PLASMA ENDOCANNABINOIDS AS POTENTIAL BIOMARKERS OF TYPE 2 DIABETES MELLITUS IN ELDERLY PATIENTS WITH MILD COGNITIVE IMPAIRMENT

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Background: Besides their role in the nervous system and the development of cognitive impairment in elderly patients, compelling evidence suggests that endocannabinoids (ECBs) are related to motivational responses in obesity and the development of insulin resistance and diabetes. Few studies indicate that ECBs modulate insulin secretion via cannabinoid receptors (CBs) in the human pancreas and alter glucose metabolism.

Objectives: The present cross-sectional study aims to evaluate the association between plasma ECBs and the incidence of type 2 diabetes mellitus (T2DM) in a cohort of elderly patients with mild cognitive impairment (MCI). We also aimed to identify possible associations between brain metabolism as determined by PET-[18]FDG in T2DM patients and plasma levels of ECBs and diabetes-related metabolites. The sample included age and gender-matched MCI patients without (non-T2DM, n = 113) and with T2DM diagnostic (n = 49).

Results: T2DM patients presented higher levels of acyl glycerols 2-AG and 2-OG, whereas DHEA was significantly decreased as compared to non-T2DM patients. Moreover, 2-AG and 2-OG were significantly associated with the triglyceride/glucose (TyG) index, a surrogate marker of insulin-resistance. 2-AG and 2-OG plasma levels were significantly associated with cognitive decline determined by MMSE and BLESSED tests, specifically in non-T2DM patients, but not in T2DM patients. T2DM patients showed hypermetabolism specifically in the hippocampus, parahippocampus and amygdala, brain regions associated with control of memory, decision-making, and social cognition. We performed binary logistic regression with stepwise selection of variables including ECBs, GLP-1, C-Peptide, insulin, glucagon, leptin, glucose, triglycerides, and cholesterol molecules in order to create a predictive model of T2DM in elderly patients with MCI. We selected glucose (standardized β: 2.215), 2-OG (standardized β: 0.519), and LDL (standardized β: -0.649), with a positive predictive power of T2DM diagnosis of 89.74%, and an AUC of 0.87 in the ROC curve. We created a surrogate marker of T2DM in elderly patients consisting of variables selected (ECB-T2DM index: (Ln(4*glucose + 2-OG)/Ln(LDL)), which was significantly associated with glucose metabolism in hippocampus, parahippocampus and amygdala.

Conclusions: Plasma 2-OG is a promising biomarker of T2DM in elderly patients with MCI and is associated with altered brain metabolism.

Keywords: endocannabinoid, biomarkers, diabetes mellitus, mild cognitive impairment.