

Blood-based Neurological Biomarkers Following Dipeptidyl Peptidase-4 Inhibitors Exposure among Older Adults with Type 2 Diabetes

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In older adults with type 2 diabetes, DPP-4i exposure is linked to lower plasma GFAP and NfL levels, suggesting a protective benefit for glial and neuronal health that merits further clinical investigation.

INTRODUCTION	METHODS	RESULTS	CONCLUSIONS																																			
•Dipeptidyl peptidase-4 inhibitors (DPP-4i) are commonly prescribed antidiabetic medications with reported neuroprotective potential. •The association between DPP-4i exposure and measures of glial activation, neurodegeneration and Alzheimer's disease pathology remains unclear. •We examined the association between DPP-4i exposure and circulating levels of Glial Fibrillary Acidic Protein (GFAP), Neurofilament Light Chain (NfL) and phosphorylated tau217 (p-tau217) in older adults with type-2 diabetes (T2D).	Data source We utilized cross-sectional digital datasets from the Israel Diabetes and Cognitive Decline study and Maccabi Healthcare Services, a large non-profit health maintenance organization in Israel Inclusion criteria: •Individuals aged 65y and older •HbA1c ≥7.25% OR two separate glucose readings above 200 mg/dL, taken at least three months apart OR purchase of antidiabetic medication twice in the previous two months •At least three HbA1c measurements Exclusion criteria: •Individuals with dementia, MCI, cholinesterase inhibitor use, or significant cognitive-impairing illnesses •Missing all three blood-based biomarkers data •Missing covariate data Exposure The DPP-4i users' group was set as individuals who used DPP-4i as a single drug or in combination with other drugs for at least a year before their first clinic visit, based on electronic health records Outcome Log-transformed blood-based biomarkers levels of GFAP, NfL, and p-tau217 Statistical analysis • Available case analyses using generalized linear regression models. • Models were adjusted for multiple potential confounders using a doubly robust approach that combined Inverse probability weights with multivariable regression adjustment • Accounting for 13 covariates: age at first clinic visit, years of education, sex, diabetes onset age, BMI, diabetes duration, HbA1c, triglycerides, LDL, systolic BP, CVD, eGFR, and apolipoprotein-E (APOE) genotype • Complete-case sensitivity analyses were performed using similar methods.	• N= 568 • Median age 71.3 (Q1-Q3: 68.1-74.8); 38.6% women • n=59 (10.4%) in the DPP-4i group • The DPP-4i group had younger T2D diagnosis age, longer diabetes duration, and higher median HbA1c levels Figure 1. Blood-base biomarkers levels in the DPP-4i group vs non-DPP-4i group (main and complete-case analyses) <table><caption>Table 1 – The associations between antidiabetic drug use (DPP-4i vs. Non-DPP-4i) and blood-based biomarkers</caption><tr><th>Biomarker</th><th>% Difference</th><th>95% CI</th><th>p-value</th><th>FDR-Adjusted p-value</th></tr><tr><td>GFAP (Main Analysis)</td><td>-10.5%</td><td>(-19.09 - -1.1)</td><td>0.030</td><td>0.044</td></tr><tr><td>GFAP (Complete-case)</td><td>-10.3%</td><td>(-19.92 - 0.38)</td><td>0.058</td><td>0.083</td></tr><tr><td>NfL (Main Analysis)</td><td>-11%</td><td>(-19.05 - -2.1)</td><td>0.017</td><td>0.044</td></tr><tr><td>NfL (Complete-case)</td><td>-12.1%</td><td>(-21.67 - -1.46)</td><td>0.027</td><td>0.081</td></tr><tr><td>p-tau217 (Main Analysis)</td><td>-15.8%</td><td>(-30.04 - 1.3)</td><td>0.068</td><td>0.068</td></tr><tr><td>p-tau217 (Complete-case)</td><td>-14.9%</td><td>(-29.14 - 2.12)</td><td>0.083</td><td>0.083</td></tr></table>	Biomarker	% Difference	95% CI	p-value	FDR-Adjusted p-value	GFAP (Main Analysis)	-10.5%	(-19.09 - -1.1)	0.030	0.044	GFAP (Complete-case)	-10.3%	(-19.92 - 0.38)	0.058	0.083	NfL (Main Analysis)	-11%	(-19.05 - -2.1)	0.017	0.044	NfL (Complete-case)	-12.1%	(-21.67 - -1.46)	0.027	0.081	p-tau217 (Main Analysis)	-15.8%	(-30.04 - 1.3)	0.068	0.068	p-tau217 (Complete-case)	-14.9%	(-29.14 - 2.12)	0.083	0.083	• In this community-based study, DPP-4i exposure was associated with lower plasma levels of GFAP and NfL • Our findings lend tentative support to the potential repurposing of DPP-4i for neuroprotection LIMITATIONS •Our cross-sectional observational study design restricts causal inference •The possibility of residual confounding cannot be ruled out •Our results do not generalize beyond to individuals with diabetes with specific characteristics CONTACT Avi Cohen, MSc acohe276@campus.haifa.ac.il Galit Weinstein, PhD gweinstei@univ.Haifa.ac.il
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