Association Between Diabetic Retinopathy and Parkinson Disease: The Korean National Health Insurance Service Database

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Context: Studies have shown an association between diabetes and Parkinson 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.

Objective: We assessed the association between DR and incident PD using a population-based database.

Design/Setting/Participants: 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 into 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. **(*J Clin Endocrinol Metab* 103: 3231–3238, 2018)**

Parkinson 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

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Abbreviations: BMI, body mass index; DB, database; DR, diabetic retinopathy; ESRD, end-stage renal disease; HR, hazard ratio; ICD-10, International Statistical Classification of Diseases and Related Health Problems, 10th revision; NHIS, National Health Insurance Service; PAD, peripheral artery disease; PD, Parkinson disease; YOPD, young-onset Parkinson disease.

(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 that 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.

Materials and Methods

Data source and study population

The Korean National Health Insurance Service (NHIS), a single-payer system, is mandatory for all residents of Korea (25). The Korean NHIS database (DB) consists of a Qualification DB, Health Checkup 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 (26). 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 (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 one 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 DR

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. The diagnosis was made by using the International Statistical Classification of

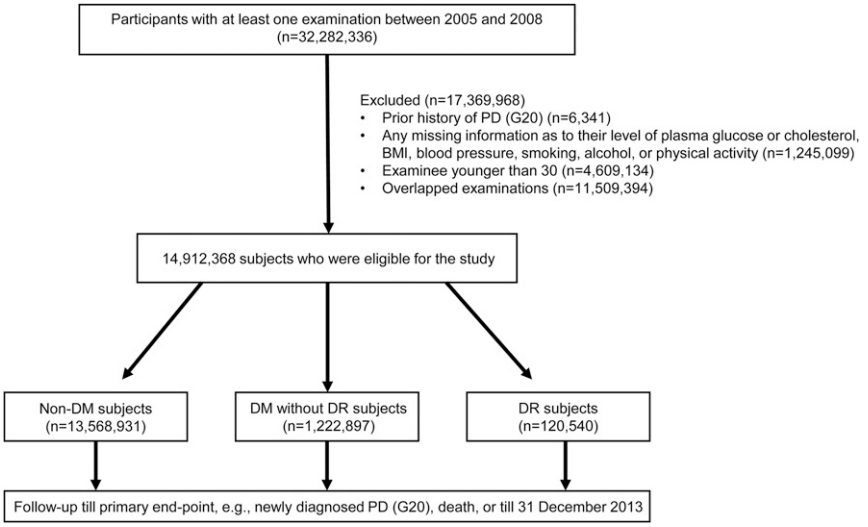

Figure 1. Study population. In total, 32,282,336 subjects who underwent regular health checkups between 2005 and 2008 were reviewed; 17,369,968 subjects were excluded for the reasons illustrated, and 14,912,368 subjects were enrolled and divided into three groups according to diabetes and retinal complications. Subjects were followed up until the primary endpoint occurred: death or date of 31 December 2013. DM, patients with diabetes mellitus; non-DM, patients without diabetes mellitus.

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 at checkup were also considered as having type 2 diabetes regardless of the use of antidiabetic drugs. Subjects with diabetes were further subclassified according to presence of DR. DR was defined by the ICD-10 code H36.0 among patients with type 2 diabetes.

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 divided 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-glutamyltranspeptidase, and hemoglobin levels (27).

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-10 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; O7011 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 one diagnosis that could lead to an overestimation of the number of cases of PD. Patients with one or more diagnoses (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 χ^2 test for categorical variables were used. When significant, Bonferroni *post hoc* analysis was performed to identify intergroup differences. The incidence rate of PD was expressed as the number of events per 10,000 person-years. Cox proportional hazards regression analysis was used to calculate the hazard ratio (HR) for PD depending on the presence of diabetes or DR. Model 2 included age and 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 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 $P < 0.001$. We also separately analyzed the impact of having ESRD or PAD on PD development among patients with diabetes to determine whether the association between DR and PD was due to DR-specific effects or those of more severe diabetes. Because ESRD and PAD can occur in patients without diabetes and are considered to be related to PD development by themselves (28, 29), we performed analyses dividing ESRD or PAD subjects into those with or without diabetes. 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 a 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

Table 1. Baseline Characteristics of Subjects Who Participated in Regular Health Checkups From 2005 to 2008

	Non-DM (n = 13,568,931)	DM	
		Without DR (n = 1,222,897)	DR (n = 120,540)
Age (y)	48.6 ± 12.6	57.2 ± 12[a]	61 ± 9.7[b]
Men (%)	53.5	60.7[a]	48.2[b]
BMI (kg/m^2)	23.7 ± 3.1	24.9 ± 3.3[a]	24.5 ± 3.1
Current smoker (%)	24.0	25.7[a]	13.4[b]
Heavy drinker (%)	9.4	13.4[a]	6.6[b]
Physically active subjects (%)	8.3	13.1[a]	20.2[b]
Comorbidities, n (%)			
Hypertension	3,651,584 (26.91)	691,109 (56.51)[a]	81,035 (67.23)[b]
Dyslipidemia	1,973,067 (14.54)	390,686 (31.95)[a]	50,922 (42.24)[b]
ESRD	5954 (0.04)	1837 (0.15)[a]	982 (0.81)[b]
PAD	356,279 (2.62)	96,409 (7.88)[a]	17,504 (14.52)[b]

Values are presented as mean ± SD or number (%).

Abbreviations: DM, patients with diabetes mellitus; non-DM, patients without diabetes mellitus.

[a] <0.001 vs patients without diabetes.

[b] <0.001 vs patients with diabetes without DR.

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 (15).

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).

We also analyzed the impact of ESRD or PAD on the development of PD (Table 4). ESRD is associated with higher risk of PD development in patients without diabetes (HR 2.67, 95% CI 1.90 to 3.75; *P* for trend <0.001), and the risk was more pronounced in patients with diabetes and ESRD (HR 5.21, 95% CI 3.81 to 7.14; *P* for trend <0.001). Likewise, patients with diabetes and PAD were at a greater risk of developing PD when compared with patients having PAD without diabetes, as well as patients without PAD (Table 4).

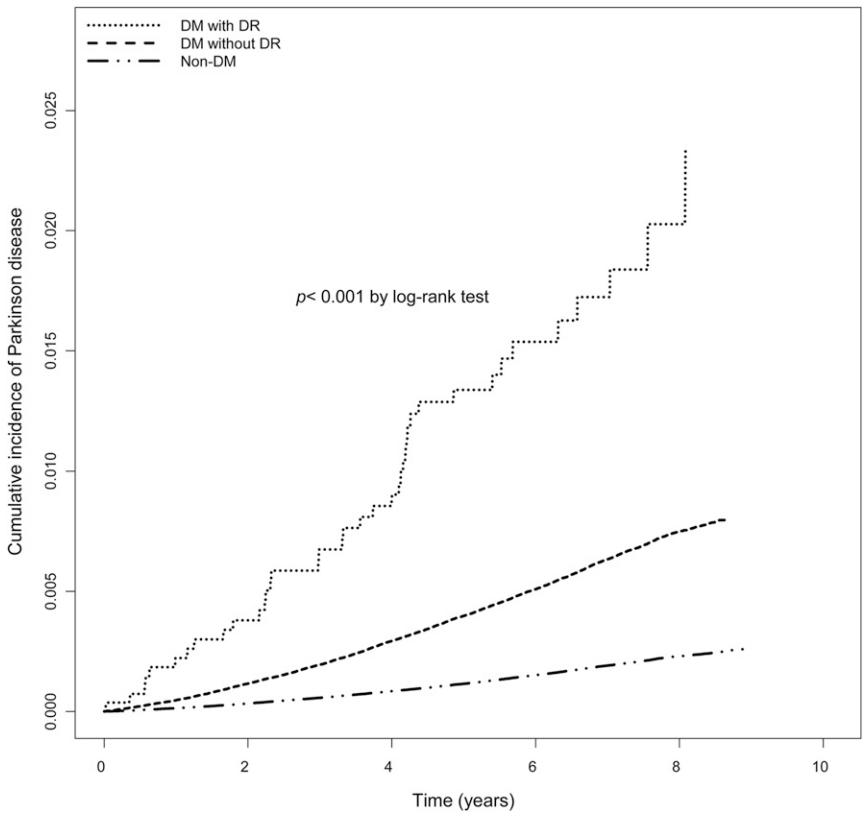

Figure 2. Cumulative incidence of PD stratified by diabetic status. DM, diabetes mellitus.

Discussion

In agreement with previous studies (12–18), we found that diabetes was

Table 2. Incidence and Risk of PD According to Diabetic Status and Sex

Variables	Initial Diabetic Status			*P* for Trend
		DM		
	Non-DM (n = 13,568,931)	Without DR (n = 1,222,897)	DR (n = 120,540)	
Total				
PD cases (n)	26,501	7066	1267	
PD incidence rate (per 10,000 person-y)	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)	<0.001
Model 2[b] HR (95% CI)	1 (reference)	1.59 (1.55–1.63)	2.52 (2.38–2.67)	<0.001
Model 3[c] HR (95% CI)	1 (reference)	1.54 (1.50–1.58)	2.39 (2.26–2.53)	<0.001
Model 4[d] HR (95% CI)	1 (reference)	1.33 (1.29–1.38)	1.75 (1.64–1.86)	<0.001
Men	7,255,888	742,239	58,096	
PD cases (n)	12,112	3188	495	
PD incidence rate (per 10,000 person-y)	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)	<0.001
Model 2[b] HR (95% CI)	1 (reference)	1.49 (1.43–1.54)	2.25 (2.05–2.46)	<0.001
Model 3[c] HR (95% CI)	1 (reference)	1.45 (1.39–1.51)	2.14 (1.95–2.34)	<0.001
Model 4[d] HR (95% CI)	1 (reference)	1.27 (1.21–1.34)	1.60 (1.45–1.78)	<0.001
Women	6,313,043	480,658	62,444	
PD cases (n)	14,389	3878	772	
PD incidence rate (per 10,000 person-y)	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)	<0.001
Model 2[b] HR (95% CI)	1 (reference)	1.70 (1.64–1.76)	2.74 (2.55–2.94)	<0.001
Model 3[c] HR (95% CI)	1 (reference)	1.63 (1.57–1.69)	2.59 (2.40–2.78)	<0.001
Model 4[d] HR (95% CI)	1 (reference)	1.39 (1.33–1.46)	1.85 (1.70–2.02)	<0.001

Abbreviations: DM, patients with diabetes mellitus; non-DM, patients without diabetes mellitus.

[a]Model 1: unadjusted.

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

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

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

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, endoplasmic reticulum stress, inflammation, and alteration of autophagy (6). To support this contention, mice with type 2 diabetes 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 (30). Insulin can cross the blood-brain barrier, resulting in enhanced dopamine release and transmission in the striatonigral area (30, 31). Indeed, patients with PD showed decreased expression of insulin receptor, as well as deactivated insulin signaling (30, 32). Results showing beneficial effect of antidiabetic drugs on PD (33, 34) 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 (35), 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, ESRD, and PAD, when compared with subjects without diabetes or patients with diabetes and 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 (35–37), 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, parallel assessments for other diabetic

Table 3. Incidence and Risk of PD According to Diabetic Status Stratified by Age Groups

	Initial Diabetic Status			
		DM		
Age Groups	Non-DM (n = 13,568,931)	Without DR (n = 1,222,897)	DR (n = 120,540)	*P* for Trend
30–39	3,657,489	95,240	2029	
PD cases (n)	627	28	2	
PD incidence rate (per 10,000 person-y)	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)	<0.001
Model 2[b] HR (95% CI)	1 (reference)	1.63 (1.11–2.38)	5.18 (1.29–20.79)	0.002
Model 3[c] HR (95% CI)	1 (reference)	1.47 (0.99–2.16)	4.21 (1.05–16.93)	0.014
Model 4[d] HR (95% CI)	1 (reference)	1.04 (0.62–1.76)	2.09 (0.44–9.99)	0.655
40–59	7,066,803	585,804	47,119	
PD cases (n)	4899	710	119	
PD incidence rate (per 10,000 person-y)	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)	<0.001
Model 2[b] HR (95% CI)	1 (reference)	1.47 (1.36–1.59)	2.74 (2.29–3.29)	<0.001
Model 3[c] HR (95% CI)	1 (reference)	1.38 (1.28–1.50)	2.52 (2.10–3.03)	<0.001
Model 4[d] HR (95% CI)	1 (reference)	1.11 (1.01–1.24)	1.53 (1.23–1.89)	<0.001
≥60	2,844,639	541,853	71,392	
PD cases (n)	20,975	6328	1146	
PD incidence rate (per 10,000 person-y)	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)	<0.001
Model 2[b] HR (95% CI)	1 (reference)	1.58 (1.54–1.63)	2.39 (2.25–2.54)	<0.001
Model 3[c] HR (95% CI)	1 (reference)	1.55 (1.51–1.59)	2.30 (2.17–2.44)	<0.001
Model 4[d] HR (95% CI)	1 (reference)	1.35 (1.30–1.40)	1.72 (1.60–1.84)	<0.001

Abbreviations: DM, patients with diabetes mellitus; non-DM, patients without diabetes mellitus.

[a]Model 1: unadjusted.

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

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

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

complications showed higher risk of PD development in subject with diabetes and ESRD or PAD (Table 4). 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 patients with diabetes.

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 (38). 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 important 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 DB. Thus, the possible inaccuracy of the claims codes can lead to the misclassification of diseases. For example, because we designated patients with diabetes without diagnostic code for DR as non-DR subjects, patients with 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 (*e.g.*, diabetic nephropathy) could not be evaluated properly. Indeed, because azotemia is considered to be related to PD development (28), analyses for nonazotemic, early-stage chronic kidney disease would be desirable to evaluate the impact of more severe or prolonged diabetes. 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, thus leading to overestimation of PD risk in patients with diabetic nephropathy. Third, as

Table 4. Incidence and Risk of PD Among Subjects With or Without DM, ESRD, and PAD

	Non-DM		DM		
	Without ESRD (n = 13,562,977)	ESRD (n = 5954)	Without ESRD (n = 1,340,618)	ESRD (n = 2819)	*P* for Trend
PD cases (n)	26,468	33	8294	39	
PD incidence rate (per 10,000 person-y)	2.74	8.76	8.99	25.83	
Model 1[a] HR (95% CI)	1 (reference)	3.28 (2.33–4.62)	3.31 (3.23–3.39)	10.09 (7.37–13.80)	<0.001
Model 2[b] HR (95% CI)	1 (reference)	2.99 (2.13–4.21)	1.68 (1.64–1.73)	5.98 (4.37–8.19)	<0.001
Model 3[c] HR (95% CI)	1 (reference)	2.67 (1.90–3.75)	1.62 (1.58–1.67)	5.21 (3.81–7.14)	<0.001
	Non-DM		DM		
	Without PAD (n = 13,212,652)	PAD (n = 356,279)	Without PAD (n = 1,229,524)	PAD (n = 113,913)	*P* for Trend
PD cases (n)	24,053	2448	7155	1178	
PD incidence rate (per 10,000 person-y)	2.55	10.23	8.42	15.90	
Model 1[a] HR (95% CI)	1 (reference)	4.08 (3.92–4.26)	3.32 (3.24–3.41)	6.41 (6.05–6.79)	<0.001
Model 2[b] HR (95% CI)	1 (reference)	1.47 (1.41–1.54)	1.69 (1.64–1.73)	2.19 (2.07–2.32)	<0.001
Model 3[c] HR (95% CI)	1 (reference)	1.41 (1.35–1.47)	1.63 (1.59–1.68)	2.07 (1.96–2.20)	<0.001

Abbreviations: DM, patients with diabetes mellitus; non-DM, patients without diabetes mellitus.

[a]Model 1: unadjusted.

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

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

detailed information of medication used to treat diabetes was not available, the possible effect of antidiabetic medications on the development of PD (33, 34) could not be evaluated. Fourth, 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 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 patients with DR complain of motor and neurologic symptoms, even young patients.

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