Diabetes in Patients With Idiopathic Parkinson's Disease

Claudia Becker, phd[1]
Gunnar P. Brobert, phd[2]
Saga Johansson, md, phd[3,4]
Susan S. Jick, dsc[5]
Christoph R. Meier, phd[1,5]

OBJECTIVE — Previous observational studies reported inconsistent results on the association between diabetes and Parkinson's disease, and data on the risk of developing incident diabetes in relation to Parkinson's disease are scarce. We aimed at comparing the diabetes prevalence between patients with or without Parkinson's disease and at exploring the risk of developing incident diabetes associated with Parkinson's disease.

RESEARCH DESIGN AND METHODS — We used the U.K.-based General Practice Research Database (GPRD) to *1*) compare the diabetes prevalence between Parkinson's disease cases and a matched comparison group free of Parkinson's disease between 1994 and 2005 and to *2*) conduct a follow-up study with a nested case-control analysis to quantify the risk of developing new-onset diabetes in association with Parkinson's disease.

RESULTS — The diabetes prevalence was similar in patients with and without Parkinson's disease (adjusted odds ratio [OR] 0.95 [95% CI 0.80–1.14]). In the cohort analysis (incidence rate ratio [IRR] 0.55 [95% CI 0.38–0.81]) and in the nested case-control analysis (adjusted OR 0.53 [95% CI 0.33–0.87]), the risk of developing diabetes was lower in patients with Parkinson's disease than in subjects without. The adjusted OR for patients with Parkinson's disease who were current levodopa users of five or more prescriptions was 0.22 (0.10–0.48) and was 1.11 (0.50–2.45) for Parkinson's disease patients not using levodopa.

CONCLUSIONS — In this observational study, diabetes prevalence was closely similar between patients with Parkinson's disease and subjects without. The risk of developing incident diabetes was lower for patients with Parkinson's disease than for patients without, a finding that was limited to Parkinson's disease patients who were using levodopa.

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Idiopathic Parkinson's disease is a common neurodegenerative disease that may be related to mitochondrial dysfunction, oxidative stress, excitotoxicity, apoptosis, and inflammation (1,2). Chronic systemic inflammation, as well as impaired mitochondrial metabolism, have also been suspected of playing a role in the development of type 2 diabetes (3–5), and the possibility of a shared pathophysiology of Parkinson's disease and type 2 diabetes has been put forth (6,7). However, observational studies investigating the association of these two disorders are scarce. Two recent case-control studies provided evidence for a possibly reduced risk for Parkinson's disease in diabetic patients (8,9), whereas others reported a higher diabetes prevalence in Parkinson's disease patients (10,11), and recent data from the Nurses Health Study suggest that the risk of developing Parkinson's disease does not differ between patients with or without diabetes (12). To our knowledge, the risk of developing an incident diagnosis of diabetes in Parkinson's disease patients has not yet been explored.

From the [1]Basel Pharmacoepidemiology Unit, Division of Clinical Pharmacology and Toxicology, University Hospital, Basel, Switzerland; [2]AstraZeneca Research and Development, Södertälje, Sweden; [3]AstraZeneca Research and Development, Mölndal, Sweden; the [4]Institute of Medicine, Sahlgrenska Academy, Göteborg University, Göteborg, Sweden; and the [5]Boston Collaborative Drug Surveillance Program, Boston University Medical Center, Lexington, Massachusetts.
Corresponding author: Christoph R. Meier, meierch@uhbs.ch.
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Studies from the 1970s described Parkinson's disease patients with hyperglycemia and hyperinsulinemia and raised the proposition that levodopa may be associated with an increased diabetes risk (13,14), whereas bromocriptine increased insulin sensitivity in an animal model (15). We conducted a large population-based study in two parts. The aim of the first part was to assess the prevalence of diabetes in patients with newly diagnosed Parkinson's disease and to compare it with patients without Parkinson's disease. The aim of the second part was to quantify the risk of new-onset diabetes in Parkinson's disease patients and to compare it with patients free of Parkinson's disease, as well as to assess the possible role of anti-Parkinson medication on the risk of developing an incident diabetes diagnosis.

RESEARCH DESIGN AND METHODS

Data source

We used the U.K.-based General Practice Research Database (GPRD), which contains computerized medical records of >5 million people who are registered with selected general practitioners (16–18). In the U.K., general practitioners are responsible for primary health care, as well as for referrals to specialists and for hospitalizations (except in emergency situations). They record information on patient demographics (age, sex, weight, and height), diagnoses, drug prescriptions, referrals, and hospital admissions, as well as some lifestyle information (e.g., smoking status). The recorded information on drug exposure and on diagnoses in the GPRD has been validated repeatedly and proven to be of high quality (19,20). The GPRD, one of the world's largest databases of anonymized patient records, is managed by the Medicines and Healthcare products Regulatory Agency in the U.K. The patients enrolled in the GPRD are representative of the U.K. population with regard to age, sex, geographic distribution, and annual turnover rate (16), and GPRD data have been used in previous studies on Parkinson's disease (21–25). The study protocol was reviewed and approved by the Independent Scientific

Advisory Committee (ISAC) for Medicines and Healthcare Products Regulatory Agency Database Research. The investigators had only access to anonymized information.

The base population consisted of all patients in the GPRD who were aged ≥40 years between 1 January 1994 and 31 December 2005. Within this base population, we identified all patients with a recorded first-time diagnosis of idiopathic Parkinson's disease and, at random, an equally sized comparison group of subjects without Parkinson's disease. We matched this comparison group to Parkinson's disease patients on age (same year of birth), sex, general practice (i.e., Parkinson's disease patients and the comparison subject had to be enrolled with the same general practitioner), date of the first Parkinson's disease diagnosis, and years of history in the GPRD before this Parkinson's disease diagnosis date. Parkinson's disease case subjects and patients from the comparison group had to have at least 3 years of medical history in the computer record before the index date. The Parkinson's disease patients and the one-for-one matched sample of Parkinson's disease–free patients (i.e., the comparison group) formed the study population.

We only included Parkinson's disease case subjects with an incident diagnosis of "idiopathic Parkinson's disease," which we defined as follows: Parkinson's disease case subjects must not have had more than one prescription for an anti-Parkinson medication recorded before the index date, which was characterized by the first recording of an OXMIS (Oxford Medical Information System) code 342 ("Paralysis agitans") or 342 D ("idiopathic parkinsonism") or READ-codes F12..00 ("Parkinson's disease"), F12z.00 ("Parkinson's disease NOS"), or F120.00 ("Paralysis agitans"); must not have received any prescription for drugs known to induce Parkinsonism ("typical" antipsychotic drugs, metoclopramide, or cinnarizine) within 180 days before the recorded Parkinson's disease diagnosis; and must have received at least two prescriptions for anti-Parkinson drugs after the index date in order to be eligible to be included in the analysis.

Part 1: assessment of the diabetes prevalence in Parkinson's disease patients and in the comparison group

We assessed and compared the prevalence of diabetes, demographic characteristics, and a range of previously recorded diagnoses of chronic diseases such as hyperlipidemia, asthma/chronic obstructive pulmonary disease (COPD), dementia, and various cardiovascular and neurological diseases before the Parkinson's disease diagnosis date (and the corresponding date in the comparison group). We expressed relative risk estimates as odds ratios (ORs) with 95% CIs, and we adjusted the crude OR for comorbidities in a multivariate conditional logistic regression analysis.

Part 2: assessment of incident diabetes in Parkinson's disease patients and in the comparison group: cohort analysis

From the study population of Parkinson's disease case subjects and matched Parkinson's disease–free comparison patients, we excluded those with a history of diabetes before the first recorded Parkinson's disease diagnosis (or the corresponding date in the matched comparison group), as well as patients with a history of cancer, HIV, alcoholism, or drug abuse. We followed both the remaining newly diagnosed Parkinson's disease patients and the matched Parkinson's disease–free comparison group, from the start of the follow-up date (i.e., the date of the Parkinson's disease diagnosis or the corresponding date in the Parkinson's disease–free comparison group) and identified all patients in the study population who developed new-onset diabetes during follow-up. We accumulated person-time from the start date until a patient developed diabetes, died, the medical record ended, or the end of the study was reached (31 December 2005), whichever came first. The date when a case subject had the first-time diagnosis of diabetes recorded will be referred to as the "index date." To be included in the analysis as a valid incident diabetes case subject, a patient had to have a documented code for diabetes recorded and must have either received treatment with antidiabetes drugs (insulin or oral antidiabetes drugs or both) after the date of the first diabetes diagnosis, or if no antidiabetes drug use was recorded in the medical record, notes such as "diabetic on diet only" had to be recorded by the general practitioner. If no treatment and no diet recommendation were recorded, we excluded the case. If a potential case had antidiabetes treatment recorded shortly before the index date, we included the case subject and corrected the index date. If a case subject had a long-standing history of antidiabetes drug use before the index date and/or if the index date was not clear for other reasons, we excluded the case subject. For the purpose of this case subject validation, we manually reviewed computer records of all potential case subjects, blinded to the subject's exposure status (i.e., Parkinson's disease or non–Parkinson's disease group). We assessed incidence rates (IRs) of first-time diagnosed diabetes in the population with Parkinson's disease and in the Parkinson's disease-free comparison group, and we calculated relative risk estimates with 95% CIs by comparing diabetes IRs between Parkinson's disease patients and the comparison group.

Nested case-control analysis

To identify potential risk factors for diabetes, to adjust the analysis on the association between Parkinson's disease and the risk of developing diabetes for such potential confounders, and to stratify Parkinson's disease patients by anti-Parkinson medication used, we conducted a nested case-control analysis. We identified, at random, for each incident diabetes case subject up to four control patients from the study population who did not develop diabetes, and we matched these control subjects to case subjects based on age (±3 years), sex, and calendar time. Control subjects had to be alive at the index date. We assessed for all diabetes case subjects and their control subjects whether they had Parkinson's disease or not, what anti-Parkinson medication (if any) they were using before the index date, how many prescriptions they had, and at what point in time the last prescription was recorded before the index date. If the last prescription was recorded within 90 days before the index date, the patient was a "current user," and if this was >3 months before the index date the patient was a "past user." We also assessed smoking status (nonsmoker, current smoker, ex-smoker, or unknown), BMI (<25, 25–29.9, ≥30 kg/m^2, or unknown), as well as recorded chronic diseases such as hypertension, hyperlipidemia, or ischemic heart disease. We conducted conditional logistic regression analyses to explore the relative risk of developing a diabetes diagnosis in association with previously recorded Parkinson's disease, expressed as ORs with 95% CIs, and adjusted this analysis by the parameters described above. In addition, since β-blockers, diuretics, and systemic steroids are known to be associated with an increased diabetes risk, we also assessed the number and the timing of previous prescriptions for these drugs and compared such drug use before the index date between diabetes case and control sub-

jects. Furthermore, we stratified the main analysis on the Parkinson's disease–diabetes association by age, sex, and anti-Parkinson medication used. All statistical analyses were performed with SAS software, version 9.1 (SAS Institute, Cary, NC).

RESULTS — The study population encompassed 7,274 subjects (3,637 Parkinson's disease case subjects and 3,637 matched subjects in the comparison group free of Parkinson's disease), of which 60% were men. Approximately 90% of the Parkinson's disease case subjects had their first Parkinson's disease diagnosis recorded after the age of 60 years.

Part 1: assessment of the diabetes prevalence in Parkinson's disease patients and in the comparison group

A prevalent diagnosis of diabetes was recorded in 291 (8%) of Parkinson's disease case subjects and in 308 (8.5%) of patients free of Parkinson's disease, yielding an OR of 0.95 (95% CI 0.80–1.14), adjusted for BMI, smoking, asthma/COPD, dementia, hypertension, ischemic heart disease, congestive heart failure, stroke/transient ischemic attack, arrhythmia, hyperlipidemia, epilepsy, affective disorders, schizophrenia, and neurotic and somatoform disorders.

Part 2: assessment of incident diabetes in Parkinson's disease patients and in the comparison group: cohort analysis

During follow-up, we identified 106 patients with an incident diabetes diagnosis who met the inclusion criteria as described above. Based on the specific codes used by the general practitioner and on the treatment pattern, all had type 2 diabetes; of these, 35 (33%) had a prior Parkinson's disease diagnosis and 71 (67%) had no history of Parkinson's disease, yielding a crude relative risk of 0.55 (95% CI 0.38–0.81) for Parkinson's disease patients compared with patients in the comparison group. The results of the person-time analyses are displayed in detail in Table 1.

Nested case-control analysis

Patient characteristics of 106 diabetic case subjects and their 424 matched control subjects in the nested case-control analyses are displayed in Table 2. A previous history of Parkinson's disease was associated with a decreased risk of developing an incident diabetes diagnosis (OR 0.53 [95% CI 0.33–0.87]), adjusted for age, sex, and calendar time (by matching) and for BMI, smoking status, hypertension, ischemic heart disease, hyperlipidemia, exposure to systemic steroids, β-blockers, or diuretics in the multivariate model. The diabetes risk for patients with Parkinson's disease tended to be slightly higher in men than in women, and stratification by age resulted in a reduced risk for patients aged <75 years (Table 3). Both *P* values for effect modification were >0.25.

We further stratified Parkinson's disease patients by use of anti-Parkinson medication before the diabetes diagnosis. The adjusted OR for developing diabetes for Parkinson's disease patients with current levodopa exposure of more than five prescriptions before the diabetes diagnosis was 0.22 (95% CI 0.10–0.48), compared with patients without Parkinson's disease (and therefore no levodopa use). The adjusted OR for Parkinson's disease patients not receiving levodopa before the diabetes diagnosis was 1.11 (0.50–2.45), compared with patients without Parkinson's disease (Table 3). A direct comparison between Parkinson's disease patients with current levodopa use with the reference group of Parkinson's disease patients without levodopa use yielded an OR of 0.30 (0.13–0.72). There were too few prescriptions for other anti-Parkinson drugs to conduct further analyses on their effects.

CONCLUSIONS — In the first part of this large primary care–based observational study, the prevalence of diabetes at the date of the first-time Parkinson's disease diagnosis was closely similar to a randomly selected, matched comparison group of patients without diagnosed Parkinson's disease (OR 0.95 [95% CI 0.80–1.14]). Two recent case-control studies (8,9) also explored the association between diabetes and Parkinson's disease. In one study (8), encompassing 352 Parkinson's disease case subjects and 484 control subjects, the risk for Parkinson's disease was significantly reduced in men with a previous diabetes diagnosis (OR 0.52 [0.28–0.97]) but not in women (0.80 [0.35–1.83]). The authors of the second study (9), a hospital-based, case-control analysis including 178 Parkinson's disease case subjects and 533 control subjects, reported a substantially lower diabetes prevalence in Parkinson's disease case subjects (3.4%) than in control subjects (10.9%), yielding a crude OR of 0.30 (0.13–0.72). The authors (9) stated, however, that the OR was no longer statistically significantly reduced when they applied a multivariate analysis, but they did not provide more details. In contrast, a prospective follow-up study (11) in Finland identified 633 incident Parkinson's disease case subjects and found an increased risk of developing Parkinson's

Table 1—*Number of diabetic case subjects and IRs per 1,000 person-years, stratified by age and sex*

	Patients with Parkinson's disease diagnosis			Patients without Parkinson's disease			
	n	Person-years	IR (95% CI)	*n*	Person-years	IR (95% CI)	IRR (95% CI)
All	35	11,307.4	3.10 (2.23–4.30)	71	12,679.1	5.60 (4.44–7.06)	0.55 (0.38–0.81)*
Men	23	6,605.6	3.48 (2.32–5.22)	42	7,327.0	5.73 (4.24–7.74)	0.61 (0.38–0.99)†
Women	12	4,701.9	2.55 (1.46–4.46)	29	5,352.1	5.42 (3.78–7.77)	0.47 (0.26–0.87)‡
Age (years)							
40–49	—	125.5	—	—	122.0	—	—
50–59	2	752.8	2.66 (0.73–9.63)	9	738.4	12.19 (6.43–23.00)	0.22 (0.07–0.71)§
60–69	10	2,331.9	4.29 (2.33–7.88)	14	2,365.3	5.92 (3.53–9.91)	0.73 (0.33–1.61)§
70–79	14	4,480.7	3.12 (1.86–5.24)	28	4,899.2	5.72 (3.96–8.25)	0.55 (0.30–1.00)§
≥80	9	3,616.5	2.49 (1.31–4.72)	20	4,554.3	4.39 (2.84–6.77)	0.57 (0.27–1.18)§

*Compared with all patients without Parkinson's disease. †Compared with male patients without Parkinson's disease. ‡Compared with female patients without Parkinson's disease. §Compared with control subjects of the same age-group.

Table 2—*Distribution of characteristics and comorbidities in case and control subjects in the nested case-control analysis*

Characteristics	Diabetic case subjects	Control subjects	Adjusted OR (95% CI)*
n	106	424	
Age (years)			
40–59	11 (10.4)	39 (9.2)	—
60–79	66 (62.3)	266 (62.7)	—
≥80	29 (27.3)	119 (28.1)	—
Sex			
Male	65 (61.3)	260 (61.3)	—
Female	41 (38.7)	164 (38.7)	—
Smoking status			
Nonsmoker	56 (52.8)	243 (57.3)	1.00 (referent)
Current smoker	9 (8.5)	47 (11.1)	0.94 (0.39–2.27)
BMI (kg/m²)			
<25	16 (15.1)	141 (33.3)	1.00 (referent)
25–29.9	42 (39.6)	135 (31.8)	2.52 (1.23–5.17)
≥30	28 (26.4)	46 (10.9)	3.80 (1.74–8.30)
Comorbidities			
IHD	50 (27.2)	163 (22.2)	1.30 (0.69–2.46)
Hypertension	58 (54.7)	144 (34.0)	1.49 (0.79–2.79)
Dyslipidemia	18 (17.0)	43 (10.1)	1.40 (0.63–3.11)
Prior drug use†			
β-Blockers	26 (24.5)	55 (13.0)	1.44 (0.70–2.93)
Diuretics	47 (44.3)	88 (20.8)	2.79 (1.41–5.53)
Systemic steroids	8 (7.6)	12 (2.8)	6.66 (2.04–21.72)

Data are *n* (%), unless otherwise indicated. *Adjusted for covariates in this Table. †Most recent drug prescription within 3 months before the index date and five or more prescriptions in total.

disease in diabetic subjects compared with patients without diabetes (hazard ratio 1.85 [95% CI 1.23–2.80]). A higher prevalence of diabetes has also been reported in Parkinson's disease patients in a cross-sectional survey (10). Finally, a recent prospective analysis of data from the Nurses' Health Study and the Health Professionals Follow-up Study encompassing 530 incident Parkinson's disease case subjects found no evidence for a difference in the risk of developing Parkinson's disease between patients with and without diabetes (relative risk 1.04 [95% CI 0.74–1.46]) (12), a finding that is consistent with our observation. Thus, previous studies exploring the association between diabetes and Parkinson's disease risk produced inconsistent results, whereby the methodology of these studies differed substantially. Furthermore, most of these studies were rather small in size with case groups of ~200–500 patients, while our study encompassed a much larger Parkinson's disease population.

Table 3—*Risk of diabetes in the nested case-control analysis*

Parameter	Case subjects (%)	Control subjects (%)	Adjusted OR (95% CI)*
n	106	424	
No Parkinson's disease	71 (67.0)	209 (49.3)	1.00 (referent)
Parkinson's disease	35 (33.0)	215 (50.7)	0.53 (0.33–0.87)
Men	23 (65.7)	136 (63.3)	0.57 (0.30–1.08)
Women	12 (34.3)	79 (36.7)	0.34 (0.13–0.91)
Age (years)			
40–74	18 (51.4)	121 (56.3)	0.44 (0.21–0.91)
≥75	17 (48.6)	94 (43.7)	0.71 (0.33–1.56)
No use of levodopa	13 (37.1)	47 (21.9)	1.11 (0.50–2.45)
Current use of levodopa†	11 (31.4)	131 (60.9)	0.22 (0.10–0.48)
Any other use of levodopa‡	11 (31.4)	37 (17.2)	0.88 (0.42–1.81)

Data are *n* (%), unless otherwise indicated. *Adjusted for covariates from Table 2. †Five or more prescriptions before the diabetes diagnosis. ‡Current use of less than five prescriptions or past use.

A potential confounder of the association between diabetes and Parkinson's disease risk may be obesity. While obesity is a well-known risk factor for type 2 diabetes (26), results from observational studies on the association between obesity and Parkinson's disease are ambiguous. Authors of a large U.S.-based observational study (27) concluded that their findings did not support a role of obesity in the Parkinson's disease pathogenesis, but others reported an association between obesity and an increased Parkinson's disease risk in observational studies (28,29). In our analysis, the BMIs of Parkinson's disease patients and Parkinson's disease–free control subjects did not differ substantially at the date of the first Parkinson's disease diagnosis or the corresponding date in the Parkinson's disease–free comparison group. Compared with the reference group of subjects with a BMI <25 kg/m^2, the relative risk estimates of developing Parkinson's disease for subjects with a BMI of 25–29.9 kg/m^2 (OR 1.00 [95% CI 0.89–1.13]) or of ≥30 kg/m^2 (0.88 [0.74–1.05]) were close to 1.0.

We not only assessed the association between diabetes and the risk of developing Parkinson's disease (part 1) but also of developing new-onset diabetes associated with a previous Parkinson's disease diagnosis (part 2). To our knowledge, the association between Parkinson's disease and the risk of developing a subsequent incident diabetes diagnosis has not been studied before. The findings of the present analysis suggest that incident diabetes occurs less frequently in patients with Parkinson's disease compared with those without Parkinson's disease (OR 0.53 [95% CI 0.33–0.87]). The substantial diabetes risk reduction seen in association with Parkinson's disease was driven by levodopa users, while the risk for developing diabetes was not altered for Parkinson's disease patients not using levodopa. We cannot tell whether this finding points to a causal association, whether it is the result of some bias, or whether it is a chance finding. It is in some contrast to a report from the 1970s in which levodopa was orally administered for 1 year to 23 patients and caused substantially impaired glucose tolerance in the majority of these patients (14). The authors explained their findings by a possibly increased glycogenolysis and

inhibition of peripheral glucose utilization caused by levodopa. This result was not confirmed by other authors (13) who exposed patients with levodopa for at least 3 months, which lead to a slight improvement of the fasting serum glucose and insulin sensitivity. However, the study was small and the observed effect did not reach statistical significance (13).

Our study has several limitations. Both Parkinson's disease and diabetes are diseases of slow onset, and, therefore, the onset of disease precedes the actual diagnosis date recorded in the database (which we used as the index date). For this reason, we only included Parkinson's disease patients who did not have anti-Parkinson medication before the first diagnosis date to reduce the likelihood of including prevalent case subjects with a longer-term history of Parkinson's disease symptoms. In addition, we only included diabetes case subjects in the follow-up portion of the study whose medical records provided evidence that the diagnosis was incident (i.e., followed by a newly introduced antidiabetes treatment). It is further possible that we did not capture all diabetes case subjects during follow-up since diabetes may go undetected due to the lack of specific clinical symptoms. Ideally, this may have occurred at random (i.e., regardless of a previous Parkinson's disease diagnosis), leading to a risk reduction toward to null. However, it is also possible that the likelihood of detecting diabetes did not occur at random but was dependent on disease status and therefore to some degree on medical attention. In this latter case, however, one might rather expect higher medical awareness in Parkinson's disease case subjects than in the comparison group of patients free of Parkinson's disease, which would have biased toward an increased diabetes risk. We adjusted the nested case-control analysis for BMI, various chronic diseases, and various drugs that reflect overall morbidity and that are known risk factors for diabetes. These adjustments did not materially change the association between Parkinson's disease and the risk of developing new-onset diabetes.

In summary, the findings of the first part of this observational study suggest that the prevalence of diabetes does not substantially differ between patients with newly diagnosed Parkinson's disease and subjects without Parkinson's disease. The results of the second part suggest that the risk of developing an incident diabetes diagnosis tends to be lower in Parkinson's disease patients than in subjects without Parkinson's disease. This effect was limited to Parkinson's disease patients who used levodopa.

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