Published in final edited form as:
Parkinsonism Relat Disord. 2013 May ; 19(5): 522–526. doi:10.1016/j.parkreldis.2013.01.016.

Diabetes is associated with Postural Instability and Gait Difficulty in Parkinson disease

Vikas Kotagal, MD[1,*], **Roger L. Albin, MD**[1,2], **Martijn L.T.M. Müller, PhD**[3], **Robert A. Koeppe, PhD**[3], **Kirk A. Frey, MD, PhD**[1,3], and **Nicolaas I. Bohnen, MD, PhD**[1,2,3]

[1]Department of Neurology, University of Michigan, Ann Arbor, MI

[2]Neurology Service and GRECC, VAAAHS, Ann Arbor, MI

[3]Department of Radiology, Division of Nuclear Medicine, University of Michigan, Ann Arbor, MI

Abstract

Background—Comorbid diabetes may be associated with more severe motor impairment in Parkinson disease. In normal elderly individuals, diabetes is associated with parkinsonian features, including gait difficulty and rigidity, though not tremor. Whether diabetes contributes to increased motor dysfunction in Parkinson disease by exacerbating nigrostriatal dopaminergic denervation or through intensification of extranigral pathology is unknown.

Methods—We performed a case-control study (n=39) involving 13 Parkinson disease subjects (age 66.4 yrs ± 5.5; duration of disease 6.9 yrs ± 4.4) with diabetes and 26 age, gender, and duration-of-disease-matched Parkinson disease controls without diabetes. All subjects underwent [^{11}C]dihydrotetrabenazine vesicular monoamine transporter type-2 positron emission tomography imaging to assess striatal dihydrotetrabenazine distribution volume ratio and Unified Parkinson disease rating scale motor examination to determine rigidity, bradykinesia, tremor, and postural instability and gait difficulty subscores. Magnetic resonance imaging scans were analyzed to assess leukoaraiosis burden.

Results—After controlling for nigrostriatal dopaminergic denervation, Parkinson disease subjects with diabetes displayed greater postural instability and gait difficulty subscores (t=3.81,

Corresponding Author: Vikas Kotagal, 2301 Commonwealth Blvd, Suite 1013, Ann Arbor MI, 48105, Phone: 734-764-6831, Fax: 734-647-8535, vikaskot@med.umich.edu.

Disclosures

None of the authors have conflict of interest regarding this specific study.
Additional disclosures for all authors are listed below.
Dr. Kotagal: Research support from National Institutes of Health T32 training grant (NS007222) and the American Academy of Neurology Clinical Research Training Fellowship.
Dr. Albin: Research support from the NIH and the VA. Dr. Albin has received compensation for expert witness testimony in litigation regarding dopamine agonist induced impulse control disorders. Dr. Albin serves on the editorial boards of Neurology, Experimental Neurology, and Neurobiology of Disease and has served on the Data Safety and Monitoring Boards for the QE3 and HORIZON trials.
Dr. Müller: Research support from the National Institutes of Health (NIH) and the Department of Veteran Affairs (VA)
Dr. Koeppe: Research support from NIH. Dr. Koeppe has served as a consultant for Johnson & Johnson and Merck and serves on the board of the International Society of Cerebral Blood Flow and Metabolism.
Dr. Frey: Research support from the NIH, GE Healthcare and AVID Radiopharmaceuticals (Eli Lilly subsidiary). Dr. Frey serves as a consultant for AVID Radiopharmaceuticals, MIMVista, Inc, Bayer-Schering and GE healthcare. He holds equity (common stock) in GE, Bristol-Myers, Merck and Novo-Nordisk.
Dr. Bohnen: Research support from the NIH and the VA.

p=0.0005). There were no differences in bradykinesia, rigidity, or tremor subscores between cases and controls. The association between diabetes and postural instability and gait difficulty persisted after controlling for comorbid hypertension and body mass index. Leukoaraiosis, distal vibratory sense, and levodopa dose equivalents did not differ significantly between cases and controls.

Conclusions—Diabetes may contribute to postural instability and gait difficulty in Parkinson disease through mechanisms other than nigrostriatal dopaminergic denervation.

Keywords

Diabetes; Parkinson disease; PET; Dopamine; Postural Instability; Gait Difficulty (PIGD)

Introduction

Motor subtype heterogeneity in idiopathic Parkinson disease (PD) is a common disease feature but the pathophysiologic factors that underlie motor heterogeneity are not well understood. Postural instability and gait difficulty (PIGD) is a motor subtype seen more frequently later in the disease course [1] and is associated with worse quality of life.[2] Although PD is historically thought of as disorder of nigrostriatal dopaminergic denervation, PIGD symptoms show a limited response to dopaminergic treatments.[3] Relatively poor response to dopaminergic treatments likely reflects the multifactorial etiology of PIGD in PD. Increased PIGD burden is perhaps the most significant motor feature contributing to higher disability scores on the Hoehn and Yahr scale [4] though the causes and factors related to PIGD progression in PD are not well understood.

The presence of diabetes in otherwise normal elderly individuals is associated with parkinsonian motor features, including gait disturbance and rigidity, though not tremor or bradykinesia.[5] Comorbid diabetes may contribute to motor impairments in PD. Cereda et al. reported a case-control study of PD subjects with and without antecedent diabetes and found that PD subjects with diabetes exhibited higher motor scores and received higher doses of dopaminergic medications.[6] A greater proportion of recently diagnosed PD subjects with antecedent diabetes were assessed as Hoehn and Yahr stage III (20.2%) compared to non-diabetic PD subjects (4.5%). These finding suggests that diabetes may preferentially exacerbate axial motor impairments. The more intensive dopamine replacement therapy documented by Cereda et al. in their diabetic PD subjects suggests that diabetes may be associated with greater nigrostriatal dopaminergic denervation. Axial motor dysfunctions, however, are generally less responsive to dopamine replacement and considerable data suggests that extranigral pathologies underlie axial motor dysfunctions.[7] We performed a case-control study of subjects with PD with and without a history of diabetes to determine if comorbid diabetes is associated with greater impairment of specific motor features of Parkinson disease, independent of the degree of nigrostriatal dopaminergic denervation.

Subjects and Methods

Subjects and clinical test battery

This case-control study involved 13 PD subjects with a history of diabetes (cases) and 26 PD subjects with no history of diabetes (controls). Diabetes status was determined through subject self-report in a standardized interview. All 13 cases had type-2 diabetes (DM2). Diabetic medications amongst cases included metformin (n = 9), sulfonylureas (n =5), insulin (n = 3), and thiazolidinediones (n =3). The two groups were matched with regards to age, gender, and duration of disease (Table 1). All subjects underwent a standardized

assessment of height and weight to calculate body mass index as well as a clinical evaluation to determine whether they carried a known history of comorbid hypertension.

All subjects met the UK Parkinson Disease Society Brain Bank Research Center clinical diagnostic criteria for PD.[8] Striatal [^{11}C]dihydrotetrabenazine (DTBZ) PET findings were consistent with the diagnosis of PD in all subjects. No subjects had evidence of previous large artery strokes on Magnetic Resonance Imaging (MRI). The Unified Parkinson Disease Rating Scale (UPDRS) was performed in the "off" state after withholding dopaminergic medications overnight. To explore associations between diabetes and motor heterogeneity in PD, UPDRS Motor exam subscores were calculated for the following categories: Bradykinesia (facial expression, right and left finger tapping, right and left hand movements, right and left pronation and supination of the hands, right and left toe tapping), Tremor (right and left upper extremity postural tremor, right and left upper extremity kinetic tremor, right and left arm rest tremor, right and left leg rest tremor), Rigidity (right arm, right leg, left arm, and left leg), and Postural Instability and Gait difficulty(posture, postural stability, gait).

Standard Protocol Approvals, Registrations, and Patient Consents

The study was approved by the Institutional Review Board of the University of Michigan. Written informed consent was obtained from all subjects.

Imaging techniques

DTBZ PET Imaging

DTBZ PET Imaging was performed in 3D imaging mode using an ECAT HR+ tomograph (Siemens Molecular Imaging, Inc., Knoxville, TN), which acquires 63 transaxial slices (slice thickness: 2.4 mm; intrinsic in-plane resolution: 4.1 mm full-width at half maximum (FWHM) over a 15.2 cm axial field-of-view. A NeuroShield (Scanwell Systems, Montreal, Canada) head-holder/ shielding unit was attached to the patient bed to reduce the contribution of detected photon events originating from the body outside the scanner field-of-view.[9] Before beginning radioligand injections, a 5-minute transmission scan was acquired using rotating ^{68}Ge rods for attenuation correction of emission data using the standard vendor-supplied segmentation and re-projection routines. All subjects were studied in the supine position, with eyes and ears unoccluded, resting quietly in a dimly lit room.

No-carrier-added (+)-[^{11}C]DTBZ (250 to 1000 Ci/mmol at the time of injection) was prepared as reported previously.[10] Dynamic PET scanning was performed for 60 minutes immediately following a bolus injection of 55% of 555 MBq (15 mCi) of (+)-[^{11}C]DTBZ dose (containing less than 50 micrograms of cold DTBZ mass) over the first 15 to 30 seconds of the study, while the remaining 45% of the dose was continuously infused over the next 60 minutes, resulting in stable arterial tracer levels and equilibrium with brain tracer levels after 30 minutes.[11] A series of 15 scan frames over 60 minutes were obtained as following: four × 30 seconds; three ×1 minute; two ×2.5 minutes; two ×5 minutes; and four ×10 minutes.

MRI Imaging

All subjects underwent brain magnetic resonance imaging on a 3T Philips Achieva system (Philips, Best, The Netherlands) utilizing either an 8-channel or 15-channel headcoil. A standard T1-weighted series of a 3D inversion recoveryprepared turbo-field-echo was performed in the sagittal plane using TR/TE/TI=9.8/4.6/1041ms; turbo factor=200; single average; FOV=240x200x160mm; acquired Matrix = 240x200. One hundred and sixty slices were reconstructed to 1mm isotropic resolution. This sequence maximizes contrast among

gray matter, leukoaraiosis, and CSF and provides high-resolution delineation of cortical and subcortical structures.

Leukoaraiosis burden MR imaging analysis

Supratentorial leukoaraiosis burden was estimated in 36 of 39 total subjects using an automated routine involving the analysis of co-registered FLAIR and SPGR MRI sequences for each subject.[12] This method was previously validated [13] and uses cerebellar white matter, a region relatively unaffected by age-associated leukoariosis, as a reference region for comparison of supratentorial hyperintensities. In comparison to visual quantitative rating scales for assessing MRI hyperintensities, our automated method may offer a more sensitive and uniform assessment of white matter burden. The cut-off of 1.65 SD was chosen on best visual discrimination of visually assessed focal white matter lesions and automatic detection by our software.

FLAIR based white matter hyperintensities were defined as 1.65 standard deviations greater than the reference region mean in intensity for bilateral frontal, parietal, temporal and occipital regions for each individual subject.[12] A similar automated analysis was conducted for the brainstem. The natural log of the number of white matter hyperintensities per region was calculated to allow normalization of data values. Supratentorial white matter volume was determined after image segmentation using the SPM5 software routine. We then used this volume to normalize the supratentorial white matter lesion burden. White matter hyperintensities were estimated qualitatively for the bilateral cerebellar hemispheres. Due to technical problems encountered in imaging processing, 3 subjects (2 cases & 1 control) were excluded from supratentorial white matter burden analysis and 4 subjects (2 cases & 2 controls) were excluded from brainstem analysis.

PET analysis

Interactive Data Language image analysis software (Research systems, Inc., Boulder, CO) was used to manually trace the striatal volume of interest (VOI) on MRI images to include the caudate nucleus and putamen of each hemisphere. Total neocortical VOI were defined using semi-automated threshold delineation of the cortical gray matter signal.

All image frames were spatially co-registered within subjects with a rigid-body transformation to reduce the effects of subject motion during the imaging session. These motion-corrected PET frames were spatially co-registered to the T1-weighted MR using standard co-registration procedures in SPM8b implemented in Matlab 2010b (The Mathworks). Time activity curves for each VOI were generated from the spatially aligned PET frames. ^{11}C-DTBZ VMAT2 distribution volume ratio (DVR) was then estimated by using the Logan plot graphical analysis method [14] with the time activity curves as the input function and neocortex as reference tissue.[11, 14, 15]

Vibratory detection analysis

Large fiber polyneuropathy may also contribute towards gait and balance problems in PD patients with comorbid diabetes. To account for the degree of large fiber polyneuropathy, a variable was created to estimate the degree of vibratory sense detection at the medial malleolus using a 128-Hertz tuning fork. Subjects were tested bilaterally and the mean duration of vibratory sense detection was calculated for each individual subject. Although this specific method has not been previously validated, a similar assessment measuring vibration sense detection at the great toe has shown favorable accuracy and reproducibility compared to monofilament testing in the detection of diabetic polyneuropathy.[16

Statistical analysis

Standard pooled-variance t-tests, chi-squared testing, and Fisher's exact test were used for comparison of demographic variables between groups (SAS version 9.3, SAS institute, Cary, North Carolina). Multivariable linear regression analysis was performed using bradykinesia, tremor, rigidity, and PIGD subscores as dependent variables in separate models with both diabetes status and striatal DTBZ DVR serving as covariates. T-values for the diabetes regression parameter estimate were calculated for each motor subtype to determine the influence of diabetes on motor subtype scores after controlling for degree of nigrostriatal dopaminergic denervation using the striatal DTBZ DVR variable. Due to the possibility that significant obesity may confound the clinical assessment of PIGD, and because BMI and a history of hypertension (HTN) were found to differ between cases and controls, a post-hoc analysis for the PIGD motor subtype was performed with the addition of BMI and a history of hypertension as covariates along with DTBZ DVR to determine if they altered the association between diabetes and PIGD.

Results

Subject comparisons

There were no significant differences between cases or controls in age, gender, duration of disease, or levodopa dose equivalents (Table 1). Hoehn and Yahr (HY) scores were slightly higher in the subjects with diabetes though this difference was not statistically significant (2.7 ±0.72 vs. 2.3 ±0.58). Diabetic subjects had more frequent comorbid hypertension (69.2% vs. 34.6%) and higher body mass index (BMI) scores (33.4 ± 6.0 vs. 27.6 ± 3.7). There were no significant differences in the degree of supratentorial or brainstem leukoaraiosis burden, or vibratory sense detection between cases and controls. Qualitative assessment of cerebellar hyperintensities showed no significant differences between diabetic subjects and those without diabetes (0.69 ±1.32 vs. 0.53 ± 1.13 cerebellar hyperintensities per subject; Fisher's exact test=0.03, p=0.87).

An exploratory subset analysis was conducted through a retrospective chart review to determine whether disease duration of either hypertension or diabetes for 2 years or greater is associated with worsened PIGD scores compared to those with a shorter known history of these two cardiovascular comorbidities. No differences were found in PIGD scores between subjects with a longer history of diabetes (5.1 ± 3.2 vs. 4.8 ± 2.1; n=7 vs. 4, t=0.18, p=0.86) or hypertension (3.9 ± 2.1 vs. 4.8 ± 2.3; n=10 vs. 6; t=0.88, p=0.40) compared to those with more recent diagnoses of either diabetes or hypertension. Classes of antihypertensive medications used amongst subjects (number of diabetic subjects vs non-diabetic subjects) are as follows: nitrates (1 vs. 0), angiotensin receptor blockers (1 vs. 1), beta-blockers (3 vs. 3), diuretics (3 vs. 6), calcium channel blockers (1 vs. 3), angiotensin converting enzyme inhibitors (5 vs. 2). There were no statistically significant differences between cases and controls in the use of any specific class of antihypertensive medication (Fisher's exact test=0.007, p=0.75).

Regression Analysis

Motor subscore values are presented in table 2. There were no significant differences seen in striatal DTBZ DVR values between cases and controls (Table 1). Individual multivariable linear regression models were performed with each of the 4 motor subscores serving as a dependent variable in separate models and striatal DTBZ and diabetes status serving as independent variables. Significant overall model effects were found for bradykinesia, rigidity, and PIGD subscores but not for tremor (Table 2) subscore. Diabetes status predicted PIGD subscores (t=3.81, p=0.0005) though not bradykinesia (t=1.99, p=0.055) or rigidity

subscores (t=1.38, p=0.176). Striatal DTBZ DVR was a significant independent predictor of bradykinesia, rigidity, and PIGD subscores

Post-hoc Analysis

We performed post-hoc analyses to determine whether BMI score or a history of comorbid hypertension might account for the increased PIGD burden seen amongst diabetic subjects. BMI and hypertension status were tested as coregressors along with diabetes status and striatal DTBZ DVR in a linear regression model using PIGD score as the dependent variable. Diabetes remained a significant predictor of PIGD score ($t = 2.29$, $p = 0.028$), after controlling for striatal DTBZ DVR, BMI, and a history of comorbid hypertension.

Discussion

We report that a history of diabetes in PD is associated with increased PIGD motor feature severity. The differences in PIGD motor feature severity between PD subjects and well-matched control PD patients without diabetes are not explained by differences in striatal dopaminergic denervation, leukoaraiosis, or large fiber polyneuropathy. The association between diabetes and PIGD persisted after controlling for BMI and comorbid hypertension. Our findings suggest that motor subtypes in PD patients with a history of diabetes may be linked to mechanisms of neural injury other than impairment of nigrostriatal dopamine projection system integrity.

PD has been associated with states of inflammation and oxidative stress [17] that could potentially be worsened by the presence of co-morbid diabetes.[18] The relationship between PD and diabetes is complex and inadequately explored. Impaired glucose metabolism may occur in anywhere from 50 to 80% of PD patients [19] though its role in PD pathogenesis is not well understood. Dopaminergic medications, including levodopa, may also promote a state of relative hyperglycemia.[20] However, diminished insulin-mediated glucose uptake has been shown even in early, treatment-naive PD subjects.[21] The recent work of Cereda et al. suggests that diabetes could influence the incidence and progression of PD. On the other hand, Miyake et al. have previously reported an inverse association between diabetes and the risk for incident PD.[22] Their analysis, however, adjusted for dietary glycemic intake and regular exercise, both of which varied between cases and controls. Our results suggest that irrespective of any effect on incidence, co-morbid diabetes influences important aspects of motor heterogeneity in PD. The higher UPDRS motor scores seen amongst diabetic subjects in the Cerada et al. cohort likely reflect increased PIGD burden rather than simply more severe and homogenous impairment across all parkinsonian motor domains.[23] The differences in dopaminergic therapy between diabetic subjects and non-diabetic subjects seen in their cohort but not ours may reflect differences in clinical practice regarding the use of dopaminergic medications. Cases and controls in our study showed no differences in nigrostriatal dopaminergic terminal integrity suggesting that extranigral pathology may mediate differential PIGD burden.

One obvious candidate for diabetes effects on PD phenotype would be increased co-morbid vascular pathology. A large postmortem study reported increased prevalence of vascular pathology, including lacunar strokes, leukoaraiosis lesions, amyloid angiopathy, and microhemorrhages in PD subjects compared to controls (44.0 % vs. 32.8%).[24] We reported previously that supratentorial leukoaraiosis is associated with axial motor features in PD.[12] Similarity between our cases and controls in supratentorial leukoaraiosis burden, however favors an alternative mechanism of extranigral neuronal injury.

Various lines of evidence have emerged from research on Alzheimer’s disease that tie together elements of the metabolic syndrome and neurodegeneration.[25] These include

dysregulation of tau protein, pathologic amyloid precursor protein processing, and cholinergic system dysfunction.[26, 27, 28] Although these pathologic factors appear to relate more closely to clinical features of cognitive impairment, PIGD is a known risk factor for dementia in PD [29] and may share mechanisms of neurodegeneration. A recent multi-center study reported that cardiovascular disease, diabetes, and non-tremor motor presentations of PD may each be risk factors for cognitive impairment.[30] Further research is needed to clarify whether diabetes and other cardiovascular comorbidities represent clear antecedent risk factors for specific PD motor features.

An alternative possibility is that impaired blood sugar regulation may be linked to mitochondrial pathology in PD. A phase-2 clinical trial of the oral antidiabetic medication pioglitazone, a peroxisome proliferator-activated receptor agonist that may augment mitochondrial metabolism, is currently underway in PD subjects.[31] Though improving mitochondrial pathology would not be expected to yield a PIGD-specific benefit, an overall improvement in systemic glucose metabolism might potentially influence the development of PIGD amongst PD subjects. These potential mechanisms are not mutually exclusive and could proceed in parallel.

Limitations of our study include our cross-sectional design which allows only for inferences of association rather than causation. Although there were no major differences in Hoehn and Yahr staging between groups, this may reflect the fact that Hoehn and Yahr staging depends heavily on performance of the single-item retropulsion test whereas the summed PIGD measure better incorporates gait function and has better metric statistical properties. Although our sample is small in size and features a higher proportion of male subjects, all subjects were recruited from the same clinical sites and careful multi-domain matching of cases and controls suggest that differential selection bias should not account for significant differences in motor impairment. Diabetes status was assessed by self-report rather than laboratory testing though recall bias would be expected to be similar amongst cases and controls. Other limitations include our use of a subjective and potentially imprecise vibratory sense detection variable as a proxy for assessing the severity of a large fiber diabetic neuropathy. The uniformity, however, of our clinical assessments is a relative strength with 35/39 subjects examined by the same investigator (N.B.). Cases and controls in our cohort showed no significant differences in levodopa-dose equivalents. Nevertheless, previous studies in PD subjects have suggested that higher doses of levodopa may associate with cyanocobalamin deficiency and an increased risk for a distal symmetric polyneuropathy,[32] which could potentially exacerbate gait impairment. PD subjects with comorbid diabetes may warrant more careful screening for vitamin B_{12} deficiency.

Diabetes may exacerbate specific nondopaminergic parkinsonian motor features. Further longitudinal studies are needed a) to determine whether impaired glucose metabolism represents an early risk factor for the development of parkinsonian gait and postural instability and b) to determine to what degree impaired glucose tolerance represents a risk factor for disease progression in early PD. Neuroprotective trials previously encountered difficulty assessing treatment efficacy in PD in part because of the lack of a clear biomarker with which to follow disease progression. Unlike many other genetic or remote exposure-based risk factors associated with PD, impaired glucose control is potentially modifiable and thus warrants further study. Clinical trials exploring central nervous system-specific therapies aimed at improving glucose metabolism are already underway in Alzheimer's disease [33] and may represent a useful therapeutic strategy in the pursuit of neuroprotection in PD.

Acknowledgments

The authors thank Christine Minderovic, Virginia Rogers, the PET technologists, cyclotron operators, and chemists, for their assistance.

Funding

Funding for this study was provided by the Michael J. Fox Foundation, the Department of Veterans Affairs, and NIH grants P01 NS015655 & R01 NS070856.

References

1. Hoehn MM, Yahr MD. Parkinsonism: onset, progression, and mortality. Neurology. 1967 Nov; 57 Suppl 3(10):S11–S26. [PubMed: 11775596]
2. Hariz GM, Forsgren L. Activities of daily living and quality of life in persons with newly diagnosed Parkinson's disease according to subtype of disease, and in comparison to healthy controls. Acta Neurol Scand. 2011 Jan; 123(1):20–27. [PubMed: 20199514]
3. Bohnen NI, Cham R. Postural control, gait, and dopamine functions in parkinsonian movement disorders. Clin Geriatr Med. 2006 Nov; 22(4):797–812. vi. [PubMed: 17000336]
4. Goetz CG, Poewe W, Rascol O, Sampaio C, Stebbins GT, Counsell C, et al. Movement Disorder Society Task Force report on the Hoehn and Yahr staging scale: status and recommendations. Mov Disord. 2004 Sep; 19(9):1020–1028. [PubMed: 15372591]
5. Arvanitakis Z, Wilson RS, Schneider JA, Bienias JL, Evans DA, Bennett DA. Diabetes mellitus and progression of rigidity and gait disturbance in older persons. Neurology. 2004 Sep 28; 63(6):996–1001. [PubMed: 15452289]
6. Cereda E, Barichella M, Cassani E, Caccialanza R, Pezzoli G. Clinical features of Parkinson disease when onset of diabetes came first: A case-control study. Neurology. 2012 Apr 25.
7. Devos D, Defebvre L, Bordet R. Dopaminergic and non-dopaminergic pharmacological hypotheses for gait disorders in Parkinson's disease. Fundam Clin Pharmacol. 2010 Aug; 24(4):407–421. [PubMed: 20163480]
8. Hughes AJ, Daniel SE, Kilford L, Lees AJ. Accuracy of clinical diagnosis of idiopathic Parkinson's disease: a clinico-pathological study of 100 cases. J Neurol Neurosurg Psychiatry. 1992 Mar; 55(3): 181–184. [PubMed: 1564476]
9. Thompson CJ, Kecani S, Boelen S. Evaluation of a neck-shield for use during neurological studies with a whole-body. PET scanner IEEE Trans Nucl Sci. 2001; 48:1512–1517.
10. Jewett DM, Kilbourn MR, Lee LC. A simple synthesis of [11C]dihydrotetrabenazine (DTBZ). Nucl Med Biol. 1997 Feb; 24(2):197–199. [PubMed: 9089713]
11. Innis RB, Cunningham VJ, Delforge J, Fujita M, Gjedde A, Gunn RN, et al. Consensus nomenclature for in vivo imaging of reversibly binding radioligands. J Cereb Blood Flow Metab. 2007 Sep; 27(9):1533–1539. [PubMed: 17519979]
12. Bohnen NI, Muller ML, Zarzhevsky N, Koeppe RA, Bogan CW, Kilbourn MR, et al. Leucoaraiosis, nigrostriatal denervation and motor symptoms in Parkinson's disease. Brain. 2011 Aug; 134(Pt 8):2358–2365. [PubMed: 21653540]
13. Bohnen NI, Bogan CW, Muller ML. Frontal and periventricular brain white matter lesions and cortical deafferentation of cholinergic and other neuromodulatory axonal projections. Eur Neurol J. 2009 Sep; 1(1):33–50. [PubMed: 22763426]
14. Logan J, Fowler JS, Volkow ND, Wang GJ, Ding YS, Alexoff DL. Distribution volume ratios without blood sampling from graphical analysis of PET data. J Cereb Blood Flow Metab. 1996; 16(5):834–840. [PubMed: 8784228]
15. Koeppe RA, Frey KA, Kuhl DE, Kilbourn MR. Assessment of extrastriatal vesicular monoamine transporter binding site density using stereoisomers of [11C]dihydrotetrabenazine. J Cereb Blood Flow Metab. 1999; 19(12):1376–1384. [PubMed: 10598942]
16. Oyer DS, Saxon D, Shah A. Quantitative assessment of diabetic peripheral neuropathy with use of the clanging tuning fork test. Endocr Pract. 2007 Jan-Feb;13(1):5–10. [PubMed: 17360294]

17. Tansey MG, Goldberg MS. Neuroinflammation in Parkinson's disease: its role in neuronal death and implications for therapeutic intervention. Neurobiol Dis. 2010 Mar; 37(3):510–518. [PubMed: 19913097]
18. Fung A, Vizcaychipi M, Lloyd D, Wan Y, Ma D. Central nervous system inflammation in disease related conditions: mechanistic prospects. Brain Res. 2012 Mar 29.1446:144–155. [PubMed: 22342162]
19. Sandyk R. The relationship between diabetes mellitus and Parkinson's disease. Int J Neurosci. 1993 Mar-Apr;69(1–4):125–130. [PubMed: 8082998]
20. Craft S, Watson GS. Insulin and neurodegenerative disease: shared and specific mechanisms. Lancet Neurol. 2004 Mar; 3(3):169–178. [PubMed: 14980532]
21. Van Woert MH, Mueller PS. Glucose, insulin, and free fatty acid metabolism in Parkinson's disease treated with levodopa. Clin Pharmacol Ther. 1971 Mar-Apr;12(2):360–367. [PubMed: 5577484]
22. Miyake Y, Tanaka K, Fukushima W, Sasaki S, Kiyohara C, Tsuboi Y, et al. Case-control study of risk of Parkinson's disease in relation to hypertension, hypercholesterolemia, and diabetes in Japan. J Neurol Sci. 2010 Jun 15; 293(1–2):82–86. [PubMed: 20347450]
23. Kawabe K, Ikeda K, Iwasaki Y, Cereda E, Barichella M, Pezzoli G, et al. Clinical features of Parkinson disease when onset of diabetes came first: a case-control study. Neurology. 2012 Oct 23; 79(17):1835–1836. [PubMed: 23091078]
24. Jellinger KA. Prevalence of cerebrovascular lesions in Parkinson's disease. A postmortem study. Acta Neuropathol. 2003 May; 105(5):415–419. [PubMed: 12677440]
25. Umegaki H. Neurodegeneration in diabetes mellitus. Adv Exp Med Biol. 2012; 724:258–265. [PubMed: 22411248]
26. Bosco D, Fava A, Plastino M, Montalcini T, Pujia A. Possible implications of insulin resistance and glucose metabolism in Alzheimer's disease pathogenesis. J Cell Mol Med. 2011 Sep; 15(9): 1807–1821. [PubMed: 21435176]
27. Muller ML, Albin RL, Koeppe RA, Frey KA, Bohnen NI. Comorbid cortical β-amyloid plaques affect postural instability and gait disorder symptoms in Parkinson disease. Society of Nuclear Medicine Meeting. 2012 Jun 12.
28. Pahapill PA, Lozano AM. The pedunculopontine nucleus and Parkinson's disease. Brain. 2000 Sep; 123(Pt 9):1767–1783. [PubMed: 10960043]
29. Alves G, Larsen JP, Emre M, Wentzel-Larsen T, Aarsland D. Changes in motor subtype and risk for incident dementia in Parkinson's disease. Mov Disord. 2006 Aug; 21(8):1123–1130. [PubMed: 16637023]
30. Jones JD, Malaty I, Price CC, Okun MS, Bowers D. Health comorbidities and cognition in 1948 patients with idiopathic Parkinson's disease. Parkinsonism Relat Disord. 2012 Jul 7.
31. Rodnitzky RL. Upcoming treatments in Parkinson's disease, including gene therapy. Parkinsonism Relat Disord. 2012 Jan. Suppl 1(18):S37–S40. [PubMed: 22166449]
32. Rajabally YA, Martey J. Neuropathy in Parkinson disease: prevalence and determinants. Neurology. 2011 Nov 29; 77(22):1947–1950. [PubMed: 22049200]
33. Craft S, Baker LD, Montine TJ, Minoshima S, Watson GS, Claxton A, et al. Intranasal insulin therapy for Alzheimer disease and amnestic mild cognitive impairment: a pilot clinical trial. Arch Neurol. 2012 Jan; 69(1):29–38. [PubMed: 21911655]

Table 1

Demographic profiles of Cases and Controls

	Mean ± SD		
	PD subjects with Diabetes (n = 13)	**PD subjects without Diabetes (n = 26)**	**Group comparison [significance]**
Gender (M/F)	11/2	22/4	$\chi^2 = 0.00$, p = 1.00
Mean Age (yrs)	66.5 ± 6.4	66.3 ± 5.1	t = 0.14, p = 0.89
Mean Duration of Disease (yrs)	6.84 ± 4.7	6.98 ± 4.4	t = 0.09, p = 0.93
Mean Hoehn & Yahr scale	2.7 ± 0.72	2.3 ± 0.58	t = 1.62, p = 0.11
Mean Striatal DTBZ DVR	2.10 ± 0.51	1.84 ± 0.26	$t^* = 1.77$, p = 0.10
Body Mass Index (BMI)	33.4 ± 6.0	27.6 ± 3.7	t = 3.73, p = 0.0006
History of statin use	46.2%	34.6%	$\chi^2 = 0.49$, p = 0.49
History of Hypertension	69.2%	34.6%	$\chi^2 = 4.2$ p = 0.04
Levodopa dose equivalency	784.2 ± 745.0	886.8 ± 681.0	t = 0.43, p = 0.67
Supratentorial White matter hyperintensity burden (n = 36)	−5.37± 2.3	−5.24 ± 1.6	t = 0.12, p = 0.91
Brainstem White matter hyperintensity burden (n = 35)	−3.75 ± 4.4	−3.78 ± 4.3	t = 0.08, p = 0.93
Mean Vibratory sense duration (seconds)	8.4 ± 4.5	8.8 ± 4.0	t = 0.29, p = 0.77
Mean Global Cognitive Z-score (n = 37)	−0.94 ± 0.85	−0.39 ± 0.95	t = 1.70, p = 0.10

Legend: PD = Parkinson disease, DTBZ DVR = [^{11}C]dihydrotetrabenazine distribution volume ratio,

*Satterthwaite t-test due to unequal variance

Table 2

Regression Analyses

UPDRS Motor Subscore Categories	Total score for PD subjects with Diabetes (±SD)	Total score for PD subjects without Diabetes (±SD)	Overall Model	Diabetes status	Striatum DTBZ DVR
Bradykinesia	13.7 ± 6.2	12.3 ± 6.2	F = 7.25, p = 0.0023	t = 1.99, p = 0.055	t = −3.73, p =0.0007
Rigidity	5.0 ± 2.6	4.6 ± 2.5	F = 3.32, p =0.048	t = 1.38, p = 0.176	t = −2.51, p = 0.017
PIGD	5.0 ± 2.5	3.6 ± 2.0	F = 14.1, p <0.0001	t = 3.81, p =0.0005	t = −4.75, p < 0.0001
Tremor	5.2 ± 4.2	3.9 ± 3.6	F = 0.48, p = 0.62	NA	NA

Legend: Legend: PD = Parkinson disease, DTBZ DVR = [^{11}C]dihydrotetrabenazine distribution volume ratio, N.A. = Not applicable.