Title: Risk of Parkinson's disease onset in patients with diabetes: A 9-year population-based cohort study with age and sex stratifications

Short title: Diabetes and Parkinson's disease

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Word count: 1,161 (not including abstract, author's contributions, acknowledgments, references, and table)

Number of tables and figures: 1

Abstract

Objective: We retrospectively assessed the age- and sex-specific incidence and relative risk of Parkinson's disease (PD) in Taiwan's diabetic population.

Research Design and Methods: Study cohort included 603,416 diabetic patients and 472,188 non-diabetic controls. Incidence rate and relative risk of PD (ICD-9-CM 332.0) were evaluated.

Results: The incidence of PD was 3.59 and 2.15 per 10,000 person-years for diabetic and control group, respectively; representing a covariate adjusted hazard ration (HR) of 1.61 (95% CI 1.56-1.66), which substantially reduced to 1.37 [1.32-1.41] after adjusting for medical visits. Diabetes was associated with a significantly elevated risk of PD in all sex and age stratifications except in young women, with the highest HR noted for young men aged 21-40 years (HR: 2.10 [1.01-4.42], followed by women aged 41-60 years (HR: 2.05 [1.82-2.30]) and >60 years (HR: 1.65 [1.58-1.73]).

Conclusions: Diabetes is associated with an increased risk of PD onset in a Chinese population, and the relation is stronger in women and younger patients.

Key words: Diabetes mellitus; Parkinson's disease; Cohort study; Incidence

A few recent studies have raised the possibility of increased risk of Parkinson's disease (PD) among diabetic patients (1-3). However, findings reported in prior studies are not consistent (4-7). Furthermore, large-scale population-based cohort studies with detailed age and sex stratifications in Asia are rare. The current study used a national cohort retrieved from Taiwan's National Health Insurance (NHI) database to retrospectively investigate the age- and sex-specific associations of diabetes with the risk of incident PD.

Research Design and Methods

Details of NHI claim data of Taiwan and methods of selection of diabetic and control groups were described in our previous reports (8-9). Briefly, eligible study subjects were adult prevalent cases of diabetes with a diagnosis of diabetes (ICD-9 250 or A code 181) in 2000 (i.e., index date), and then experienced another one or more diabetic diagnosis within the subsequent 12-month follow-up period. The first and last outpatient visits within one year had to be >30 days apart to avoid accidental inclusion of miscoded patients. The index date for subjects in the control group was the first date of enrollment to NHI. If their first date of enrollment was before January 1, 2000, the index date was set as January 1, 2000. The original study subjects consisted of 615,532 diabetic patients and 614,871 age- and sex-matched controls randomly selected from the registry of beneficiaries (8-9). Cases with a prior diagnosis of PD (ICD-9 332.xx, *n*=2,977) or secondary Parkinsonism (*n*=3,639) from January 1, 1997 to the index date were excluded. Cases aged <20 years were also excluded (*n*=5,500). The same exclusion criteria were also applied to controls (PD, *n*=1,699; secondary Parkinsonism, *n*=1,398; age<20, *n*=5,497). The controls treated for diabetes (ICD-9: 250.xx) during follow-up (i.e., 2000-2008) (*n*=134,089) were also excluded to reduce the likelihood of disease misclassification. The final cohort consisted of 603,416 diabetic patients and 472,188 controls.

We identified the first diagnoses of PD (ICD-9: 332.0) from outpatient claims or hospitalization records from 2000 to 2008 as the study end point. Only those with end point onset one year after the index date were retrieved to establish the temporal link between diabetes and PD. All the study subjects were followed from the index date to occurrence of end point, withdrawal from the NHI, or December 31, 2008, whichever date came first; and the later two were considered as censoring observations.

The age- and sex-specific incidence densities (IDs) were determined under Poisson assumption. Cox proportional hazard regression models were performed with adjustment for age, sex, geographic area, urbanization status, and comorbidities including hypertension (ICD-9: 401-405), hyperlipidemia (ICD-9: 272), and cardiovascular disease (ICD-9: 410-414, 430-438). We also tested the interactive effects of diabetes with age or sex on risk of PD. We adjusted for geographic area to minimize the potential confounding by differential accessibility and availability of medical care (10). Adjustment for urbanization was to account for the possible urban-rural difference in prevalence of certain environmental factors, such as well water drinking, herbicides, pesticides exposure and neurotoxins, which have been considered as risk factors for PD (11). All statistical analyses were performed with SAS (version 9.2; SAS Institute, Cary, NC). A statistical significance was declared at a type I error of 0.05.

Results

The overall ID for diabetic men and women was 3.34 and 3.82 per 10,000 patient-years, respectively, while the corresponding figures for control men and women were 2.12 and 2.18 per 10,000 patient-years. Irrespective of sex, the ID increased with age in both groups, with a dramatically high ID noted for those aged >65 years.

Compared with controls, diabetic patients showed a significantly increased risk of PD with an adjusted hazard ratio (HR) of 1.61 with 95% confidence interval (CI) 1.56-1.66. The adjusted HR was significantly higher (β=0.109657, P<0.0001) in diabetic women (HR: 1.70 [1.63-1.77]) than in male diabetes (HR: 1.51 [1.44-1.57]). The interaction of diabetes with age was also statistically significant for both men (β=0.18082, P=0.0014) and women (β=0.30550, P<0.001). For men, the age-specific HR was highest in young diabetes aged 21-40 years (HR: 2.10), then it declined to 1.60 and 1.49 for age of 41-60 years and >60 years, respectively. The age-specific HR was lower for young women (HR: 1.10), and was higher for middle-aged (HR: 2.05) and older women diabetes (HR: 1.65). To test the proportionality assumption of Cox model, we performed stratified analysis according to the period of follow-up. The adjusted HR tended to be higher in earlier years (i.e., 2000-2004; HR: 1.83 [1.75-1.91]) than in later years (i.e., 2005-2008; HR: 1.44 [1.39-1.50]). We also calculated the respective HR for diabetes whose index date being

in 1997, 1998-1999, or 2000, and observed an adjusted HR of 1.72 [1.66-1.77], 1.38 [1.32-1.44], and 1.25 [1.18-1.33], respectively.

To examine the potential bias arising from higher ambulatory care frequency in diabetic patients, we limited controls to those with >=21 times of ambulatory visits (the average number of ambulatory visit for non-diabetic causes in diabetes) for all causes in 2000, and noted an overall adjusted HR of 1.37 [1.32-1.41].

Conclusions

This retrospective study supports the putative link between diabetes and risk of PD (1-3). Our study provides additional information suggesting significant effect-modifications by age and sex. We found a significantly higher HR of PD in diabetic women than in diabetic men. Moreover, young diabetic men aged 21-40 years or diabetic women aged 41-60 years are more vulnerable to the increased risk.

The association between diabetes and PD has not been fully illustrated. It is possible that chronic inflammation and oxidative stress noted in diabetes may also lead to higher risk of PD years later (3). Besides, animal and in vitro studies have shown a role for insulin in the regulation of brain dopaminergic activity. Insulin dysregulation and changes in insulin action have been of concern in the pathophysiology and clinical symptoms of PD (12). Furthermore, reduced expression of certain genes in type 2 diabetes is related to impaired mitochondrial oxidative pathway, while mitochondrial dysfunction has been suggested as a pathogenesis in PD (2; 13). Our finding indicated a stronger association of diabetes with early-onset PD (age <60 years), which is consistent with one recent report (2).

The limitation of this study was that we could not differentiate between type 1 and type 2 diabetes, despite that type 1 diabetes constitutes only 1.8% of all diabetes in Taiwan (14). We

limited the diabetic patients to those diagnosed after 20 or older to further minimize this problem. In addition, due to a lack of complete information on one's lifestyle and environmental or occupational exposure, our study was unable to directly adjust for the potential confounding of those variables. The HR in diabetes was substantially decreased from 1.61 to 1.37 after adjusting for frequency of ambulatory care, suggesting major confounding by medical attention which may explain also some of the remaining risk elevation.

Over a nine-year study period, the diabetic patients in Taiwan experienced significantly increased risks of PD in both genders and most ages, a stronger link between diabetes and young-onset PD deserves further investigations.

Authors' contributions

Sun Y: Wrote the manuscript and researched data; **Chang YH**: Analyzed data and draft the results; **Chen HF**: Managed data, contributed to discussion and reviewed/edited the manuscript; **Su YH**: Contributed to discussion and draft conclusion; **Su HF**: Contributed to discussion and draft conclusion; **Li CY**: Principal investigator, researched data and reviewed/edited the manuscript.

Acknowledgements

This study was supported by a National Scientific Council grant (NSC100-2314-B-006 -052). The interpretation and conclusions contained herein do not represent those of BNHI, Department of Health or NHRI. The authors have no relevant conflict of interest to disclose. Professor Chung-Yi Li is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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Table 1—*Overall and age- and sex-specific incidence densities and relative hazards of Parkinson's disease in the diabetic and control groups*

Variables *	Control group			Diabetic group			HR † (95% CI †) in association with diabetes	AHR †§ (95% CI†) in association with diabetes
	No. of subjects	No. of events	ID †,‡ (per 10,000 patient-years) (95% CI †)	No. of subjects	No. of events	ID †,‡ (per 10,000 patient-years) (95% CI †)		
Men								
21-40	20,660	2	0.09 (0.05-0.14)	21,310	4	0.22 (0.16-0.30)	2.57 (1.42-4.67)	2.10 (1.01-4.42)
41-60	102,883	47	0.55 (0.50-0.60)	128,217	108	1.06 (0.99-1.12)	1.96 (1.76-2.18)	1.60 (1.41-1.81)
>60	109,636	338	4.29 (4.15-4.44)	140,593	599	6.41 (6.25-6.58)	1.52 (1.46-1.59)	1.49 (1.42-1.56)
Total	233,179	387	2.12 (2.06-2.19)	290,120	711	3.34 (3.26-3.42)	1.59 (1.53-1.65)	1.51 (1.44-1.57)
Women								
21-40	14,718	2	0.11 (0.06-0.19)	14,881	3	0.22 (0.15-0.32)	2.00 (1.05-3.79)	1.10 (0.48-2.55)
41-60	97,508	52	0.62 (0.56-0.67)	125,561	156	1.51 (1.44-1.59)	2.48 (2.25-2.74)	2.05 (1.82-2.30)
>60	126,783	368	3.80 (3.67-3.92)	172,210	743	6.18 (6.04-6.32)	1.66 (1.59-1.72)	1.65 (1.58-1.73)
Total	239,009	422	2.18 (2.11-2.24)	312,652	902	3.82 (3.74-3.90)	1.77 (1.71-1.84)	1.70 (1.63-1.77)
Overall	472,188	809	2.15 (2.10-2.20)	603,416	1,613	3.59 (3.53-3.64)	1.69 (1.64-1.73)	1.61 (1.56-1.66)

* Inconsistency between total population and population summed for individual variable was due to missing information

† ID= incidence density, CI=confidence interval; HR=hazard ratio; AHR= adjusted hazard ratio

‡ Based on Poisson assumption

§ Based on Cox proportional hazard regression with adjustment for age, sex, geographic area, urbanization status, hypertension,

hyperlipidemia, and cardiovascular disease