Abstract

JAMA Neurol. 2015 Jul 27. [Epub ahead of print]

Association of Insulin Resistance With Cerebral Glucose Uptake in Late Middle-Aged Adults at Risk for Alzheimer Disease.


Department of Food Science and Human Nutrition, Iowa State University, Ames; Neuroscience Interdepartmental Program, Iowa State University, Ames; Clinical Science Center, Wisconsin Alzheimer's Disease Research Center, University of Wisconsin School of Medicine and Public Health, Madison; Wisconsin Alzheimer's Institute, University of Wisconsin School of Medicine and Public Health, Madison; Clinical Science Center, Wisconsin Alzheimer's Disease Research Center, University of Wisconsin School of Medicine and Public Health, Madison.

IMPORTANCE: Converging evidence suggests that Alzheimer disease (AD) involves insulin signaling impairment. Patients with AD and individuals at risk for AD show reduced glucose metabolism, as indexed by fludeoxyglucose F 18-labeled positron emission tomography (FDG-PET).

OBJECTIVES: To determine whether insulin resistance predicts AD-like global and regional glucose metabolism deficits in late middle-aged participants at risk for AD and to examine whether insulin resistance-predicted variation in regional glucose metabolism is associated with worse cognitive performance.

DESIGN, SETTING AND PARTICIPANTS: This population-based, cross-sectional study included 150 cognitively normal, late middle-aged (mean [SD] age, 60.7 [5.8] years) adults from the Wisconsin Registry for Alzheimer's Prevention (WRAP) study, a general community sample enriched for AD parental history. Participants underwent cognitive testing, fasting blood draw, and FDG-PET at baseline. We used the homeostatic model assessment of peripheral insulin resistance (HOMA-IR). Regression analysis tested the statistical effect of HOMA-IR on global glucose metabolism. We used a voxelwise analysis to determine whether HOMA-IR predicted regional glucose metabolism. Finally, predicted variation in regional glucose metabolism was regressed against cognitive factors. Covariates included age, sex, body mass index, apolipoprotein E ε4 genotype, AD parental history status, and a reference region used to normalize regional uptake.

MAIN OUTCOME MEASURES: Regional glucose uptake determined using FDG-PET and neuropsychological factors.

RESULTS: Higher HOMA-IR was associated with lower global glucose metabolism ($\beta = -0.29; P < .01$) and lower regional glucose metabolism across large portions of the frontal, lateral parietal, lateral temporal, and medial temporal lobes ($P < .05$, familywise error corrected). The association was especially robust in the left medial temporal lobe ($R^2 = 0.178$). Lower glucose metabolism in the left medial temporal lobe predicted by HOMA-IR was significantly related to worse performance on the immediate memory ($\beta = 0.317; t148 = 4.08; P < .001$) and delayed memory ($\beta = 0.305; t148 = 3.895; P < .001$) factor scores.

CONCLUSIONS AND RELEVANCE: Our results show that insulin resistance, a prevalent and increasingly common condition in developed countries, is associated with significantly lower regional cerebral glucose metabolism, which in turn may predict worse memory performance. Midlife may be a critical period for initiating treatments to lower peripheral insulin resistance to maintain neural metabolism and cognitive function.

PMID: 26214150