Visceral Abdominal Adipose Tissue and Insulin Resistance Respectively Influence Alzheimer's Disease Amyloid Pathology and Neurodegeneration in Midlife

PURPOSE

Obesity and adiposity at midlife, evidenced by high body mass index (BMI), are increasingly understood as risk factors for Alzheimer's disease (AD). Importantly, visceral fat is known to be associated with insulin resistance and a proinflammatory state, the mechanisms involved in AD pathology. Herein, we aimed to assess the association between brain MRI volumes as well as amyloid and tau uptake with obesity, insulin resistance, and abdominal adipose tissue in the cognitively normal midlife population.

METHODS AND MATERIALS

A total of 34 middle-aged (age: 51.27 ± 6.12 years, BMI: 32.28 ± 6.39 kg/m2), cognitively normal participants, underwent bloodwork, brain, and abdominal MRI, as well as amyloid and tau PET scan. Homeostatic Model Assessment for Insulin Resistance (HOMAIR) > 1.9 was used as a measure of insulin resistance. Visceral and subcutaneous adipose tissue (VAT, SAT) were semi-automatically segmented using VOXel Analysis Suite (Voxa). FreeSurfer 7.1.1 was used for the automatic segmentation of cortical and subcortical brain regions using a probabilistic atlas. Dynamic amyloid imaging was performed with a bolus injection of ~15 mCi of [11C]PiB, followed by a 60-min scan. A single intravenous bolus of between 7.2-10.8 mCi of AV-1451 was administered. Data from the 30-60 minute, and 80-100 minute post-injection window for PiB and AV-1451 were used for the analysis, respectively. The association of brain volumes and PiB and AV-1451 standardized uptake value ratios (SUVRs) within the default mode network areas with BMI and VAT/SAT ratio were assessed using linear regression models.

RESULTS

We observed lower right entorhinal white matter volumes in obese participants with insulin resistance compared to metabolically normal non-obese group (p=0.004), without any significant difference in PiB or AV-1451 SUVRs. Regression models with sex, age and education as covariates showed a significant positive association between VAT/SAT ratio and left precuneus white matter PiB SUVRs (R2=0.31, p=0.005), but no significant associations with AV-1451 SUVRs.

CONCLUSIONS

In our midlife obese sample with insulin resistance, there was lower right entorhinal white matter volume, which is involved in relaying information to the hippocampus. We also demonstrated higher early amyloid pathology in AD-signature areas such as the precuneus in mid-life persons with high VAT/SAT ratio, a marker of visceral obesity.

CLINICAL RELEVANCE/APPLICATIONS

These findings prompt designing interventions targeted at reducing abdominal visceral fat, obesity, and insulin resistance in midlife to prevent against Alzheimer disease pathology and neurodegeneration.