http://rjdnmd.org
Rom J Diabetes Nutr Metab Dis. **26**(1):079-084
doi: 10.2478/rjdnmd-2019-0009

THE RELATION BETWEEN TYPE 2 DIABETES MELLITUS AND PARKINSON DISEASE UP TO DATE

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received: February 18, 2019 *accepted*: March 10, 2019
available online: April 10, 2019

Abstract

Parkinson's disease is defined nowadays as a neurodegenerative disease with prominent motor symptoms accompanied by a wide range of comorbidities, some of them, like type 2 diabetes mellitus, probably implicated in the pathogenesis and progression of the disease. In order to achieve this article, which aimed to realize an up to date synthesis of published dedicated papers, a PubMed search was performed; it revealed increasing evidence that these two morbid conditions share many pathogenic pathways and current studies are trying to finally transform the accumulated knowledge into curative therapy or effective prevention for these frequent and complex diseases.

key words: *diabetes, Parkinson disease, comorbidities*

Introduction

Parkinson's disease (PD) is defined nowadays as a neurodegenerative disease with prominent motor symptoms accompanied by a wide range of non-motor conditions, some of them appearing as early features of this complex morbid process. On the other hand, the mechanisms by which some of these comorbidities like type 2 diabetes mellitus (T2DM) may be implicated in the pathogenesis and progression of PD are still uncertain; very importantly, recent scientific work trying to investigate these mechanisms has revealed novel diagnostic biomarkers and therapy targets [1,2].

In order to achieve this article, which aimed to realize an up to date synthesis of published dedicated papers, a PubMed search was performed in December 2018, using the keywords "diabetes", "Parkinson disease" and "comorbidities".

Common pathogenic pathways

The search revealed that PD has been linked to diabetes for more than 15 years ago, even from the discovery that brain is an insulin-dependent organ, that insulin has multiple and very complex functions within the brain and hyperglycemia can destroy the blood brain barrier, but this relation is still described by hypothesis like:

– α-synuclein (deeply involved in PD etiopathogenesis) interacts with the Kir6.2 subunit of the ATP-sensitive potassium channel (K-ATP) and insulin-secretory granules in pancreatic β-cells and downregulates the glucose stimulated insulin

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secretion; K-ATP channels also inhibit brain dopamine secretion, so that intracellular α-synuclein aggregates located in brain or pancreas could impair the secretion of the two essential compounds [3,4];

- common cellular pathways between neurodegeneration in PD, abnormal mitochondrial function and impaired glucose metabolism: peroxisome proliferator activated receptor gamma coactivator 1-α, a key regulator of enzymes involved in mitochondrial respiration and insulin resistance [5];
- insulin can stimulate dopamine release and dopamine is produced by beta cells of the pancreas, inhibiting insulin secretion [4,6,7];
- inflammation (especially mediated by blood myeloid dendritic cells, tumor necrosis factor, interferon gamma), endoplasmic reticulum stress, mitochondrial dysfunction, autophagy and altered insulin signaling have been proposed as common pathogenic mechanisms for both diseases [8,9,10];
- common genetic factors (such as AKT1 gene polymorphisms, involved in the regulation of cell survival and apoptosis) or environmental factors (heavy metals and pesticides) [4,11].

The role of insulin within the central nervous system proved its importance to the point that brain insulin resistance (sometimes even named "diabetes mellitus type III"), associated or not with peripheral resistance to insulin, is nowadays recognized at least as a part of the pathogenic mechanism of major neurodegenerative diseases like Alzheimer's disease, Parkinson's disease, Huntington's disease, amyotrophic lateral sclerosis, depression [12,13].

Epidemiological evidence

A lot of worldwide epidemiological studies suggested that diabetes variably increase the risk of PD in global population (from 23% to more than 50%) or in specific subpopulations like: women, men, younger onset PD patients, PD patients with dementia [14-21].

Even a meta-analysis of 14 case-control studies found a negative association between Parkinson Disease and Type 2 Diabetes, this study reported a higher proportion of PD patients having diabetes, compared to controls [22].

A recently published English retrospective cohort study (2,017,115 individuals admitted for hospital care with a coded diagnosis of T2DM was compared to a reference cohort of 6,173,208 subjects) found statistically significant increased rates of PD following T2DM (hazard ratio 1.32), even greater in subjects with complicated T2DM (HR 1.49) and in youngers (HR 3.81 in age group 25-44 years) [23].

Another recent longitudinal study revealed diseases of the circulatory system (hypertension) and endocrine and metabolic diseases (diabetes) as the most frequent comorbidities in PD patients [4,24].

Romanian data

The PubMed search showed no Romanian dedicated published papers. Nevertheless, a study conducted in the northern region of Romania, which aimed to assess the cardiovascular risk factors in PD patients, found a prevalence of type 2 diabetes among 126 studied parkinsonian subjects comparable with those reported by international literature. The study used laboratory tests (fasting blood glucose test, serum lipid fractions dosage) as well as an interview regarding the personal history of hypertension, diabetes, cerebro-vascular and cardiovascular diseases [25].

A personal, clinical, cross-sectional, observational study which aimed to assess the non-motor symptoms and comorbidities in Parkinson's disease patients from the South-

eastern Romania, revealed a prevalence of 41.86% (95%CI 31.43-52.29) for T2DM in a group of 86 consecutive patients with idiopathic Parkinson's disease from 5 Outpatients Clinics of Constanta, Diabetes was found to be more prevalent in women PD subjects, but not statistically significant.

Study details

The study has been performed between 01 January 2017 and 31 May 2018.

Main characteristics of the studied population: PD patients aged 51 to 89 years, 56% males; mean age of studied subjects = 70.6 years (95% CI 68.5-72.6); mean age in women =71.8 years (95% CI 69.6-73.9); mean age in men = 69.6 years (95% CI 67.6-71.5); mean disease duration in the studied group was 6.33 years (95% CI 5.7-6.9), 6.25 years (95% CI 5.8-6.8) in women and 6.35 years (95% CI 5.7-7) in men.

Inclusion criteria: diagnosis of idiopathic Parkinson's disease according to the UK Parkinson's Disease Society Brain Bank Diagnostic Criteria [26].

Exclusion criteria: atypical neurological features, suggestive for other causes for parkinsonism (e.g. multiple system atrophy).

The patients and their caregivers have been asked about disease duration (period, in years, between the diagnosis date and the date of assessment), associated medical conditions and current medications. Subsequently, the subjects have been assessed using the Scale for Outcomes in Parkinson's Disease for Autonomic Symptoms (SCOPA-AUT) [27] as a self-administered questionnaire.

Statistical analysis: calculation of mean or median values and/or percentages, together with the corresponding standard deviations, 95% confidence intervals and parametric tests for statistical relevance, using Word Excel and MedCalc applications.

Emerging biomarkers

The study of the molecular mechanisms underlying the link between PD and diabetes, by so called "network-based approaches" which try to identify common molecular networks between diabetes and PD, resulted in proposing some biomarkers (added to classical blood glucose level): hepatocyte nuclear factor 4 alpha, polypyrimidine tract-binding protein 1, superoxide dismutase 2, amyloid precursor protein, tumor necrosis factor, interferon gamma and myeloid dendritic cells [4].

Regarding clinical picture, it seems that PD patients associating diabetes have more severe motor manifestations (especially postural instability and gait troubles), bigger cognitive impairment, and more rapid disease progression compared to PD patients without diabetes [4,21,28-31].

It has been observed that impaired glucose metabolism appears early in PD: blood glucose levels over 100 mg/dL have been identified in early stage untreated PD patients and PD patients with mild cognitive impairment [4,31].

Very interestingly, comparing 25 patients with PD and diabetes to 25 with PD without diabetes, and 14 patients with diabetes to 14 healthy controls, it has been found that:

– In PD patients, the presence of diabetes induces higher motor scores, lower striatal dopamine transporter binding, and higher tau CSF levels;
– In diabetic patients without PD, the presence of diabetes induces higher tau and α-synuclein CSF levels and lower striatal dopamine transporter binding compared to healthy controls [30].

Emerging therapeutic approaches

As a result of the pathogenic connection between diabetes and PD, older or novel antidiabetic drugs reduced the risk of PD (metformin-sulfonylurea) or proved positive effects on motor symptoms in PD patients (glucagon-like peptide 1 mimetics) [4,32,33]. Glucagon-like peptide 1 mimetics (exenatide, liraglutide and lixisenatide) are able to cross the blood brain barrier and influence crucial biological processes as neuroinflammation, mitochondrial function and brain insulin resistance [4,32,34]. Particularly, exenatide proved additional efficacy on cognitive impairment in PD subjects but weight loss and GI side effects may limit its tolerability [34,35].

Thiazolidinediones (a class of medications that act like agonist of peroxisome proliferation-activated receptor gamma), especially glitazone, showed the capacity to reduce the incidence of PD in a retrospective cohort study in United Kingdom [36].

For a more appropriate therapeutic approach, some authors have even proposed that chronic comorbidities such as type 2 diabetes should be taken into consideration when identifying PD subtypes for promoting individualized treatment (personalized medicine) for these patients [4].

Conclusions

There is increasing evidence (from molecular, epidemiological, experimental, clinical and therapeutic studies) that implicates type 2 diabetes mellitus in the pathogenesis of the neurodegenerative diseases like Parkinson disease. Further studies should finally transform the accumulated knowledge into curative therapy or effective prevention for these frequent and complex diseases.

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