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NEWS

The Association Between Body Fat Localization, Insulin Resistance, and Amyloid Burden in Midlife

PURPOSE

Obesity in midlife is a risk factor for developing Alzheimer disease later in life. However, the metabolic and inflammatory effects of body fat vary based on its anatomical localization. In this study, we aimed to investigate the association of MRI-derived abdominal visceral and subcutaneous adipose tissue (VAT and SAT), liver proton-density fat fraction (PDFF), thigh fat-to-muscle ratio (FMR), and insulin resistance with whole-brain amyloid burden in cognitively normal midlife individuals.

METHODS AND MATERIALS

A total of 62 cognitively normal midlife individuals (Age: 50.35 years, 61.3% female, BMI: 32.30 kg/m2>, 53.2% obese) underwent brain PET scan, body MRI, and metabolic assessment. Homeostatic Model Assessment for Insulin Resistance (HOMAIR) was used for measuring insulin resistance. Dynamic amyloid imaging was performed with a bolus injection of ~15mCi [11C] PiB, and a 60-min scan. Data from the 30-60-minute post-injection window was used for calculating whole-brain amyloid Centiloid. VAT and SAT were semi-automatically segmented using an in-house MATLAB-based software. The PDFF maps were generated from liver chemical shift encoded MR images and segmented using a 3D CNN model and manual correction. After preprocessing and N4ITK bias correction on mid-thigh slices between the ischial ramus and the medial knee condyle, an in-house MATLAB program was used for segmenting thigh total fat (subcutaneous, inter-, and intra-muscular fat) and muscle volumes. Total thigh fat-to-muscle ratio (FMR) was calculated. Using linear regression, the association between Centiloid and BMI, HOMAIR, VAT, SAT, PDFF, and FMR was assessed, with age and sex as covariates.

RESULTS

Obese individuals had higher Centiloids compared to the non-obese ($p=0.008$). Centiloids were significantly associated with VAT (Adj-$R^2=0.25$, $p<0.0001$), HOMAIR (Adj-$R^2=0.08$, $p=0.02$), SAT (Adj-$R^2=0.08$, $p=0.02$), and BMI (Adj-$R^2=0.09$, $p=0.01$), but not other fat metrics. A mediation analysis showed that the effects of BMI on Centiloid is fully mediated by VAT (ACME= 0.282, $p <2e-16$, and ADE= 0.061, $p=0.56$) and there is a significant direct effect of VAT (ADE=0.0104, $p<2e-16$) on amyloid burden, not explained by HOMAIR (ACME=-0.003, $p=0.86$).

CONCLUSIONS

Obesity, higher visceral fat, and to a lesser extent insulin resistance, BMI, subcutaneous fat, but not liver or thigh fat, are associated with higher whole-brain amyloid in midlife. This highlights the importance of anatomical characterization of body fat for Alzheimer risk, where obesity-related amyloid pathology is fully explained by visceral fat.

CLINICAL RELEVANCE/APPLICATIONS

Modifying visceral adipose tissue can be considered to reduce obesity-related risk of Alzheimer pathology in midlife years before its development.

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Cerebral Blood Flow in Midlife Obesity: Associations with Visceral and Subcutaneous Abdominal Adipose Tissue

PURPOSE

Obesity and higher adiposity in midlife are recognized as contributors to Alzheimer disease, where vascular compromise and brain hypoperfusion play a role. In this study, we aimed to investigate the associations of body mass index (BMI), abdominal visceral and subcutaneous adipose tissue (VAT, SAT) with brain cerebral blood flow (CBF) in cognitively normal midlife individuals.

METHODS AND MATERIALS

A total of 66 middle-aged cognitively normal adults (age: 49.86 years, females: 66.7%, obesity: 51.5 %, BMI: 31.72 kg/m2) underwent abdominal and brain MRI, and brain PET scan. Using an in-house MATLAB-based program, abdominal VAT and SAT were automatically segmented followed by manual editing. A 3D Pseudo-Continuous Arterial Spin Labeling (pCASL) sequence, with a single post-labeling delay of 2.025 s, was used for assessing CBF. SPM 12 was used to generate ASL difference and absolute CBF (aCBF) maps with a single compartment model, co-registered to the gray matter segmentations, normalized to MNI space, and spatial smoothing with a 6mm FWMH Gaussian kernel. Using AAL3 atlas and Matlab, region of interest masks were created for amygdala, hippocampus, posterior cingulate, precuneus, parahippocampal, medial orbitofrontal, middle temporal, and Calcarine cortices, and applied to absolute CBF (aCBF) maps. The whole-brain and regional aCBF differences between the obese vs. non-obese, the low- vs. high-VAT, and low- vs. high-SAT group, and the association between whole-brain amyloid PET Centiloids were assessed. Also, BMI, VAT, and SAT as separate predictor variables, were used for voxel-wise analysis, with age and sex as covariates.

RESULTS

The high-VAT group showed lower whole-brain aCBF (p=0.004), particularly in the bilateral Calcarine gyri (p=0.001, 0.002). A lower whole-brain aCBF was found in the obese group (p=0.005), more prominent in the left middle temporal lobe (p=0.002). No significant difference was observed in global and regional aCBF in the high-SAT vs. low-SAT groups. Voxel-wise analyses showed significantly lower aCBF in association with BMI in small temporal, occipital, and frontal lobe clusters after false discovery rate correction. No association was found between whole-brain Centiloids and aCBF.

CONCLUSIONS

Obesity and increased visceral abdominal fat are associated with a lower cerebral blood flow, with a more prominent decrease in the middle temporal cortex, as an AD-signature area, in cognitively normal midlife individuals. These findings highlight the role of obesity, especially visceral obesity, in brain hypoperfusion and potentially Alzheimer disease risk, as early as midlife.

CLINICAL RELEVANCE/APPLICATIONS

Modifying visceral obesity can potentially improve brain perfusion and reduce the risk of Alzheimer disease.