Neurology Asia 2022; 27(2) : 345 – 352

A negative effect of poorly controlled diabetes mellitus on the treatment of Parkinson's disease

[1]Jae Jung Lee, [2]Jin Yong Hong, [3]Jong Sam Baik

[1]Department of Neurology, Ilsan Paik Hospital, Inje University College of Medicine, Goyang; [2]Department of Neurology, Wonju Seveance Christian Hospital, Yonsei University Wonju College of Medicine, Wonju; [3]Department of Neurology, Sanggye Paik Hospital, Inje University College of Medicine, Seoul, Korea

Abstract

Objective: Converging evidence ranging from basic pathophysiology to epidemiological and clinical data has described a potential relationship between Parkinson's disease (PD) and diabetes mellitus (DM). This study aimed to explore the effect of sugar control on the treatment of motor manifestations in PD. *Methods:* A total of 124 *de novo* PD patients were included in the study. The participants were classified into three groups, non-DM (n = 45), well-controlled (n = 41) and less-controlled DM (n = 38), based on the glycated hemoglobin (HbA1c) cut-off value of 7.0. Clinical parameters including Unified Parkinson's Disease Rating Scale (UPDRS), Mini-Mental State Examination (MMSE), and Montreal Cognitive Assessment (MoCA) were evaluated serial twice apart from 1 year. *Results:* The less-controlled DM group revealed significantly lesser improvement in UPDRS III (baseline to follow-up, 38.1 ± 9.6 to 29.9 ± 7.8; $p < 0.001$) than those of either non-DM (36.6 ± 8.9 to 22.9 ± 5.7) and well-controlled group (37.0 ± 8.8 to 24.0 ± 6.0) after standard PD treatment for 1 year. A higher HbA1c was correlated with a lesser decline of UPDRS III (β, 0.47; $p < 0.001$) among PD with DM population. Less-controlled DM effectively predicted a lesser decline of UPDRS III ($\beta = + 5.426$; $p < 0.001$).
Conclusions: Our results demonstrated a potential negative effect of sub-optimally controlled blood sugar on treating motor manifestations of PD. Careful glucose management might be a beneficial strategy to improve the burden of motor symptoms in PD who have coexisting DM.

Keywords: Parkinson's disease, diabetes mellitus, glycated hemoglobin, glucose, treatment.

INTRODUCTION

A hidden association between Parkinson's disease (PD) and diabetes mellitus (DM) can be speculated despite the two entities are seemingly unrelated to each other. A growing body of evidence ranging from a basic experiment to epidemiological or clinical data has suggested a potential relationship between the two disorders. The mean prevalence of PD[1], over 10%, in populations with DM has been demonstrated to be slightly higher than that in the general populations.[2] Conversely, the incidence of DM has also been reported to be modestly but more frequent in the PD populations than in the healthy populations.[3] Of note, socio-economic alterations including rapid industrialization and urbanization in conjunction with westernized dietary pattern are leading to the higher rates of DM in Asian-Pacific region.[4] Each disorder shares a few risk factors in common, such as aging[5,6], depression[7,8], pesticide[6,9] vitamin D deficiency[10,11], and metabolic disorders.[12] However, the issue of which one came first remains unclear. A few epidemiological or observational studies have demonstrated the DM as a preceding risk factor for the PD[3] or vice versa.[1] Besides, an independent[13] or even an inverse association[14] has also been reported between the two conditions. According to the advanced prospective cohort studies, diabetic populations demonstrated almost 80% higher risk for the development of PD than non-diabetic populations.[3] A meta-analysis from 1.7 million individuals revealed an increased risk of PD by 40% in diabetic groups.[15] Although some differences among the studies in terms of study design, methods, analysis, and study population do

Address correspondence to: Jong Sam Baik, MD, PhD, Department of Neurology, Sanggye Paik Hospital, Inje University College of Medicine, 1342 Dongilro, Nowongu, Seoul, Korea. 01757. Tel: +82-2-950-1090, E-mail: jsbaik@paik.ac.kr

Date of Submission: 15 April 2021; Date of Acceptance: 3 October 2021

https://doi.org/10.54029/2022vsp

exist, we can presume the putative link between the two morbidities.

PD and DM share very similar mechanisms of etiopathogenesis, such as the protein misfolding error. Amylin and islet amyloid polypeptide accumulated in the central nervous system as well as the pancreatic islet cell lead to toxic neuronal degenerations[16] which is very similar to the misfolding and toxic aggregation of the α-synuclein taking place in the PD. Additional mechanisms of action including insulin resistance, mitochondrial dysfunction, and neuroinflammation also play a certain role in the progression of two disorders.[17]

Fewer investigations on the longitudinal relationship between DM and clinical manifestations of PD have been performed. Therefore, we examined the effect of sugar control on the treatment of clinical manifestations of PD who have a comorbid DM.

METHODS

Study populations

In the current retrospective cohort study, the patients were consecutively selected from the longitudinal joint cohort registry of the movement disorders run by the department of neurology in Ilsan Paik and Sanggye Paik Hospital. All individuals were patients with *de novo* PD who were previously diagnosed with DM or not. Clinical diagnosis of PD was based on the diagnostic criteria of United Kingdom PD Brain Bank Society.[18] Patients were excluded when they met 1) clinical features of atypical parkinsonism, 2) any kind of secondary parkinsonism, 3) delayed diagnosis of DM following PD, and 4) comorbid DM gastropathy or absorption disorders. Additionally, baseline neurologic examination screened out the patients who had any type of neurologic deficit including somatic motor or sensory deficit. Imaging studies were performed for every participant including both [^{18}F] N-(3-Fluoropropyl)-2β-carbon ethoxy-3β-(4-iodophenyl) nortropane positron emission tomography scan and brain magnetic resonance imaging at the time of their diagnoses. The institutional review board approved the clinical investigation of study participants. (Approval identifier, 2020-07-014)

Clinical assessment

All targeted patients were classified into three subgroups including non-DM, well-controlled (glycated hemoglobin (HbA1c) ≤ 7.0) and less-controlled DM (HbA1c > 7.0) on the basis of the mean HbA1c value of 7.0 which were serially assessed during 1 year of follow-up. Evaluation of Unified Parkinson's Disease Rating Scale (UPDRS), Korean version of the Mini Mental State Examination (MMSE), and Montreal Cognitive Assessment (MoCA) were performed twice, at baseline and 1 year later, respectively. UPDRS was examined during the "off" state at the baseline, while during the "on" state at the follow-up. Every patient received a standard treatment for PD which was individually tailored and optimally scheduled throughout the follow-up period.

UPDRS was employed to determine the motor subtype of each PD individual following the original classification method.[19] The ratio of the tremor (item 16 in the UPDRS II and item 20 to 21 in the UPDRS III) to PIGD (item 13 to 15 in the UPDRS II and item 29 to 30 in the UPDRS III) sub-scores defined the case by whom would fall into tremor-dominant (≥1.5), postural instability/gait difficulty (≤1.0), or indeterminate (>1.0 and <1.5) subtype.

Statistical analysis

Data were analyzed longitudinally and cross-sectionally. To assess the demographic characteristics, analysis of variance and Cochran-Mantel-Haenszel test were performed to compare group difference for each variable. The normality of the continuous variable was evaluated using the Kolmogorov–Smirnov test. Comparison of group difference in the longitudinal changes of clinical parameters were analyzed using repeated measures analysis of variance with the Bonferroni correction for family-wise error rate. Additionally, Pearson's correlation was performed to examine the relationship between the HbA1c and longitudinal changes of the UPDRS III. Multiple linear regression analysis was carried out to determine the contributing factor for changes in the UPDRS III, which employed covariates including group (HbA1c < 7.0 or otherwise), age, sex, disease duration, hypertension, hyperlipidemia, levodopa equivalent daily dose (LEDD), motor subtype, and UPDRS II and III scores at baseline. A two-tailed level of $p < 0.05$ was considered to be significant. All statistical analyses were performed using R (R version 3.6.0; R Foundation for Statistical Computing, Vienna, Austria) and Rex (Version 3.0.3, RexSoft Inc., Seoul, Korea).[20]

RESULTS

Demographic characteristics

A total of 124 PD patients, of whom 45 non-DM, 41 well-controlled and 38 less-controlled DM, were included in the present study. Demographic characteristics and clinical data are summarized in the table 1. The mean HbA1c was 6.3 ± 0.3 and 8.1 ± 0.7 in the well- and less-controlled DM group, respectively. Multiple assessment of the serum HbA1c was completed twice in 39 and thrice in 16 out of the 41 well-controlled, while in 36 and in 29 out of the 38 patients in the less-controlled group, respectively. LEDD, which was determined after 1 year from the initial PD diagnosis, and the profile of medications for respective PD and DM are presented in the table 2. We did not find any difference between well- vs less-controlled DM group. Among DM subpopulations, a majority of patients were being treated with polytherapy (well- vs less-controlled DM group; n, 36/41 (87.8%) vs 3/38 (86.8)), of whom subset of patients were combined with insulin treatment (8/41 (19.5) vs 10/38 (26.3)). A section of DM patients who underwent oral medication alone (31/41 (75.6%) vs 33/38 (86.8%)) or insulin treatment alone (2/41 (4.9%) vs 1/38 (2.6%)) did not demonstrate group difference either. A portion of participants who spared levodopa during the whole follow-up period did not present between-group differences (n (%); non-DM, 9/45 (20%); well-controlled DM, 10/43 (23.3%); less-controlled DM, 9/36 (25.0%)). Moreover, we did not find any differences either as to the distribution of motor subtypes among each group.

Comparative analysis for longitudinal changes of clinical parameters of Parkinson's disease

No significant difference in the longitudinal changes of the UPDRS I (gap, non-DM vs well-controlled vs less-controlled, -0.07 ± 1.86 vs 0.29 ± 2.48 vs 0.55 ± 2.09; $p = 0.422$) and UPDRS II (-1.64 ± 3.84 vs -2.02 ± 4.85 vs -1.32 ± 3.94; $p = 0.758$) were noted between the two groups. (Table 3) Meanwhile, the UPDRS III exhibited significant longitudinal decline within each three group after 1 year (non-DM group, -13.60 ± 5.39, $p < 0.001$; well-controlled group, -13.02 ± 6.14, $p < 0.001$; less-controlled group, -8.21 ± 4.08, $p < 0.001$), yet the less-controlled group alone demonstrated a lesser decline than otherwise two groups (group by time interaction, $p < 0.001$). The UPDRS IV score did not differ among the groups following 1 year of standard PD treatment. Longitudinal alterations of MMSE and MoCA were not evident within each group and not even different between the groups either.

Contribution of sugar control on treatment of motor manifestations in PD

A scatter plot of HbA1c versus longitudinal

Table 1: Baseline demographics

	Non-DM (n = 45)	Well-controlled DM (n = 41)	Less-controlled DM (n = 38)	*p*
Age, yr	63.7 ± 10.8	64.1 ± 11.3	65.9 ± 9.5	0.621
Male, n (%)	25 (55.6)	19 (46.3)	20 (52.6)	0.761
Age of onset, yr	62.7 ± 11.1	63.1 ± 11.6	64.7 ± 9.6	0.678
Disease duration, yr				
Parkinson's disease	1.1 ± 0.8	1.1 ± 0.9	1.2 ± 0.5	0.837
Diabetes mellitus		3.6 ± 2.3	3.5 ± 2.9	0.918
Education, yr	9.2 ± 5.2	9.1 ± 5.1	9.2 ± 5.5	0.986
Hypertension, n (%)	20 (44.4)	19 (46.3)	22 (57.9)	0.233
Hyperlipidemia, n (%)	15 (33.3)	17 (41.5)	21 (55.3)	0.082
Motor subtype				
Tremor dominant, n (%)	12 (26.7)	8 (19.5)	9 (23.7)	0.552
PIGD, n (%)	23 (51.1)	24 (58.5)	21 (55.3)	0.683
Indeterminate, n (%)	10 (22.2)	9 (22.0)	8 (21.1)	0.837

DM, diabetes mellitus; PIGD, postural instability/gait difficulty.

Table 2: The medication profile of respective Parkinson's disease and diabetes mellitus in the entire study population

	Non-DM (n = 45)	Well-controlled DM (n = 41)	Less-controlled DM (n = 38)	p
LEDD, mg	411.8 ± 95.5	401.4 ± 105.0	422.2 ± 130.6	0.704
Levodopa, n (%)	34 (75.6)	30 (73.2)	29 (76.3)	0.742
Dopamine agonist, n (%)	21 (46.7)	17 (41.5)	15 (39.5)	0.621
MAO-B inhibitor, n (%)	15 (33.3)	16 (41.9)	14 (33.3)	0.531
COMT inhibitor, n (%)	5 (11.1)	3 (7.0)	2 (5.6)	0.736
Amantadine, n (%)	2 (4.4)	3 (7.0)	2 (5.6)	0.813
Biguanides, n (%)		32 (78.0)	29 (76.3)	0.841
Sulfonylureas, n (%)		15 (36.6)	14 (36.8)	0.806
Thiazolidinediones, n (%)		3 (7.3)	1 (2.6)	0.453
DPP-4 inhibitors, n (%)		23 (56.1)	20 (52.6)	0.678
SGLT2 inhibitors, n (%)		8 (19.5)	7 (18.4)	0.716
Insulins, n (%)		10 (24.4)	11 (28.9)	0.639

LEDD, levodopa equivalent daily dose; MAO-B, monoamine oxidase-B; DPP-4, dipeptidyl peptidase-4; SGLT2, sodium glucose co-transporter 2.

changes in UPDRS III demonstrated that higher HbA1c was correlated well with lesser decline in UPDRS III (coefficient of correlation r, 0.47; $p < 0.001$). (Figure 1) The result of multiple linear regression is presented in the Table 4. Univariate analysis revealed that the less-controlled group was strongly associated with the lesser decline of UPDRS III ($\beta = +4.814, p < 0.001$). Furthermore, it remained a strong predictor ($\beta = +5.426, p < 0.001$) even after further control of covariates including age, sex, disease duration, hypertension, hyperlipidemia, LEDD, motor subtype, and scores of UPDRS II and III at the baseline.

DISCUSSION

Based on the comparative analysis among PD with or without DM, the present study demonstrated that the less-controlled DM patients might experience poor improvements in the motor manifestation albeit the standard treatment of PD. The HbA1c level was correlated very well

Table 3: Comparison of longitudinal changes of clinical parameters in Parkinson's disease with or without diabetes mellitus

	Non-DM (n = 45)		Well-controlled DM (n = 41)		Less-controlled DM (n = 38)		
	Baseline	1-year-after	Baseline	1-year-after	Baseline	1-year-after	p*
UPDRS I	2.6 ± 1.7	2.5 ± 1.9	2.4 ± 1.9	2.7 ± 2.1	2.5 ± 2.0	3.1 ± 2.1	0.422
UPDRS II	7.6 ± 5.6	5.9 ± 4.1	7.5 ± 6.3	5.4 ± 3.9	8.2 ± 5.8	6.5 ± 3.9	0.758
UPDRS III	36.6 ± 8.9	22.9 ± 5.7	37.0 ± 8.8	24.0 ± 6.0	38.1 ± 9.6	29.9 ± 7.8	< 0.001
UPDRS IV		2.0 ± 1.3		1.8 ± 1.5		2.0 ± 1.2	0.790
MMSE	24.9 ± 3.7	23.8 ± 3.9	25.2 ± 3.6	23.8 ± 3.9	23.9 ± 3.9	22.8 ± 4.6	0.651
MoCA	19.9 ± 4.2	18.3 ± 4.4	20.2 ± 4.3	18.5 ± 4.7	19.1 ± 4.7	17.7 ± 5.3	0.757

*Group by time interaction. Correction for multiplicity by Bonferroni method was applied ($p < 0.0083$).
DM, diabetes mellitus; UPDRS, unified Parkinson's disease Rating Scale; MMSE, mini mental state examination; MoCA, Montreal cognitive assessment.

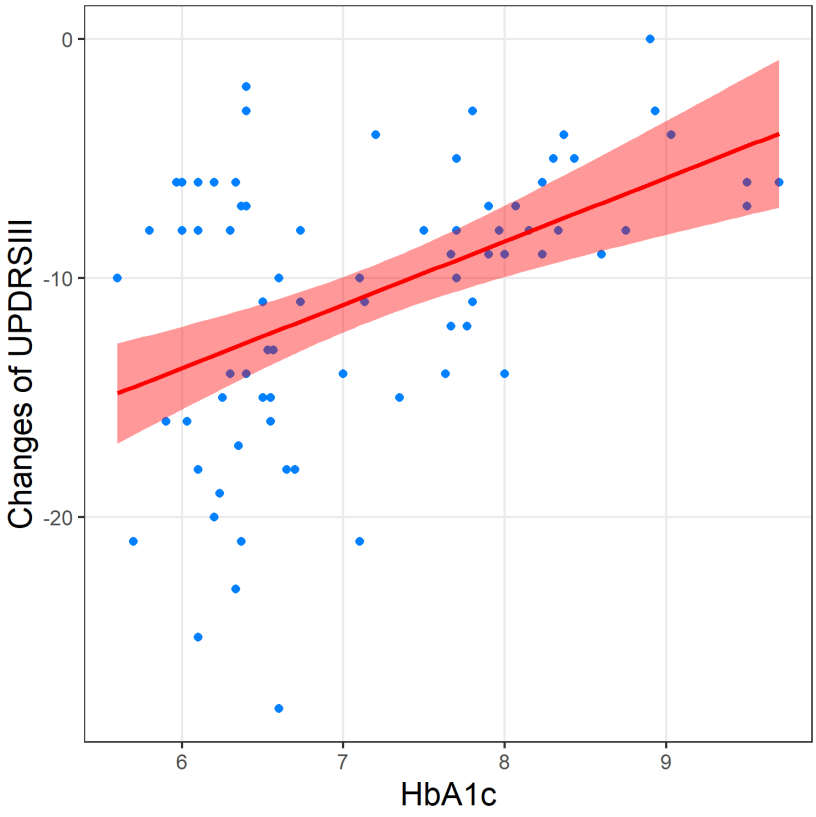

Figure 1. Relationship between mean HbA1c and changes of Unified Parkinson's Disease Rating Scale III score over 1 year.

Table 4: Potential effect of sugar control on longitudinal changes of UPDRS III in Parkinson's disease

	Crude			Adjusted	
	***β* (SE)**	***p***		***β* (SE)**	***p***
Group			Group		
Well-controlled	Reference		Well-controlled	Reference	
Less-controlled	4.814 (1.183)	< 0.001	Less-controlled	5.426 (0.859)	< 0.001
			Age	-0.164 (0.057)	0.006
			Sex	0.384 (0.888)	0.667
			Disease duration	0.104 (0.637)	0.871
			HTN	-0.946 (0.988)	0.342
			HL	0.813 (0.968)	0.404
			LEDD	-0.001 (0.004)	0.799
			Motor subtype		
			Tremor	Reference	
			PIGD	-0.668 (1.090)	0.542
			Indeterminate	-1.528 (1.604)	0.344
			UPDRS II, baseline	-0.007 (0.080)	0.934
			UPDRS III, baseline	-0.299 (0.053)	< 0.001

HTN, hypertension; HL, hyperlipidemia; LEDD, levodopa equivalent daily dose; PIGD, postural instability/gait difficulty; UPDRS, unified Parkinson's disease Rating Scale.

with the extent of motor improvement over time. Sugar control was observed to be a potential contributing factor in the treatment of motor manifestations in PD.

Mounting evidence has underpin the implication of the clinical aspect between the PD and DM. PD patients with DM showed worse cognitive performance[21,22] and exhibited corresponding structural abnormalities, such as fronto-temporal cortical atrophy[21] or ischemic insult across the white matter regions.[22] Exenatide, a glucagon-like peptide-1 receptor agonist, has demonstrated a promising effect of significant motor improvement in the advanced PD.[23] Experimental studies presented metformin[24] and thiazolidinediones[25] to undermine the oxidative stress and mitochondrial dysfunction, that eventually led to the potential protection for dopaminergic neurons in the striatum. Functional neuroimaging studies found that the striatal dopamine transporter binding was lower in the patients with PD having DM[21,26], which were even observed slower rate of decline following treatment with exenatide.[23]

However, there has been a paucity of studies concerning the motor manifestations of PD. Patients with comorbid PD and DM had worse performance on either motor symptoms and activities of daily living.[27] They featured noticeable impairments in terms of the balance and gait in particular.[28] One observational study reported an onset of motor complication 1 year earlier in the group with DM comorbidity.[29] However, a majority of the previous studies were based on the cross-sectional design of case-control comparison, which offered some limitation in the interpretation of their outcomes. One longitudinal study[26] where examined the data from the Parkinson's Progression Markers Initiative have demonstrated that the DM was associated with faster progression in both the motor and cognitive function over a 36-month study period in the *drug naïve* early stage PD. Notably, PD suggesting pathology, including lower striatal dopamine and greater amounts of tau in cerebrospinal fluid, were even evident in the PD with DM comorbidity. Our longitudinal data presenting negative effect of sub-optimally controlled blood sugar on motor control in PD is in line with such outcomes and might underpin the potential detrimental effect of DM on PD.

The specific mechanism of action of high serum glucose on the motor manifestation in PD is not fully understood yet. However, a number of precedent studies have suggested the negative effect of high glucose on the dopaminergic neurons in the nigrostriatal pathway. Experimental models using rat demonstrated hyperglycemia-induced attenuation of dopaminergic firing in the substantia nigra[30], which was resolved by the insulin treatment.[17] Renaud *et al*[31] investigated altering patterns of the dopaminergic pathway from hyperglycemia-induced rat during a 6-month observation period. Their immunohistochemical analyses revealed preferential loss of the dopaminergic neurons and an increased number of the astroglial cells in the both substantia nigra pars compacta (SNc) and dorsal striatum, although the ventral tegmental area was less affected. The hyperglycemic rats even exhibited deteriorated motor behaviors, including delayed initiation and slowed adjustment, which are reminiscent of the classic clinical features of PD. Alternatively, methylglyoxal, a highly reactive glycating agent, may be another key compound accounting for the effect of DM on the motor pathway in PD. A structural similarity does exist between the methylglyoxal and 3,4-dihydroxyphenylacetaldehyde or dopamine-quinone, an auto-oxidized toxic reactive oxygen species derived from the dopamine placed in the nigrostriatal pathway.[32] Such an oxidative effect has already been reported from the dopaminergic neurons in the SNc[33] and further implicated to the disruption of α-synuclein clearance in the transgenic mice model expressing human α synuclein.[34]

Insulin also accounts for the role of the uncontrolled glucose on PD, which takes part around the intracellular organelle, the mitochondria. A peroxisome proliferator activated receptor gamma coactivator 1 alpha (PGC1α) is one of the essential enzyme regulators to suppress the reactive oxygen species in the mitochondria.[35] The PGC1α is decreased in the both insulin resistant individuals[36] and patient with PD.[37] In addition, parkin interacting substrate, a zinc-finger protein that suppresses the expression of PGC1α, was found to be significantly upregulated in the SNc of patients with PD, which may result in neurodegeneration by the inactivation of parkin protein. Otherwise, given the neurotrophic effect of insulin on the neural tissue, a defective insulin signaling , such as insulin resistance in DM, might interact with the pathogenesis of PD through the impairment of the PI3k/AKT pathway, one of the critical cascades belongs to the regulation of cell survival.[38]

Nevertheless, the potential role of DM is not specific to the PD alone, but is also associated to a variety of other neurodegenerative disorders

including Huntington disease, mitochondrial disorders, certain types of hereditary ataxia syndrome, and Alzheimer's disease.[39] A greater volume of scientific evidence has been proposed between the DM and AD.[40] Further identification of specific co-pathways between the PD and DM which can advance future clinical therapeutics is warranted.

The current study obtained data from the patients with *de novo* PD whose diagnoses were thoroughly confirmed by the neurologic examination in conjunction with dopamine transporter functional imaging. We presented the longitudinal data regarding the effect of DM on the motor management in PD. Our study, however, includes a lack of evidence for cause-and-effect relationship between the two morbidities because of the essential limitation of the case-control approach. Potential confounder, such as individual DM medications or physical activity level which has shown strong evidence of positive effect on functional capacity or neurotrophic factor in the brain, were not controlled in the scientific analysis and might be another source of bias of the current outcomes. Since the patients with better glycemic control may have better compliance in the daily physical activities in particular, further investigations are encouraged to involve this information in the future.

Despites these limitations, our data have demonstrated that the sugar-control may be coupled with the treatment of motor manifestations in PD. More stringent glucose management might be beneficial in the control of motor severity in the PD patients with comorbid DM. In the days to come, more advanced prospective and larger-scale cohort or interventional studies would be warranted to best clarify the association between the two common disorders.

DISCLOSURE

Financial support: None

Conflict of interest: None

REFERENCES

1. Cereda E, Barichella M, Pedrolli C, *et al*. Diabetes and risk of Parkinson's disease: a systematic review and meta-analysis. *Diabetes Care* 2011;34:2614-23. https://doi.org/10.2337/dc11-1584.
2. Sarwar N, Gao P, Seshasai SR, *et al*. Diabetes mellitus, fasting blood glucose concentration, and risk of vascular disease: a collaborative meta-analysis of 102 prospective studies. *Lancet* 2010;375:2215-22. https://doi.org/10.1016/S0140-6736(10)60484-9.
3. Xu Q, Park Y, Huang X, *et al*. Diabetes and risk of Parkinson's disease. Diabetes care 2011;34:910-5. https://doi.org/10.2337/dc10-1922.
4. Nanditha A, Ma RC, Ramachandran A, *et al*. Diabetes in Asia and the Pacific: Implications for the global epidemic. *Diabetes Care* 2016;39:472-85. https://doi.org/10.2337/dc15-1536.
5. Chang AM, Halter JB. Aging and insulin secretion. *Am J Physiol Endocrinol Metab* 2003;284:E7-12. https://doi.org/10.1152/ajpendo.00366.2002.
6. de Lau LM, Breteler MM. Epidemiology of Parkinson's disease. *Lancet Neurol* 2006;5:525-35. https://doi.org/10.1016/S1474-4422(06)70471-9.
7. Gustafsson H, Nordstrom A, Nordstrom P. Depression and subsequent risk of Parkinson disease: A nationwide cohort study. *Neurology* 2015;84:2422-9. https://doi.org/10.1212/WNL.0000000000001684
8. Rotella F, Mannucci E. Depression as a risk factor for diabetes: a meta-analysis of longitudinal studies. *J Clin Psychiatry* 2013;74:31-7. https://doi.org/10.4088/JCP.12r07922.
9. Montgomery MP, Kamel F, Saldana TM, Alavanja MC, Sandler DP. Incident diabetes and pesticide exposure among licensed pesticide applicators: Agricultural Health Study, 1993-2003. *Am J Epidemiol* 2008;167:1235-46. https://doi.org/10.1093/aje/kwn028.
10. Knekt P, Kilkkinen A, Rissanen H, Marniemi J, Saaksjarvi K, Heliovaara M. Serum vitamin D and the risk of Parkinson disease. *Arch Neurol* 2010;67:808-11. https:// doi:10.1001/archneurol.2010.120.
11. Song Y, Wang L, Pittas AG, *et al*. Blood 25-hydroxy vitamin D levels and incident type 2 diabetes: a meta-analysis of prospective studies. *Diabetes Care* 2013;36:1422-8. https://doi.org/10.2337/dc12-0962.
12. Nam GE, Kim SM, Han K, *et al*. Metabolic syndrome and risk of Parkinson disease: A nationwide cohort study. *PLoS Med* 2018;15:e1002640. https://doi.org/10.1371/journal.pmed.1002640.
13. Palacios N, Gao X, McCullough ML, *et al*. Obesity, diabetes, and risk of Parkinson's disease. *Mov Disord* 2011;26:2253-9. https://doi.org/10.1002/mds.23855.
14. Miyake Y, Tanaka K, Fukushima W, *et al*. Case-control study of risk of Parkinson's disease in relation to hypertension, hypercholesterolemia, and diabetes in Japan. *J Neurol Sci* 2010;293:82-6. https://doi.org/10.1016/j.jns.2010.03.002.
15. Yue X, Li H, Yan H, Zhang P, Chang L, Li T. Risk of Parkinson disease in diabetes mellitus: An updated meta-analysis of population-based cohort studies. *Medicine* 2016;95:e3549-e3549. https://doi: 10.1097/MD.0000000000003549.
16. May PC, Boggs LN, Fuson KS. Neurotoxicity of human amylin in rat primary hippocampal cultures: similarity to Alzheimer's disease amyloid-beta neurotoxicity. *J Neurochem* 1993;61:2330-3. https://doi.org/10.1111/j.1471-4159.1993.tb07480.x.
17. Sergi D, Renaud J, Simola N, Martinoli MG. Diabetes, a contemporary risk for Parkinson's disease: Epidemiological and cellular evidences. *Front Aging Neurosci* 2019;11:302. https://doi.org/10.3389/fnagi.2019.00302.
18. 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;55:181-4. http://dx.doi.org/10.1136/jnnp.55.3.181.
19. Stebbins GT, Goetz CG, Burn DJ, Jankovic J, Khoo TK, Tilley BC. How to identify tremor dominant and postural instability/gait difficulty groups with the movement disorder society unified Parkinson's disease rating scale: comparison with the unified Parkinson's disease rating scale. *Mov Disord* 2013;28:668-70. https://doi.org/10.1002/mds.25383.
20. RexSoft (2018). Rex: Excel-based statistical analysis software. URL http://rexsoft.org/.
21. Chung SJ, Jeon S, Yoo HS, *et al*. Detrimental effect of type 2 diabetes mellitus in a large case series of Parkinson's disease. *Parkinsonism Relat Disord* 2019;64:54-9. https://doi.org/10.1016/j.parkreldis.2018.08.023.
22. Ong M, Foo H, Chander RJ, *et al*. Influence of diabetes mellitus on longitudinal atrophy and cognition in Parkinson's disease. *J Neurol Sci* 2017;377:122-6. https://doi.org/10.1016/j.jns.2017.04.010.
23. Athauda D, Maclagan K, Skene SS, *et al*. Exenatide once weekly versus placebo in Parkinson's disease: a randomised, double-blind, placebo-controlled trial. *Lancet* 2017;390:1664-75. https://doi.org/10.1016/S0140-6736(17)31585-4.
24. Martin-Montalvo A, Mercken EM, Mitchell SJ, *et al*. Metformin improves healthspan and lifespan in mice. *Nat Commun* 2013;4:2192. https://doi.org/10.1038/ncomms3192.
25. Dehmer T, Heneka MT, Sastre M, Dichgans J, Schulz JB. Protection by pioglitazone in the MPTP model of Parkinson's disease correlates with I kappa B alpha induction and block of NF kappa B and iNOS activation. *J Neurochem* 2004;88:494-501. https://doi.org/10.1046/j.1471-4159.2003.02210.x.
26. Pagano G, Polychronis S, Wilson H, *et al*. Diabetes mellitus and Parkinson disease. *Neurology* 2018;90:e1654-e1662. https://doi.org/10.1212/WNL.0000000000005475.
27. 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;78:1507-11. https://doi.org/10.1212/WNL.0b013e3182553cc9.
28. Kotagal V, Albin RL, Müller MLTM, Koeppe RA, Frey KA, Bohnen NI. Diabetes is associated with postural instability and gait difficulty in Parkinson disease. *Parkinsonism Relat Disord* 2013;19:522-6. https://doi.org/10.1016/j.parkreldis.2013.01.016.
29. Mohamed Ibrahim N, Ramli R, Koya Kutty S, Shah SA. Earlier onset of motor complications in Parkinson's patients with comorbid diabetes mellitus. *Mov Disord* 2018;33:1967-8. https://doi.org/10.1002/mds.27526.
30. Saller CF, Chiodo LA. Glucose suppresses basal firing and haloperidol-induced increases in the firing rate of central dopaminergic neurons. *Science* 1980;210:1269-71. https://doi.org/10.1126/science.6254155.
31. Renaud J, Bassareo V, Beaulieu J, *et al*. Dopaminergic neurodegeneration in a rat model of long-term hyperglycemia: preferential degeneration of the nigrostriatal motor pathway. *Neurobiol Aging* 2018;69:117-28. https://doi.org/10.1016/j.neurobiolaging.2018.05.010
32. Rees JN, Florang VR, Eckert LL, Doorn JA. Protein reactivity of 3,4-dihydroxyphenylacetaldehyde, a toxic dopamine metabolite, is dependent on both the aldehyde and the catechol. *Chem Res Toxicol* 2009;22:1256-63. https://doi.org/10.1021/tx9000557.
33. Bayarsaikhan E, Bayarsaikhan D, Lee J, *et al*. Microglial AGE-albumin is critical for neuronal death in Parkinson's disease: a possible implication for theranostics. *Int J Nanomedicine* 2015;10 Spec Iss:281-92. https://doi.org/10.2147/IJN.S95077.
34. Vicente Miranda H, Szego ÉM, Oliveira LMA, *et al*. Glycation potentiates α-synuclein-associated neurodegeneration in synucleinopathies. *Brain* 2017;140:1399-419. https://doi.org/10.1093/brain/awab175.
35. Stark R, Roden M. ESCI Award 2006. Mitochondrial function and endocrine diseases. *Eur J Clin Invest* 2007;37:236-48. https://doi.org/10.1111/j.1365-2362.2007.01773.x.
36. Heilbronn LK, Gan SK, Turner N, Campbell LV, Chisholm DJ. Markers of mitochondrial biogenesis and metabolism are lower in overweight and obese insulin-resistant subjects. *J Clin Endocrinol Metab* 2007;92:1467-73. https://doi.org/10.1210/jc.2006-2210
37. Shin JH, Ko HS, Kang HC, *et al*. PARIS (ZNF746) repression of PGC-1α contributes to neurodegeneration in Parkinson's disease. *Cell* 2011;144:689-702. https://doi.org/10.1016/j.cell.2011.02.010.
38. Brunet A, Datta SR, Greenberg ME. Transcription-dependent and -independent control of neuronal survival by the PI3K–Akt signaling pathway. *Curr Opin Neurobiol* 2001;11:297-305. https://doi.org/10.1016/S0959-4388(00)00211-7
39. Ristow M. Neurodegenerative disorders associated with diabetes mellitus. *J Mol Med* (Berl) 2004;82:510-29. https://doi.org/10.1007/s00109-004-0552-1.
40. Akter K, Lanza EA, Martin SA, Myronyuk N, Rua M, Raffa RB. Diabetes mellitus and Alzheimer's disease: shared pathology and treatment? *Br J Clin Pharmacol* 2011;71:365-76. https://doi.org/10.1111/j.1365-2125.2010.03830.x.