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Beneficial effects of dipeptidyl peptidase-4 inhibitors in diabetic Parkinson's disease

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Dipeptidyl peptidase-4 inhibitors (DPP-4i) are widely used hypoglycaemic agents. In a retrospective study, Jeong *et al.* show that DPP-4i reduce baseline striatal dopamine depletion and improve long-term motor outcomes in diabetic patients with Parkinson's disease.

Dipeptidyl peptidase 4 (DPP4) inhibitors are widely used hypoglycaemic agents and improve glucose metabolism by enhancing the bioavailability of active glucagon-like peptide-1. In this study, we hypothesized that treatment with DPP4 inhibitors may have beneficial effects on nigrostriatal dopamine and longitudinal motor performance in diabetic patients with Parkinson's disease. We classified 697 drug naive patients with *de novo* Parkinson's disease who had undergone dopamine transporter imaging into three groups according to a prior diagnosis of diabetes and use of DPP4 inhibitors: diabetic patients with Parkinson's disease being treated with ($n = 54$) or without DPP4 inhibitors ($n = 85$), and non-diabetic patients with Parkinson's disease ($n = 558$). Diabetic patients with Parkinson's disease being treated with DPP4 inhibitors had a higher baseline dopamine transporter availability in the anterior (2.56 ± 0.74 versus 2.10 ± 0.50; $P = 0.016$), posterior (1.83 ± 0.69 versus 1.40 ± 0.50; $P < 0.001$), and ventral putamina (1.72 ± 0.58 versus 1.35 ± 0.37; $P = 0.001$) than that in diabetic patients with Parkinson's disease without DPP4 inhibitors. Additionally, diabetic patients with Parkinson's disease being treated with DPP4 inhibitors had higher dopamine transporter availability in the posterior putamen than that in non-diabetic patients with Parkinson's disease (1.83 ± 0.69 versus 1.43 ± 0.59; $P < 0.001$). After adjusting for age, sex, disease duration, and vascular risk factors, linear regression models showed that a prior treatment of DPP4 inhibitors remained independently and significantly associated with dopamine transporter availability in the anterior ($\beta = -0.186$, $P = 0.012$; $\beta = -0.207$, $P = 0.003$), posterior ($\beta = -0.336$, $P < 0.001$; $\beta = -0.286$, $P < 0.001$), and ventral putamina ($\beta = -0.204$, $P = 0.005$; $\beta = -0.250$, $P < 0.001$). A linear mixed model revealed that the diabetic group with Parkinson's disease being treated with DPP4 inhibitors had a slower longitudinal increase in levodopa-equivalent dose than the other groups ($P = 0.003$). Survival analyses showed that the rate of levodopa-induced dyskinesia was significantly lower in the diabetic group with a prior treatment with DPP4 inhibitors than the diabetic group without DPP4 inhibitors (hazard ratio = 0.194, $P = 0.037$). These findings suggest that DPP4 inhibitors may confer beneficial effects on the baseline nigrostriatal dopamine degeneration and long-term motor outcomes in diabetic patients with Parkinson's disease and may extend its role into non-diabetic patients with Parkinson's disease.

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Abbreviations: DPP4i = DPP4 inhibitors; DAT = dopamine transporter; LED = levodopa-equivalent dose; LID = levodopa-induced dyskinesia; PD-DM = Parkinson's disease with diabetes mellitus; WMH = white matter hyperintensities

Introduction

Type 2 diabetes mellitus, as a metabolic disorder, is regarded as a protein misfolding disease.[1] Progressive loss of beta cell function and mass in patients with diabetes mellitus could result from toxic aggregates of islet amyloid polypeptide or amylin which is closely linked to defects in toxic protein-removing cellular systems, including the proteasome and autophagy.[2,3] Parkinson's disease is characterized by the progressive loss of dopaminergic neurons in the substantia nigra of the midbrain and the presence of Lewy bodies that are composed mainly of aggregated α-synuclein. Similarly, the accumulation of misfolded α-synuclein via the dysregulation of the cellular clearing system plays a key role in the pathogenesis of Parkinson's disease. Moreover, recent clinical studies have demonstrated a close association between type 2 diabetes mellitus and Parkinson's disease. Patients with diabetes mellitus have a 35% increased risk of developing Parkinson's disease,[4] and diabetes mellitus has a deteriorating impact on the prognosis of motor and cognitive performance in patients with Parkinson's disease.[5–7] Given that diabetes mellitus and Parkinson's disease might share common mechanisms, anti-diabetic medications may potentially serve as a treatment for Parkinson's disease.

Dipeptidyl peptidase-4 inhibitors (DPP4i) are widely used hypoglycaemic agents associated with a low risk of hypoglycaemia and weight gain.[8] DPP4i improve glucose metabolism by enhancing the bioavailability of active glucagon-like peptide-1 (GLP-1) by inhibiting its degradation. Beside their glycaemic properties, DPP4i have neuroprotective properties via pleotropic effects, such as modulating prosurvival and anti-apoptotic signalling, inhibiting phosphorylation of toxic proteins, inhibiting neuroinflammation, or enhancing synaptic plasticity.[9–11] Preclinical and clinical studies have demonstrated that DPP4i confer neuroprotective effects in patients with Alzheimer's disease and stroke.[12–14] In patients with Parkinson's disease, along with preclinical evidence showing neuroprotective properties of DPP4i,[15–17] a recent nationwide case-control study demonstrated that treatment with DPP4i was associated with a decreased risk of future development of Parkinson's disease.[18] Until now, the potential beneficial effects of DPP4i on nigrostriatal dopaminergic degeneration and its related longitudinal prognosis in patients with Parkinson's disease have not yet been investigated using *in vivo* neuroimaging. In the present study, we hypothesized that treatment with DPP4i may confer protective effects on the nigrostriatal dopamine system in *de novo* patients with Parkinson's disease. We, therefore, performed a comparative analysis of striatal dopamine transporter (DAT) availability and clinical parameters of longitudinal disease progression, including longitudinal increases in doses of dopaminergic medications and the rates of levodopa-induced dyskinesia (LID) and wearing-off in diabetic and non-diabetic patients with Parkinson's disease depending on treatment with DPP4i.

Materials and methods

Subjects

We retrospectively reviewed the database of the Yonsei Parkinson Center (719 consecutive patients with *de novo* Parkinson's disease who visited the Movement Disorders outpatient clinic at Severance Hospital from April 2009 to December 2016). Parkinson's disease was diagnosed according to the clinical diagnostic criteria of the UK Parkinson's Disease Society Brain Bank. *N*-(3-[^{18}F]fluoropropyl)-2β-carbon ethoxy-3β-(4-iodophenyl) nortropane (^{18}F-FP-CIT PET) scans revealed decreased DAT availability in the posterior putamen on all subjects. The exclusion criteria included drug-induced patients with parkinsonism, evidence of atypical parkinsonism, and bedridden status due to other disorders, as well as Parkinson's disease patients who were not drug-naive (Supplementary Fig. 1). Parkinsonian motor symptoms were assessed using the Unified Parkinson's Disease Rating Scale Part III (UPDRS-III) at initial visit under dopaminergic naive status, 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) was used to assess general cognition.[19] We classified patients with Parkinson's disease according to clinical phenotypes as having tremor dominant or postural instability/gait difficulty parkinsonism.[20] All patients were investigated for medical history, and vascular risk factors including hypertension, dyslipidaemia, cardiac disease, and ischaemic stroke in addition to diabetes mellitus. New-onset diabetes was defined by patient-reported physician-diagnosed diabetes, initiation of anti-diabetic medication or by fasting plasma glucose $>$125 mg/dl or HbA1c 6.5% or higher among individuals with no prior record of diabetes based on electronic medical record of Severance Hospital, Seoul, Korea.[21] Patients with Parkinson's disease were classified into three groups according to the presence of diabetes mellitus and whether they were being treated with DPP4i: non-diabetic patients with Parkinson's disease (PD-DM– group, n = 558), diabetic patients with Parkinson's disease who were not being treated with DPP4i (PD-DM+/DPP4i– group, n = 85), and diabetic patients with Parkinson's disease who were being treated with DPP4i (PD-DM+/DPP4i+ group, n = 54). We also investigated the patients' prescriptions, including other oral hypoglycaemic agents and insulin in addition to DPP4i. We investigated other anti-diabetic drugs as well as the type of DPP4i that the patients were taking (sitagliptin, n = 30; linagliptin, n = 10; vildagliptin, n = 6; gemigliptin, n = 3; alogliptin, n = 2; saxagliptin, n = 2; teneligliptin, n = 1). There were no diabetic patients with Parkinson's disease who were being treated with a GLP-1 agonist. This study was approved by the Yonsei University Severance Hospital institutional review board

(IRB No. 4-2014-0637), and the need for informed consent was waived because of the retrospective nature of the study.

Acquisition and quantitative analyses of ^{18}F-FP-CIT PET scans

The ^{18}F-FP-CIT PET scans were acquired using a GE PET-CT DSTe scanner (GE Discovery STE; GE Healthcare), which obtains images with a 3D resolution of 2.3-mm full-width at half-maximum. After the subjects fasted for at least 6 h, they were intravenously injected with 5 mCi (185 MBq) of ^{18}F-FP-CIT. Ninety minutes after the injection, PET images were acquired for 20 min in the 3D mode at 12 kVp and 380 mA. Image processing was performed using SPM8 (Wellcome Department of Imaging Neuroscience, Institute of Neurology, UCL, London, UK) with MATLAB 2013a for Windows (MathWorks, Natick, MA, USA). Quantitative analyses were based on volumes of interests, which were defined based on a template in standard space. All reconstructed PET images were spatially normalized to the Montreal Neurological Institute (MNI) template space using a standard ^{18}F-FP-CIT PET template, which was generated from ^{18}F-FP-CIT PET and -weighted MRI scans of 13 normal controls. Twelve volumes of interest of bilateral striatal subregions and one occipital volume of interest were drawn on a co-registered spatially normalized single T_1-weighted magnetic resonance and ^{18}F-FP-CIT PET template image on MRIcro version 1.37 (Chris Rorden, Columbia, SC, USA).[22] Briefly, the striatum was divided along the anterior-posterior commissure line on the transverse plane into dorsal and ventral portions. The ventral portion comprised two subregions: the ventral putamen and ventral striatum. Subsequently, the dorsal portion was divided along the coronal anterior commissure plane into the following anterior and posterior subregions: the anterior caudate, posterior caudate, anterior putamen, and posterior putamen. These volumes of interest were adjusted by a minor translation in our in-house editing software ANIQUE.[23] DAT availability was calculated by the non-displaceable binding potential, which was defined as follows: (mean standardized uptake value of the striatal subregions volume of interest—mean standardized uptake value of the occipital volume of interest)/(mean standardized uptake of the occipital volume of interest).[24]

Acquisition of FLAIR sequence images and grading white matter hyperintensities

Of the 697 enrolled patients, 527 (75.6%) patients underwent brain MRI scans at Severance Hospital using a 3.0 T scanner (Achieva; Philips Medical Systems) at initial assessment, including fluid-attenuated inversion recovery (FLAIR) sequence images. The FLAIR sequence images were acquired with the following parameters: matrix, 512 × 512; slice number, 22; pixel spacing, 0.449 × 0.449 mm^2; slice thickness, 5 mm; gap, 2 mm; field of view, 230 mm; repetition time, 11 000 ms; echo time, 125 ms; inversion time, 2800 ms; flip angle, 90°. The other 170 (24.4%) patients underwent brain MRI scans including FLAIR sequence images at other hospitals before being referred to our hospital. The visual rating scale of the white matter hyperintensities (WMH) was assessed by two neurologists (Y.H.L. and H.S.Y.) using the Scheltens scale in which the periventricular and lobar (frontal, parietal, temporal, and occipital) WMH, as well as basal ganglia and infratentorial signal hyperintensities were rated separately in a semi-quantitative manner.[25] The intra- and inter-rater reliability of total WMH were high (intra class correlation coefficients = 0.984 and 0.966, respectively). A final consensus rating between the two raters was used for the analysis.

Longitudinal assessment of the changes in levodopa-equivalent daily doses over time

Of the 697 patients with Parkinson's disease, 605 patients with Parkinson's disease (PD-DM–, $n = 483$; PD-DM + /DPP4i–, $n = 76$; PD-DM + /DPP4i + , $n = 46$) treated with dopaminergic medications for at least 2 years were included in the assessment of the longitudinal changes in levodopa-equivalent doses (LED) (Supplementary Fig. 1). The median follow-up duration was 65 months (range: 24–129 months). The patients visited the outpatient clinic every 3–6 months, and the median number of visits was 20 (range: 6–56). Their dopaminergic medications were adjusted for effective symptom control by P.H.L. and Y.H.S. according to the patients' response. At each visit, the doses of dopaminergic medications were checked, and the levodopa equivalent dose (LED) was calculated using the following formula: levodopa × 1 + controlled-release levodopa × 0.75 + ropinirole × 20 + pramipexole × 100 + levodopa × 0.33 if they were on entacapone + selegiline × 10 + rasagiline × 100.[26] A linear mixed model was used to compare the rate of longitudinal changes in LED among the groups. Ten fixed effects were included in the model: eight were between subject effects [Parkinson's disease group according to age of symptom onset, sex, disease duration, hypertension, dyslipidaemia, body mass index (BMI), total WMH, and baseline DAT availability in the posterior putamen] and one was a within-subject effect (time). Because most of the increases in LED occurred within the first 6 months, and then the doses of dopaminergic medications were adjusted every 3 to 6 months thereafter, time was treated as a categorical variable with a 6-month interval, up to 60 months (when > 40% of the patients were followed-up). The effects of the Parkinson's disease group on longitudinal changes in LED were tested using a group × time interaction term.

Assessment of the development of levodopa-induced dyskinesia and wearing-off

The participants visited our outpatient clinic every 3–6 months, and two movement disorder experts (Y.H.S., P.H.L.) carefully assessed the presence of LID[27] and wearing-off[28] through a history obtained from patients and caregivers or by direct neurological examination at every visit. The date on which the patients with Parkinson's disease or their caregivers reported that LID or wearing-off occurred or the date on which LID or wearing-off was first seen in the clinic was regarded as the date of occurrence of LID or wearing-off. The time from treatment initiation to the onset of LID and wearing-off assessed with Kaplan-Meier estimates in 606 patients with Parkinson's disease who had a follow-up duration ⩾ 2 years (Supplementary Fig. 1).

A log-rank test was used to compare the Kaplan-Meier plots among the groups. To assess the effects of DPP4i on the development of LID and wearing-off, the Cox regression model was used to estimate hazard ratio (HR) and 95% confidence intervals (CIs) while adjusting for age of symptom onset, sex, disease duration, hypertension, dyslipidaemia, total WMH, baseline DAT availability in the posterior putamen, and levodopa doses per body weight at LID or wearing-off onset in patients with dyskinesia or at the last visit to the outpatient clinic in those without dyskinesia.

Statistical analyses

To compare the baseline demographic characteristics among the Parkinson's disease groups, one-way ANOVA with *post hoc* Bonferroni correction was used for continuous variables, and Pearson's χ^2 tests or Fisher exact tests were used for categorical variables. Independent sample *t*-test was used to compare diabetes mellitus duration between the diabetic Parkinson's disease groups. To compare the DAT availability of each striatal subregion among the Parkinson's disease groups, Bonferroni correction for multiple comparisons were used. A multivariate linear regression analysis was used to determine the independent effects of DPP4i after adjusting for age of symptom onset, sex, disease duration, hypertension, dyslipidaemia, BMI, and total WMH. A linear mixed model was used to compare the rates of the longitudinal LED changes among the three Parkinson's disease groups. The effects of DPP4i on the development of LID and wearing-off was assessed with a log-rank test and the Cox regression model as described above. The statistical analyses were performed with SPSS (version 25.0; IBM Corporation, Armonk, NY, USA) and R (v3.6, http://www.r-project.org/). Results with a two-tailed $P < 0.05$ were considered statistically significant.

Data availability

The de-identified data that support the findings of this study are available from the authors upon reasonable request.

Results

Demographic and clinical characteristics

Demographic and clinical characteristics of the PD-DM–, PD-DM + /DPP4i–, PD-DM + /DPP4i + groups enrolled in this study are summarized in Table 1. Age of symptom onset was higher in the PD-DM + /DPP4i– and PD-DM + /DPP4i + groups than in the PD-DM– group. Disease duration, UPDRS III score, education, CCSIT, and BMI did not differ among the three groups. The PD-DM– group tended to have higher K-MMSE scores than the PD-DM + /DPP4i– group. The PD-DM + /DPP4i + group tended to have a lower BDI score when compared with the PD-DM + /DPP4i– group. In terms of vascular factors, hypertension and dyslipidaemia were more prevalent in the PD-DM + than in the PD-DM– group. Vascular risk factors including hypertension, cardiac disease and ischemic stroke were comparable between the PD-DM + /DPP4i– and PD-DM + /DPP4i + groups. Dyslipidaemia was more prevalent in the PD-DM + /DPP4i + than in the PD-DM + /DPP4i– groups. The co-prescribed other anti-diabetic drugs such as metformin, sulfonylurea, thiazolidinedione, alpha-glucosidase, and insulin did not differ significantly between the groups. The mean score of WMH was significantly higher in the Parkinson's disease group with diabetes mellitus relative to the PD-DM– group (9.52 ± 7.62) and comparable between the PD-DM + /DPP4i– (13.0 ± 9.17) and PD-DM + /DPP4i + (12.6 ± 8.11) groups. In terms of motor phenotype, the predominant phenotype did not differ among the groups. Additionally, all PD-DM + / DPP4i + patients were exposed to DPP4i during entire follow-up period except for one patient who was taking DPP4i for 28 months at the 39-month follow-up point.

Comparison of striatal DAT availability among the groups

The DAT availability for the whole striatum and each striatal subregion in each group are shown in Table 1 and Fig. 1. The PD-DM + /DPP4i + group had a significantly higher DAT availability in the whole striatum compared to the PD-DM + /DPP4i– or PD-DM– group (Table 1). When the PD-DM + /DPP4i + group was compared to the PD-DM + / DPP4i– group with regards to subregional striatum DAT availability, the PD-DM + /DPP4i + group showed more preserved DAT availability in the anterior putamen (2.56 ± 0.74 versus 2.10 ± 0.50; $P = 0.016$), posterior putamen (1.83 ± 0.69 versus 1.40 ± 0.50; $P < 0.001$), and ventral putamen (1.72 ± 0.58 versus 1.35 ± 0.37; $P = 0.001$) (Fig. 1). Additionally, the PD-DM + /DPP4i + group had higher DAT availability in the posterior putamen compared to the PD-DM– group (1.83 ± 0.69 versus 1.43 ± 0.59; $P < 0.001$). A multivariate linear regression analysis revealed that the PD-DM + /DPP4i + group was significantly and independently associated with less severely decreased DAT availability in the whole striatum ($\beta = -0.148$, $P = 0.011$; $\beta = -0.185$, $P = 0.001$), the anterior putamen ($\beta = -0.186$, $P = 0.012$; $\beta = -0.207$, $P = 0.003$), posterior putamen ($\beta = -0.336$, $P < 0.001$; $\beta = -0.286$, $P < 0.001$), and ventral putamen ($\beta = -0.204$, $P = 0.005$; $\beta = -0.250$, $P < 0.001$) relative to the PD-DM– or PD-DM + /DPP4i– group after adjusting for age of symptom onset, sex, disease duration, hypertension, dyslipidaemia, BMI, and total WMH (Table 2). Absolute values of standardized coefficients (β) were the highest in the model of posterior putamen.

Longitudinal assessment of the changes in levodopa-induced dyskinesia between groups

The 605 patients with Parkinson's disease who were treated with dopaminergic medications for at least two years had similar demographic characteristics and striatal DAT availability as all enrolled patients (Supplementary Table 1). There was a significant group × time interaction in the

Table 1 Demographic characteristics and dopamine transporter availability in patients with Parkinson's disease

	PD-DM– (*n* = 558)	PD-DM + /DPP4i– (*n* = 85)	PD-DM + /DPP4i + (*n* = 54)	*P*-value
Demographic characteristics				
Age of symptom onset, years	63.69 ± 10.40	68.48 ± 7.73	69.37 ± 8.64	<0.001[a, b]
Female, *n* (%)	294 (52.7)	42 (49.4)	29 (53.7)	0.836
Disease duration, m	17.40 ± 17.50	18.01 ± 18.32	14.20 ± 13.71	0.392
DM duration, years		11.43 ± 6.48	12.52 ± 7.12	0.357
UPDRS-III	22.46 ± 9.85	24.08 ± 9.48	20.96 ± 9.26	0.186
Education, years	9.41 ± 5.10	8.45 ± 5.47	10.12 ± 4.98	0.149
K-MMSE	26.63 ± 2.99	25.77 ± 3.63	26.24 ± 2.97	0.049
CCSIT	6.68 ± 2.39	6.58 ± 2.78	6.21 ± 2.09	0.456
BDI	12.65 ± 8.56	13.67 ± 9.57	10.33 ± 7.06	0.089
Clinical phenotype, *n* (%)				0.345
TD	107 (23.3%)	14 (17.5%)	11 (21.2%)	
PIGD	316 (68.7%)	61 (76.2%)	40 (76.9%)	
Intermediate	37 (8.0%)	5 (6.2%)	1 (2.3%)	
Vascular risk factors				
Hypertension	211 (37.8%)	51 (60.0%)	36 (66.7%)	<0.001[a, b]
Dyslipidaemia	73 (13.1%)	23 (27.1%)	24 (44.4%)	<0.001[a, b, c]
Cardiac disease	53 (9.5%)	15 (17.6%)	6 (11.1%)	0.075[a]
Ischaemic stroke	20 (3.6%)	6 (7.1%)	1 (1.9%)	0.219
BMI, kg/m^2	23.46 ± 2.93	24.07 ± 2.79	23.19 ± 2.53	0.134
Anti-diabetic drugs				
Metformin		71 (83.5%)	49 (90.7%)	0.228
Sulfonylurea		44 (51.8%)	21 (38.9%)	0.241
Thiazolidinedione		16 (18.8%)	5 (9.3%)	0.150
α-glucosidase inhibitors		6 (7.1%)	2 (3.7%)	0.484
Insulin		6 (7.1%)	3 (5.6%)	1.000
Brain MRI				
Total WMH	9.52 ± 7.62	13.0 ± 9.17	12.6 ± 8.11	<0.001[a, b]
Baseline DAT availability				
Total striatum	1.89 ± 0.55	1.69 ± 0.44	2.03 ± 0.64	0.003[a, c]

Values are expressed as mean ± standard deviation or *n* (%). *P*-values are the results of analyses of variance, independent sample *t*-test, χ^2 tests or Fisher exact tests as appropriate. BDI = Beck Depression Inventory; BMI = body mass index; CCSIT = Cross-Cultural Smell Identification Test; PIGD = postural instability and gait difficulty; TD = tremor-dominant; UPDRS III = Unified Parkinson's Disease Rating Scale Part III.

[a]Significantly different in comparison between PD-DM– and PD-DM + /DPP4i–.

[b]Significantly different in comparison between PD-DM– and PD-DM + /DPP4i + .

[c]Significantly different in comparison between PD-DM + /DPP4i– and PD-DM + /DPP4i–.

mixed model ($P = 0.002$) after adjusting for age of symptom onset, sex, hypertension, dyslipidaemia, BMI, total WMH, baseline DAT availability in the posterior putamen, time, and group × time, indicating that the pattern of longitudinal changes in LED differed among the groups. Throughout the follow-up period, the PD-DM + /DPP4i + group required lower doses of dopaminergic medications compared to the PD-DM + /DPP4i– group. The LED changes in the PD-DM + /DPP4i + group were smaller even in the comparison with the PD-DM– group (Table 3 and Fig. 2). Information on anti-parkinsonian medications among the groups is available in Supplementary Table 2.

Development of levodopa-induced dyskinesia and wearing-off relation to DPP4 inhibitor use

During the follow-up period, LID developed in 123 (25.4%) of the 484 patients in the PD-DM– group (follow-up duration, 6.00 ± 2.10 years; the number of visits 22.61 ± 9.43), 18 of 76 patients (23.7%) in the PD-DM + /DPP4i– group (follow-up duration, 5.45 ± 2.15 years; the number of visits 20.21 ± 9.87), and 2 of 46 patients (4.4%) in the PD-DM + /DPP4i + group (follow-up duration, 4.77 ± 1.37 years; the number of visits 16.83 ± 6.07). Wearing-off developed in 135 (27.9%) in the PD-DM– group, 21 (27.6%) in the PD-DM + /DPP4i– group, and 3 (6.5%) in the PD-DM + /DPP4i + group. The Kaplan-Meier analyses revealed that the PD-DM + /DPP4i + group had a lower risk of developing LID than the PD-DM + /DPP4i– group or PD-DM– group ($P_{log\text{-}rank}$ = 0.047 and 0.039, Fig. 3A). In addition, the PD-DM + /DPP4i + group had a lower risk of developing wearing-off than the PD-DM + /DPP4i– group or PD-DM– group in the Kaplan-Meier analyses ($P_{log\text{-}rank}$ = 0.041 and 0.036; Fig. 3B). After adjusting for covariates, the PD-DM + /DPP4i + group tended to have lower risks of developing LID (HR, 0.294; 95% CI, 0.071–1.213; $P = 0.091$) and wearing-off

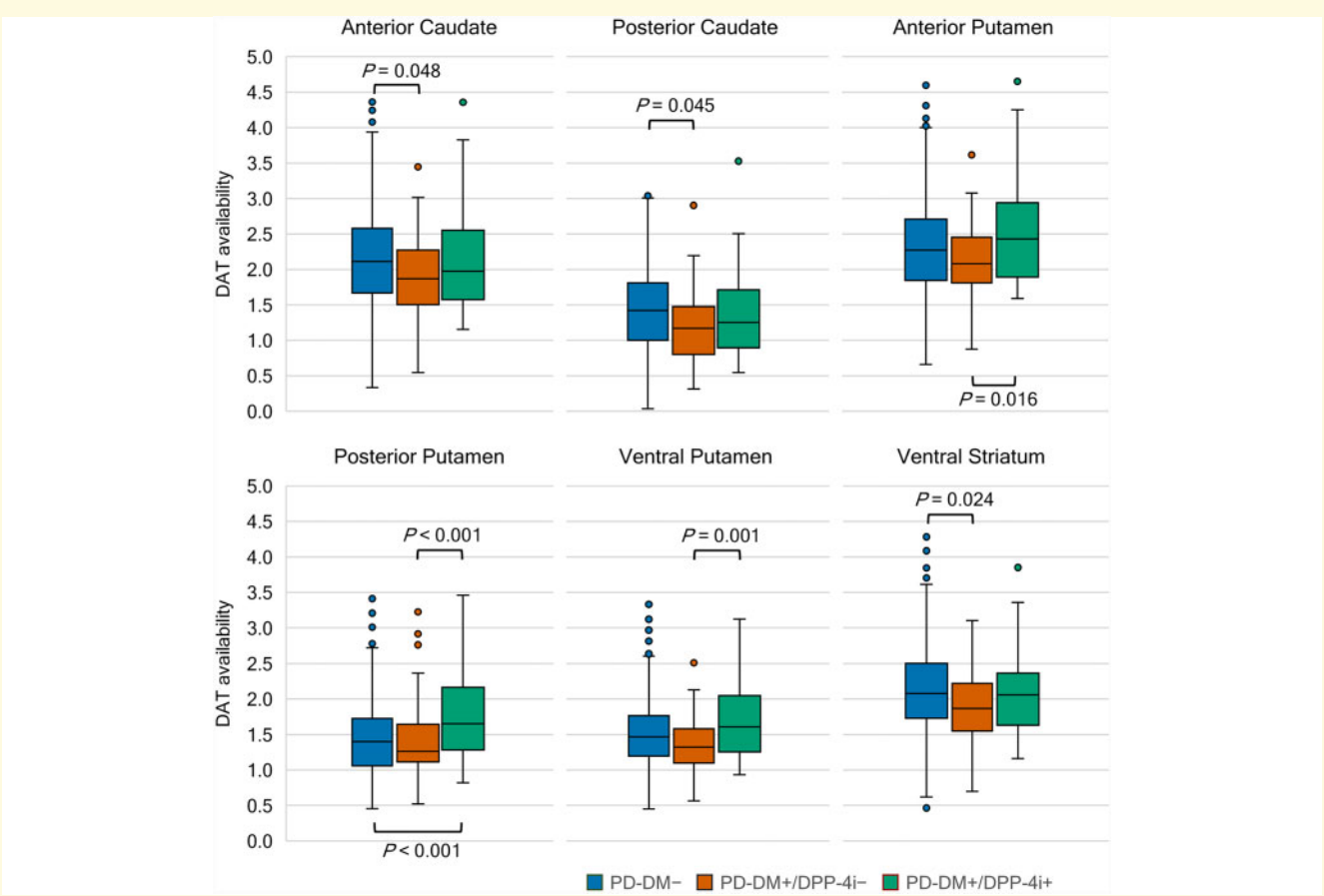

Figure 1 Box-and-whisker plots of the dopamine transporter availability of the striatal subregions. Significant *P*-values were based on both the *post hoc* Bonferroni correction after one-way ANOVA and Bonferroni correction for multiple comparison.

Table 2 Multiple linear regression analysis of dopamine transporter availability in each striatal subgroup

Striatal subgroup	Total striatum		Anterior caudate		Posterior caudate		Anterior putamen		Posterior putamen		Ventral putamen		Ventral striatum	
	β	*P*	β	*P*	β	*P*	β	*P*	β	*P*	β	*P*	β	*P*
PD-DM + /DPP4i +	Reference		Reference		Reference		Reference		Reference		Reference		Reference	
PD-DM + /DPP4i–	–0.185	0.001	–0.095	0.435	–0.074	1.000	–0.207	0.003	–0.286	<0.001	–0.250	<0.001	–0.085	0.863
PD-DM–	–0.148	0.011	–0.062	1.000	–0.033	1.000	–0.186	0.012	–0.336	<0.001	–0.204	0.005	–0.016	1.000

Results of multivariate linear regression analysis for the whole striatum and striatal subgroup after controlling for age of symptom onset, sex, disease duration, hypertension, dyslipidaemia, total WMH, and BMI. *P*-values of striatal subgroups are the results of Bonferroni correction for multiple comparison. β = standardized beta coefficient; BMI = body mass index.

than the PD-DM– group (HR, 0.323; 95% CI, 0.099-1.051; $P = 0.060$; Table 4). When analysing diabetic patients with Parkinson's disease, the PD-DM + /DPP4i + group had a lower risk of developing LID than the PD-DM + /DPP4i– group (HR, 0.194; 95% CI, 0.041–0.907; $P = 0.037$; Table 4). However, the hazard ratio for developing wearing-off in the PD-DM + /DPP4i + group relative to the PD-DM + /DPP4i– group was not significant. The predictability of LID or wearing-off was reliable (Harrel's C indices were >0.7).

Discussion

In this study, we investigated the effects of DPP4i on nigrostriatal dopaminergic denervation and the clinical course of drug-naive patients with Parkinson's disease. The major findings are as follows. First, the PD-DM + /DPP4i + group had a higher baseline mean DAT availability in the anterior, posterior, and ventral putamina than the PD-DM + /DPP4i– group. Additionally, the PD-DM + /DPP4i + group had higher DAT availability in the posterior putamen compared

Table 3 Longitudinal changes of levodopa-equivalent doses in patients with Parkinson's disease

	PD-DM–	PD-DM + /DPP4i–	PD-DM + /DPP4i +	Overall *P*	*P* at each time point
Month 6	400.60 (10.34)	427.04 (21.56)	376.63 (27.55)		0.320
Month 12	432.00 (10.35)	465.02 (21.56)	391.40 (27.55)		0.102
Month 18	455.58 (10.35)	498.11 (21.56)	408.31 (27.55)		0.032[c]
Month 24	473.90 (10.36)	524.12 (21.58)	443.30 (27.55)	Group: 0.013	0.038[c]
Month 30	497.92 (10.37)	552.85 (21.62)	467.80 (27.76)	Time: < 0.001	0.024[a, c]
Month 36	526.30 (10.40)	574.17 (21.74)	479.52 (27.87)	Group × Time: 0.002	0.021[a, c]
Month 42	555.63 (10.47)	601.02 (22.14)	489.93 (28.08)		0.008[b, c]
Month 48	586.12 (10.58)	642.68 (22.64)	526.55 (28.82)		0.005[a, c]
Month 54	618.33 (10.73)	683.48 (23.46)	550.78 (29.98)		0.002[a, b, c]
Month 60	652.26 (10.97)	707.79 (24.42)	576.66 (31.31)		0.004[a, b, c]

Values are expressed as the estimated mean (standard error) for the levodopa-equivalent doses after controlling for age of symptom onset, sex, disease duration, hypertension, dyslipidaemia, BMI, total WMH, baseline DAT availability in the posterior putamen, time, and group × time. *P*-values are calculated by a linear mixed model analysis. BMI = body mass index.

[a]Significantly different in comparison between PD-DM– and PD-DM + /DPP4i–.

[b]Significantly different in comparison between PD-DM– and PD-DM + /DPP4i + .

[c]Significantly different in comparison between PD-DM + /DPP4i– and PD-DM + /DPP4i + .

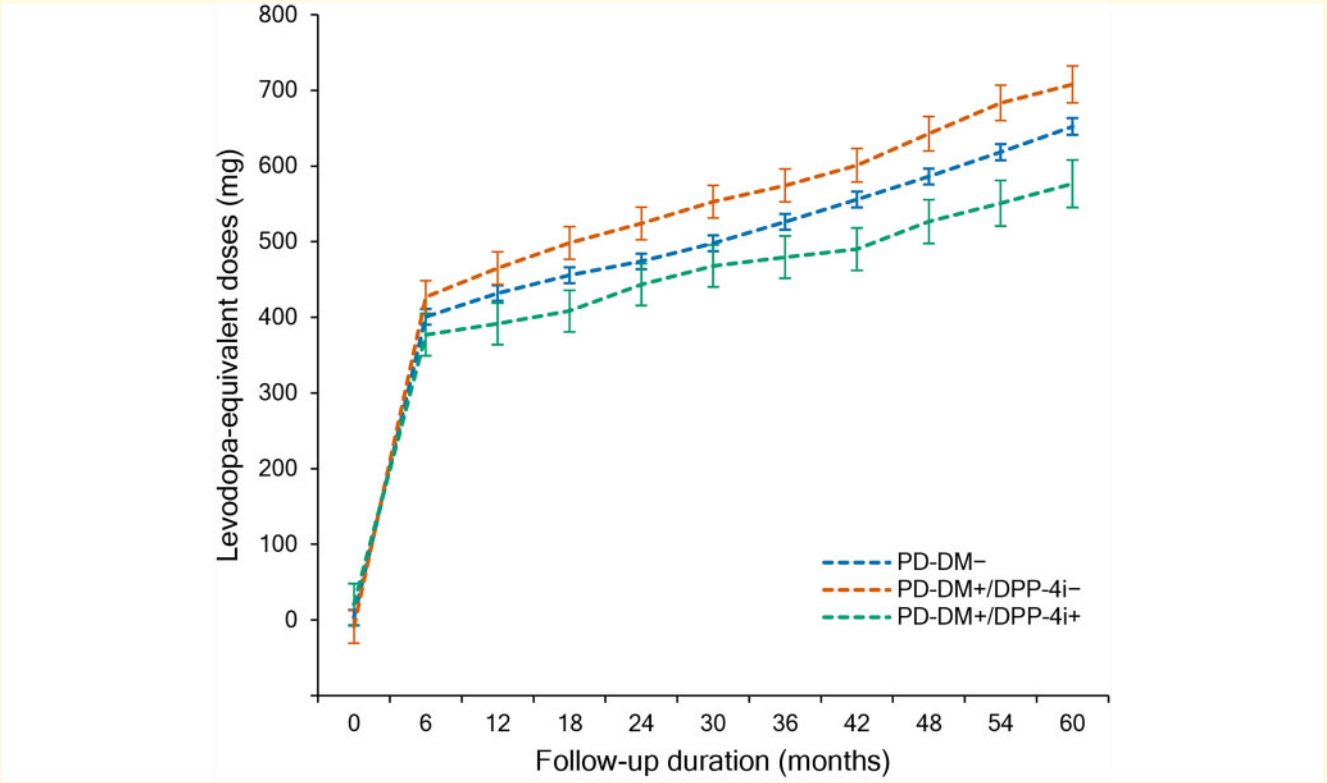

Figure 2 Longitudinal increases in levodopa-equivalent doses. A linear mixed model analysis showed significant difference among the PD-DM– (in blue), PD-DM + /DPP4i– (in vermion), and PD-DM + /DPP4i + groups (in bluish green) (group × time interaction, $P = 0.002$). The error bars represent standard errors of the estimated means.

to the PD-DM– group. Second, the PD-DM + /DPP4i + group showed a slower longitudinal increase in LED compared to the PD-DM + /DPP4i– or PD-DM⁻ group. Finally, the PD-DM + /DPP4i + group had a lower risk of developing LID than the PD-DM + /DPP4i– groups, after adjusting for confounding factors. These findings suggest that DPP4i may confer beneficial effects on the baseline striatal dopamine depletion and long-term motor outcomes in diabetic patients with Parkinson's disease.

Along with beneficial effects of DPP4i on a variety of neurologic disorders,[13,14] the protective effects of DPP4i on dopaminergic neurons in Parkinson's disease had also been

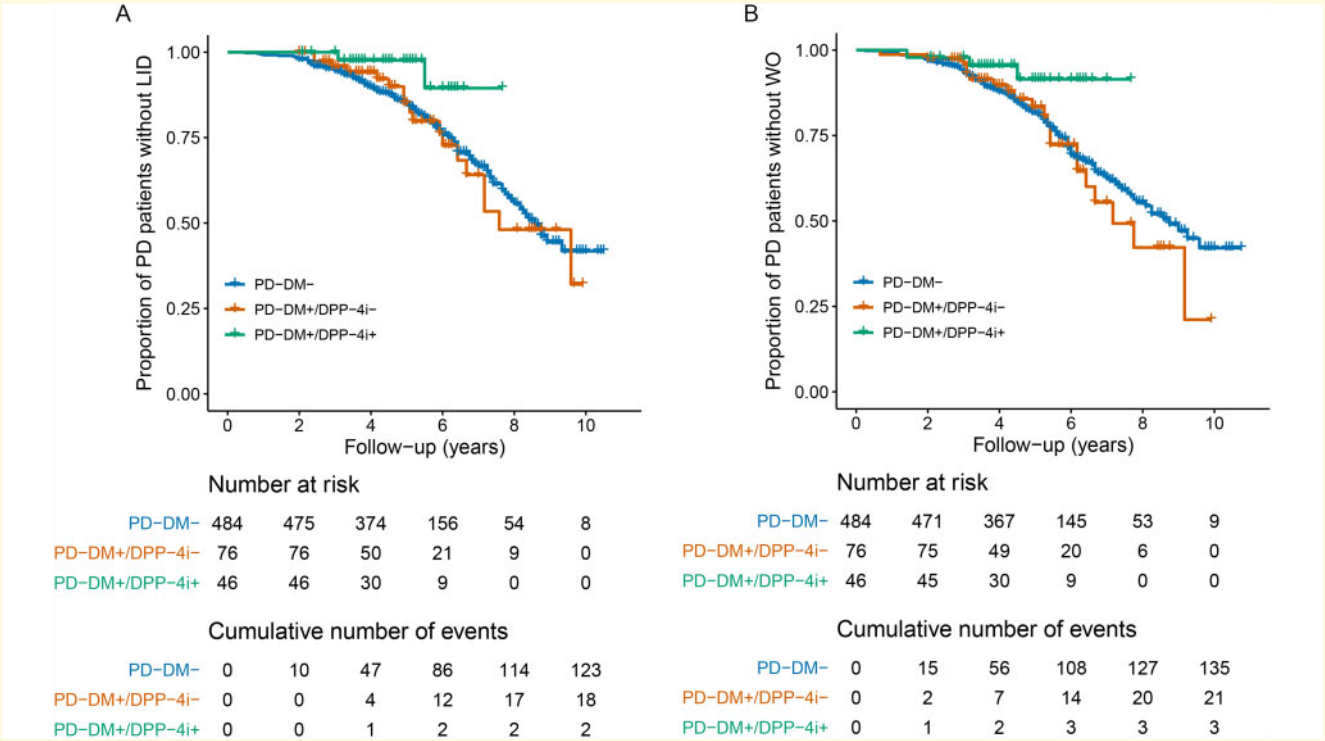

Figure 3 Kaplan-Meier survival curve of levodopa-induced dyskinesia. Curves of Kaplan-Meier estimates of the onset of levodopa-induced dyskinesia after treatment initiation in the PD-DM– (in blue), PD-DM + /DPP4i– (in orange), and PD-DM + /DPP4i + groups (in bluish green). The PD-DM + /DPP4i + group had a lower risk of early development of levodopa-induced dyskinesia than either the PD-DM– ($P_{log\text{-}rank}$ = 0.039) or PD-DM + /DPP4i– group ($P_{log\text{-}rank}$ = 0.047). The PD-DM + /DPP4i + group had a lower risk of early development of wearing-off than either the PD-DM– ($P_{log\text{-}rank}$ = 0.041) or PD-DM + /DPP4i– group ($P_{log\text{-}rank}$ = 0.036). The crosses in the graphs indicate censored data.

Table 4 Cox regression analyses for the development of levodopa-induced dyskinesia and wearing-off in patients with Parkinson's disease according to the use of DPP4i

	Levodopa-induced dyskinesia				Wearing-off			
	PD-DM–/DPP4i + versus PD-DM– (C index = 0.713)		PD-DM + /DPP4i + versus PD-DM + /DPP4i– (C index = 0.755)		PD-DM–/DPP4i + versus PD-DM– (C index = 0.729)		PD-DM + /DPP4i + versus PD-DM + /DPP4i– (C index = 0.762)	
	HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P
Age of symptom onset	0.950 (0.930–0.971)	<0.001	0.947 (0.893–1.005)	0.071	0.927 (0.908–0.947)	<0.001	0.913 (0.860–0.970)	0.003
Female	1.280 (0.882–1.858)	0.194	2.710 (0.963–7.624)	0.059	0.909 (0.645–1.282)	0.587	2.967 (1.130–7.794)	0.027
Disease duration	1.005 (0.994–1.017)	0.352	0.996 (0.964–1.028)	0.790	1.001 (0.990–1.012)	0.858	0.982 (0.945–1.021)	0.373
Hypertension	0.981 (0.652–1.475)	0.925	0.667 (0.254–1.755)	0.412	1.199 (0.814–1.766)	0.358	1.063 (0.429–2.632)	0.895
Dyslipidaemia	1.538 (0.947–2.496)	0.082	1.009 (0.309–3.296)	0.989	1.130 (0.684–1.865)	0.633	1.152 (0.394–3.365)	0.796
Total WMH	1.038 (1.011–1.066)	0.006	0.992 (0.929–1.060)	0.810	0.999 (0.971–1.028)	0.960	1.034 (0.976–1.096)	0.259
DAT availability in posterior putamen	0.853 (0.561–1.296)	0.457	0.678 (0.198–2.319)	0.535	1.168 (0.798–1.711)	0.424	0.237 (0.066–0.845)	0.026
Levodopa doses per body weight	1.092 (1.059–1.126)	<0.001	0.925 (0.833–1.028)	0.148	1.137 (1.104–1.171)	<0.001	0.983 (0.902–1.071)	0.695
DPP4i +	0.294 (0.071–1.213)	0.091	0.194 (0.041–0.907)	0.037	0.323 (0.099–1.051)	0.060	0.360 (0.101–1.285)	0.116

Results of Cox regression analyses for the development of levodopa-induced dyskinesia and wearing-off after controlling for age of symptom onset, sex, disease duration, hypertension, dyslipidaemia, total WMH, baseline DAT availability in the posterior putamen, and levodopa doses per body weight.

demonstrated in several preclinical studies. Sitagliptin treatment conferred a neuroprotective effect on nigrostriatal degeneration via modulation of anti-inflammatory and anti-apoptotic properties.[17] Additionally, vildagliptin had neuroprotective effect in the rotenone-induced Parkinson's disease model via an interception with the RAGE-induced NFκB signalling pathway and the activation of Nrf2-antioxidant signalling.[15] However, in contrast to a GLP-1 receptor agonist, which seems to have a potential disease-modifying property in Parkinson's disease, DPP4i cannot cross the blood–brain barrier.[29,30] Thus, the neuroprotective effects of DPP4i may be conferred indirectly through an increase in the levels of GLP-1 and GLP-2 in the peripheral blood, which can cross blood–brain barrier. To date, preclinical studies demonstrated that GLP-1 had a neuroprotective property on nigrostriatal dopaminergic neurons via elevation in cAMP, modulation of antiapoptotic and proapoptotic proteins, or inhibition of microglial activation and matrix metalloproteinase 3 expression.[31–33] Moreover, a randomized clinical trial demonstrated that exenatide, a GLP-1 agonist, is associated with positive and persistent effects on practically defined off-medication motor disability in patients with Parkinson's disease, although the symptomatic effects of GLP-1 agonist cannot be excluded.[34]

The present study demonstrated that the PD-DM + /DPP4i + group had higher DAT availability in the putamen than the PD-DM + /DPP4i– group, with the posterior putamen having the most contrast. The posterior and ventral putamen, as the sensorimotor striatum, receiving projections from the dopaminergic neurons in the ventrolateral substantia nigra,[35] connect with the primary motor and somatosensory cortices.[36] The result of this study suggests that DPP4i might exert a neuroprotective effect preferentially on nigrostriatal dopaminergic neurons that are mainly affected by Parkinson's disease pathology. Additionally, we found that compared to the PD-DM + /DPP4– group, the PD-DM + /DPP4 + group had preserved DAT availability in the anterior putamen, which has been reported to be associated with neuropsychiatric symptoms such as depression or anxiety in patients with Parkinson's disease.[37] Considering that depression and anxiety were related to DPP4 activity,[38] and the PD-DM + /DPP4i + group tended to have lower BDI scores than the PD-DM + /DPP4i–, further studies are needed to assess whether DPP4i can have effects on neuropsychiatric symptoms. Interestingly, the present study showed that the PD-DM + /DPP4i + group had higher DAT availability in the posterior putamen compared to the PD-DM– group. Ample evidence has demonstrated that diabetes mellitus has a detrimental effect on motor performance, arguing that onset of diabetes mellitus prior to Parkinson's disease is a risk factor for more severe parkinsonian symptoms.[5,6] Accordingly, the results of this study implicate that DPP4i may counteract the detrimental effect of diabetes mellitus on nigrostriatal dopaminergic neurons, thus exhibiting DAT availability above the range observed in patients with PD-DM$^-$. Since there have been no previous reports regarding the effects of DPP4i on DAT activity, our results may provide indirect neuroprotective evidence of DPP4i on dopaminergic neurons in Parkinson's disease regardless of DM. However, due to a lack of clinical evidence, further epidemiological or imaging studies are required to uncover whether DPP4i would delay development of motor symptoms or lead to different patterns of nigrostriatal DAT availability in patients with idiopathic REM sleep behaviour disorder.

In this study, we found that the PD-DM$^+$/DPP4i$^+$ group showed a slower longitudinal increase in LED during follow-up compared to the PD-DM + /DPP4i– or PD-DM– group. Until now, there have been no clinical studies of the contribution of DPP4i on progression of Parkinson's disease. We previously reported in a large case series that coexistent of diabetes mellitus in patients with Parkinson's disease may accelerate disease progression in terms of longitudinal LED requirement.[39] Despite considering the detrimental effects of diabetes mellitus on prognosis, the PD-DM + /DPP4i + group in the present study exhibited a slower longitudinal increase in the estimated LED change compared with patients with Parkinson's disease who were not taking DPP4i regardless of the presence of DM, even after adjusting for confounding factors including disease duration, vascular factors, total WMH, and baseline DAT availability in the posterior putamen. Although a longitudinal change in LED may not accurately reflect disease progression, LED is indirectly associated with parkinsonian disability.[40] In terms of the prognostic role of DPP4i, the results of this study suggest that DPP4i can modulate longitudinal progression of parkinsonian motor deficits. However, since GLP-1 agonists may have symptomatic effects on the control of parkinsonian motor symptoms,[34] it is also possible that the beneficial effects of DPP4i in LED requirement would not be direct but would be merely secondary to symptomatic effects.

Finally, the present study showed that the development of LID was significantly lower in the PD-DM + /DPP4i– group than in the PD-DM + /DPP4i– group, even after adjusting for confounding factors. A recent preclinical study demonstrated that sitagliptin and liraglutide modulate levodopa effects and alleviate dyskinetic movements in a rotenone-induced Parkinson's disease model.[41] Considering the complex presynaptic and postsynaptic mechanisms of LID,[42,43] DPP4i may involve not only the protection of nigral dopaminergic neurons, but also postsynaptic down-signalling pathways via modulation of neuroplasticity like that observed for a GLP-1 agonist,[44] which may directly lead to lower incidences of LID in the PD-DM + /DPP4i + group. However, less severe baseline DAT availability and longitudinal levodopa requirement, which are known to be an important risk factor of LID, may also contribute to a decreased development of LID in the PD-DM + /DPP4i + group. In terms of wearing-off, the PD-DM + /DPP4i + group tended to have lower risks of its development than the PD-DM– group, suggesting that DPP4i may also modulate the development of wearing-off in Parkinson's disease. Collectively, the results of this study may imply that as a disease modifying strategy, beneficial effects of DPP4i on nigral dopaminergic neurons and longitudinal motor performance extend its role into non-diabetic

patients with Parkinson's disease. However, this generalization should be cautiously interpreted due to the lower age of onset in the PD-DM– group despite adequately adjusting for onset age. A previous case-control study reported that age of onset was higher in the PD-DM+ group than in the PD-DM– group, which are consistent with the results of the present study.[45] Considering that the risk of Parkinson's disease was elevated only in patients who had diabetes mellitus for more than 10 years,[4] the age of onset in our data is also explainable. Nevertheless, a robust study is needed to better inform the evidence for this issue.

Our study has some limitations. First, because of the nature of this retrospective study, the lack of uniformity in baseline measurements and occurrences of LID and wearing-off based on medical records may have introduced potential bias. Second, the use of DPP4i can induce selection bias because there is preference of DPP4i in diabetic patients who are vulnerable to hypoglycaemia, such as elderly patients,[46] despite there being no specific limitations of DPP4i according to the guideline. Also, because of DPP4i's weight neutrality compared with other anti-diabetic agents, BMI tended to be lower in the PD-DM+/DPP4i+ group than in the PD-DM+/DPP4i+ group in our study, although this was not statistically significant. We minimized this possible bias as much as possible by controlling for BMI, or body weight in addition to age, vascular risk factors and WMH in sequential analyses. Third, the number of patients with diabetes and Parkinson's disease who were taking DPP4i and exhibited LID events was relatively small; therefore, caution should be exercised in the interpretation of our results. Further studies with larger numbers of patients with Parkinson's disease being treated with DPP4i are necessary to draw a more solid conclusion. Fourth, even though a consensus for clinically meaningful endpoints has not been established, LED and its longitudinal changes to control parkinsonian motor symptoms may indirectly reflect the severity of Parkinson's disease and disease progression marker.[40] However, since global disability in patients with Parkinson's disease is complexly influenced by motor and non-motor symptoms,[47] an increase in LED may not accurately reflect the progression of Parkinson's disease. Finally, while we adjusted for hypertension, dyslipidaemia, and total WMH, other vascular risk factors within the spectrum of metabolic syndromes and the degree of glycaemic control during follow-up may act as confounding factors. Furthermore, although most patients with DPP4i continued taking this drug, controlling the changes in the use of anti-diabetic drugs was challenging.

In conclusion, the present study demonstrated that DPP4i had a protective effect on the clinical prognosis as well as the baseline nigrostriatal striatal DAT availability in drug-naive diabetic patients with *de novo* Parkinson's disease.

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Competing interests

The authors report no competing interests.

Supplementary material

Supplementary material is available at *Brain* online.

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