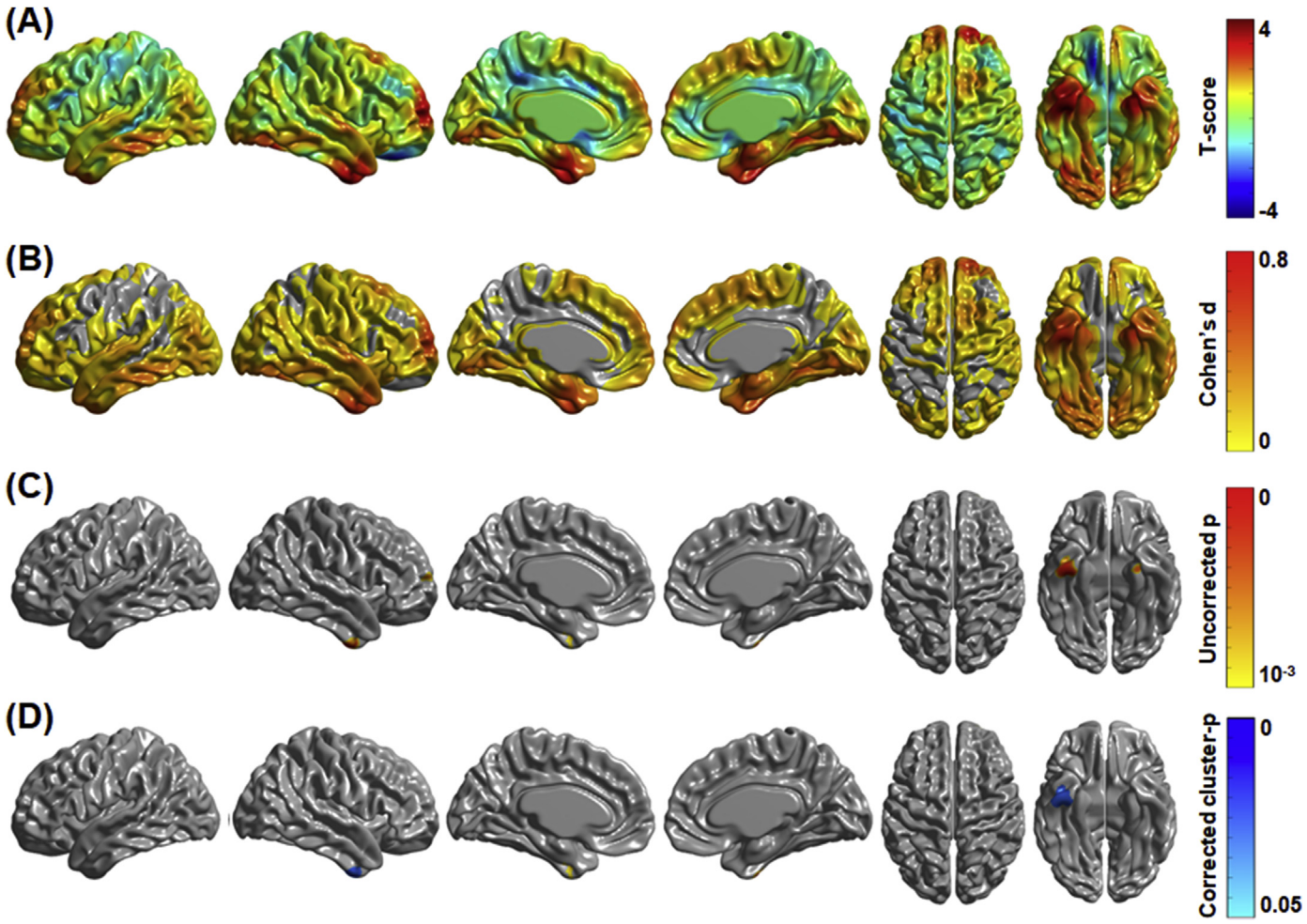

Fig. 1. Analysis of cortical thickness comparison between the PD-DM + and PD-DM- groups. (A) The t-map shows differences in cortical thickness between the groups. The blue and red color indicate greater and lesser cortical thickness in the PD-DM + group compared to the PD-DM- group, respectively. (B) The effect size (Cohen's d) map shows a large magnitude of difference between the groups. (C) The reddish spots of the p-map indicates the regions of significant cortical thinning in the PD-DM + group compared to the PD-DM- group (thresholding at uncorrected $p < 0.001$). (D) Significant cluster was found in the right inferior temporal cortex after multiple comparisons correction using the random field theory (corrected $p < 0.05$). No areas were found in which the PD-DM- group exhibited statistically significant cortical thinning compared to the PD-DM + group. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

Table 2
Longitudinal changes in LED across time in PD patients with follow-up duration > 2 years.

	Estimated slope (standard error)					
	PD-DM+	p-value	PD-DM-	p-value	Difference	p-value
Overall series (86 vs. 463)						
Δ LED	9.5403 (0.4229)	< 0.001	7.0906 (0.1816)	< 0.001	2.4497 (0.4584)	< 0.001
Propensity score-matched pairs (86 vs. 86)						
Δ LED	9.4431 (0.4070)	< 0.001	7.8992 (0.4949)	< 0.001	1.5439 (0.6384)	0.016

The estimate (β) is the change in LED per month (Δ LED), i.e., positive value indicates the dose-up of PD medications. The propensity score for the predicted probability of the presence of DM in each patient was estimated with the use of a logistic regression model with the following variables: age at onset, sex, PD duration, and DAT binding in the posterior putamen. The effect of the PD subgroup on the change in LED across time was tested using the time × PD subgroup interaction term, and the PD-DM + group exhibited a faster rate of dose-up of PD medications than the PD-DM- group. Abbreviations: LED, levodopa-equivalent dose; PD, Parkinson's disease; PD-DM+, PD with diabetes mellitus; PD-DM-, PD without diabetes mellitus.

[22], and atrophy in the bilateral caudate head [23] compared to those without DM. Thus, it is possible that the lesional effect of the susceptible caudate may result in dopamine depletion in this structure. However, further study is required to determine whether DM-related neurodegenerative process in PD would induce the selective vulnerability in the medial portion of SN neurons or on the caudate-related structures.

In terms of the cognitive aspects, the PD-DM + group showed poor cognitive performances in attention/working memory and frontal executive function domain. The general cognition measured by the K-MMSE also tended to decline more rapidly in the PD-DM + group compared to the PD-DM- group. To the best of our knowledge, only a limited number of studies have reported the effects of DM on cognition in PD: PD patients with comorbid DM had lower cognitive scores with the greatest impairments in attention and executive functions [11,24], and a more rapid decline in MMSE scores at a three-year follow-up than those without DM [25]. Our neuropsychological findings are in accordance with the pattern of striatal dopamine depletion and structural changes shown in the PD-DM + group in this study. Several studies have reported a significant association between striatal dopamine depletion, especially in the caudate, and frontal lobe-based cognitive dysfunction in PD [26]. In addition, several cortical structures such as

Table 3
Differences in cortical thickness between the PD groups according to the presence of DM.

	Region	t-score	Corrected cluster-p	Uncorrected p	Cohen's d	x	y	z
Rt	Inferior Temporal Cortex	4.10.	0.025	< 0.001	0.78	39.0	−8.0	−43.8
Lt	Entorhinal Cortex	3.45	NS	< 0.001	0.63	−27.0	−5.8	−34.6

Abbreviations: PD, Parkinson's disease; DM, diabetes mellitus; NS, not significant.

the dorsolateral frontal and mesial temporal cortices are related to cognitive function as well as the prognosis of cognitive decline in patients with PD [27]. In this regard, cortical thinning in the frontal and temporal regions of the PD patients with DM might additionally influence the level of cognitive performance.

Interestingly, the PD-DM + group showed a more rapid longitudinal increase in LED compared to the PD-DM- group. The contribution of DM to PD progression has been rarely reported: A single case-control study demonstrated that patients with a diagnosis of DM prior to PD onset required higher treatment doses of levodopa than those without DM [9]. One possible explanation for this finding is that DM shares similar dysregulated pathways with PD, including protein aggregation [1], mitochondrial dysfunction, and inflammatory response [3]. Multiple misfolded proteins may interact with each other in the process of seeding-nucleation (i.e., cross-seeding) [28]; thus, coexistent DM may accelerate disease progression in patients with PD. Given that the initial UPDRS-III scores and DAT availability in the posterior putamen were comparable between the PD groups in this study, the synergistic effects seem to appear after PD has progressed to a more advanced stage. Indeed, a large prospective study demonstrated that the risk elevation of PD was limited to diabetic patients with a disease duration of more than 10 years [6], which may also explain why the PD patients with a prior diagnosis of DM had relatively older ages of PD onset compared to those without DM in our cohort and why there was no significant correlation between the disease duration of DM and clinical progression or brain structural alterations in the PD-DM + group.

Our study has some limitations. First, the subgroups for the cognitive assessment, neuroimaging analyses, and longitudinal assessment of PD progression were not identical due to the retrospective nature of this study; however, demographic characteristics and baseline striatal DAT availability were similar between these subgroups. Second, a longitudinal change in LED might not accurately reflect the PD progression, even though a consensus for assessing this clinical endpoint has not been established. Third, a serial neuropsychological assessment was not performed often enough to assess the longitudinal changes in cognitive performances. Although the PD patients with DM tended to show a rapid decline in K-MMSE scores relative to those without PD, a detailed evaluation of each cognitive domain, especially the frontal executive function, would provide evidence for a firm conclusion regarding the cognitive prognosis. Fourth, other vascular risk factors within the spectrum of metabolic syndrome and the degree of glycemic control during follow-up might act as confounding factors. Furthermore, antidiabetic drugs may have positively impacted on the disease progression of PD. In particular, glucagon-like peptide-1 (GLP-1) receptor agonists appear to have neuroprotective properties [29] and clinical studies of GLP-1 receptor agonists have shown the possible disease modifying effects in PD [30]. Finally, we cannot completely exclude the possibility that older ages in the PD-DM + group might suggest a protective effect of DM on the development of PD, even though other clinical and neuroimaging findings have supported the detrimental effect of DM.

In conclusion, coexistent DM had a detrimental effect on the clinical prognosis as well as the baseline striatal DAT availability, brain structural change, and level of cognitive performances in patients with PD.

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Declarations of interest

None.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.parkreldis.2018.08.023.

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