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Diabetes and Neuroaxonal Damage in Parkinson's Disease

We read with interest Uyar and colleagues' recent report on the association between diabetes, nondiabetic elevated glycated hemoglobin levels (HbA1c), and neuroaxonal damage in Parkinson's disease (PD) patients from the MARK-PD study.[1] The authors confirmed previously established findings of an inverse association between diabetes and cognitive and motor status. The authors also demonstrated higher serum neurofilament light (NfL) levels (a marker of neuroaxonal damage)[2] in PD patients with prevalent type 2 diabetes and in PD patients with nondiabetic elevated HbA1c levels. These associations persisted after adjustment for age, body mass index (BMI), and vascular risk factors (prevalent arterial hypertension, hypercholesterolemia, and history of stroke). We recently noted similar motor and cognitive associations in PD patients with diabetes[3] in the Tracking Parkinson's study, although only a nonsignificant trend toward an association in the overall PD cohort between NfL levels and more severe motor and cognitive status at baseline,[4] which may reflect the reduced disease duration in the Tracking Parkinson's cohort, compared with the MARK-PD cohort.

Considering the authors' novel findings of an association between diabetes and neuroaxonal damage, we explored the relationship between serum NfL and diabetes in our previously defined subgroup of the Tracking Parkinson's study.[4] The analysis was performed using Stata V.17.0 (Stata, RRID:SCR_012763), and differences were compared using Kruskal–Wallis tests for continuous data and $\chi 2$ tests for categorical data, whereas the association between NfL and diabetes was further explored using univariate and multivariate (age, BMI, and vascular risk factors) linear regression analysis.

Of the 280 patients studied, 29 suffered from prevalent type 2 diabetes. PD-DM patients were older (74.1 years ± SD 7.7 vs. 68.1 years ± 8.7, $P < 0.001$), with higher BMIs (31.1 ± SD [standard deviation] 5.7 vs. 27.1 ± SD 4.4, $P < 0.001$), whereas a higher proportion had coexistent vascular risk factors than PD patients without diabetes ($P = 0.032$). Serum NfL levels were higher in PD-DM patients (39.5 ± SD 18.9 vs. 29.6 ± SD 16.0, $P < 0.001$). Using regression analysis, NfL levels were significantly associated with patients' diabetic status (coefficient: 0.82, 95% CI [confidence interval]: 0.45–1.19, $P < 0.0001$), which persisted (coefficient: 0.52, 95% CI: 0.18–0.86, $P = 0.003$) after adjustment for age, BMI, and vascular risk factors (history of angina, myocardial infarction, stroke, hypertension, and hypercholesterolemia).

Our findings affirm Uyar et al's report of an association between PD-DM and more severe neuroaxonal damage. Furthermore, the data indicate that the more severe phenotype in PD-DM noted to date by several studies is likely to be mediated by additional factors other than vascular risk factor burden that tends to coexist in these cases. T2DM and PD share several pathological processes encompassing neuroinflammation, lysosomal dysfunction, mitochondrial dysfunction, and the development of central insulin resistance that leads to neurodegeneration.[5] This process is in part mediated by hyperglycemia as demonstrated by the MARK-PD study and its downstream impact on α-synuclein aggregation.[6] It is also possible that some of the observed associations are explained by diabetic neuropathy, as other peripheral neuropathies are known to increase blood NfL concentrations.[7] Disentangling the mechanistic factors that contribute to this more rapidly progressive axonal damage is of critical importance in the development of disease-modifying therapies for PD.

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Data Availability Statement

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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Reply to: "Diabetes and Neuroaxonal Damage in Parkinson's Disease"

We appreciate the letter by Vijiaratnam and colleagues, which confirms the association of diabetes with increased neuronal damage in patients with Parkinson's disease (PD) independent of age, body mass index, and vascular risk factors.[1] PD patients with diabetes revealed increased serum neurofilament light (sNfL) chain levels in both the biomarkers in Parkinson's disease (MARK-PD) and Tracking Parkinson's Disease studies.[1,2] However, disease duration was much longer (12 years vs. 1 year), Hoehn & Yahr stage was more advanced (2.5 vs. 1.8), and Movement Disorder Society–Sponsored Revision of the Unified Parkinson's Disease Rating Scale III score was slightly higher (26 vs. 23) in the MARK-PD study, whereas age and Montreal Cognitive Assessment scores were identical (ie, 68 years and 25 points, respectively).[1,2] Despite these differences, prevalent diabetes was associated with increased neuronal damage quantified by sNfL in early- and late PD underlining the robustness of this finding. Although sNfL is highly specific for neuronal damage, the underlying neuronal subtype and pathomechanisms leading to neuronal injury are not. In cross-sectional studies, blood NfL was increased not only in PD patients with motor impairment but also in PD patients with cognitive decline, postural instability and gait disorder subtype, and subclinical cardiac damage (ie, troponin and N-terminal brain natriuretic peptide), reflecting different central and peripheral neuronal subtypes.[3,4] Therefore, findings of increased sNfL in both early and advanced diabetic PD patients, however, might be caused by a different type of neuronal damage involving central dopaminergic or nondopaminergic as well as peripheral motor,

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