Obesity and type 2 diabetes : cardiovascular and cerebral aspects

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Chapter 9

Visceral adipose tissue is associated with microstructural brain tissue damage

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ABSTRACT

Background

Obesity has been associated with microstructural brain tissue damage. Different fat compartments demonstrate different metabolic and endocrine behaviors. The aim was to investigate the individual associations between abdominal visceral adipose tissue (VAT) and subcutaneous adipose tissue (SAT) and microstructural integrity in the brain.

Methods

This study comprised 243 subjects aged 65.4 ± 6.7 years. The associations between abdominal VAT and SAT, assessed by CT, and magnetization transfer imaging markers of brain microstructure for gray and white matter were analyzed and adjusted for confounding factors.

Results

VAT was associated with normalized magnetization transfer ratio (MTR) peak height in gray (β −0.216) and white matter (β −0.240) (both $P < 0.01$) after adjustment for confounding factors. After adjustment for sex, age, and descent, SAT was associated with normalized MTR peak height in gray and white matter, but not after additional correction for BMI, hypertension, current smoking, statin use, and type 2 diabetes (respectively, β −0.055 and β 0.035, both $P > 0.05$). Stepwise linear regression analysis showed that only VAT was associated with normalized MTR peak height in gray and white matter (both $P < 0.001$).

Conclusions

Our data indicate that increased abdominal VAT rather than SAT is associated with microstructural brain tissue damage in elderly individuals.

INTRODUCTION

Obesity has been linked to brain atrophy, and many studies have suggested that body mass index (BMI) is associated with brain damage and cognitive decline[1-4]. The distribution of body fat is crucial to understanding the adverse effects of obesity. Excess fat is stored subcutaneously, as well as at ectopic sites, such as the visceral fat depot. Visceral adipose tissue (VAT), as opposed to subcutaneous adipose tissue (SAT), is considered to play a key role in the atherogenic effects of obesity[5] and is associated with incident cardiovascular disease and cancer[6]. VAT is increasingly appreciated as an endocrine organ which produces cytokines, such as interleukin-6 and tumor necrosis factor alpha, which induce hepatic production of the acute phase protein C-reactive protein[7, 8]. Production of these cytokines and systemic low-grade inflammation are considered as important mechanisms for the adverse effects of obesity on the vessel wall. It can be hypothesized that inflammation also induces subtle microstructural brain changes, which by themselves may lead to cognitive decline[9, 10]. Magnetization transfer imaging (MTI) is an MRI technique that is more sensitive to subtle microstructural changes in the brain than conventional techniques[11-13]. Although the association between high BMI and brain damage is apparent, the individual contributions of VAT and SAT are unknown. Accordingly, the aim of the present study was to investigate the individual associations between abdominal VAT and SAT and the integrity of the microstructure in the brain.

METHODS

Subjects

This study comprises subjects from the Leiden Longevity Study, which is described extensively elsewhere[14]. In summary, in the Leiden Longevity Study subjects genetically enriched for familial longevity are compared with their partners to determine genetic factors contributing to longevity. Inclusion criteria for the study as a whole were: [1] men must be aged ≥ 89 years and women ≥ 91 years; [2] subjects must have at least one living brother or one living sister who fulfilled the first criterion and was willing to participate; [3] the sib pairs have an identical mother and father; [4] the parents of the sibship are Dutch and Caucasian. The Leiden Longevity Study cohort included 421 Dutch Caucasian families consisting of 943 long-lived siblings with 1671 of their offspring and 745 of the partners thereof. The offspring carries on average 50% of the genetic propensity of their long-lived parent and were shown to have a lower mortality (standardized mortality ratio 0.65) compared with their birth cohort[14]. Their partners, with who most have shared the same environment for decades were included as matched controls. There was no selection on demographic or health characteristics[14, 15].

Participants for the current study were recruited from the offspring of the long-lived siblings and their partners. The subjects were pooled for analysis. After exclusion of subjects with contraindications for MRI, the current study included 243 nondemented subjects (127 offspring and 116 controls) who underwent MTI of the brain and abdominal CT on the same day.

This study was approved by the Medical Ethical Committee of the Leiden University Medical Center and was conducted in accordance with the Declaration of Helsinki. Written informed consent was obtained from all participants.

Abdominal adipose tissue measurement

Measures of abdominal adiposity were assessed by nonenhanced CT (Toshiba Aquilion ONE, Toshiba Medical Systems, Otawara, Japan). The examinations were performed between September 2009 and December 2010. A single-slice 8.0 mm acquisition was planned at the L4/L5 vertebra level. Tube voltage was 120 kV, tube current 310 mA, rotation time 0.5 s. Imaging was performed during breath hold after expiration. Analysis of visceral fat and subcutaneous fat was performed with dedicated fat measurement software available at the CT scanner console. The single slice image was selected within the software program. An automated tool was used for recognizing fat, using predefined thresholds for adipose tissue ranging from −150 to −30 HU. Visceral fat was defined as fat enclosed by the peritoneal cavity. Abdominal subcutaneous fat was defined as fat outside the peritoneal cavity.

MRI acquisition

Imaging was performed on an MR system operating at a field strength of 3 Tesla (Philips Medical Systems, Best, the Netherlands). MTI was part of a more extended protocol described previously[16], which included T1-w, T2-w, FLAIR, and DTI MRI scans. MTI was performed with the following parameters: TR = 100 ms, TE = 11 ms, FA = 9°, FOV = 224 × 180 × 144 mm, matrix size 224 × 169, and 20 slices with a 7 mm thickness, no slice gap.

MRI processing

Magnetization transfer ratio (MTR) was investigated for gray and white matter separately. Nonsaturated and saturated MTI images were co-registered to the three-dimensional T1-weighted images and subsequently processed with FSL tools[17, 18]. For creation of individual brain masks for cortical gray and white matter, three-dimensional T1-weighted images were skull stripped[19] and subsequently segmented[20] into cortical gray and white matter. For all analyses basal ganglia, hippocampus, and amygdala were excluded from data analysis. Individual MTR maps were calculated voxel by voxel following the equation MTR = (M0 − M1) / M0. Mean MTR and normalized MTR peak height were determined[11] after masking the MTR maps with the respective brain masks. For correction for possible partial volume effects, 1 voxel eroded gray and white matters masks were applied.

Statistical analysis

All descriptive data were presented as mean ± standard deviation or as percentage. Offspring and partners were pooled. Multivariate linear regression and stepwise backward regression analyses were performed to investigate the associations between VAT and SAT and MTI markers of brain microstructure. First, analyses were adjusted for sex, age, and descent (being partner or offspring of long lived siblings) (Model 1). Second, analyses were additionally adjusted for BMI, hypertension, current smoking, statin use, and type 2 diabetes (Model 2). Regression coefficients, 95% confidence intervals (CI), *P* values, and R^2 values are reported. $P < 0.05$ was considered statistically significant. Statistical analyses were performed using IBM SPSS Statistics for Windows, version 20.0 (IBM Corp., Armonk, NY).

RESULTS

This analysis comprised 243 subjects. Subject characteristics are shown in **Table 1**. Mean age was 65.4 ± 6.7 years and mean BMI 26.3 ± 3.8 kg/m^2. The gray matter and white matter MTI parameters (mean MTR and normalized MTR peak height) of the entire group are summarized in **Table 2**. BMI was associated with normalized MTR peak height in both gray matter (standardized β: −0.217, $P < 0.001$) and white matter (standardized β: −0.208, $P < 0.001$) after adjustment for sex, age, and descent. BMI was associated neither with mean MTR in gray matter ($P = 0.957$) nor in white matter ($P = 0.315$).

Table 1. Subject characteristics

Men, *n* (%)	112 (46)
Age (years)	65.4 ± 6.7
BMI (kg/m^2)	26.3 ± 3.8
VAT (cm^2)	128.9 ± 61.7
SAT (cm^2)	236.1 ± 91.7
Systolic blood pressure (mmHg)	138.9 ± 19.6
Diastolic blood pressure (mmHg)	83.3 ± 9.4
Hypertension, *n* (%)	55 (23)
Current smokers, *n* (%)	27 (11)
Type 2 diabetes, *n* (%)	16 (7)
Statin use, *n* (%)	19 (8)
History of stroke	5 (2)
History of myocardial infarction	3 (1)
Total cholesterol (mmol/L)	5.6 ± 1.2
HDL cholesterol (mmol/L)	1.5 ± 0.4

Values are means ± standard deviation or *n* (%).
BMI = body mass index, VAT = visceral adipose tissue, SAT = subcutaneous adipose tissue, HDL = high-density lipoprotein.

Table 2. Magnetization transfer imaging parameters

	Normalized MTR peak height (pixel count x 10^3)	Coefficient of variation
Gray matter	76 ± 11	0.14
White matter	117 ± 23	0.20
	Mean MTR (value x 10^3)	**Coefficient of variation**
Gray matter	335 ± 9	0.03
White matter	394 ± 9	0.02

MTR = magnetization transfer ratio.

Table 3 shows the associations between VAT and MTI parameters in gray and white matter. VAT was associated with normalized MTR peak height in both gray matter ($P < 0.001$) and white matter ($P < 0.001$) after adjustment for sex, age, and descent. After additional adjustment for BMI, hypertension, current smoking, statin use, and type 2 diabetes, the associations remained for gray matter ($P = 0.003$) and white matter ($P < 0.001$). An increase of VAT with 1 cm^2 reduced normalized MTR peak height in the gray matter with 46.1 (95% CI −85.4, −6.7), which roughly corresponds to an overall decrease in normalized MTR peak height of 0.1%. In the white matter, 1 cm^2 increase in VAT resulted in a MTR peak height decrease of 103.6 (95% CI −190.2, −17.1), which also roughly corresponds to a 0.1% overall decrease. No significant associations between VAT and mean MTR in the gray and white matter were found.

Table 4 shows the associations between SAT and MTI parameters in gray and white matter. SAT was associated with normalized MTR peak height in both the gray matter ($P < 0.001$) and white matter ($P = 0.001$) after adjustment for sex, age, and descent. However, after additional

Table 3. Associations between visceral adipose tissue and magnetization transfer imaging parameters

	Standardized β	*P*	R^2
Normalized MTR peak height - gray matter			
Model 1	-0.361	< 0.001	0.283
Model 2	-0.216	0.003	0.262
Normalized MTR peak height - white matter			
Model 1	-0.396	< 0.001	0.305
Model 2	-0.240	< 0.001	0.287
Mean MTR - gray matter			
Model 1	0.006	0.923	0.169
Model 2	0.058	0.475	0.171
Mean MTR - white matter			
Model 1	0.033	0.611	0.106
Model 2	0.076	0.110	0.255

Model 1: Adjusted for sex, age and descent. Model 2: Adjusted for sex, age, descent, BMI, hypertension, current smoking, statin use, and type 2 diabetes.
β = regression coefficient, R^2 = proportion of explained variance; MTR = magnetization transfer ratio.

adjustment for BMI, hypertension, current smoking, statin use, and type 2 diabetes, the associations for both gray matter ($P = 0.284$) and white matter ($P = 0.938$) were abolished. No significant associations between SAT and mean MTR in the gray and white matter were found.

When analyzing both VAT and SAT in a stepwise backward regression model adjusted for sex, age, and descent, only VAT remained associated with normalized MTR peak height in gray and white matter (both $P < 0.001$). Additional adjustment for BMI, hypertension, current smoking, statin use, and type 2 diabetes did not alter these findings.

Table 4. Associations between subcutaneous adipose tissue and magnetization transfer imaging parameters

	Standardized β	*P*	R^2
Normalized MTR peak height - gray matter			
Model 1	-0.274	< 0.001	0.233
Model 2	-0.055	0.284	0.235
Normalized MTR peak height - white matter			
Model 1	-0.217	0.001	0.207
Model 2	0.035	0.938	0.233
Mean MTR - gray matter			
Model 1	-0.003	0.965	0.168
Model 2	0.052	0.501	0.171
Mean MTR - white matter			
Model 1	0.052	0.434	0.108
Model 2	-0.024	0.580	0.106

Model 1: Adjusted for sex, age and descent. Model 2: Adjusted for sex, age, descent, BMI, hypertension, current smoking, statin use, and type 2 diabetes.
β = regression coefficient, R^2 = proportion of explained variance; MTR = magnetization transfer ratio.

DISCUSSION

In the current study, we observed lower integrity of the microstructure in the brain with increasing VAT, as well as SAT. When entered in one regression model, VAT appeared to have a much stronger association with microstructural brain tissue damage than SAT.

It has been shown that obesity is related to neurodegenerative, vascular, and metabolic processes that affect brain structures underlying cognitive decline and dementia, with increasing evidence of a greater role of visceral rather than subcutaneous adiposity[8, 21]. It has also been shown that visceral rather than subcutaneous fat, expressed as a percentage of total fat, was significantly correlated with the volume of white matter lesions in subjects with acute ischemic stroke. In that particular study, study population was small ($n = 25$), consisted mostly of men, and adjustments for potential confounders were not performed[22]. A more recent study reported a link between having more than 100 cm^2 visceral fat and the presence of white matter lesions and silent lacunar infarctions in subjects free of symptomatic cerebrovascular

disease, suggesting a role of visceral fat on the development of cerebral small vessel disease. This association was found to be independent of age ≥ 60 years, waist circumference, BMI ≥ 25 kg/m^2, and hypertension[23]. In a large cohort study, it was found that VAT and total brain volume were associated; however, VAT was not associated with markers of vascular brain injury such as volume of white matter lesions and brain infarcts[8]. In the latter study no associations between VAT or SAT and temporal horn volume, a surrogate measure for hippocampal volume, was found. In a study with healthy nondemented elderly subjects it was demonstrated that VAT was significantly associated with verbal memory and low hippocampal volume after accounting for SAT, indicating an adverse effect of VAT on cognitive performance[24]. In general, these studies demonstrate associations between VAT and brain damage.

The current study shows that VAT is strongly associated with MTI parameters reflecting discrete brain lesions that may not be detected by conventional imaging. MTI has the potential to quantify the pathologic changes in central nervous system disorders in the normal appearing white and gray matter on conventional MRI sequences[11, 13, 25]. MTI offers a way of examining tissue structure and structural components, normally not resolvable with conventional MRI[12]. This allows for examination of structural integrity in a different and possibly more sensitive manner than volumetric changes alone. MTI contrast is based on magnetization transfer between protons, which are bound to macromolecules and therefore restricted in motion, and protons in water, which can move freely[26]. The MTR, representing the percentage of variation in the MR signal between the saturated and unsaturated acquisitions, is an effective and simple MTI measure to use as a clinical application. Within the brain, myelin water contributes disproportionately to the MTR, which therefore has been suggested to be a relatively specific quantitative measure of myelin integrity[27-29]. MTR histogram analysis is a technique which displays MTR values of the segmented brain. MTR histograms of normal brains are characterized by the presence of a single, sharp peak, indicating that most normal brain voxels have approximately the same MTR values[30]. In general mean MTR and histogram peak height are reported both. It should be realized that both measures reflect different processes and may show different sensitivity to demonstrate brain changes. In most cases histogram peak height is a more sensitive marker than mean MTR[31-33]. On the other hand it has also been reported that both measures demonstrate a comparable sensitivity[34]. Therefore, although both measures are related, they may demonstrate a different sensitivity in detecting structural changes in the brain.

Widespread MTI changes are associated with cognition. Previously, patients with Alzheimer disease, and mild cognitive impairment were shown to have lower mean MTR and normalized MTR peak height in gray and white matter compared to controls[35]. In the current study, VAT was associated with normalized MTR peak height in gray and white matter, however not with mean MTR. It may be hypothesized that subtle brain changes in the state of overweight and obesity might not yet be detected by the mean MTR parameter. Unfortunately, we did not measure cognition in this study.

The pathophysiological pathways linking obesity and structural brain changes are not completely understood, but systemic low-grade inflammation associated with inflamed and expanded VAT has been a proposed mechanism. Compared to SAT, VAT was stronger associated with systemic biomarkers including C-reactive protein, interleukin-6, monocyte chemoattractant protein-1, and isoprostanes reflecting inflammation and oxidative stress[7]. Excess visceral fat accumulation has been associated with various atherogenic and diabetogenic abnormalities[36], and weight loss decreased VAT[37], carotid intima-media thickness[38], arterial stiffness[39], and improves inflammatory profile[38]. Altogether, there is growing evidence that VAT has a unique metabolic and endocrine function with deleterious effects on multiple organs, which may also include the brain.

Strengths of this study are the availability of combined data of abdominal adipose tissue distribution and microstructural brain tissue damage in a large cohort. A few limitations should be addressed. The study population is an elderly population, consisting of offspring of long-lived siblings and their partners. The cross-sectional nature of our study limits to differentiate cause and effect. It can be hypothesized that the observed relationship between VAT and microstructural brain tissue damage is merely a result of the potential confounding factor ageing. In this study, we attempted to correct for age in the multivariate linear regression analysis. However, because the age range is relatively small, we cannot completely exclude that age in part affects our results. Furthermore, part of our study population is offspring of long-lived persons and therefore may be different than the general population, which could limit the generalizability of our results. Because of the cross-sectional design of the study, it could be postulated that microscopic brain tissue damage may lead to obesity. However, it has been shown that obese nondiabetic adolescents with metabolic syndrome have lower cognitive performance compared to adolescents without metabolic syndrome. Moreover, smaller hippocampal volumes and reductions of white matter microstructural integrity were found[40]. It is not very likely that these brain impairments were pre-existing. Thus the observations in this early stage of life strengthen the hypothesis that obesity leads to reductions in cognitive function and structural brain changes, and not vice versa.

Further research in a general population with a wider age range is necessary to study whether the relationship between visceral adiposity and microstructural brain tissue damage is merely a result of ageing, or exists independently of age. Furthermore, cognition tests could be of additional value for evaluating the clinical consequences of these findings.

In conclusion, this study indicates that increasing VAT rather than SAT is associated with microstructural brain tissue damage in elderly individuals. This association cannot be accounted for by BMI, which is an easily obtainable clinical measure of obesity but does not discriminate different fat compartments. Awareness of differences in the underlying mechanisms between body fat patterns and brain damage may offer more focused individual advice or treatment than considering BMI only.

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