Revista Portuguesa de Diabetes. 2021; 16 (4): 162-163

Can We Prevent the Development of Parkinson's Disease in Type-2 Diabetes *Mellitus* Patients?

Podemos Prevenir o Desenvolvimento da Doença de Parkinson em Pacientes com Diabetes Mellitus Tipo 2?

Hugo Vicente Miranda

Invited Assistant Professor, NOVA Medical School/Faculdade de Ciências Médicas; Researcher, Centro de Estudos de Doenças Crónicas (CEDOC), Lisboa, Portugal

During the last years, several epidemiological evidence demonstrated that individuals with type-2 diabetes *mellitus* present a higher risk of developing Parkinson's disease. It is also clear that individuals with both pathologies present a higher decline and faster progression of Parkinson's disease. [1]

Parkinson's disease is the second most common neurodegenerative disorder, characterized by several well-known motor impairments including tremor, difficulty in initiating movement (bradikynesia) and loss of balance. It is probably less known that these patients also develop several non-motor issues such as loss of smell (which occurs several years prior diagnostic), severe depression, sleep disorders and cognitive deficits that may in fact evolve to dementia. Parkinson's disease remains an incurable disease. However, there is a plethora of therapeutical options that are effective in the management of several symptoms. Their major issue is that they do not prevent neurodegeneration, therefore their efficacy significantly reduces with disease development, with severe impact in the well-being of the patients.

The major challenge in developing a therapy that prevents Parkinson's disease progression is to identify the major causes of neurodegeneration. We know that the loss of dopamine production, mainly caused by the significant loss of dopaminergic neurons, is responsible for the motor impairment outcomes. This is mainly due to the important role of this neurotransmitter in specific regions of the brain that are responsible for motor control and coordination. It is also known that Parkinson's disease patients accumulate protein aggregates in the brain, mainly composed by the protein α-synuclein. This phenomenon is accepted to drive to neuronal loss. In fact, mutations in the gene coding this protein are a known genetic cause of Parkinson's disease. However, most Parkinson's disease cases are sporadic, with only 5% of the patients presenting known genetic causes. It is therefore highly interesting and crucial to understand why type-2 diabetes *mellitus* patients are more vulnerable to develop Parkinson's disease.

Both type-2 diabetes *mellitus* and Parkinson's share several molecular changes. For example, insulin signaling, and glucose intolerance are present in both diseases. [2] Moreover, with ageing, several problems in the clearance and folding of proteins (process that facilitates and maintains a functional structure of proteins) occurs.

Hyperglycemia is one of the major characteristics of type-2 diabetes *mellitus*. In the process of glucose metabolism, to obtain energy, several byproducts are formed. Methylgloxal is one of this off-pathway metabolites that can react with proteins in a process known as glycation. [3] In fact, higher protein glycation occurs in type-2 diabetes *mellitus* patients since they present higher glucose levels. Interestingly, in Parkinson's disease a higher glycemic index is also present, which may result in higher protein glycation in the *substantia nigra pars compacta*, one of the most affected brain areas in Parkinson's disease and where dopaminergic neurons are mainly localized. [4] Moreover, glycated proteins can be found next to α-synuclein aggregates, [5] suggesting that glycation may be involved in α-synuclein pathology.

To understand if increased glycation may contribute for the degeneration of dopaminergic neurons, we challenged the brain of mice (preclinical models of Parkinson's disease) with methylglyoxal and investigated if increased brain glycation

impacts neuronal survival and animal behavior. These experiments allowed to demonstrate that increased brain glycation induces the accumulation and aggregation of α-synuclein. Glycation also induces neurodegeneration and motor and non-motor changes that are typically present in Parkinson's disease. Molecularly, it was possible to understand how the brain is responding to increased glycation, which allowed to identify novel therapeutic targets. [6,7] This is extremely important as it will facilitate the development of novel therapies for Parkinson's disease and strategies that can decrease the increased vulnerability of type-2 diabetes *mellitus* patients to develop this neurodegenerative disease.

We are also investigating how other dysregulated pathways in type-2 diabetes *mellitus* can contribute for the development of Parkinson's disease. One characteristic of this metabolic disease is the decrease of insulin-degrading enzyme levels and activity. Remarkably, this enzyme has potential to decrease the aggregation of α-synuclein. [8] Recent research from our laboratory showed that insulin-degrading enzyme is also decreased in the brain of mice with pre-diabetes. Using cellular models, we also determined that this enzyme decreases α-synuclein toxicity. Altogether, we are following our hypothesis that an increase of insulin-degrading enzyme levels in the brain can protect neurons from α-synuclein-induced toxicity. If we prove our hypothesis, we will be one step closer for the development of a novel therapeutic avenue for Parkinson's disease.

It was extremely important and a privilege to be awarded the Big Prize from the Portuguese Society of Diabetology (Sociedade Portuguesa de Diabetologia). It will allow us to investigate in preclinical models if the increase of this enzyme in the brain has therapeutic potential against α-synuclein neurotoxicity. It will also allow to determine if insulin-degrading enzyme is a blood biomarker for Parkinson's disease and that allows to identify type-2 diabetes *mellitus* patients at higher risk of developing Parkinson's disease. This translational project will bring together several research groups from CEDOC (Chronic diseases Research Center) at NOVA Medical School, from New University of Lisbon and clinical research groups at APDP-Portugal (Associação Protectora dos Diabéticos de Portugal).

In conclusion, we strongly believe that a bad management of type-2 diabetes *mellitus* may increase the risk of developing Parkinson's disease. Taking into consideration that insulin-resistance and hyperglicemia are risk factors for Parkinson's disease, strategies that improve glucose management, that prevent insulin-degrading enzyme dysfunction and that prevent glycation are promising therapeutic avenues to prevent the development of Parkinson's disease in type-2 diabetes *mellitus* patients.

REFERENCES

1. De Pablo-Fernandez E, Goldacre R, Pakpoor J, Noyce AJ, Warner TT. Association between diabetes and subsequent Parkinson disease: A record--linkage cohort study. Neurology. 2018; 91(2): e139-e142.
2. Bosco D, Plastino M, Cristiano D, Colica C, Ermio C, De Bartolo M, et al. Dementia is associated with insulin resistance in patients with Parkinson's disease. J Neurol Sci. 2012 Apr 15; 315(1-2): 39-43.
3. Vicente Miranda H, El-Agnaf OM, Outeiro TF. Glycation in Parkinson's disease and Alzheimer's disease. Mov Disord. 2016; 31(6): 782-790.
4. Uchiki T, Weikel KA, Jiao W, Shang F, Caceres A, Pawlak D, et al. Glycation-altered proteolysis as a pathobiologic mechanism that links dietary glycemic index, aging, and age-related disease (in nondiabetics). Aging Cell. 2012 Feb; 11(1): 1-13.
5. Castellani R, Smith MA, Richey PL, Perry G. Glycoxidation and oxidative stress in Parkinson disease and diffuse Lewy body disease. Brain Res. 1996; 737(1-2): 195-200.
6. Chegão A, Guarda M, Alexandre BM, Shvachiy L, Temido-Ferreira M, Marques-Morgado I, et al. Glycation modulates glutamatergic signalling and exacerbates Parkinson's disease-like phenotypes. bioRxiv 2021: 2021.2008.2024.457507.
7. Vicente Miranda H, Szego ÉM, Oliveira LMA, Breda C, Darendelioglu E, de Oliveira RM, et al. Glycation potentiates α-synuclein-associated neurodegeneration in synucleinopathies. Brain. 2017 May 1;140(5): 1399-1419. doi: 10.1093/brain/awx056. Erratum in: Brain. 2021 Jul 28; 144(6): e58.
8. Sousa L, Guarda M, Meneses MJ, Macedo MP, Vicente Miranda H. Insulin-degrading enzyme: an ally against metabolic and neurodegenerative diseases. The Journal of Pathology. 2021; 255(4): 346-361.