Multicentre analysis of 178,992 type 2 diabetes patients revealed better metabolic control despite higher rates of hypertension, stroke, dementia and repeated inpatient care in patients with comorbid Parkinson’s disease

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A B S T R A C T

Background: Especially in older people, physicians are faced with the coexistence of type 2 diabetes mellitus (T2DM) and Parkinson’s disease (PD). Therefore, this research aimed to compare diabetes endpoints between T2DM with and without PD.

Methods: Based on the standardized, multicenter, prospective DPV database, 178,992 T2DM patients (>40 years) were analyzed. 1579 were diagnosed with PD and/or received specific treatment. Hierarchical multivariable regression models were used for group comparisons; adjusted estimates based on observed marginal frequencies were calculated.

Results: PD patients were significantly older (77.9 vs. 70.0 years; p < 0.0001) and had a longer diabetes duration (10.3 vs. 8.4 years; p < 0.0001). In young PD patients (<50 years), percentage of females was significantly higher compared to age-matched T2DM patients without PD or people of the German population (66.7 vs. 38.1 vs. 49.0%; p < 0.0001, p < 0.02).

After demographic adjustment, T2DM patients with PD showed a significantly lower HbA1c (58.0 vs. 60.3 mmol/mol; p < 0.0001), OAD/GLP-1 treatment (41.9 vs. 45.9%; p < 0.01) and frequency of dyslipidemia (62.0 vs. 64.5%; p < 0.05). In contrast, rates of insulin therapy (57.8 vs. 54.8%; p < 0.05), hypertensive medication (60.4 vs. 56.1%; p < 0.01), stroke (12.0 vs. 7.3%; p < 0.0001), dementia (5.2 vs. 2.6%; p < 0.0001) and repeated inpatient care (15.7 vs. 12.0%; p < 0.0001) were significantly higher and duration of hospital stay (5.2 vs. 4.7 days; p < 0.0001) was significantly longer in T2DM with PD.

Conclusion: Clear demographic and clinical differences were observed between T2DM with and without PD. In PD patients, metabolic control is better, potentially due to more intensive medical care.

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1. Introduction

Parkinson’s disease (PD) is one of the most frequent neurodegenerative diseases in aging people, due to a decrease of dopamine producing neurons in the substantia nigra. Typical symptoms include slowing of movements, muscle stiffness, difficulties in performing...
automatic sequential and simultaneous movements, tremor at rest, personality changes, increased salivation, loss of facial expression and dysphagia. Consequently, quality of life is dramatically impaired.

Among the general European population, PD prevalence amounts to 0.1–0.3% [1]. According to cohort studies, about 0.3%–2.4% of PD patients are additionally affected by diabetes mellitus [2–5]. The association between the two diseases was investigated in several previous studies, but with inconsistent results. Some showed an increased risk for PD in diabetes patients [2,4] while others found no association [3,5] or even an inverse association [6,7]. However, diabetes endpoints like HbA1c, anti-hyperglycemic therapy, rates of complications or frequency of repeated inpatient care were not yet studied. Therefore, the purpose of this research was to investigate these parameters in a large cohort of type 2 diabetes mellitus (T2DM) patients with comorbid PD compared to T2DM patients without PD. The following questions should be answered:

1. Is gender distribution in T2DM with PD different from T2DM without PD?
2. Is body mass index (BMI) in T2DM with PD lower than in T2DM without PD?
3. Are there differences in anti-hyperglycemic therapy?
4. Are complications and comorbidities more prevalent in T2DM with PD than in T2DM without PD?
5. Is repeated inpatient care more frequent or longer in T2DM with PD than in T2DM without PD?

2. Methods

2.1. Subjects

Basis for the present research was the standardized, prospective, multicenter DPV database (www.d-p.v.de). DPV stands for the German Diabetes Prospective Documentation, a computer-based documentation program for diabetes diagnosis and patient’s care currently used by 382 specialized centers of the DPV initiative from Germany and Austria. For central analyses [8,9], locally documented data were semi-annually transmitted to the University of Ulm, Germany in anonymous form. To ensure plausibility, the transmitted data are checked and correction is requested from participating centers in case of inconsistent data. For a cumulative database all data of each participating center are aggregated. The DPV initiative has been approved by the local Ethical Committee.

Until September 2012, 178,992 T2DM patients aged 40 years or older with plausible data on demographic and clinical variables were registered in DPV by 148 German and 5 Austrian centers. Patients with other forms of diabetes were excluded from the present analysis. For the selection of patients with PD, the database was searched for the diagnosis and treatment of PD according to ICD-10-codes, search terms like "parkinson", "paralysis agitans", "schüttelfühlmung", "parkinsonmittel", "parkinsonmedikament" and specific drugs against PD listed in the German drug catalog "yellow list Pharmindex" from the Medical Information GmbH, Neu-Issenburg, Germany. Patients were selected if either diagnosis or specific treatment or both were registered. Subjects with atypical or drug-induced parkinsonism were not included. Besides drugs with the agent levodopa, only specific anti-Parkinson drugs with PD as sole indication were considered as selection criteria. Patients on PD medication, but with other clinical diagnoses such as restless-legs-syndrome, Huntington’s chorea, multiple sclerosis or brain tumor, were not selected as PD patients. Also not selected were patients with PD medication and additional drugs used in the treatment of restless-legs-syndrome. Due to these selection criteria 1579 adult T2DM patients with PD were found and included in the present analysis. All other adult T2DM patients (n = 177,413) served as controls for the comparison between T2DM with and without PD. For each patient, datasets were aggregated over the last year of care.

2.2. Diabetes endpoints and their definitions

Metabolic control was assessed by hemoglobin A1c (HbA1c). Based on local reference ranges, HbA1c values were standardized to the DCCT reference range (20.7–42.6 mmol/mol) by the multiple of the mean (MOD) method [10]. Anti-hyperglycemic therapy was categorized as i) insulin therapy (insulin alone or with additional glucose lowering medication), ii) oral antidiabetic drug medication (OAD)/glucagon-like peptide-1 agonists (GLP-1), iii) non-pharmacological treatment only (physical activity, dietary advice). In patients treated with insulin, daily insulin dosage per kilogram body weight as well as rates of severe hypoglycemia and hypoglycemia with coma were additionally analyzed. Severe hypoglycemia was defined as “an event requiring assistance of another person to actively administer carbohydrate, glucagon, or other resuscitative actions" [11] and hypoglycemia with coma was defined as the state, when the episode previously described is associated with sufficient neuroglycopenia to induce coma [11].

Antihypertensive or lipid lowering medication was defined as documentation of drugs at least once during the last year of care. Criteria for hypertension were an elevated median blood pressure as described in Refs. [8,12] and/or the use of antihypertensive medication. Dyslipidemia was diagnosed in patients with lipid lowering medication and/or with at least one blood lipid value on average above (below) the ATP III thresholds [13] as described elsewhere [8]. In patients without antihypertensive or lipid lowering medication, blood pressure or lipid status were additionally analyzed. Renopathy (proliferative and non-proliferative) was diagnosed if patients had at least one abnormal retinal examination documented during the last year of care. Microalbuminuria was diagnosed if at least two of three tests according to the guidelines of the American Diabetes Association were abnormal [14]. Threshold was a urinary albumin excretion >30 mg/24 h (>20 μg/min on a timed sample or >30 μg/g creatinine on a random collection) [14]. Diabetic foot syndrome, according to the guidelines of the German Diabetes Association [15], myocardial infarction, stroke and dementia were each ascertained by ICD-codes and/or free text. Renal failure was diagnosed in patients with glomerular filtration rate (GFR) <60 ml/min/1.73 m2 during the last treatment year and/or renal transplantation or dialysis. GFR was estimated by the Modification of Diet in Renal Disease (MDRD) formula according to Silvero et al. [16]. For males: GFR [ml/min/1.73m2] = 175 × [serum creatinine [mg/dl] × 0.742]−1.154 × [age [a]]−0.203 \( a \geq 18 \) years. For females: GFR [ml/min/1.73m2] = 175 × [serum creatinine [mg/dl] × 0.742]−1.154 × [age [a]]−0.203 \( a < 18 \) years. Rate of repeated inpatient care and duration of hospital stay were also studied. At least two inpatient admissions during the last treatment year were defined as repeated inpatient care.

2.3. Statistical analysis

Descriptive statistics were implemented for demographic variables for the whole study population and for T2DM patients with and without PD separately. Data

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Demographics of the whole study population and of T2DM patients with and without PD separately.</th>
</tr>
</thead>
<tbody>
<tr>
<td>All (n = 178,992)</td>
<td>T2DM without PD (n = 177,413)</td>
</tr>
<tr>
<td><strong>Age [year]</strong></td>
<td>70.1 [61.1; 77.4]</td>
</tr>
<tr>
<td><strong>Age at diabetes onset [year]</strong></td>
<td>58.8 [40.4; 68.1]</td>
</tr>
<tr>
<td><strong>Diabetes duration [year]</strong></td>
<td>8.4 [3.1; 15.0]</td>
</tr>
<tr>
<td><strong>Gender ratio [male/female, %]</strong></td>
<td>51.1/48.9</td>
</tr>
<tr>
<td><strong>Body weight [kg]</strong></td>
<td>84.3 [73.0; 97.6] (n = 158,106)</td>
</tr>
<tr>
<td>Male</td>
<td>85.2 [79.0; 102.0] (n = 81,110)</td>
</tr>
<tr>
<td>Female</td>
<td>79.0 [68.0; 91.4] (n = 76,996)</td>
</tr>
<tr>
<td><strong>BMI [kg/m²]</strong></td>
<td>29.6 [26.1; 33.8] (n = 158,106)</td>
</tr>
<tr>
<td>Male</td>
<td>29.3 [26.2; 33.1] (n = 81,110)</td>
</tr>
<tr>
<td>Female</td>
<td>30.0 [26.0; 34.6] (n = 76,996)</td>
</tr>
</tbody>
</table>

Data are presented as median with lower and upper quartile (median [Q1; Q3]) for continuous variables or as percentage (%) for dichotomous variables.

p-Values are shown for comparisons between T2DM with and without PD. BMI, body mass index (BMI), not significant (ns).

\( ^a \) No independent comparison.
are presented as median with lower and upper quartile (median [Q1; Q3]) for continuous variables and as percentage (%) for dichotomous variables. For group comparisons of continuous variables, Kruskal–Wallis test was used; dichotomous variables were compared by χ²-test.

In order to adjust for the difference in age, gender and diabetes duration between T2DM with and without PD (Table 1), multivariable regression models were created for BMI, body weight and each diabetes endpoint as target variable. For continuous variables linear regression was used; for dichotomous variables logistic regression, and for count data Poisson regression. Demographically (age, gender, diabetes duration) adjusted estimates based on observed marginal frequencies were calculated. In all adjustments, the confounder “age” was categorized as 40–<50 years, 50–<70 years, 70–<90 years and ≥90 years and the confounder “diabetes duration” was divided in tertiles. In addition, sensitivity analyses were conducted for several models. Beside adjustments for demographics, additional adjustments were made for therapeutic regimen, insulin therapy, metformin use, BMI, HbA1c or interaction between age and gender. To consider the multicenter nature of the data collected, treatment center was entered as random intercept in all models using Cholesky covariance structure. Denominator degrees of freedom were calculated using Satterthwaite approximation. Adjustments were made for the confounders age, gender and diabetes duration, respectively. P-Values are presented for the comparison between T2DM with and without PD. Only indicators with significant difference are included in the table. p < 0.05 was considered statistically significant and two-sided test hypotheses were used. All statistical analyses were implemented with SAS 9.3 (Statistical Analysis Software, SAS Institute, NC, USA).

3. Results

3.1. Description of study population

0.9% of adult T2DM patients analyzed in this research had a diagnosis of PD and/or received specific PD treatment. With increasing age, PD prevalence rose continuously from 0.1% in the youngest age group (40–<50 years) to 0.3% and 1.4% in the middle age groups (50–<70 years and 70–<90 years) and 2.2% in the oldest age group (≥90 years). As described in Fig. 1, percentage of females was significantly higher in young T2DM patients with comorbid PD compared to age-matched T2DM patients without PD or people of the German population (GP [17]). Above 50 years, gender ratio differed only significantly in the age group 50–<70 years between T2DM patients with comorbid PD and people of the German population (Fig. 1). As we reported previously [18], between 40 and 69 years, a male predominance in T2DM without PD was observed (Fig. 1). Above 90 years, a female preponderance existed in all three groups (Fig. 1).

Table 1 shows further demographics of the whole study population as well as of T2DM with and without PD, separately. PD patients were significantly older, median age at diabetes onset was significantly higher and median diabetes duration significantly longer compared to T2DM without PD (Table 1). After adjustment for demographics, body weight and BMI were similar between T2DM with and without PD in both genders (body weight: males: 90.5 ± 0.8 vs. 91.7 ± 0.3 kg, females: 79.0 ± 0.7 vs. 81.1 ± 0.2 kg, p < 0.01; BMI: males: 29.7 ± 0.2 vs. 30.1 ± 0.1 kg/m², females: 29.9 ± 0.3 vs. 30.8 ± 0.1 kg/m², p < 0.01). The significant differences in females are without clinical relevance. Further adjustment for therapeutic regimen or insulin therapy and metformin use did not alter these findings.

3.2. Comparison of diabetes endpoints

3.2.1. Diabetes treatment

As described in Table 2, HbA1c, OAD/GLP-1 treatment and frequency of dyslipidemia were significantly lower in T2DM with comorbid PD after adjustment for demographics. Diastolic blood pressure was also significantly lower in PD patients if adjusted for demographic data, although clinical relevance is doubtful (Table 2). In contrast, rates of insulin therapy, hypertension, antihypertensive medication and repeated inpatient care were significantly higher and duration of hospital stay was significantly longer in T2DM patients with PD after adjustment for demographics (Table 2). Adjustment for further confounders did not alter these findings, except for insulin therapy. HbA1c remained significantly lower in T2DM with PD if additionally adjusted for therapeutic regimen (57.4 ± 0.8 vs. 59.9 ± 0.7 mmol/mol; p < 0.0001). Insulin therapy (60.0 vs. 57.0%) was still higher and OAD/GLP-1 treatment (44.1 vs. 47.8%; p < 0.02) significantly lower in PD patients after additional adjustment for BMI. However, difference in insulin therapy was no longer statistically significant (p = 0.054). Rate of repeated inpatient care and duration of hospital stay remained significantly higher in T2DM with PD after additional adjustment for BMI (16.4 vs. 12.6%, 6.6 ± 0.08 vs. 5.0 ± 0.01 days per year; each p < 0.0001) or BMI plus therapeutic regimen (15.9 vs. 12.3%, 6.1 ± 0.07 vs. 4.8 ± 0.01 days per year; each p < 0.0001).

Daily insulin dosage, systolic blood pressure, lipid values, frequencies of lipid lowering medication and non-pharmacological treatment were comparable between T2DM with and without PD if adjusted for demographic data or additionally for therapeutic regimen/BMI (data not shown).

Table 2

<table>
<thead>
<tr>
<th>Adjusted estimates</th>
<th>T2DM with PD</th>
<th>T2DM without PD</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>HbA1c [±SE, mmol/mol]</td>
<td>58.0 ± 0.9</td>
<td>60.3 ± 0.7</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Insulin therapy [%]</td>
<td>57.8</td>
<td>54.8</td>
<td>0.0256</td>
</tr>
<tr>
<td>OAD/GLP-1 treatment [%]</td>
<td>41.9</td>
<td>45.9</td>
<td>0.0024</td>
</tr>
<tr>
<td>Diastolic blood pressure [±SE, mmHg]</td>
<td>76.4 ± 0.4</td>
<td>77.8 ± 0.2</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Hypertension [%]</td>
<td>73.3</td>
<td>68.6</td>
<td>0.0002*</td>
</tr>
<tr>
<td>Antihypertensive drugs [%]</td>
<td>60.4</td>
<td>56.1</td>
<td>0.0010</td>
</tr>
<tr>
<td>Dyslipidemia [%]</td>
<td>62.0</td>
<td>64.5</td>
<td>0.0434</td>
</tr>
<tr>
<td>Stroke [%]</td>
<td>12.0</td>
<td>7.3</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Dementia [%]</td>
<td>9.2</td>
<td>2.6</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Repeated inpatient care [%]</td>
<td>15.7</td>
<td>12.0</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Hospital duration [±SE, days per year]</td>
<td>6.2 ± 0.07</td>
<td>4.7 ± 0.01</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

Displayed are adjusted estimates based on hierarchical, multivariable regression models. Adjustments were made for the confounders age, gender and diabetes duration, respectively. p-Values are presented for the comparison between T2DM with and without PD. Only indicators with significant difference are included in the table. *No independent comparison.
3.2.2. Diabetes complications

Rates of stroke and dementia were significantly higher in T2DM with comorbid PD after adjustment for demographics (Table 2). Additional adjustment for therapeutic regimen and HbA1c did not change the significantly higher prevalence of stroke in PD patients (11.9 vs. 7.3%; p < 0.0001).

Other diabetes complications studied like rates of severe hypoglycemia and hypoglycemia with coma, frequencies of diabetic retinopathy, microalbuminuria, renal failure, myocardial infarction and diabetic foot syndrome were comparable between T2DM with and without PD after adjustment for demographics (data not shown). Adjustment for further confounders such as therapeutic regimen, BMI, HbA1c or interaction between age and gender did not alter these findings.

Analysis of rates of severe hypoglycemia and hypoglycemia with coma in all patients (with and without insulin therapy) showed for hypoglycemia with coma a significantly but non-clinically relevant higher rate in T2DM with PD after adjustment for demographics plus insulin therapy (0.011 ± 0.0021 vs. 0.006 ± 0.0002 events per year).

4. Discussion

In this large multicenter research of prospectively collected data, demographic and clinical differences between T2DM with and without PD were observed. T2DM patients with comorbid PD were older and had longer diabetes duration. Compared to T2DM without PD or the German population, a female preponderance was observed particularly in young diabetic PD patients. Furthermore, Parkinson’s disease contributed to a lower HbA1c, less frequent OAD/GLP-1 treatment and reduced frequency of dyslipidemia beside a higher tendency for insulin therapy and higher rates of antihypertensive medication, hypertension and stroke. As expected frequencies of dementia and repeated inpatient care were higher and duration of hospital stay was longer in T2DM with comorbid PD. In contrast to previous reports [19, 20] of a progressive weight loss in PD due to increased energy expenditure (e.g. rigidity and dyskinesia), reduced energy intake (e.g. restricted food intake, dysphagia) and/or levodopa treatment, this research revealed in both genders no clinically relevant differences in body weight and BMI for T2DM patients with and without PD.

Compared to other studies [2–5], the PD prevalence among T2DM patients (0.3%) in this research is similar to previously reported frequencies (0.3%–2.4%) among diabetes patients. The increasing PD prevalence with age confirms the well-known fact, that PD is a typical age related neurodegenerative disease. As reported in 2012 by Sun et al. [2] the incidence rate of PD among diabetes patients increased with age and was dramatically high in patients aged >65 years.

Contrary to the customary belief of a higher PD prevalence in men, the present study in T2DM patients indicates a similar prevalence of PD in men and women aged 70–<90 years, and even a higher prevalence in young (<30 years) as well as old females (≥90 years). The latter can be confirmed by investigations from Sun et al. [2] and Powers et al. [6]. They both found a higher risk for PD in female diabetes patients compared to males. A possible reason for the higher PD prevalence in older female T2DM patients can be the fact that life expectancy is higher in females. Above 90 years, in the German population [17] as well as in T2DM patients without PD, a female preponderance was also observed (Fig. 1).

Possible explanations for the significantly lower HbA1c in T2DM with PD can be the PD medication and PD itself. A clinical trial in obese T2DM patients treated with bromocriptine, commonly used to treat PD, showed lower HbA1c values compared to placebo groups [21]. Bromocriptine is a dopamine agonist and has been proposed to improve glucose and energy metabolism, because metabolic control of the central nervous system is partly modulated by dopamine [22]. A case control study from Italy reported in 178 untreated idiopathic PD patients lower blood glucose values compared to age- and sex-matched controls [7]. The authors explained this by the often reported reduction of sympathetic activity in PD and the impaired hypothalamic–pituitary–adrenal axis that resulted in reduced catecholamine and cortisol production [7].

Somewhat surprising in our study, insulin therapy tended to be more frequent and OAD/GLP-1 treatment was less frequent in T2DM with PD than in patients without PD. Non-pharmacological therapy was comparable between the two groups. One hypothesis could be that PD patients are more often in hospitals or residential and nursing homes. For these institutions, it is maybe more practicable and time as well as cost-effective to inject insulin instead of administering OAD or adhere to physical activity and dietary advice. Another explanation might be that due to PD itself, it is difficult to adhere to physical activity and dietary advice or to swallow OAD.

As recently reported by Cereda et al. [23] PD patients seem to have a more favorable lipid profile. This confirms our result of a significantly lower frequency of dyslipidemia in T2DM with comorbid PD.

In line with our finding of a higher frequency of stroke in T2DM with PD, Skeie et al. [24] reported a higher prevalence of prior stroke in PD patients compared to controls. One reason for the higher rate of stroke in PD patients can be the fact that stroke contributes to PD. A higher rate of dementia in T2DM with PD compared to T2DM without PD was expected, and is comprehensible because PD is a neurodegenerative disease. About 30–40% of PD patients are affected by dementia [25]. In recent years, it is assumed that T2DM and recurrent episodes of hypoglycemia also increase dementia risk [26, 27]. In our population, 2.6% of T2DM patients without PD are affected by dementia.

The higher rate of repeated inpatient care and the longer duration of hospital stay in T2DM with PD confirm the assumption that PD and its complications (e.g. aspiration pneumonias, infections, falls and fractures or psychiatric problems) require more intensive clinical care than T2DM alone. Consequently, we suppose that the more frequent and longer clinical care in PD contributes also to a better and more intensive diabetes care and with this to a better metabolic control in T2DM patients with comorbid PD.

The strength of this research is its large number of patients included from routine care. Due to the multicenter data collection, variances in the documented data cannot be fully eliminated, even though assessments and laboratory procedures are standardized by guidelines. One possible limitation could be that PD diagnosis or treatment may be underreported in the database. For example, patients who allowed entries of diabetes diagnosis and care but not of PD diagnosis or treatment were only selected as T2DM patients instead of diabetic PD patients. We are aware of this possible limitation, but due to the similar prevalence of PD among diabetes patients to earlier studies, we believe that this can be neglected.

Conflict of interest

No potential conflicts of interest relevant to this article were reported.

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