Hyperglycemic crisis and Parkinson disease: a retrospective cohort study based on nationwide data

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Abstract

Introduction: Hyperglycemic crisis episode (HCE) suggests poor control of diabetes, which may increase the risk of Parkinson disease (PD). This study aimed to clarify this issue since the literature remains unclear.

Material and methods: Patients with diabetes with and without HCE matched at a 1 : 1 ratio by age, sex, and index date between 2000 and 2002 from the Taiwan National Health Insurance Research Database were identified for analyses. Comparison of PD between patients with diabetes with and without HCE was performed by follow-up until 2012. Independent predictors for PD were also investigated among all patients.

Results: A total of 10,056 patients with diabetes with HCE and an identical number of patients with diabetes without HCE were included in the study. The mean age and male ratio were 62.0 years and 52.1%, respectively in both cohorts. Patients with HCE were found to have higher prevalence rates of hypertension, renal disease, hyperlipidemia, mental disorder, chronic obstructive pulmonary disease, liver disease, and head injury than those without HCE. Patients with HCE ≥ 3 times had a higher risk for PD (adjusted hazard ratio: 1.27; 95% CI: 1.05–1.54) compared to those without HCE; however, patients with HCE 1 or 2 times were not at high risk. Older age except ≥ 85 years, hypertension, hyperlipidemia, and mental disorder were also independent predictors for PD.

Conclusions: HCE ≥ 3 times is associated with PD. Close follow-up in older patients with HCE and control of hypertension, hyperlipidemia, and mental disorder are warranted.

Key words: diabetes, hyperglycemic crisis, Parkinson disease.

Introduction

Diabetes is one of the most important public health issues globally, especially in the aging society [1–5]. In the United States (US) in 2020, the prevalence of diabetes was 13.0% in all adults and 26.8% in older people (age ≥ 65 years) [6]. In Taiwan between 2015 and 2018, the prevalence of diabetes was about 9% in all adults and 26.5% in older people [7]. In the US, the total estimated cost of diagnosed diabetes reached $327 billion in 2017, with an increase of 26% from 2012 [8]. The increased cost is due to an increased cost per person with diabetes and increased prevalence of diabetes, especially in the older population [8].

Hyperglycemic crises, including diabetic ketoacidosis (DKA), hyperosmolar hyperglycemic state (HHS), and mixed syndromes, are the most common and acute complications of diabetes [9]. Hyperglycemic crisis episode (HCE) suggests poor control of diabetes and increased risk for subsequent complications, including death [10–13], end-stage renal disease [14], stroke [15], and dementia [16]. Parkinson disease (PD) is a common neurological disorder mainly due to a dopaminergic activity reduction of the substantia nigra in the midbrain, which presents movement problems such as rigidity, slowness, and tremor [17, 18]. Possible causes of PD include age, gene, environmental factors, and nutrition [17, 18]. Previous studies have shown that patient with type 2 diabetes had a higher risk for PD than those without [19–21]. Insulin dysregulation affecting the regulation of brain dopaminergic activity is suggested to be the possible cause [22, 23]. In addition, diabetes is a risk factor for neurodegenerative diseases, including diabetic neuropathy, stroke, dementia, and Alzheimer's disease [19]. Therefore, it is plausible for HCE to be associated with PD. However, there is no study about the association between HCE and PD in the literature. Therefore, the present study was conducted.

Material and methods

Data source

The Longitudinal Cohort of Diabetes Patients (LHDB) was used, a sub-dataset of the Taiwan National Health Insurance Research Database (NHIRD), which contains randomized selected data (120,000 patients per year) from patients with newly diagnosed diabetes [14, 16]. Taiwan NHIRD, a large and powerful data source, provides an important research resource for public health issues, which has been validated in many studies [24, 25]. Because there was no hemoglobin A_{1c} level, fasting plasma glucose level ≥ 126 mg/dl, and 2-hour plasma glucose in the Taiwan NHIRD, we adopted the definitions of diabetes as the follows: (1) hospitalization: a prescription for anti-diabetes medication or at least one diagnosis of diabetes during the hospitalization; or (2) outpatient clinic: at least two diagnoses of diabetes made by the same or different physicians, or at least one diagnosis of diabetes with a prescription for anti-diabetes medication in the outpatient clinic [14, 16]. The definitions of diabetes and HCE using the same database have been validated to be useful in previous studies [25, 26].

Study design and participants

Patients with diabetes (≥ 45 years) who were newly diagnosed with HCE (International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) code: DKA 250.1 or HHS 250.2) in the emergency department or hospitalized between January 1, 2000, and December 31, 2002, were identified as the study cohort. The diagnosis of HCE was made according to the following criteria: (1) DKA: glucose > 250 mg/dl, a high anion gap metabolic acidosis (anion gap > 10, serum HCO_3 < 18 mmol/l, and pH < 7.3), and positive urine ketones or serum ketones; (2) HHS: plasma glucose > 600 mg/dl, increased effective serum osmolality > 320 mOsm/kg, anion gap < 12, no significant acidosis (HCO_3 > 15 mmol/l or pH > 7.3), small urine ketones or serum ketones, and alteration in mental state [11, 14]. Most patients with PD are > 50 years old [27]. In early-onset PD, the mean age is 45 years old; therefore 45 years was used as the cut-off point for inclusion [27]. Patients in the study cohort who had PD diagnosis (ICD-9-CM code: 332) before the index date (i.e., the date of diagnosis of HCE) were excluded. Patients with diabetes without diagnosis of HCE were identified by exactly matching the index date, age, and sex at 1 : 1 ratio with the study cohort as the comparison cohort between January 1, 2000, and December 31, 2002. Because the effect of HCE times on PD may have a dose response, the identified study cohort (i.e., patients with HCE) was classified into three subgroups for the analyses: HCE 1 time, HCE 2 times, and HCE ≥ 3 times after counting their HCEs between January 1, 2000, and December 31, 2002. In the comparison cohort, patients who had a PD diagnosis before the index date were also excluded.

Definitions of variables and outcome

We classified age into subgroups of 45-55, 55-65, 65-75, 75-85, and ≥ 85 years [18]. Comorbidities or past histories included the following: (1) hypertension (ICD-9-CM code: 401–405); (2) renal disease (ICD-9-CM code: 580–593); (3) hyperlipidemia (ICD-9-CM code: 272); (4) mental disorder (ICD-9-CM code: 290–302, 306–319); (5) chronic obstructive pulmonary disease (COPD)

(ICD-9-CM code: 490–492, 494, or 496); (6) liver disease (ICD-9-CM code: 571.2, 571.4, 571.5, 571.6, 456.0–456.2, 572.2–572.8); (7) head injury (ICD-9-CM code: 310.2, 800, 801, 803, 804, 850, 852, 853, 854, 959.0, 959.01, 959.09); (8) pesticide or herbicide poisoning (ICD-9-CM code: 989, E861.4, E863, E980.7, E950.6, E950.0–950.5, E950.7–E950.9); (9) carbon monoxide poisoning (ICD-9-CM code: 986); and (10) vitamin B deficiency (ICD-9-CM code: 266.9). These comorbidities or past histories are the risk factors for PD and possible confounding factors for the present study [19, 28]. We did not include medications such as oral antihyperglycemic agents, insulin, steroids, and statins in this study because the medications recorded in the database we used may not be the true medications that the patient took due to the fact that many patients with HCE had poor drug compliance. In addition, these medications were not considered to be risk factors or confounding factors in previous studies [19, 28]. Outcome was defined as PD development (ICD-9-CM code: 332) in the follow-up until 2012. The comorbidity and PD development were counted only when the patient had the diagnosis of comorbidity or PD in at least one hospitalization or at least three outpatient clinic visits. There was no wash-out period for PD development.

Ethical statements

The present study was conducted with the approval of the Institutional Review Board at Chi Mei Medical Center. All methods were carried out in accordance with relevant guidelines and regulations and the Declaration of Helsinki. All data in the present study were deidentified; thus, informed consent was waived and did not affect the rights and welfare of participants.

The research was accepted by the Bioethics Committee (approval number 10405-E02).

Statistical analysis

The independent *t*-test was used for continuous variables and χ^2 test for categorical variables to compare demographic characteristics, comorbidities or past histories, and monthly incomes between the two cohorts. Cox proportional hazards regression analysis was used to compare PD development between the two cohorts and investigate the independent predictor of PD in all participants. The SAS for Windows 9.3.1 (SAS Institute, Cary, NC, USA) was used for all analyses, with the significance threshold set at $p < 0.05$ (two-tailed test).

Results

A total of 10,056 patients with HCE and an identical number of patients without HCE were included in the present study (Table I). The mean age and percentage of male sex were 62.0 years and 52.1%, respectively, in both cohorts from matching. Patients with HCE had higher prevalence of hypertension, renal disease, hyperlipidemia, mental disorder, COPD, liver disease, head injury, and lower monthly income compared to those without HCE. The percentages of intensive care unit admission and in-hospital mortality were 14.8% and 9.8%, respectively.

In the overall analysis, patients with HCE did not have a higher risk for PD than patients without HCE after adjusting hypertension, renal disease, hyperlipidemia, mental disorder, COPD, liver disease, head injury, and monthly income (adjusted hazard ratio – AHR: 1.02; 95% confidence interval – CI: 0.88–1.18) (Table II). Stratified analyses showed that patients with HCE had a higher risk of PD in the follow-up period of < 1 year (AHR: 1.52; 95% CI: 1.07-2.16) and 2–4 years (AHR: 1.39; 95% CI: 1.01-1.93).

Cox proportional hazards regression analysis showed that patients with HCE ≥ 3 times had a higher risk of developing PD (AHR: 1.27; 95% CI: 1.05-1.54) compared with 0 time HCE (i.e., patients without HCE) (Table III). However, patients with 1 or 2 times HCE did not have higher risk for PD than those without HCE. In addition to HCE ≥ 3 times, older age except ≥ 85 years (AHRs were 2.62, 4.11, and 3.63 in the age subgroups of 55–65 years, 65–75 years, and 75–85 years, respectively), hypertension (AHR: 1.22; 95% CI: 1.03-1.44), hyperlipidemia (AHR: 1.30; 95% CI: 1.05-1.61), and mental disorder (AHR: 2.74; 95% CI: 2.28-3.30) were also independent predictors for PD.

Discussion

The present study showed that HCE ≥ 3 times was associated with a higher risk of PD; however, HCE 1 or 2 times did not have high risk. In addition to HCE ≥ 3 times, older age except ≥ 85 years, hypertension, hyperlipidemia, and mental disorder were also independent predictors for PD.

The study results suggested a positive association between HCE and PD. The reason those 1 or 2 HCEs did not have high risk may be the insufficiency of disease severity. The association between increasing number of HCEs and the risk of PD strengthens the causal relationship between HCE and PD. The same finding was also obtained in a study which reported that only HCE ≥ 3 times was associated with subsequent dementia [16]. One possible explanation is the relationship between PD pathogenesis and glucose regulation and insulin resistance [23]. Previous studies revealed that dopaminergic neurons of the substantia nigra pars compacta have dense insulin

Table I. Comparison of demographic characteristics, comorbidities, and monthly income between patients with diabetes with and without HCE

Variable	With HCE *n* = 10,056	Without HCE *n* = 10,056	*P*-value
Age at diabetes [years]	62.0 ±10.5	62.0 ±10.5	> 0.999
Age at diabetes subgroup:			0.999
45–55	3,131 (31.1)	3,131 (31.1)	
55–65	2,896 (28.8)	2,896 (28.8)	
65–75	2,788 (27.7)	2,788 (27.7)	
75–85	1,093 (10.9)	1,093 (10.9)	
≥ 85	148 (1.5)	148 (1.5)	
Sex:			> 0.999
Female	4,819 (47.9)	4,819 (47.9)	
Male	5,237 (52.1)	5,237 (52.1)	
Comorbidity or past history:			
Hypertension	4,069 (40.5)	1,130 (11.2)	< 0.001
Renal disease	2,340 (23.3)	310 (3.1)	< 0.001
Hyperlipidemia	1,554 (15.5)	390 (3.9)	< 0.001
Mental disorder	1,187 (11.8)	351 (3.5)	< 0.001
COPD	998 (9.9)	320 (3.2)	< 0.001
Liver disease	749 (7.5)	182 (1.8)	< 0.001
Head injury	203 (2.0)	67 (0.7)	< 0.001
Pesticide or herbicide poisoning	8 (0.1)	4 (0.04)	0.388
Carbon monoxide poisoning	1 (0.01)	1 (0.01)	> 0.999
Vitamin B deficiency	0 (0.0)	4 (0.04)	0.125
Monthly income (NTD):			< 0.001
< 20,000	8,679 (86.3)	8,159 (81.1)	
20,000–40,000	920 (9.2)	1,100 (10.9)	
≥ 40,000	457 (4.5)	797 (7.9)	

Data were expressed as n (%) or mean ± SD. HCE – hyperglycemic crisis episode, COPD – chronic obstructive pulmonary disease, NTD – New Taiwan Dollars.

receptors [23], indicating the effect of glucose regulation in dopaminergic neurons. Magnetic resonance spectroscopy and fluorodeoxyglucose-PET demonstrated abnormal glucose utilization in the brain of patients with PD, suggesting that PD is a systemic disorder due to the derangement of oxidative energy metabolism [23]. Animal studies suggest that insulin plays a role in the regulation of brain dopaminergic activity [22, 29, 30]. Elevation of blood glucose suppresses dopamine-containing neurons located within the substantia nigra [29] and administration of glucose decreases the dopamine turnover in both the striatum and the olfactory tubercle [30]. Chronic hyperglycemia may lead to oxidative stress and production of reactive oxygen species, causing dopaminergic cell loss [31] and subsequent PD development.

Both insulin resistance and PD are suggested to be related to mitochondrial dysfunction [23]. A study reported that rates of mitochondrial adenosine triphosphate (ATP) production are reduced by 30% in the muscle of pre-diabetic subjects with insulin resistance [32]. In addition, insulin resistance is related to mitochondrial mutations [33] and PGC1α, which is an important regulator of enzymes involved in mitochondrial respiration [34]. 1-methyl 4-phenyl 1,2,3,6-tetrahydropyridine may cause degeneration of dopaminergic neurons by selective inhibition of complex I (NADH (nicotinamide adenine dinucleotide) coenzyme Q dehydrogenase), which plays a crucial role in ATP generation as it is the first enzyme of the mitochondrial respiratory chain [35]. In the substantia nigra of patients with PD, complex I deficiency and damage were found, suggesting a direct relationship between mitochondrial dysfunction and PD [36, 37].

The present study revealed that older age except ≥ 85 years; hypertension, hyperlipidemia, and mental disorder were independent predictors for PD, which is compatible with previous studies [38]. A large cohort study with follow-up of 23 years in the US reported that the annual incidence rate of PD ranged from 5.83 per 100,000 person-years at 44–49 years to the peak of 614.74 per 100,000

Table II. Comparison of Parkinson's disease development between patients with diabetes with and without HCE by Cox proportional hazards regression analysis

Variable	With HCE			Without HCE			Crude HR (95% CI)	AHR (95% CI)*
	PD (%)	PY	Rate@	PD (%)	PY	Rate@		
Overall analysis	460 (4.6)	71209.8	6.5	385 (3.8)	70931.9	5.4	1.20 (1.04–1.37)	1.02 (0.88–1.18)
Stratified analysis								
Age [years]:								
45–55	60 (1.9)	22033.1	2.7	33 (1.1)	22031.9	1.5	1.82 (1.19–2.78)	1.30 (0.81–2.08)
55–65	132 (4.6)	19932.5	6.6	97 (3.4)	19713.7	4.9	1.36 (1.05–1.77)	1.15 (0.86–1.53)
65–75	189 (6.8)	19542.2	9.7	184 (6.6)	19443.8	9.5	1.03 (0.84–1.26)	0.92 (0.74–1.15)
75–85	75 (6.9)	8362.4	9.0	67 (6.1)	8394.1	8.0	1.13 (0.81–1.57)	0.88 (0.62–1.26)
≥ 85	4 (2.7)	1339.7	3.0	4 (2.7)	1348.4	3.0	1.04 (0.26, 4.15)	1.06 (0.22–5.03)
Sex:								
Female	221 (4.6)	33351.8	6.6	187 (3.9)	33340.3	5.6	1.18 (0.97–1.43)	1.01 (0.82–1.24)
Male	239 (4.6)	37858.1	6.3	198 (3.8)	37591.6	5.3	1.21 (1.01–1.47)	1.02 (0.83–1.25)
Comorbidity or past history:								
Hypertension	234 (5.8)	26104.4	9.0	74 (24.0)	7786.8	9.5	1.00 (0.77–1.30)	1.09 (0.83–1.42)
Renal disease	94 (4.0)	14816.0	6.3	15 (4.8)	2166.3	6.9	1.01 (0.59–1.75)	1.06 (0.61–1.84)
Hyperlipidemia	83 (5.3)	9793.5	8.5	29 (7.4)	2576.8	11.3	0.88 (0.57–1.34)	0.95 (0.62–1.47)
Mental disorder	126 (10.6)	7556.6	16.7	45 (12.8)	2481.7	18.1	0.94 (0.67–1.33)	1.02 (0.72–1.44)
COPD	62 (6.2)	7175.0	8.6	34 (10.6)	2418.3	14.1	0.60 (0.40–0.92)	0.69 (0.45–1.06)
Liver disease	30 (4.0)	5489.8	5.5	13 (7.1)	1368.1	9.5	0.65 (0.34–1.26)	0.89 (0.44–1.78)
Head injury	9 (4.4)	1462.0	6.2	8 (11.9)	489.3	16.4	0.36 (0.14–0.96)	0.28 (0.09–0.85)
Monthly income (NTD):								
< 20,000	424 (4.9)	61675.6	6.9	348 (4.3)	57832.5	6.0	1.18 (1.02–1.36)	1.01 (0.86–1.17)
20,000–40,000	23 (2.5)	6403.0	3.6	24 (2.2)	7391.8	3.3	1.13 (0.64–2.01)	0.90 (0.49–1.67)
≥ 40,000	13 (2.8)	3131.2	4.2	13 (1.6)	5707.6	2.8	1.69 (0.78–3.66)	1.28 (0.54–3.06)
Follow-up period [years]:								
< 1	124 (20.0)	322.8	384.2	61 (10.4)	305.3	199.8	1.90 (1.38–2.60)	1.52 (1.07–2.16)
1–2	72 (11.3)	958.9	75.1	62 (9.5)	983.2	63.1	1.14 (0.80–1.61)	0.86 (0.57–1.30)
2–4	110 (7.7)	4288.5	25.7	76 (5.6)	4073.8	18.7	1.45 (1.08–1.94)	1.39 (1.01–1.93)
4–6	69 (5.0)	6892.9	10.0	69 (4.8)	7271.8	9.5	1.02 (0.73–1.43)	0.92 (0.63–1.33)
6–8	44 (2.9)	10721.9	4.1	66 (4.0)	11484.3	5.8	0.68 (0.46–1.00)	0.88 (0.58–1.32)
≥ 8	41 (0.9)	48024.9	0.9	51 (1.2)	46813.5	1.1	0.78 (0.52–1.18)	0.97 (0.63–1.49)

*HCE – hyperglycemic crisis episode, PY – person-year, AHR – adjusted hazard ratio, PD – Parkinson's disease, COPD – chronic obstructive pulmonary disease, NTD – New Taiwan Dollars. *Adjusted for hypertension, renal disease, hyperlipidemia, mental disorder, COPD, liver disease, head injury, and monthly income. @Rate: per 1000 person-years.*

person-years at 85–89 years and declined after 90 years [38]. Other studies also showed a decline in PD incidence in men after age 75 or 79 years [38]. The decreased incidence of PD in the population with advancing age in previous studies is like the finding of decreased influence of age after 85 years in the present study. Underdiagnosis due to easier lost follow-up, less intensive survey, and difficulty of diagnosis of PD in the population of advancing age is suspected to be the reason [38]. Furthermore, survivorship bias may be another possible explanation. Hypertension may cause hypertensive vasculopathy in the brain and affect the dopaminergic cells in the pars compacta and connections between neurons in the substantia nigra and the striatum [39]. A meta-analysis showed that the risk ratio of PD was 1.70 (95% CI: 1.60–1.80) in participants with hypertension compared to those without hypertension [39]. A previous study showed that the risk of PD increases with an increasing total cholesterol level [40]. Several putative mechanisms are proposed, including disturbed cholesterol homeostasis in the brain and excess body weight [40]. Psychiatric symptoms (PS), especially depression and anxiety, may be the prodromal phase of PD [41]. These PS may be diagnosed as mental disorder before the diagnosis of PD. Therefore, more attention should be paid to patients with mental disorder for subsequent PD development [41].

Table III. Independent predictors for PD in all patients with diabetes by Cox proportional hazards regression analysis

Variable	Crude HR (95% CI)	AHR (95% CI)*
HCE:		
0 times	1 (reference)	1 (reference)
1 time	1.12 (0.95–1.31)	0.93 (0.78–1.10)
2 times	1.09 (0.85–1.40)	0.87 (0.67–1.12)
≥ 3 times	1.41 (1.17–1.69)	1.27 (1.05–1.54)
Age subgroup [years]:		
45–55	1 (reference)	1 (reference)
55–65	2.72 (2.14–3.46)	2.62 (2.06–3.35)
65–75	4.53 (3.61–5.68)	4.11 (3.24–5.22)
75–85	4.07 (3.14–5.29)	3.63 (2.76–4.78)
≥ 85	1.48 (0.72–3.05)	1.36 (0.66– 2.82)
Sex:		
Female	1 (reference)	1 (reference)
Male	0.95 (0.83–1.09)	1.03 (0.90–1.19)
Comorbidity or past history:		
Hypertension	1.80 (1.56–2.07)	1.22 (1.03–1.44)
Renal disease	1.07 (0.88–1.31)	0.80 (0.65–0.99)
Hyperlipidemia	1.57 (1.28–1.91)	1.30 (1.05–1.61)
Mental disorder	3.30 (2.79–3.91)	2.74 (2.28–3.30)
COPD	1.78 (1.44–2.21)	1.12 (0.90–1.40)
Liver disease	1.07 (0.79–1.45)	0.99 (0.73–1.36)
Head injury	1.48 (0.91–2.39)	0.99 (0.61–1.60)
Monthly income:		
< 20,000 NTD	2.20 (1.49–3.24)	1.22 (0.82–1.83)
20,000–40,000 NTD	1.15 (0.71–1.86)	1.09 (0.68–1.76)
≥ 40,000 NTD	1 (reference)	1 (reference)

*PD – Parkinson disease, AHR – adjusted hazard ratio, HCE – hyperglycemic crisis episode, COPD – chronic obstructive pulmonary disease, NTD – New Taiwan Dollars. *Adjusted for hypertension, renal disease, hyperlipidemia, mental disorder, COPD, liver disease, head injury, and monthly income.*

The present study has the major strength of delineating an unclear issue using a nationwide population-based design with a large sample size. Limitations include the following. First, some variables, including family history and genetic factors, smoking, dietary information, exercise, HbA_{1c}, blood glucose, and body mass index, which are possible confounders, are not available in the NHIRD. However, most associated comorbidities, past histories, and monthly income were adjusted to minimize the potential confounding effect. Second, the present study showed a positive association between HCE and PD; however, it is not necessarily a causal relationship, because PD patients may have impaired glucose control and the putative latency of PD pathogenesis has been suggested to be long (several years). Therefore, reverse causation cannot be discarded with respect to the causal relationship between PD and HCE [20, 21]. Third, the study result may not be generalized to other nations due to race, health care, and culture differences. Fourth, HCEs during follow-up were not considered in this study due to the fact that we wanted to conduct a cohort study. The exposure (i.e., HCE) should be defined at the stage of identifying patients. Therefore, we decided not to count the development of HCE in both study and comparison cohorts during the follow-up. Fifth, the definition of diabetes for the outpatient clinic may be too loose. Misclassification for diabetes may exist. However, all the included patients in both cohorts were diagnosed with diabetes using the same criteria. Therefore, the misclassification is non-differential, which may minimize its effect on this study. Sixth, some early-onset PD patients would be excluded from the analyses because we used 45 years (i.e., the mean age of early-onset PD) as the cut-off point for inclusion. Therefore, the results would be dominated by PD that was not of early onset. Seventh, not all HCE events are

symptomatic, not all require hospitalization, and not all are diagnosed or registered in the medical records. Eighth, there were no data about how many HCE events merited hospitalization and how many HCE events received emergency department care. Ninth, there is the possibility that drug-induced or lesion-induced parkinsonism associated with HCE and dysglycemia-related non-PD parkinsonism might be confused with PD. Further studies are warranted to clarify these limitations.

The prevalence of diabetes is increasing and HCE, the most common acute complication of diabetes, is plausibly associated with PD. This retrospective cohort study based on nationwide data showed a positive association between HCE and PD. The possible mechanism is the link between pathogenesis of PD and glucose regulation and insulin resistance. A close follow-up is suggested for patients with HCE, especially in patients with ≥ 3 HCEs, older age, hypertension, hyperlipidemia, and mental disorder, for early detection and treatment of PD development. Further studies including clarifying the causal relationship between HCE and PD and validation in other nations are warranted.

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Conflict of interests

The authors declare no conflict of interests.

References

1. Wierzba W, Sliwczynski A, Karnafel W, et al. The association of diabetes with all-cause mortality in patients with end-stage renal disease compared to the general population in Poland – a comparative analysis. Arch Med Sci 2022; 18: 314-9.
2. Jankowska A, Golicki D. Self-reported diabetes and quality of life: findings from a general population survey with the Short Form-12 (SF-12) Health Survey. Arch Med Sci 2022; 18: 1157-68.
3. Klisic A, Radoman Vujacic I, Munjas J, Ninic A, Kotur-Stevuljevic J. Micro-ribonucleic acid modulation with oxidative stress and inflammation in patients with type 2 diabetes mellitus – a review article. Arch Med Sci 2022; 18: 870-80.
4. Alswat K. Type 2 diabetes control and complications and their relation to serum magnesium level. Arch Med Sci 2022; 18: 307-13.
5. Huang YL, Tsay WI, Her SH et al. Chronic pain and use of analgesics in the elderly: a nationwide population-based study. Arch Med Sci 2020; 16: 627-34.
6. Prevention CfDCa. National Diabetes Statistics Report 2020. In. 2020.
7. Welfare MoHa. Prevalance of diabetes accoring to age and sex. In. 2020.
8. American Diabetes Association. Economic costs of diabetes in the U.S. in 2017. Diabetes Care 2018; 41: 917-28.
9. Kitabchi AE, Umpierrez GE, Miles JM, Fisher JN. Hyperglycemic crises in adult patients with diabetes. Diabetes Care 2009; 32: 1335-43.
10. Huang CC, Chien TW, Su SB, et al. Infection, absent tachycardia, cancer history, and severe coma are independent mortality predictors in geriatric patients with hyperglycemic crises. Diabetes Care 2013; 36: e151-2.
11. Huang CC, Kuo SC, Chien TW, et al. Predicting the hyperglycemic crisis death (PHD) score: a new decision rule for emergency and critical care. Am J Emerg Med 2013; 31: 830-4.
12. Huang CC, Weng SF, Tsai KT, et al. Long-term mortality risk after hyperglycemic crisis episodes in geriatric patients with diabetes: a national population-based cohort study. Diabetes Care 2015; 38: 746-51.
13. Kao Y, Hsu CC, Weng SF, et al. Subsequent mortality after hyperglycemic crisis episode in the non-elderly: a national population-based cohort study. Endocrine 2016; 51: 72-82.
14. Kao Y, Feng IJ, Hsu CC, Wang JJ, Lin HJ, Huang CC. Association of hyperglycemic crisis with an increased risk of end-stage renal disease: a nationwide population-based cohort study. Diabetes Res Clin Pract 2018; 138: 106-12.
15. Wang JY, Wang CY, Huang YS, et al. Increased risk of ischemic stroke after hyperosmolar hyperglycemic state: a population-based follow-up study. PLoS One 2014; 9: e94155.
16. Chou CH, Feng IJ, Chen YC, et al. Risk of dementia in diabetic patients with hyperglycemic crisis: a nationwide taiwanese population-based cohort study. Neuroepidemiology 2020; 54: 419-26.
17. 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.
18. Armstrong MJ, Okun MS. Diagnosis and treatment of Parkinson disease: a review. JAMA 2020; 323: 548-60.
19. Hu G, Jousilahti P, Bidel S, Antikainen R, Tuomilehto J. Type 2 diabetes and the risk of Parkinson's disease. Diabetes Care 2007; 30: 842-7.
20. Cheong JLY, de Pablo-Fernandez E, Foltynie T, Noyce AJ. The association between type 2 diabetes mellitus and Parkinson's disease. J Parkinsons Dis 2020; 10: 775-89.
21. Hassan A, Sharma Kandel R, Mishra R, Gautam J, Alaref A, Jahan N. Diabetes mellitus and Parkinson's disease: shared pathophysiological links and possible therapeutic implications. Cureus 2020; 12: e9853.
22. Craft S, Watson GS. Insulin and neurodegenerative disease: shared and specific mechanisms. Lancet Neurol 2004; 3: 169-78.
23. Aviles-Olmos I, Limousin P, Lees A, Foltynie T. Parkinson's disease, insulin resistance and novel agents of neuroprotection. Brain 2013; 136: 374-84.
24. Lin LY, Warren-Gash C, Smeeth L, Chen PC. Data resource profile: the National Health Insurance Research Database (NHIRD). Epidemiol Health 2018; 40: e2018062.
25. Hsieh CY, Su CC, Shao SC, Sung SF, Lin SJ, Yang YHK, et al. Taiwan's National Health Insurance Research Database: past and future. Clin Epidemiol 2019; 11: 349-58.
26. Sung SF, Hsieh CY, Lin HJ, Chen YW, Yang YHK, Li CY. Validation of algorithms to identify stroke risk factors in patients with acute ischemic stroke, transient ischemic attack, or intracerebral hemorrhage in an administrative claims database. Int J Cardiol 2016; 215: 277-82.
27. Pagano G, Ferrara N, Brooks DJ, Pavese N. Age at onset and Parkinson disease phenotype. Neurology 2016; 86: 1400-7.

28. Belvisi D, Pellicciari R, Fabbrini A, Costanzo M, Pietracupa S, De Lucia M, et al. Risk factors of Parkinson disease: simultaneous assessment, interactions, and etiologic subtypes. Neurology 2020; 95: e2500-8.
29. 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.
30. Montefusco O, Assini MC, Missale C. Insulin-mediated effects of glucose on dopamine metabolism. Acta Diabetol Lat 1983; 20: 71-7.
31. Stranahan AM, Arumugam TV, Cutler RG, Lee K, Egan JM, Mattson MP. Diabetes impairs hippocampal function through glucocorticoid-mediated effects on new and mature neurons. Nat Neurosci 2008; 11: 309-17.
32. Petersen KF, Dufour S, Befroy D, et al. Impaired mitochondrial activity in the insulin-resistant offspring of patients with type 2 diabetes. N Engl J Med 2004; 350: 664-71.
33. Gerbitz KD, van den Ouweland JM, Maassen JA, Jaksch M. Mitochondrial diabetes mellitus: a review. Biochim Biophys Acta 1995; 1271: 253-60.
34. Stark R, Roden M. ESCI Award 2006. Mitochondrial function and endocrine diseases. Eur J Clin Invest 2007; 37: 236-48.
35. Perier C, Tieu K, Guegan C, et al. Complex I deficiency primes Bax-dependent neuronal apoptosis through mitochondrial oxidative damage. Proc Natl Acad Sci USA 2005; 102: 19126-31.
36. Mann VM, Cooper JM, Daniel SE, et al. Complex I, iron, and ferritin in Parkinson's disease substantia nigra. Ann Neurol 1994; 36: 876-81.
37. Keeney PM, Xie J, Capaldi RA, Bennett JP, Jr. Parkinson's disease brain mitochondrial complex I has oxidatively damaged subunits and is functionally impaired and misassembled. J Neurosci 2006; 26: 5256-64.
38. Driver JA, Logroscino G, Gaziano JM, Kurth T. Incidence and remaining lifetime risk of Parkinson disease in advanced age. Neurology 2009; 72: 432-8.
39. Chen J, Zhang C, Wu Y, Zhang D. Association between hypertension and the risk of Parkinson's disease: a meta-analysis of analytical studies. Neuroepidemiology 2019; 52: 181-92.
40. Hu G, Antikainen R, Jousilahti P, Kivipelto M, Tuomilehto J. Total cholesterol and the risk of Parkinson disease. Neurology 2008; 70: 1972-9.
41. Szatmari S, Jr., Ajtay A, Oberfrank F, Dobi B, Bereczki D. The prevalence of psychiatric symptoms before the diagnosis of Parkinson's disease in a nationwide cohort: a comparison to patients with cerebral infarction. PLoS One 2020; 15: e0236728.