Central Obesity and the Aging Brain

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Background: Central adiposity as an indicator of visceral fat is linked to vascular and metabolic factors that in turn are related to cognitive decline and dementia.

Objective: To determine whether larger waist-hip ratio (WHR) is associated with structural brain changes that underlie cognitive decline and dementia.

Design: Cross-sectional analysis of an epidemiologic cohort study of cognitive and functional decline (Sacramento Area Latino Study on Aging).

Setting: California Central Valley.

Participants: A total of 112 individuals selected from an ongoing cohort study of 1789 older Latino individuals. Baseline anthropomorphic measures (WHR) and measurements of fasting blood glucose, cholesterol, and insulin levels and blood pressure were obtained.

Main Outcome Measures: Baseline magnetic resonance images were analyzed quantitatively to determine the hippocampal volumes in the right and left hemispheres and rated for the percentage of white matter hyperintensities.

Results: Greater WHR (P=.02) and older age ($P<.001$) were negatively related to hippocampal volumes. The WHR and age were positively related to white matter hyperintensities (P=.02 and P=.001, respectively). A 1-SD increase in WHR was associated with a 0.2-SD decrease in hippocampal volume and a 27% increase in white matter hyperintensities. These relationships were not affected by adjustment for body mass index, total cholesterol, fasting blood glucose, and insulin levels or systolic blood pressure in the models.

Conclusion: A larger WHR may be related to neurodegenerative, vascular, or metabolic processes that affect brain structures underlying cognitive decline and dementia.

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INCREASING RATES OF OBESITY IN the United States have led to widespread public concerns about an epidemic with profound negative health consequences.[1] Although obesity is defined as a body mass index (BMI) of 30 or greater, the greatest association with vascular and metabolic disease involves abdominal obesity, measured as waist-hip ratio (WHR) or waist circumference, which is also increasing.[2] The factors of abdominal obesity, hyperlipidemia, hypertension, and glucose intolerance frequently coexist and constitute the metabolic syndrome, an important risk factor for diabetes mellitus and cardiovascular disease. The metabolic syndrome is also prevalent in the United States, with some of the highest rates in Mexican American individuals.[3]

Obesity has recently been linked to both Alzheimer disease and alterations in brain structure seen with computed tomography.[4-6] A host of potential factors may mediate these associations, including diabetes,[7] hypertension,[8] and vascular disease.[9]

Based on associations among obesity, metabolic and vascular disease, and dementia, it seems reasonable to further investigate changes in brain structure that may underlie these relationships. Magnetic resonance imaging (MRI) measures that have been linked to cognitive impairment and dementia are hippocampal volume (HV) and white matter hyperintensities (WMHs). Although it is also seen in other conditions, HV is highly associated with Alzheimer disease.[10,11] Although also not entirely specific, WMHs are associated with cerebrovascular risk factors and cognitive decline.[12,13] We recently reported that HV and WMHs both contribute independently to the risk of dementia in an epidemiologic cohort.[14] Therefore, we sought to evaluate how WHR, considered a predictor of cardiovascular disease and a component of the metabolic syndrome, might be associated with changes in brain structure in this cohort.

Table 1. Subject Characteristics

Variable	Mean (SD)	Range
Age, y	69.7 (6.3)	60-83
Education, y	8.2 (5.2)	0-20
Weight, kg	76.11 (13.6)	46.27-122.02
Body mass index*	29.2 (4.9)	19.8-45.6
Waist-hip ratio	0.91 (0.08)	0.75-1.14
Mini-Mental State Examination score	78.8 (19.1)	12-100
Fasting glucose, mg/dL [mmol/L]	122 (46.2) [6.77 (2.56)]	72-331 [4.00-18.37]
Cholesterol, mg/dL [mmol/L]	207 (40.3) [5.35 (1.04)]	113-317 [2.92-8.20]
HDL-C, mg/dL [mmol/L]	50.8 (13.6) [1.31 (0.35)]	25-93 [0.65-2.40]
LDL-C, mg/dL [mmol/L]	124.6 (32.9) [3.22 (0.85)]	63-229 [1.63-5.92]
Triglycerides, mg/dL [mmol/L]	179.7 (109.4) [2.03 (1.24)]	45-622 [0.51-7.02]
Ankle-arm blood pressure index, mm Hg	1.03 (0.0)	0.62-1.29
Systolic blood pressure, mm Hg	149.8 (24.5)	107-215

Abbreviations: HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol.
*Calculated as weight in kilograms divided by the square of height in meters.

Table 2. Multiple Regression Models for Hippocampal Volume and White Matter Hyperintensities

Variable	Estimate (SE)	*P* Value	Partial R^2*
Hippocampal volume			
Age, y	−0.074 (0.013)	<.001	0.213
Waist-hip ratio (*z* score)	−0.201 (0.083)	.02	0.040
White matter hyperintensities			
Age, y	0.056 (0.016)	.001	0.088
Waist-hip ratio (*z* score)	0.254 (0.104)	.02	0.047

*Partial R^2 is the percentage of variability in the dependent measure explained by each independent variable alone.

METHODS

SUBJECTS

Subjects were recruited for neuroimaging from a sample of community-dwelling Latino individuals 60 years and older who were residing in the Sacramento, Calif, area. Detailed information about sampling, screening, evaluation, and dementia ascertainment has been previously described.[15] A subgroup of 122 subjects was selected for an imaging substudy from the larger cohort of 1789 individuals.[14] Of the MRI subgroup, 112 individuals had complete data available for analysis for this report. The study was approved by the institutional review boards of participating institutions.

The WHR was measured twice and averaged by field staff in the subjects' homes. The waist measurement was taken at the midpoint between the iliac crest and lower rib using an insertion tape and measured at the end of a normal expiration. Hip circumference was the maximum circumference over the buttocks below the iliac crest. The WHR was calculated as the ratio of waist circumference to hip circumference. The BMI was calculated as weight in kilograms (measured with a portable digital scale) divided by the square of height in meters (measured with a portable stadiometer). Brachial and ankle blood pressures were measured with a handheld Doppler probe. Morning fasting blood samples were taken for measurement of total cholesterol, glucose, and insulin levels.

MRI ACQUISITION AND ANALYSIS

Subjects underwent MRI (GE Signa system; General Electric, Milwaukee, Wis) using a sagittal fast spin-echo T2 sequence, an axial oblique spin-echo T2-weighted/proton density sequence, and a T1-weighted, coronal 3-dimensional spoiled gradient recalled echo inversion recovery prepped sequence.[14] Measurement of HV and WMHs has previously been described.[14] The HV measurements on the T1 images included CA1 through CA3, dentate gyrus, and subiculum. The WMHs were rated using a semiquantitative rating scale in which a rater evaluated uniformly formatted axial proton-density images with respect to a series of image standards that had quantitated magnetic resonance WMHs.

DATA ANALYSIS

Strategy for data analysis used linear regression with model building that was the same across analyses. The WMHs were not normally distributed and so were increased by 1 (to shift the lowest value from 0 to 1) and log transformed. The HV and WHR were transformed into *z* scores for all analyses for ease of interpretation. Subsequent analyses included multiple regression models accounting for potential confounders.

We performed unadjusted linear regressions to assess the relationship between measures of interest. Since our primary hypothesis concerned the relationship between WHR and MRI variables, we constructed models with WHR and age as the independent variables and HV or WMHs as the dependent variables. Subsequently, the models were adjusted for the effects of a group of covariates that largely reflected metabolic and vascular disease.

RESULTS

Characteristics of the sample are given in **Table 1**. A total of 25% of the group was obese, with BMIs of 30 or greater. Ten percent of subjects were cognitively impaired but did not have dementia, an additional 21% had dementia, and the rest were cognitively healthy. Values for WMHs, HV, and cognitive function were previously reported to differ among these groups.[14] However, these groups did not differ by WHR ($P=.19$ for a group by WHR analysis of variance). The high mean fasting glucose level reflects the 39% prevalence of type 2 diabetes mellitus as identified by either a medical history of the disease or prescription of hypoglycemic agents.

The results of multiple regression modeling for the average of the right and left HVs are presented in **Table 2**. The WHR and age together accounted for 25% of the variability in HV, whereas WHR alone accounted for 4%. A 1-SD increase in age was associated with a 0.5-SD decrease in HV, whereas a 1-SD increase in WHR was associated with a 0.2-SD decrease in HV. Relationships between covariates and HV were evaluated and none, including sex, BMI, cholesterol level, systolic blood pressure, ankle-arm blood pressure index, fasting blood glucose level, or insulin level, were associated with HV. The

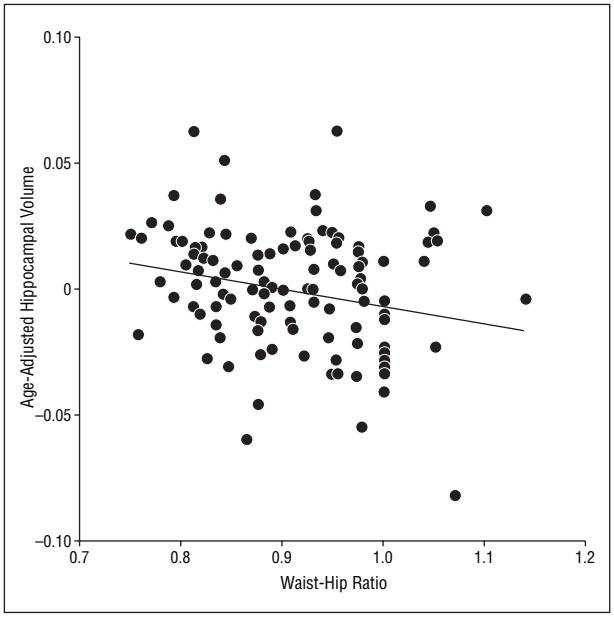

Figure 1. Plot of waist-hip ratio vs age-adjusted hippocampal volume. There is a significant association between the 2 variables (r=0.2, P=.02).

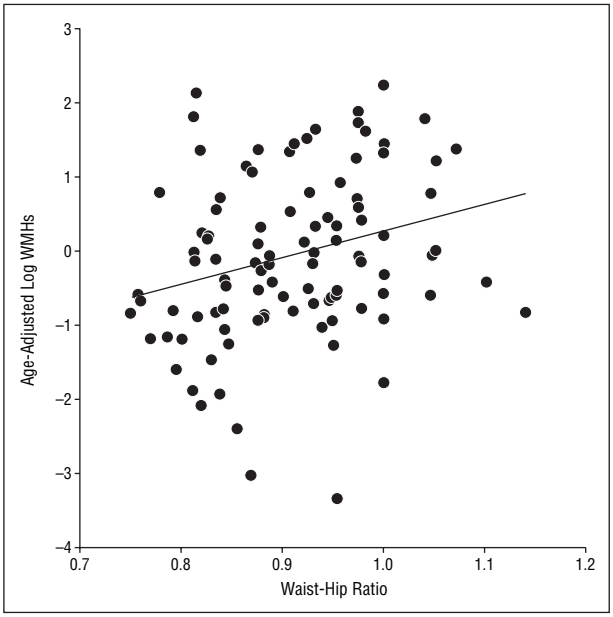

Figure 2. Plot of waist-hip ratio vs age-adjusted log of white matter hyperintensities (WMHs). There is a significant association between the 2 variables (r=0.22, P=.02).

strongest associations were seen with blood glucose level (partial R^2=0.02, P=.10) and systolic blood pressure (partial R^2=0.02, P=.15). When these covariates were added to the model with WHR and age, they did not significantly affect the results. Results using the individual values for right and left hemisphere HVs were similar to those for the average of the right and left. The regression for WHR and HV, controlling for the effects of age, is shown in **Figure 1**.

The results of the multiple regression model for WMHs are presented in Table 2. Both WHR and age accounted for 13.5% of the variability in WMHs, and WHR alone accounted for 4.7% of the variability. Both variables were significantly associated with WMHs. A 1-SD increase in age was associated with a 42% increase in WMHs, whereas a 1-SD increase in WHR was associated with a 27% increase. Among the covariates, including sex, BMI, cholesterol level, systolic blood pressure, ankle-arm blood pressure index, and glucose and insulin levels, we found that the fasting glucose level and systolic blood pressure were significantly associated with WMHs (for glucose, partial R^2=0.05, P=.01; and for systolic blood pressure, partial R^2=0.14, P<.001). The only other variables that came close to a significant association were sex (partial R^2=0.03, P=.07) and cholesterol level (partial R^2=0.02, P=.15). When these confounders were included in the multivariate model, however, the relationship between WHR and WMHs did not change (the estimate was 0.29, partial R^2=0.05, P=.05). **Figure 2** shows the relationship between WHR and WMHs after controlling for the effects of age.

COMMENT

We found that distribution and amount of body fat accounted for a small, but significant, proportion of variance in the size of the hippocampus and the amount of WMHs in this cohort of individuals with a high prevalence of obesity and glucose intolerance. Adjustment for covariates that included both generalized obesity (BMI) and a variety of cardiovascular variables did not affect these relationships. Although the strength of the associations is small, the estimates indicate moderate effects of increases in WHR on HV and WMHs. These effects are likely to be behaviorally relevant, since we have previously reported significant effects of both WMHs and HV on cognition in this cohort.[14]

Considerable evidence exists to support the idea that the MRI variables we chose for analysis are intimately related to metabolic and vascular disease. Smaller HVs have been reported in association with diabetes mellitus and poor glucose tolerance.[16,17] Similarly, changes in brain white matter are well known to be associated with a variety of vascular factors, including hypertension and diabetes.[12,13]

Nevertheless, changes in glucose metabolism and vascular risk factors do not entirely explain the relationship between these changes in brain structure and WHR because inclusion of these variables in the regression models did not affect the associations. A number of other potential mechanisms might mediate these associations. Such possibilities include inflammatory mechanisms, mediated by proinflammatory cytokines such as interleukin 6 and tumor necrosis factor α, which are produced by adipose tissue.[18,19] In addition, central adiposity has been suggested as an outcome related to chronic stress or allostatic load.[20] Although chronic stress effects on the brain are poorly understood, cumulative effects have been proposed to exert deleterious adaptation of the hypothalamic-pituitary-adrenal axis that in turn produces hippocampal dysfunction.[21] Although relationships between central obesity and such physiologic and anatomical changes are highly speculative, evidence exists that relates stress and hypothalamic-pituitary-adrenal axis dysfunction to hippocampal atrophy.[22,23] Increased cortisol levels in aging

are also associated with poor performance on memory tests and smaller HVs.[24]

The strength of the associations are small and could potentially be explained by residual confounding or comorbid illnesses. Nevertheless, standard measures of vascular and metabolic disease and cognitive status do not appear to account for the results.

These results are consistent with a growing body of evidence that links obesity, vascular disease, and inflammation to cognitive decline and dementia and provide additional evidence of the brain mechanisms that may mediate these associations. Vascular risk factors are well known to increase the risk of dementia, cognitive decline, and Alzheimer disease.[12,15,25] Women, but not men, who develop dementia between the ages of 79 and 88 years had a higher BMI an average of 18 years earlier.[5] In the same cohort, higher BMI (but not WHR) was associated with greater temporal lobe atrophy by visual rating of computed tomographic scans.[6] These findings were not accounted for by vascular factors. In another cohort, variables that reflect the metabolic syndrome, including BMI, increased dementia risk independently of one another and were not simply reflective of cardiovascular disease or atherosclerosis.[4] Our findings extend these observations by defining brain regions and potential pathophysiologic processes that may mediate these associations.

The findings reported herein are thus congruent with a wealth of data that indicate negative effects of obesity on cognitive function and also with data that implicate diabetes,[26] inflammation,[27] and stress[28] as factors related to cognitive decline. Evidence that suggests that physical exercise may reduce the risk of dementia[29] is also consistent with these results, since it can affect weight, insulin function, and potentially stress and is associated with diminished loss of brain tissue with age.[30] The finding that a greater WHR is associated with both smaller hippocampi and more WMH demonstrates evidence of structural brain damage that should be at least partially modifiable by lifestyle changes.

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