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당뇨망막병증과 파킨슨병의 관계

Association between diabetic retinopathy and Parkinson disease: evidence from a nationwide Korean study

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백 지 연

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이 논문을 의학석사 학위논문으로 제출함

2018 년 12 월

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백지연의 의학석사 학위 논문을 인준함

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Abstract

Background: Studies have shown an association between diabetes and Parkinson's disease (PD). The retina is a part of the central nervous system; it was proposed that diabetic retinopathy (DR) and PD share common pathophysiology of dopamine deficiency. However, no epidemiologic studies have investigated the relationship between these two diseases.

Method: Using the Korean National Health Insurance Service database, 14,912,368 participants who underwent regular health checkup from 2005 to 2008 were included. Subjects were classified as non-diabetes, diabetes without DR, and diabetes with DR groups at baseline and followed up until the date of PD incidence, death, or 31 December 2013. Cox proportional hazards regression analysis was used to evaluate the association between DR and incident PD.

Results: During the period, 34,834 subjects were newly diagnosed with PD. The incidence of PD was 2.74, 8.39 and 15.51 per 10,000 person-years for the non-diabetes, diabetes without DR and diabetes with DR groups, respectively. In multivariate Cox proportional hazard models, DR groups were associated with significantly higher risk of PD than non-diabetes or diabetes without DR groups even after adjusting for age, sex, fasting plasma glucose level, insulin usage, and other possible risk factors

Conclusion: Concurrent DR was associated with an increased risk of incident PD. Future studies are necessary to investigate the mechanism of increased risk of PD in DR including dopamine deficiency in the central nervous system and long-lasting poor glycemic control.

Key words: diabetes, diabetic retinopathy, Parkinson disease

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Introduction

Parkinson's disease (PD) is the second most common neurodegenerative disorder [1]. Patients with PD exhibit not only motor parkinsonism, but also other systemic manifestations, including cognitive impairment, sleep disturbance, and autonomic dysfunction [2], resulting in poor quality of life. During the past several decades, the incidence of PD has increased gradually [3] and it was expected that its prevalence would continually increase along with the increasing life expectancy [4]. Early treatment of PD can provide symptomatic benefit [5]. Also, the early use of agents such as dopamine receptor agonists and monoamine oxidase B inhibitors can delay the initiation of levodopa use, which is effective but has major adverse effects including motor fluctuations and dyskinesia [5]. Therefore, it is imperative to investigate the risk factors of PD to facilitate its early diagnosis and treatment.

PD and diabetes are both age-associated chronic diseases, and a growing body of evidence suggests that they share common pathophysiologic pathways, such as mitochondrial dysfunction, endoplasmic reticulum stress, and inflammation [6]. In addition, hyperglycemia and impaired insulin action can also induce neurodegeneration [7, 8]. Even though some studies denied the association of PD with history of diabetes [9-11], it is generally agreed that diabetes is associated with an increased risk of PD [12-18].

A previous study suggested not only retinal vasculature but also retinal neurons are altered in patients with diabetes[19]. The retina is a part of the central nervous system and uses dopamine as a key neurotransmitter [20]. Loss of dopaminergic amacrine cells in the retina was also found in diabetic mice[21]. In accordance, retinal levels of dopamine have been found to decrease significantly in diabetic mice with visual dysfunction [22]. Notably, treatment with dopamine precursor improved retinal and visual functions in these mice[22]. Furthermore, PD causes a progressive loss of dopaminergic cells predominantly in the retina[23]. Based on these results, it was recently proposed that diabetic retinopathy (DR) and PD share a common pathophysiology of dopamine deficiency [24]. Nevertheless, there have been no epidemiologic studies investigating the relationship between DR and PD so far. Thus, we aimed to assess the association between DR and incident PD.

Design and Methods

Data source and study population

The Korean National Health Insurance (KNHI), a single-payer system, is mandatory for all residents in Korea[25]. The Korean National Health Insurance Service (NHIS) database consists of Qualification DB, Health Check-up DB, and Claim DB[25]. Among these, the Health Checkup DB generally comprises four areas: regular health checkup, lifetime transition period health checkup, cancer checkup, and baby/infant health checkup. The Korean National Health Insurance provides annual or biannual regular health checkups without cost to all applicable examinees including (1) employee subscribers and regional insurance subscribers who are regional householders, (2) dependents and household members of employee subscribers (40 years or older), and (3) medical aid beneficiaries who are householders aged 19 to 64 years and household members aged 41 to 64 years and household members aged 41 to 64 years[25]. Among these, nonoffice workers who are employee subscribers are requested to have annual health checkups, whereas the others are biannually examined.

In this study, we combined data from regular health checkups during the years 2005 to 2008 and the Claim DB of 2005 to 2013, for which hospitals claimed their health care costs from the NHIS. Regular health checkup comprises filling of questionnaires, interviews, and laboratory examinations, and the Claim DB mostly comprises diagnostic codes and prescriptions[25]. A total of 32,282,336 people who underwent at least on examination between 2005 and 2008 were included. Among these, subjects were excluded if (1) they had a history of PD (n=6341); (2) there was any missing information as to their level of plasma glucose or cholesterol, body mass index (BMI), blood pressure, smoking, alcohol, or physical activity at the time of examination (n=1,245,099); or (3) the examinee was younger than 30 years (n=4,609,134). In addition, if subjects had two or more examinations between 2005 and 2008, only the first checkup was considered (n=11,509,394). The final sample size was 14,912,368 and they were classified according to the presence or absence of prevalent diabetes or DR at inclusion (Fig.1). The study protocol was approved by the Korean National Institute for

Bioethics Policy (P01-201504-21-005). Anonymized and deidentified information was used for the analyses.

Definitions of type 2 diabetes and diabetic retinopathy

At baseline, individuals were defined as having type 2 diabetes if they had a diagnostic code of type 2 diabetes, having been treated with antidiabetic drugs at least once[25]. The diagnosis was made by using the International Statistical Classification of Diseases and Related Health Problems, 10th revision (ICD-10) codes, E11 to E14, and the relevant prescriptions were as follows: sulfonylureas, metformin, meglitinides, thiazolidinediones, dipeptidyl peptidase-4 inhibitors, α-glucosidase inhibitors, and insulin. Besides, subjects with fasting plasma glucose levels ≥126 mg/dL were also considered as having type 2 diabetes regardless of the use of antidiabetic drugs. Subjects with diabetes were further sub-classified according to presence of DR. DR was defined by the ICD-10 code H36.0 among type 2 diabetic patients[26].

Demographic factors at baseline

All participants in the regular health checkup were required to fill out self-administered questionnaires, which included questions about smoking status (never, ex, and current smoker), alcohol consumption, and physical activity. Current smokers were defined as those who smoked 100 or more cigarettes in their lifetime and until now. Heavy drinkers were defined as those who drunk 5 or more days per week. Subjects were defined as physically active if they exercised on 1 or more days per week. BMI was calculated as the weight dived by height squared (kg/m^2). Venous samples were drawn after an overnight fast to determine fasting plasma glucose, total cholesterol, triglyceride, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, aspartate aminotransferase, alanine aminotransferase, γ-glutamyl transpeptidase, and hemoglobin levels.

Baseline comorbidities

Hypertension, dyslipidemia, end-stage renal disease (ESRD), and peripheral artery disease (PAD) were evaluated as baseline comorbidities in this study. If individuals had systolic blood pressure ≥140 mm Hg and/or diastolic blood pressure ≥90 mm Hg at regular health checkup, or an ICD-10 code of hypertension (I10-13, I15), having been treated with antihypertensive medications, they were defined as having hypertension. Total cholesterol level ≥240 mg/dL at regular health checkup or ICD code of dyslipidemia (E78) concurrent with lipid-lowering agents was used for diagnosis of dyslipidemia. Subjects with diagnostic codes for kidney disease (N18 to N19, Z49, Z94, Z992, Z90) were defined as ESRD patients if they also had (1) a procedure code (R3280, kidney transplantation; O07011 to O7020, hemodialysis; O7071 to O7075, peritoneal dialysis) or (2) a rare/incurable disease code (V001, hemodialysis; V003, peritoneal dialysis; V005, treatment with immune suppressants after kidney transplantation). PAD was diagnosed when subjects had two or more diagnoses (I70 and I73) in the outpatient setting and one or more diagnoses (I70 and I73) in the inpatient setting.

Follow up

The primary endpoint was newly diagnosed PD during the follow-up period. PD was determined using ICD-10 code G20. We defined PD if patients had two or more diagnoses (G20) during outpatient clinic visits rather than on diagnosis that could lead to an overestimation of the number of cases of PD. Patients with one or more diagnosis (G20) during hospitalization were also considered to have PD. Subjects without PD were followed up until the date of death or 31 December 2013, whichever came first (Fig 1).

Statistical analysis

To compare the baseline characteristics of the participants, one-way analysis of variance for continuous variables, and the chi-square test for categorical variables were used. When significant, Bonferroni post-hoc analysis was performed to identify inter-group differences. The incidence rate of

PD was expressed as the number of events per 1000 person-years. Cox proportional hazards regression analysis was used to calculate hazard ratio (HR) for PD depending on the presence of diabetes or DR. Model 2 included age, sex, whereas model 3 included other possible risk factors including BMI, smoking, heavy drinking, exercise, hypertension, and dyslipidemia. To evaluate the influence of diabetes severity, model 4 further included ESRD, PAD, fasting plasma glucose, and insulin usage at baseline. The cumulative incidence of PD according to the presence of diabetes or DR was calculated by using Kaplan–Meier curves and the log-rank test. The P value was calculated to three decimal places, and P values smaller than 0.001 were reported as $P < 0.001$. For data management and analysis, SAS survey procedure was used (version 9.2; SAS Institute, Cary, NC).

Results

Baseline characteristics of the study subjects

In all, 1,343,437 patients were identified as having type 2 diabetes at baseline. Table 1 shows the baseline characteristics of the study subjects. Patients with diabetes were older and had more comorbidities including hypertension, dyslipidemia, ESRD, and PAD when compared with patients without diabetes. As could be expected, patients with DR showed higher values of these indices than those of patients with diabetes and without DR (**Table 1**). Unexpectedly, however, patients with DR showed a lower proportion of current smokers and heavy drinkers and higher proportion of physically active subjects than those of patients without DR.

Incidence and risk of PD depending on diabetic status

By the end of the follow-up period, the incidence of PD was significantly higher among patients with diabetes than patients without diabetes, and higher among patients with diabetes and DR than patients with diabetes and without DR (log-rank test, $P < 0.001$) (Fig. 2). The incidence rates of PD among patients without diabetes, patients with diabetes and without DR, and patients with DR were 2.74, 8.39, and 15.51 per 10,000 person-years, respectively (Table 2). This difference remained significant

after adjusting for age and sex (model 2) or additional clinical characteristics (model 3). Even after adjusting for ESRD, PAD, fasting plasma glucose, and insulin use (model 4), patients with DR had a significantly strong association of PD than those in other groups (without DR group: HR 1.33, 95% CI 1.29 to 1.38; DR group: HR 1.75, 95% CI 1.64 to 1.86; P for trend <0.001). When the men and women were examined separately, the association persisted, with modestly higher hazard in women than men, in agreement with previous studies performed in Asia [16].

We next compared the incidence rate of PD according to age groups (Table 3). Having DR was significantly associated with the development of PD in subjects aged > 40 years after adjustment for confounding factors. The association between DR and PD was significant after adjustment for age, sex, and clinical characteristics in younger patients aged 30 to 39 years (HR 4.21, 95% CI 1.05 to 16.93; *P* for trend 0.014); this association was not significant after adjusting for ESRD, PAD, fasting plasma glucose, and insulin usage (HR 2.09, 95% CI 0.44 to 9.99, P for trend 0.655).

Table 1. Baseline characteristics of subjects who participated in regular health check-up from 2005 to 2008.

	Non-DM (n = 13,568,931)	DM	
		without DR (n = 1,222,897)	DR (n = 120,540)
Age (years)	48.6±12.6	57.2±12*	61±9.7†
Men (%)	53.5	60.7*	48.2†
BMI (kg/m^2)	23.7±3.1	24.9±3.3*	24.5±3.1
Current smoker (%)	24.0	25.7*	13.4†
Heavy drinker (%)	9.4	13.4*	6.6†
Physically active subjects (%)	8.3	13.1*	20.2†
Comorbidities, n (%)			
Hypertension	3,651,584 (26.91)	691,109 (56.51)*	81,035 (67.23)†
Dyslipidemia	1,973,067 (14.54)	390,686 (31.95)*	50,922 (42.24)†
ESRD	5,864(0.04)	1,789 (0.15)*	957 (0.79)†
PAD	356,279 (2.62)	96,409 (7.88)*	17,504 (14.52)†

Values are presented as mean ± standard deviation or proportion (%).

Non-DM, patients without diabetes; without DR, diabetic patients without diabetic retinopathy; DR, patients with diabetic retinopathy; BMI, body mass index; ESRD, end-stage renal disease.

* <0.05 vs. non-DM.

† <0.05 vs. DM without DR

Table 2. Incidence and risk of Parkinson's disease according to diabetic status and gender

Variables	Initial Diabetic Status			P for trend
	Non-DM (n = 13,568,931)	DM		
		Without DR (n = 1,222,897)	DR (n = 120,540)	
Total				
PD cases (n)	26,501	7,066	1,267	
PD incidence rate (per 10,000-person-years)	2.74	8.39	15.51	
Model 1[a] HR (95% CI)	1 (reference)	3.08 (3.00-3.16)	5.72 (5.41-6.05)	<0.05
Model 2[b] HR (95% CI)	1 (reference)	1.59 (1.55-1.63)	2.52 (2.38-2.67)	<0.05
Model 3[c] HR (95% CI)	1 (reference)	1.54 (1.50-1.58)	2.39 (2.26-2.53)	<0.05
Model 4[d] HR (95% CI)	1 (reference)	1.34 (1.30-1.39)	1.79 (1.68-1.91)	<0.05
Men	7,255,888	742,239	58,096	
PD cases (n)	12,112	3,188	495	
PD incidence rate (per 10,000-person-years)	2.33	6.23	12.67	
Model 1[a] HR (95% CI)	1 (reference)	2.70 (2.60-2.81)	5.54 (5.06-6.06)	<0.05
Model 2[b] HR (95% CI)	1 (reference)	1.49 (1.43-1.54)	2.25 (2.05-2.46)	<0.05
Model 3[c] HR (95% CI)	1 (reference)	1.45 (1.39-1.51)	2.14 (1.95-2.34)	<0.05
Model 4[d] HR (95% CI)	1 (reference)	1.28 (1.22-1.35)	1.65 (1.49-1.82)	<0.05
Women	6,313,043	480,658	62,444	
PD cases (n)	14,389	3,878	772	
PD incidence rate (per 10,000-person-years)	3.23	11.73	18.10	
Model 1[a] HR (95% CI)	1 (reference)	3.65 (3.52-3.78)	5.64 (5.25-6.07)	<0.05
Model 2[b] HR (95% CI)	1 (reference)	1.70 (1.64-1.76)	2.74 (2.55-2.94)	<0.05
Model 3[c] HR (95% CI)	1 (reference)	1.63 (1.57-1.69)	2.59 (2.40-2.78)	<0.05
Model 4[d] HR (95% CI)	1 (reference)	1.40 (1.34-1.47)	1.89 (1.74-2.06)	<0.05

Non-DM, patients without diabetes; Non-DR, diabetic patients without diabetic retinopathy; DR, patients with diabetic retinopathy; PD, Parkinson's disease; HR, hazard ratio.

[a] Model 1: unadjusted.

[b] Model 2: adjusted for age and gender.

[c] Model 3: adjusted for age, gender, BMI, smoking, alcohol, exercise, hypertension, and dyslipidemia.

[d] Model 4: adjusted for age, gender, BMI, smoking, alcohol, exercise, hypertension, dyslipidemia, glucose, and insulin use

Table 3. Incidence and risk of Parkinson's disease according to diabetic status stratified by age groups

Age groups	Initial Diabetic Status			P for trend
	Non-DM (n = 13,568,931)	DM		
		Without DR (n = 1,222,897)	DR (n = 120,540)	
30-39	3,657,489	95,240	2,029	
PD cases (n)	627	28	2	
PD incidence rate (per 10,000-person-years)	0.24	0.41	1.38	
Model 1[a] HR (95% CI)	1 (reference)	1.70 (1.17-2.49)	5.70 (1.42-22.85)	<0.05
Model 2[b] HR (95% CI)	1 (reference)	1.63 (1.11-2.38)	5.18 (1.29-20.79)	<0.05
Model 3[c] HR (95% CI)	1 (reference)	1.47 (0.99-2.16)	4.21 (1.05-16.93)	<0.05
Model 4[d] HR (95% CI)	1 (reference)	1.05 (0.63-1.77)	2.18 (0.46-10.44)	???
40-59	7,066,803	585,804	47,119	
PD cases (n)	4,899	710	119	
PD incidence rate (per 10,000-person-years)	0.96	1.72	3.62	
Model 1[a] HR (95% CI)	1 (reference)	1.80 (1.66-1.95)	3.81 (3.18-4.57)	<0.05
Model 2[b] HR (95% CI)	1 (reference)	1.47 (1.36-1.59)	2.74 (2.29-3.29)	<0.05
Model 3[c] HR (95% CI)	1 (reference)	1.38 (1.28-1.50)	2.52 (2.10-3.03)	<0.05
Model 4[d] HR (95% CI)	1 (reference)	1.12 (1.01-1.24)	1.58 (1.28-1.96)	<0.05
≥60	2,844,639	541,853	71,392	
PD cases (n)	20,975	6,328	1,146	
PD incidence rate (per 10,000-person-years)	10.64	17.51	24.17	
Model 1[a] HR (95% CI)	1 (reference)	1.66 (1.62-1.71)	2.30 (2.17-2.44)	<0.05
Model 2[b] HR (95% CI)	1 (reference)	1.58 (1.54-1.63)	2.39 (2.25-2.54)	<0.05
Model 3[c] HR (95% CI)	1 (reference)	1.55 (1.51-1.59)	2.30 (2.17-2.44)	<0.05
Model 4[d] HR (95% CI)	1 (reference)	1.36 (1.31-1.41)	1.75 (1.64-1.87)	<0.05

Non-DM, patients without diabetes; Non-DR, diabetic patients without diabetic retinopathy; DR, patients with diabetic retinopathy; PD, Parkinson's disease; HR, hazard ratio.

[a] Model 1: unadjusted.

[b] Model 2: adjusted for age and gender.

[c] Model 3: adjusted for age, gender, BMI, smoking, alcohol, exercise, hypertension, and dyslipidemia.

[d] Model 4: adjusted for age, gender, BMI, smoking, alcohol, exercise, hypertension, dyslipidemia, glucose, and insulin use

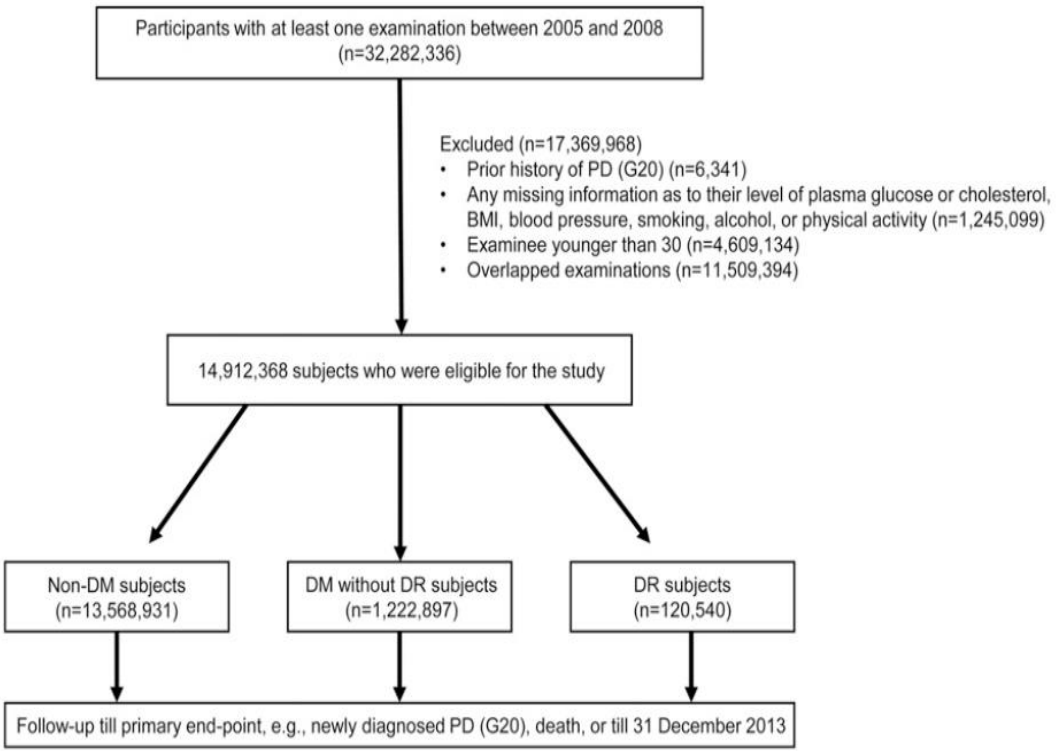

Figure 1. Study population. In total, 32,282,336 subjects who underwent regular health check-ups between 2005 and 2008 were reviewed. 17,369,968 subjects were excluded for the reasons illustrated. 14,912,368 subjects were enrolled and divided to 3 groups according to diabetes and retinal complication. Subjects were followed-up until primary endpoint occur, death, or 31 December 2013.

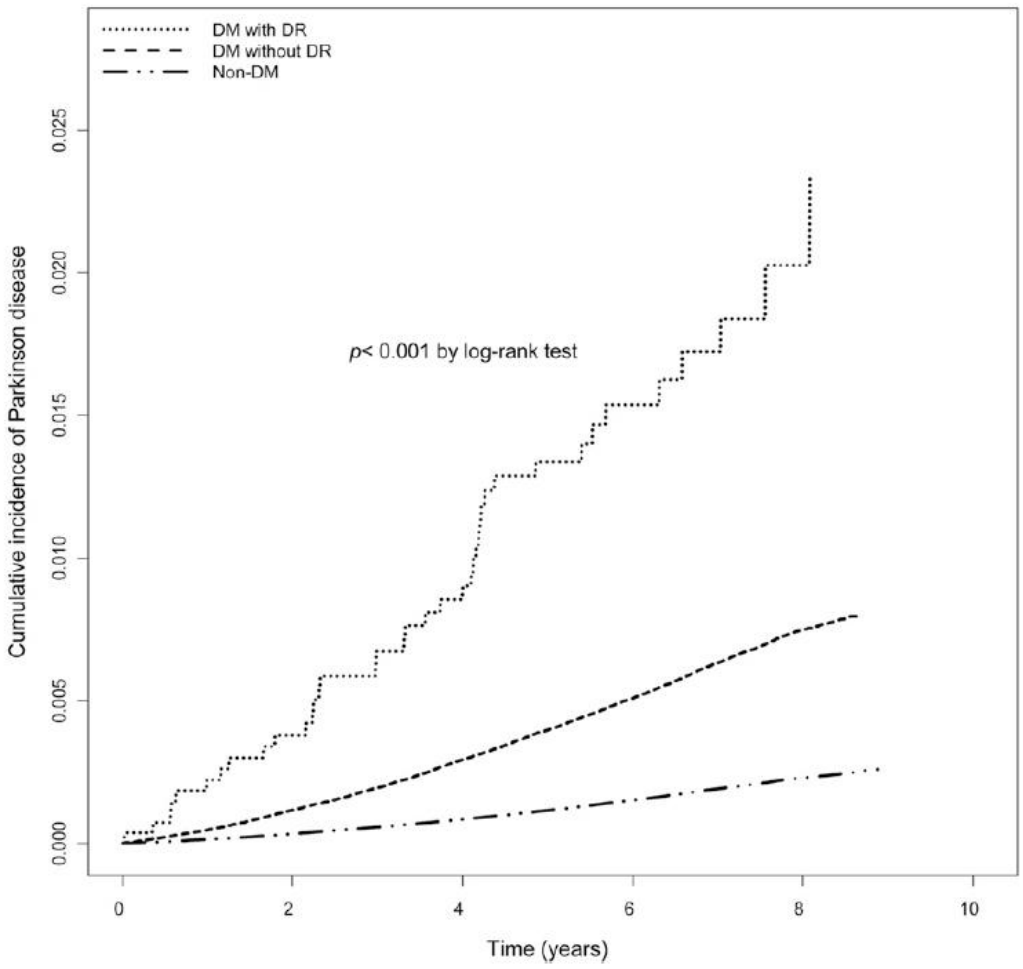

Figure 2. Cumulative incidence of Parkinson's disease stratified by diabetic status. Non-DM, patients without diabetes; without DR, diabetic patients without diabetic retinopathy; DR, patients with diabetic retinopathy.

Discussion

In agreement with previous studies[12-18], we found that diabetes was associated with an increased risk of incident PD. In addition, this association was more pronounced among patients with DR.

The higher PD risk in patients with diabetes may be explained by common dysregulated pathways such as mitochondrial dysfunction, ER stress, inflammation, and alteration of autophagy [6]. To support this contention, type 2 diabetic mice showed accelerated loss of dopamine neurons when treated with 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine, a toxin used for inducing PD [22]. Accumulating evidence suggests insulin resistance as a common mechanism explaining the links between PD and type 2 diabetes [27]. Insulin can cross the blood-brain-barrier, resulting in enhanced dopamine release and transmission in the striatonigral area [27, 28]. Indeed, patients with PD showed decreased expression of insulin receptor, as well as deactivated insulin signaling [29, 30]. Results showing beneficial effect of antidiabetic drugs on PD [31, 32] further support the importance of insulin resistance linking PD and diabetes.

The mechanism underlying the stronger association with incident PD among patients with DR is uncertain. A significant association between DR and PD in our study after adjustment for ESRD, PAD, fasting glucose level, and insulin usage (Table 2, model 4) suggests the possibility of a glucose-independent mechanism linking these two diseases. A recent study proposed a hypothesis that dopamine deficiency may be the common pathophysiologic mechanism of DR and PD [24]. Because DR can be developed even in some subjects with well-controlled diabetes [33], this hypothesis may explain why some patients with diabetes are more susceptible to the development of DR as well as PD. However, there exist several other possible explanations. In our study, patients with DR had more comorbidities including

hypertension, dyslipidemia, and end-stage renal disease when compared with subjects without diabetes or diabetic patients without DR (Table 1), raising the possibility that these risk factors might increase the incidence of PD. Alternatively, poor glycemic control, well established to cause diabetic microvascular complications [34-36] may be the common mechanism underlying co-occurrence of DR and PD. Although DR was significantly associated with incident PD after adjusting for fasting glucose level and insulin usage, this decreased the relative risk ratio in DR group (Table 2). This result suggests the possibility that severe or prolonged diabetes is a common mechanism between DR and PD. Future studies are warranted to test whether proper glycemic control can mitigate the risk of PD development in diabetic patients.

In our study, DR subjects also exhibited a higher incidence rate of PD than those without DR among younger patients aged 30 to 39 years. In relation to this, there is a subtype of PD called young-onset PD (YOPD), commonly defined as PD occurring in those aged 21 to 49 years[37]. Treatment of patients with YOPD is of importance because they are productive and have long life expectancy. Our study suggests that DR may be one of the risk factors of YOPD. However, we have to be cautious about interpreting the results from Cox proportional hazards regression analysis because statistical power might be of limited value due to the very low absolute number of patients with PD in this age group. Studies of longer duration are required to ascertain the association between DR and PD in younger patients with diabetes.

Our study has several limitations. First, we defined non-DR, DR, and PD using the claim data from the Korean NHIS database. Thus, the possible inaccuracy of the claims codes can lead to the misclassification of diseases. For example, because we designated diabetic patients without diagnostic code for DR as non-DR subjects, patients having undiagnosed

retinopathy could be misclassified as non-DR patients. This can underestimate the effect of DR on PD development. Second, data regarding the duration of diabetes, glycated hemoglobin and plasma creatinine level were not available; thus, the influence of severity of diabetes or other diabetic complications (i.e., diabetic nephropathy) could not be evaluated properly. However, we could not stratify chronic kidney disease by severity levels due to lack of data regarding creatinine levels. In addition, the Claim DB only provided information on more advanced diabetic nephropathy, the leading to overestimation of PD risk in patients with diabetic nephropathy. Third, as detailed information of medication used to treat diabetes was not available, possible effect of anti-diabetic medications on the development of PD [31, 32] could not be evaluated. Forth, alternative etiologies of PD such as drug, trauma, or brain injury were not considered. Despite these limitations, the large sample size would be the major strength of our study and may have helped make our study results valid.

In summary, the results of this large population-based study suggest that having DR as well as diabetes is an independent risk factor for the development of PD. Future studies are necessary to investigate the mechanism of increased risk of PD in DR, Possible mechanisms may include either a shared pathophysiology of dopamine deficiency in the central nervous system and retina, or long lasting poor glycemic control. At the same time, physicians should pay attention to the possibility of PD, in addition to diabetic neuropathy, when a patient with DR complains about motor and neurologic symptoms, even young patients.

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국문 요약

제목: 당뇨망막병증과 파킨슨병의 관계

배경: 당뇨병과 파킨슨병의 연관성은 이전의 많은 연구에서 다루어진 바 있으며 특히 당뇨망막병증의 경우 파킨슨병의 주된 병인인 도파민 부족과 연관되어 있을 가능성이 제시된 적 있다. 그러나 현재까지 이를 뒷받침할 만한 역학 연구가 없는 상태이다.

방법: 국민건강보험공단의 자료를 바탕으로 2005 년부터 2008 년까지 일반적인 건강 검진을 받은 14,912,368 명의 성인을 대상으로 하였다. 대상자들은 연구 시작 시점부터 비 당뇨병군, 당뇨망막병증이 없는 당뇨병군, 당뇨망막병증이 있는 당뇨병군으로 나뉘었으며, 파킨슨병의 발병시점이나 사망 혹은 2013 년 12 월 31 일까지 추적관찰 되었다. 통계학적 방법으로는 당뇨망막병증과 파킨슨병 발생과의 연관성을 분석하기 위해 Cox proportional hazard regression model 이 사용되었다.

결과: 관찰기간 동안 총 34,834 명의 대상자가 새로 파킨슨병을 진단 받았다. 파킨슨병의 발병율은 비 당뇨병군, 당뇨망막병증이 없는 당뇨병군, 당뇨망막병증이 있는 당뇨병군에 서 각각 10,000 인년 당 2.74, 8.39, 15.5 로 확인되었다. Multivariate Cox proportional hazard 모델에서, 당뇨망막병증이 있는 당뇨병군이 비 당뇨병 및 당뇨망막병증이 없는 당뇨병군에 비해 파킨슨병의

발병 위험도가 의미 있게 높았다. 이 결과는 나이, 성, 공복혈당 수치, 인슐린 사용 유무 및 다른 위험 요인들을 보정한 이후에도 변하지 않았다.

결론: 당뇨망막병증을 동반한 당뇨병군은 파킨슨병의 발생률을 의미 있게 높였다. 추후 이에 대한 메커니즘을 규명하는 후속 연구가, 중추신경계의 도파민 부족 및 장기간의 불량한 혈당 조절을 포함하여 진행되어야 할 필요가 있다.

중심단어: 당뇨병, 당뇨망막병증, 파킨슨병