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Dementia is associated with Insulin Resistance in patients with Parkinson's Disease

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ABSTRACT

Background: Parkinson's disease is a neurodegenerative disorder involving the basal ganglia. Type-2 Diabetes Mellitus is an important risk factor for Alzheimer disease and vascular dementia. However, the association between Parkinson's disease and Diabetes Mellitus is controversial.
Objective: To investigate glucose metabolism abnormalities in 110 Parkinson's disease patients with and without dementia.
Subjects and Methods: We evaluated Insulin Resistance, glucose and insulin levels after a 2-h-oral-glucose-tolerance-test in 53 Parkinson's disease with dementia and 57 with Parkinson's disease without dementia, with normal fasting glucose.
Results: BMI, waist circumference, fasting glucose and insulin values, HbA1c, triglycerides, blood lipid profile, depression rating, educational levels, levodopa-dosage and antipsychotic use were similar in both groups. Disease duration and motor impairment were higher in patients with Parkinson's disease and dementia group. After 2-h-oral-glucose-tolerance-test, the prevalence of glucose metabolism abnormalities was significantly higher in group with Parkinson's disease and dementia group ($p = 0.03$). The insulin resistance was present in 62% patients with Parkinson's disease with dementia, of whom 30% had also impaired glucose tolerance, 5,6% newly diagnosed Diabetes Mellitus and 26% only Insulin Resistance. These percentages were significantly higher in group with Parkinson's disease and dementia, also after adjustment for disease duration and motor disability.
Conclusions: Our study suggests that PD patients with dementia are two times more likely to have insulin resistance than patients with PD

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Parkinson's disease (PD) is a degenerative disease manifesting with bradykinesia, resting tremor, muscular rigidity, gait disturbance and postural reflex impairment [1]. The underlying pathologic lesion is the loss of pigmented neurons of the substantia nigra, and selected brain stem dopaminergic cell groups. However, the causes of PD are not well known [2]. There is evidence that genetic factors play a key role in the development of PD. Studies of twins have provided strong evidence for an important role of environmental factors in the aetiology of typical PD [3,4]. The development of PD involves an interaction between genes and environmental factors.[3] Prospective studies have identified type-2 diabetes as an independent risk factor for several diseases, including neurodegenerative diseases, such as diabetic neuropathy [5], stroke [6], Alzheimer disease (AD) [7]. The association between diabetes mellitus (DM) and PD is controversial [8–10]. The aim of this study was to investigate glucose metabolism abnormalities and insulin sensitivity, in a group of consecutive normoglycemic PD patients with dementia (PD-D) or without dementia.

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2. Methods

2.1. Participants

All patients gave their informed consent, in accordance with the official standards of the 1964 declaration of Helsinki, local laws and regulations. This is a population-based case–control study, comprising 57 subjects with PD based on criteria from the UK Parkinson's Disease Society Brain Bank [11] and 53 patients with PD-D according to 2007 consensus criteria [12]. All patients showed normal fasting glycaemia. The study was performed between October 2007 and November 2010. If cognitive impairment arose within the first year from the appearance of presence of parkinsonian signs, cases were excluded as likely to be Lewy Body Dementia (DLB) or AD. We did not recruit subjects treated with drugs potentially responsible of cognitive impairment (i.e. anticholinergic agents, tricycles antidepressant, benzodiazepines), cholesterol-lowering or anti-diabetic agents. Differential diagnoses have been made according to the National Institute of Neurological and Communicative Disorders and Stroke–Alzheimer's disease and Related Disorders Association International pour la Recherché et l'Enseignement en Neurosciences criteria for vascular dementia [13].

2.2. Neuropsychological and clinical assessment

Patients were evaluated by an endocrinologist and a neurologist expert in movement disorders. All patients with PD underwent Mini-Mental State Examination (MMSE) as a general cognitive screening. Depression score was assessed with Montgomery Asberg Depression Rating Scale (MADRS) [14]. Patients were categorized as having dementia according to Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) criteria [15], with MMSE score less than 24. All patients underwent magnetic resonance imaging (MRI) to exclude cerebral vascular lesions. Patients without vascular lesions underwent more detailed cognitive examination included neuropsychological battery of tests to assess verbal and non verbal memory, orientation, language, attention, abstract reasoning and visuo-spatial ability. Examinations included the Stroop Interference Test, Rey Auditory Verbal Learning Test, Benton Visual Retention Test, Verbal Fluency Tests, Reitan Trail Making Test (parts A and B), verbal subtests of the Wechsler Adult Intelligence Scale, and the Clock Drawing Test. The composite score was summarized by a neuropsychologist and compared with series of established cut-off scores for age and level of educational achievement. The control group (non-demented PD patients) had MMSE scores of 24 or greater, and scored above all cut-off scores. Motor and functional assessment included the Unified Parkinson's Disease Rating Scale (UPDRS) [16] motor score (ME) and Hoehn-Yahr staging [17]. Recorded medical data for both groups included: anamnestic data (health and behaviour status, disease duration, levodopa dosage, antidepressant or antipsychotics use, smoking habits), education level (measured as the total number of school years) and demographic informations (age, sex), smoking use. All subjects were classified as non-smokers if they had never smoked before the onset of disease and as smokers. Smokers were further categorized according to the amount of cigarettes smoked daily (1–9, 10–19, or ≥ 20 cigarettes/day). Data on smoking history were not available for three patients and four controls (Table 1). We also assessed: glucose and insulin values at fasting and after 2 h-OGTT, serum HbA_{1c}, and blood lipid profile, waist circumference (WC) and Body Mass Index (BMI). To rule out potentially reversible causes of cognitive impairment, laboratory tests included: thyroid function, complete blood count, blood chemistry, folic acid and vitamin B12 level and syphilis tests. Procedure for the 2 h-OGTT required fasting after mid-night, to obtain a baseline glycaemia value, followed by administration of the 75 grams oral glucose load within a 5-minute period. Blood specimens to determine plasma glucose and insulin levels were subsequently drawn at 120 minutes, timed from the beginning of the glucose load. Patients and controls were established to have impaired glucose tolerance (IGT) if the 120-minute venous plasma glucose value fell between 140 and 200 mg/dL and newly diagnosed DM (NDDM) if the 120-minute venous plasma glucose level higher than 200 mg/dL [18]. Finally, insulin resistance (IR) was calculated by the homoeostasis model assessment (HOMA) formula [19].

Table 1
Clinical features of 53 patients with Parkinson's disease and dementia (PD-D) and 57 PD without dementia.

	PD-D	PD	*p*
No	53	57	.34
Demographic, Clinical features	65 (6.2)	64.2 (6.3)	1.8
Age (years)			
Sex (M/F)	36/17	36/21	1.2
Waist circumference (cm)	84 (1.9)	83.5 (2.3)	2.1
BMI	23.3 (1.7)	22.7 (1.9)	3.1
Duration of symptoms (years)	8.5 (3.2)	5.8 (3.3)	.05
Levodopa dosage (mg/day)	593 (167)	570 (190)	2.1
Antipsycotic use	8	9	1.2
Smoking habits§	22	24	1.6
Smokers	28	29	1.4
no smokers	3	4	.3
not available			
Motor Performance:	19 (3.9)	17.2 (3.7)	.05
UPDRS			
UPDRS-ME	17.7 (3.6)	15.7 (3.2)	.01
Hoehn Yahr Scale	2.3 (0.5)	2 (0.3)	.05
Neuropsychological Assessment	16.6 (3.9)	26.1 (1.6)	.01
MMSE			
MADRS Score	15.7 (9.5)	16.1 (7.4)	.43
Education Level (years)	10.4 (4.3)	11 (4.2)	.66
Metabolic features	80.8 (8.6)	81.6 (9.2)	1.3
Fasting glycaemia (mg/dl)			
Fasting insulinemia (UI/ml)	15 (6.7)	13.6 (5.4)	.05
HOMA-index	4,2 (2,1)	2,5 (1)	.01
2 h-OGTT (mg/dl)	114 (53)	98 (48)	.05
HbA1c (%)	4 (0.6)	4.2 (1.4)	1.5
Triglycerides (mg/dl)	136.7 (16)	142.8 (18)	2.6
Serum lipid (mg/dl)	150.8 (29.5)	147.3 (29)	1.3

Abbreviations: UPDRS: Unified Parkinson's Disease Rating Scale; UPDRS-ME: UPDRS-Motor Examination; MMSE: Mini-Mental State Examination; MADRS: Montgomery Asberg Depression Rating Scale. Body Mass Index: BMI [Weight (kg)/height^2 (h^2]. Insulin resistance (IR) was calculated by the homeostasis model assessment (HOMA) formula. HOMA-Index: Basal Glucose Plasma (mg/dl) x Basal Insulin Plasma (UI/ml)/405; Differences between the proportions with Insulin Resistance ≥ 2.7 on the HOMA formula.
§PD-D smokers (n = 22): 6 smoked: 1–9 cigarettes/day, 9 smoked: 10–19 cigarettes/day, and 7 smoked: ≥ 20 cigarettes/day.
§PD smokers (n = 24): 7 smoked: 1–9 cigarettes/day, 11 smoked: 10–19 cigarettes/day, and 6 smoked: ≥ 20 cigarettes/day.
Values are expressed as mean (SD) unless otherwise indicated. **[a]*P* = .01**, **[b]*P* = .05.**

2.3. Statistical analyses

Data were expressed as mean ± SD. An ANOVA test for independent samples was performed to compare the means. A χ^2 test was performed to compare prevalences. Analysis of covariance was used to test for differences in HOMA-index and glycaemia value after 2 h-OGTT test in PD patients with and without dementia, after adjustment for parameters that resulted in differences determined by the ANOVA. Stepwise multivariate forward analysis has been used for confounding variables defined as variables that correlated to MMSE in univariate analysis. Besides, we included variables that are usually associated with higher risk of dementia (i.e. age, sex, glycaemia, BMI, duration disease, levodopa dosage, antipsychotic use, smoking habit, depression rating and educational level).

We conducted conditional logistic regression analysis to explore the relative risk of developing dementia in association with previously recorded PD, expressed as Odds Ratios (ORs), with 95% Cis, and adjusted this analysis by the parameters described above. In all cases, a *P* value of 0.05 was considered statistically significant. All comparisons were performed using the statistical package SPSS 17.0 for Windows (SPSS, Chicago, IL).

3. Results

3.1. Demographic features

During a period of three years, from 2007 to 2010, we screened prospectively 53 (17 women and 36 men) patients with PD-D and 57 (21 women and 36 men) without dementia. Disease duration was higher in PD-D group, but age, sex, educational level and smoking habits were similar in both groups (Table 1).

3.2. Clinical and metabolic features

BMI, waist circumference, triglycerides, blood lipid profile, levodopa dosage, antipsychotic use and depression rating were not significantly different between PD-D and PD. Six patients with PD-D and seven patients with PD assumed clozapine; two patients with PD-D and two with PD assumed quietiapine. Among smokers, 22 were PD-D and 24 PD. Motor impairment was greater in PD-D compared to PD (UPDRS-ME: 17.7 ± 3.6 vs 15.7 ± 3.2, $P = .01$; Hoehn-Yahr Scale: 2.3 ± 0.5 vs 2 ± 0.3, $p = 0.05$) (Table 1).

3.3. Glucose metabolism and Insulin Resistance

Mean fasting glucose value was 81.6 ± 9.2 mg/dl in PD and 80.8 ± 8.6 mg/dl in PD-D respectively (Table 1). Following 2 h-OGTT, we found glucose metabolism abnormalities in 19 (36%) PD-D patients (16 with IGT and 3 with DM) and in 13 (23%) PD patients (10 with IGT and 3 with DM). The IR calculated with HOMA formula was present in 33 patients with PD-D (62%), of whom 16 (30%) had also IGT (IGT + IR), 3 (5,6%) had NDDM (NDDM + IR) and 14 (26%) IR alone. Twenty of the 53 (38%) patients in the PD-D group had normal glucose metabolism (NGM) and were not IR. In nondemented PD, IR was found in 20 (35%) subjects, of whom 10 (17%) had IGT (IGT + IR), 3 (5.3%) had NDDM (NDDM + IR) and 7 (12%) had IR alone (**Fig. 1**). Thirty-seven of the 57 (65%) patients in PD group were NGM without IR. HOMA-index and 2 h-OGTT values were significantly higher in PD-D than in PD patients. Because many clinical differences existed between PD-D and nondemented PD subjects, we performed an analysis of covariance to adjust HOMA and 2 h-OGTT values for confounding variables. A multiple regression analysis was performed entering MMSE as dependent variable, and HOMA-index as independent variable, because the latter was alone significantly correlated with MMSE scores in univariate analysis ($r = 0.17$, $p = 0.01$). We assessed, also as independent variables, potential confounders known to be risk factors for dementia in PD (i.e. age, sex, duration disease, BMI, levodopa dosage, motor impairment, antipsychotic use, smoking habits, depression rating and educational level). A second model was produced including also UPDRS-ME constant. In this model, only HOMA and UPDRS-ME were correlated with MMSE (Table 2).

3.4. Insulin resistance and dementia in patients with Parkinson's disease

In our findings, we observed that increased risk of dementia in PD was associated with IR (ORs = 1,5), while glycaemia value after 2 h-OGTT showed a moderate increase in the ORs (ORs = 1,2) (Table 3). After adjustment for confounding variables, the association between HOMA and the risk of dementia showed a moderate change (ORs = 2), while 2 h-OGTT linked did not show significant risk increasing (ORs = 1,03). When association of IGT + IR was considered the outcome of interest, the ORs was unchanged if compared to IR alone (ORs = 1,6 vs 1,8). Table 3, shows the association between HOMA and dementia in PD in different subgroups.

4. Discussion

In this study, performed in our country (Calabria, Southern Italy) we investigated the prevalence of abnormal glucose metabolism by 2 h-OGTT and IR-index in 53 patients with PD-D and 57 with PD, with normal fasting glucose. The results of this case control study showed that PD-D patients had higher prevalence of abnormal glucose metabolism, mainly IR, than nondemented PD. PD patients

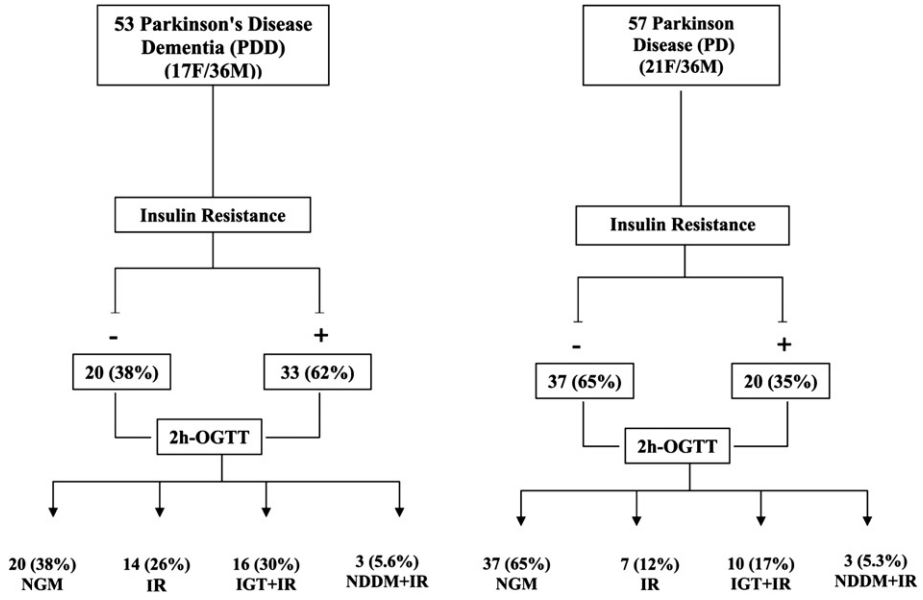

Fig. 1. Prevalence of abnormal glucose metabolism in 53 patients with "Parkinson Disease and Dementia (PD-D)" and in 57 patients with PD without patients.Abbreviations:-PD with Dementia: PD-D; NGM: Normal Glucose Metabolism; Insulin Resistance: IR; NGM + IGT: NGM with Impaired Glucose Tolerance; Newly Diagnosed Diabetes Mellitus with IR: NDDM + IR.

Table 2
Multiple regression analysis of predictions of MMSE (stepwise forward analysis).

		B	*SE*	*p*
Model I	**HOMA**	-,373	,228	,006
Model II	**UPDRS-ME**	,329	,141	,024
	HOMA	-,763	,223	,001

Dependent variable MMSE. Excluded variables: Model I: educational level, Glycaemia, Glycaemia after 2 h-OGTT, HbA1c, cholesterol, BMI, duration disease, UPDRS and habit smoking. Model II: educational level, Glycaemia, Glycaemia after 2 h-OGTT, HbA1c, cholesterol, BMI, duration disease, UPDRS, HY Score, levodopa dosage and habit smoking.

with dementia were two times more likely to have IR than controls (PD without dementia). Cases and controls showed also a significant difference in disease duration and motor disability. After adjustment for these parameters, a significant correlation was found between HOMA-index and MMSE. This association was unchanged, also after adjustment for confounding variables usually associated with higher dementia risk in PD.

4.1. Prevalence of Insulin Resistance in health subjects

Few studies assessed the prevalence of isolated IR in the italian general population [20,21]. IR is thought to be a common finding in several metabolic disorders (i.e. glucose intolerance, dyslipidemia, DM, hyperuricemia, etc.) [20–24]. Bonora et al. found that IR is common in subjects with metabolic disorders, although its prevalence varies among clinical condition. Higher rate of IR were found in NIDDM, hypertriglyceridemia and low-HDL cholesterol subjects. The same authors showed that an appreciable number of subjects (9,6%; aged: 40–79 years) was IR but free of metabolic disorders. Moreover, in our previous work, 12% of the general population (aged: 50,5 ± 6,8 years) consisted of normal-weight subjects showed isolated IR [21]. These values are similar to the prevalence rate of IR that we found in the control group of the present study (nondemented PD, DM or IGT free).

4.2. Parkinson Disease and Diabetes Mellitus

A recent study explored brain impairment in insulin, insulin-like growth factor (IGF) and neurotrophin signaling in patients with PD or DLB; the authors concluded that IGF-I, IGF-II, and neurotrophin signaling are more impaired in DLB than in PD [25]. However, the association between DM and PD remains controversial. Two case–control studies explored the association between DM and PD [8,26]. In one study [8], encompassing 352 PD case subjects and 484 control subjects, the risk of PD was significantly reduced in men with a previous diabetes diagnosis, but not in women. In the second case–control analysis, including 178 PD case subjects and 533 controls, the authors reported a significantly lower diabetes prevalence in PD case than in controls (3,4% vs 10.9%) [26]. In contrast, a prospective follow-up study performed in Finland found an increased risk of PD in diabetic subjects compared to patients without DM [9]. A prospective analysis of data from the Nurse's Health Study and the Health Professional Follow-up Study found no difference in the risk of PD between patients with and without diabetes [10]. Similarly, a recent study suggests that the prevalence of DM does not substantially differ in patients with newly diagnosed PD and subjects without PD and that the risk of an incidental diabetes diagnosis tends to be lower in PD patients [27].

4.3. Potential risk factors in Parkinson's Disease

Many demographic and clinical features have been assessed as potential risk factors for dementia in PD [28–31]. Several longitudinal studies confirmed that patients with more severe and advanced parkinsonism have higher risk for dementia than those with less advanced PD [31,32]. Our findings are in agreement with the literature, in fact, our patients with dementia and PD had more severe disability than nondemented patients. Nevertheless, after adjusted for motor disability, the association between IR and MMSE remained strongly significant. Another potential confounder about the association between DM and PD risk may be obesity. While obesity is a well-known risk factor for type-2 DM [33], results from observational studies on the association between obesity and PD are controversial. Authors of a large US based observational study concluded that their findings did not support a role of obesity in PD pathogenesis [34], but others reported a significant association between obesity and increased PD risk [29]. In our analysis, the BMI of PD and PD-D did not differ substantially and the BMI value was lower than 25 in both groups. An extra potential bias was the effect of levodopa use and the risk of diabetes; previous studies produced confounding results [30,35]. However, these studies were small and the observed effect did not reach statistical significance [29].

4.4. Parkinson's Disease with dementia and glucose metabolism

We supposed that “dementia" in PD is frequently associated with IR "status" in the form of prediabetes and IR seems to be an independent risk factor for cognitive impairment. In a previous case–control study performed on 104 patients with AD and DM, we found that insulinic therapy could be effective in slowing cognitive decline in AD [36]. Therefore, we supposed that IR could have an independent effect on cognitive performance, through several mechanisms: 1. *The glucose metabolism*, low concentrations of exogenous insulin may increase cerebral glucose metabolism and then modulate selective brain functions such as memory [37]; 2. *neuro-transmitter modulation*, notably, low doses of insulin can reverse the anamnestic effects of cholinergic blockade [38]; moreover, in humans, rising plasma insulin levels increase *CSF norepinephrine* [39]. Besides, from our study emerges that the prevalence of DM in PD patients without dementia was similar to that of general population [21]; on the other side, the prevalence of “prediabetes” was strongly associated with dementia in our PD-D patients. Sixty-two percent of PD-D patients had IR of whom, following a 2 h-OGTT, the 30% had also IGT and 26% IR only. These percentages were significantly higher than those reported in our control group.

Table 3
Prevalence of abnormal glucose metabolism in 53 patients with “Parkinson Disease and Dementia (PD-D)” and in 57 patients with PD without patients, after adjusted for duration disease and motor impairment. Data are n (%), unless otherwise indicate.

No	PD-D	PD	Unadjusted ORs	*p*	Adjusted Ors	*p*
	53	57	(95% CI)		(95% CI)*	
2 h-OGTT n°, (%)	19 (36)	13 (23)	1,2 (0,92-1,25)	.05	1,03 (0,86-1,1)	NS
HOMA n°, (%)	33 (62)	20 (35)	1,5 (1,41-1,68)	.001	2,1 (1,9-2,4)	.001
NDDM + IR n°, (%)	3 (5.6)	3 (5.3)	-	NS	-	NS
IGT + IR n°, (%)	16 (30)	10 (17)	1,3 (1,1-1,5)	.04	1,6 (1,42-1,9)	.04
NGM + IR n°, (%)	14 (26)	7 (12)	1,5 (1,3-1,7)	.001.	1,8 (1,54-2)	.001.
NGM-IR n°, (%)	20 (38)	37 (65)	0,56 (,32-,61)	.001	0,8 (0,7-0,9)	.001

Insulin resistance (IR) was calculated by the homeostasis model assessment (HOMA) formula. HOMA-Index: Basal Glucose Plasma (mg/dl) x Basal Insulin Plasma (UI/ml)/405; Differences between the proportions with Insulin Resistance ≥ 2.7 on the HOMA formula.
Abbreviations:
NGM-IR: Normal Glucose Metabolism (NGM) without Insulin Resistance (IR); NGM + IR: NMG with IR; NGM + IGT, NGM with Impaired Glucose Tolerance; NDDM + IR: Newly Diagnosed Diabetes Mellitus with IR.

4.5. Study limitations

Our study has some limitations. In fact, the disease duration was higher in patients with PD-D than in patients with PD: both diabetes and dementia are diseases with late onset and slow progression, so we cannot exclude the occurrence of dementia and/or diabetes at a later stage. Also, after adjustment for confounding variables, the association between IR and dementia in PD remained strongly significant. Moreover, our study could be criticized because the diagnosis of PD has been performed by clinical criteria, although the evaluation was accurate and complete. Another limitation could be that our results report the IR prevalence in a population sample of our country. These data may be different studies performed on other populations with different characteristics (i.e. ethnic background, life-style or dietary habits).

5. Conclusions

Finally, the findings of our study suggest that the prevalence of IR is significantly higher in PD-D vs nondemented PD. Further studies to replicate our finding in other populations should be acknowledged. HOMA-index may be considered to be a useful tool and, if confirmed, could identify a new risk factor for developing dementia in PD.

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