Reduced Lean Mass in Early Alzheimer Disease and Its Association With Brain Atrophy

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Objective: To examine body composition in individuals with early AD and without dementia and its relation to cognition and brain volume.

Design: Cross-sectional case-control study.

Participants: Individuals without dementia (Clinical Dementia Rating, 0; n=70) and with early-stage AD (Clinical Dementia Rating, 0.5 or 1; n=70) in the Alzheimer and Memory Program at the University of Kansas School of Medicine.

Main Outcome Measures: Participants were evaluated with brain magnetic resonance imaging (MRI), neuropsychological testing, and dual-energy x-ray absorptiometry to determine whole-body fat and lean masses. Body mass index was calculated as weight in kilograms divided by height in meters squared.

Results: Lean mass was reduced in persons with early AD compared with controls without dementia ($F=7.73$; $P=.006$) after controlling for sex. Whole-brain volume ($\beta=.20$; $P<.001$), white matter volume ($\beta=.19$; $P<.001$), and global cognitive performance ($\beta=.12$; $P=.007$) were associated with lean mass (dependent variable) when controlling for age and sex. The total body fat and percentage of body fat values were not different across groups or related to cognition and brain volume.

Conclusion: Loss of lean mass is accelerated in AD and is associated with brain atrophy and cognitive performance, perhaps as a direct or indirect consequence of AD pathophysiology or through shared mechanisms common to both AD and sarcopenia.

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ALZHEIMER DISEASE (AD) IS associated with unintended weight loss[1] that begins years prior to the recognition of AD-related clinical symptoms[2-4] and may be a marker of preclinical AD.[5] Weight loss in AD is associated with dementia severity and faster clinical progression.[1] Epidemiological studies suggest a complex relationship between body composition and dementia that may be variable across the age spectrum. Although obesity in midlife is a risk factor for developing dementia,[6,7] overweight and obesity in late life are associated with lower dementia risk.[8,9] Most studies of body composition in dementia and AD are limited by nonspecific measures of body composition such as total body weight or body mass index (BMI; calculated as weight in kilograms divided by height in meters squared) rather than specific measures of body fat and muscle mass. As normal aging is associated with increases in body fat and declines in lean mass without overall weight loss, nonspecific adiposity measures such as BMI have limited value in capturing these changes.

We used dual-energy x-ray absorptiometry (DEXA) to quantify body composition in subjects with early-stage AD and without dementia. We examined whether alterations in specific components of body composition (ie, lean mass vs fat mass) were apparent in individuals in the earliest clinical stages of AD. Given previous studies relating body composition to AD severity and progression, we also examined the relationship of body composition to cognition. Additionally, AD-related brain changes including medial temporal lobe atrophy[10] and neuropathological burden (plaques and tangles)[11] are associated with reduced BMI, suggesting that neurodegenerative processes may contribute to alterations in body composition. Thus, we further examined the relationship of components of body composition to imaging measures of neurodegeneration (ie, brain atrophy). Because weight loss is associated with AD progression and altered body composition, we hypothesized that body composition would be associated with brain volume and cognitive performance.

SAMPLE AND RECRUITMENT

Participants were aged 60 years and older and either did not have dementia (Clinical Dementia Rating [CDR], 0; n=70) or were diagnosed with early-stage AD (CDR, 0.5; n=56 and CDR, 1; n=14) as detailed below. Participants without dementia and 63% of the participants with AD were self-referred from the community (primarily through media coverage and word of mouth), while 37% of the participants with AD were recruited from a referral-based memory clinic. Study exclusions included neurologic disease other than AD, diabetes mellitus, recent (<2 years) history of ischemic heart disease, clinically significant depressive symptoms, use of antipsychotic and investigational medications, and significant sensory impairment or systemic illness that could impair completion of the study. All participants were required to be accompanied by a study partner who was knowledgeable about the participant's daily activities. We have previously reported results from subsamples of this cohort.[12-14]

CLINICAL ASSESSMENT

All participants were evaluated using a semistructured interview of the participant and a study partner to determine the presence or absence of dementia and its severity, if present, using the CDR.[15] Diagnostic criteria for AD require the gradual onset and progression of impairment in memory and at least 1 other cognitive and functional domain.[16] These diagnostic methods have an accuracy of 93% for AD[17] and sensitively detect the earliest stages of AD by focusing on intraindividual change rather than comparison with group reference values.[18] Additionally, they accurately identify the subset of individuals who meet criteria for mild cognitive impairment and have early-stage AD.[19] A global CDR score is derived from individual ratings in each domain, with a CDR of 0 indicating no dementia; 0.5, very mild dementia; and 1, mild dementia. Subjects with moderate (CDR, 2) or severe (CDR, 3) dementia were not enrolled in the study.

A nurse clinician collected medication information, medical history, education, and demographics from the study partner. A neurologist performed a standard physical and neurological examination. Functional activity level was estimated using the Mild Cognitive Impairment Activities of Daily Living Scale.[20] The Geriatric Depression Scale[21] was given to the collateral source for all participants and used as a continuous variable for analysis. Apolipoprotein E genotyping was conducted using restriction enzyme isotyping.[22]

NEUROPSYCHOLOGICAL ASSESSMENT

A trained psychometrician gave a standardized psychometric battery of tests to all participants, as previously described.[12-14] The battery included the standard measures of Logical Memory I and II, Free and Cued Selective Reminding Task, Boston Naming Test-15 item, Verbal Fluency, Digit Span Forward and Backward, Letter-number sequencing, Trail making A and B, Stroop Color-Word Test, and Block Design. Cognitive performance scores were converted to z scores based on the mean and standard deviations of subjects without dementia. The means of each participant's z scores served as an index of global cognitive performance. The Mini-Mental State Examination (MMSE) was also given as a measure of global cognition.

BODY COMPOSITION

Dual-energy x-ray absorptiometry (GE Lunar Corp, Madison, Wisconsin) was used to determine total body measures of lean and fat mass. Percentage of body fat represents the percentage of total body mass (determined by DEXA) composed of fat (ie, total fat × 100/total body mass). We used total body mass determined by DEXA. Mass determined by DEXA was highly correlated with our manually measured (by scale) body weight (r=0.99; P<.001) and also minimized the influence of clothing. Height was measured using a standard stadiometer.

OTHER CLINICAL MEASURES

We also examined potential covariates that may mediate brain and body composition relationships including habitual level of physical activity, frailty, and laboratory assessments of insulin, lipids, inflammation, and apolipoprotein E4 allele status, as previously described.[12-14] Briefly, level of habitual physical activity was estimated using the Physical Activity Scale in the Elderly, a reliable and valid measure of physical activity developed specifically for older individuals.[23] The Physical Activity Scale in the Elderly estimates an individual's level of physical activity in the last 7 days by assessing the frequency and duration of participation in a variety of activities. The Physical Activity Scale in the Elderly was given to both the subject and the study partner and, for individuals with AD, data collected from the study partner were used in the analyses. We assessed peripheral insulin levels by radioimmunoassay using a fasting, 14-sample, 3-hour intravenous glucose tolerance test as previously described.[13] Total 3-hour area under the curve (AUC) values for glucose and insulin served as overall indices of glucose and insulin levels. The Physical Performance Test was used as a measure of physical performance and frailty.[24] Fasting venous blood samples were assessed using commercial enzymatic assays for total cholesterol (Diagnostic Chemicals, Ltd, Oxford, Connecticut). Highly sensitive C-reactive protein was determined in fasting blood by turbidimetric assay (Roche Diagnostics Systems, Basel, Switzerland).

NEUROIMAGING

Structural magnetic resonance imaging was obtained for all participants using a Siemens 3.0 Tesla Allegra MRI scanner (Siemens Medical Solutions, Erlangen, Germany). High-resolution T1-weighted anatomic images were acquired to provide detailed gross anatomy with high gray/white matter contrast (magnetization-prepared 180° radiofrequency pulses and rapid gradient-echo; $1 \times 1 \times 1$ mm^3 voxels; time to repetition, 2500 milliseconds; echo time, 4.38 milliseconds; time following inversion pulse, 1100 milliseconds; field of view, 256 × 256 mm^2 with 18% oversample; flip angle, 8 degrees). Normalized whole-brain volume (WBV) was computed for each imaging session using validated imaging tools from the FMRIB Software Library (http://www.fmrib.ox.ac.uk/fsl), as previously described,[12] using the Laboratory of Neuro Imaging Pipeline (University of California Los Angeles; http://pipeline.loni.ucla.edu). Briefly, the images were preprocessed and skull-stripped using the Brain Extraction Tool. Skull-stripped images were then segmented into white matter, gray matter, and cerebrospinal fluid using FMRIB's Automated Segmentation Tool by registering them to the Montreal Neuroimaging Institute avg152 template. Normalized volumes for white matter (WMV), gray matter (GMV), and the whole brain (WBV; sum of white and gray matter) were calculated by dividing each by the total intracranial volume (the sum of white, gray, and cerebrospinal fluid volumes) and expressed as the percentage of the total intracranial volume. Normalized brain volumes minimize sex differences and produce an estimate of brain atrophy. Imaging data was unavailable for 3 participants without dementia and 1 with early AD.

Table 1. Characteristics of Study Population

| Characteristic | Mean (SD) | | |
	Control (n=70)	Early AD (n=70)	P Value
Age, y	73.3 (7.3)	74.9 (6.7)	.17
Education, y	16.5 (2.7)	15.2 (3.3)	.01
Sex, male/female	30/40	29/41	.86
Apolipoprotein E4 carrier, No. (%)	19 (27.9)	59.1 (39)	<.001
Mini-Mental State Examination score	29.4 (0.8)	26.0 (3.5)	<.001
Global cognitive performance, z score	0.0 (1.0)	−1.7 (1.8)	<.001
Whole-brain volume, % ICV	78.0 (2.9)	75.3 (3.3)	<.001
White matter volume, % ICV	35.0 (1.9)	34.6 (2.4)	.32
Gray matter volume, % ICV	43.0 (2.5)	40.6 (2.4)	<.001
Activities of daily living	48.5 (3.3)	40.2 (7.8)	<.001
Physical performance test	30.5 (3.4)	27.6 (3.9)	<.001
Physical activity level, PASE score	130.4 (51.8)	88.9 (56.7)	<.001
Total cholesterol, mg/dL	182.6 (34.0)	188.1 (37.4)	.37
C-reactive protein, mg/L	2.3 (2.4)	1.8 (1.5)	.11
Insulin area under the curve[a]	2540 (1361)	2903 (1747)	.18
Glucose area under the curve[a]	22 475 (2851)	23 049 (4541)	.38

Abbreviations: AD, Alzheimer disease; % ICV, percentage of intracranial volume; PASE, Physical Activity Scale in the Elderly.

SI conversion factors: to convert total cholesterol to millimoles per liter, multiply by 0.0259; C-reactive Protein to nanomoles per liter, 9.524.

[a] Area under the curve generated from a 3-hour intravenous glucose tolerance test.

Table 2. Body Composition in Participants With Early AD and Controls

| Variable | Mean (SD) | | |
	Control	Early AD	P Value[a]
Body mass index[b]	25.7 (3.6)	25.0 (3.9)	.38
Weight, kg	73.2 (14.0)	69.1 (12.9)	.10
Height, cm	169.6 (11.2)	166.2 (9.1)	.14
Fat mass, kg	25.8 (8.3)	24.7 (8.7)	.41
Body fat, %	35.3 (8.7)	35.4 (9.7)	.93
Lean mass, kg	44.6 (10.4)	41.9 (9.3)	.02

[a] Group comparison by general linear model, controlling for age and sex.
[b] Calculated as weight in kilograms divided by height in meters squared.

STATISTICAL ANALYSIS

Analyses were conducted using SPSS 16.0 (SPSS Inc, Chicago, Illinois). Continuous variables were summarized by means and standard deviations and categorical variables were summarized by frequency and percentage. The t test was used to compare continuous demographic and imaging variables in groups with early AD and without dementia. A χ^2 test was used to compare categorical variables. Pearson correlation coefficients were calculated to assess simple relationships between variables.

A multistep hierarchical linear regression was conducted to examine the relationship between clinical predictors (ie, brain volume, cognition) with body composition (ie, BMI, lean mass, and fat mass as dependent variables). All analyses controlled for age and sex. Variables correlating with body composition (ie, dementia status, physical activity, and insulin [3-hour AUC]) were used as covariates, and the increment in R^2 assessed the additional variance predicted from each new variable entered into the model. A final exploratory regression model examined the influence of all variables of interest and covariates on body composition. Age and sex were forced into the model in step 1, with covariates later entered in a stepwise fashion.

RESULTS

DESCRIPTIVE STATISTICS

Participant characteristics are summarized in **Table 1**. The control and early-AD groups were well matched with respect to age (mean [SD], 74.1 [6.8] years) and sex (58% female). Participants with early AD were slightly less educated than controls (15.2 years vs 16.5 years; t=2.60; P=.01). As expected, they also demonstrated mild global cognitive dysfunction. On average, they scored 3.4 points lower on the MMSE (of 30 points) and 1.7 SD (z scored) lower on the global cognitive composite index than controls without dementia. More participants with early AD were carriers of the apolipoprotein E4 allele. The groups did not differ on clinical indices of metabolic function (total cholesterol, C-reactive protein, insulin AUC, and glucose AUC).

Brain volumetrics demonstrated evidence of whole-brain and gray matter atrophy in early AD, with no difference in WMV across groups, suggesting that differences in WBV were driven by reduced GMV in the participants with AD.

Indices of physical function were significantly lower in early AD. Individuals with early AD had impairments in activities of daily living (Mild Cognitive Impairment Activities of Daily Living Scale) and physical function (Physical Performance Test) and lower levels of habitual physical activity (Physical Activity Scale in the Elderly).

BODY COMPOSITION IN PARTICIPANTS WITH AD AND WITHOUT DEMENTIA

Body mass index, body weight, and body fat measures were not different across the control and early-AD groups (**Table 2**). Total lean mass was reduced in individuals with early AD compared with controls after controlling for known sex differences in lean mass (F=7.73; P=.006). There were no dementia group × sex interactions, suggesting that AD-related differences in lean mass were not different in men and women.

To identify potential mediators of reduced lean mass in AD, we performed a series of linear regressions that examined the relationship of individual covariates with lean mass (dependent variable). Because age and sex influence lean mass and all of the clinical covariates tested (all β>.10; P<.01), we included age and sex as the first step in all regression analyses and report resultant partial correlations as standardized β values (**Table 3**).

The strongest predictor of lean mass was WBV (**Figure**), largely driven by a relationship between WMV and lean mass. Gray-matter volume was not related to lean mass. Additional significant correlates related to lean mass included cognitive indices (global cognitive performance and MMSE), insulin levels (3-hour AUC), and habitual physical activity levels. Glucose, C-reactive pro-

Table 3. Standardized Coefficients (β) Predicting Lean Mass After Controlling for Age and Sex[a]

Variable	β	P Value
Whole-brain volume, normalized	.20	<.001
Gray matter volume, normalized	.06	.27
White matter volume, normalized	.19	<.001
Global cognitive performance	.12	.007
Mini-Mental State Examination	.11	.009
Insulin, AUC	.11	.02
Glucose, AUC	.09	.05
C-reactive protein	.003	.94
Physical activity (PASE)	.14	.001
Activities of daily living	.07	.09
Physical performance task	.07	.16
Depression	−.05	.21
Apolipoprotein E4 carrier	−.05	.24

Abbreviations: AUC, area under the curve; PASE, Physical Activity Scale in the Elderly.
[a] Age and sex included in all analyses as covariates.
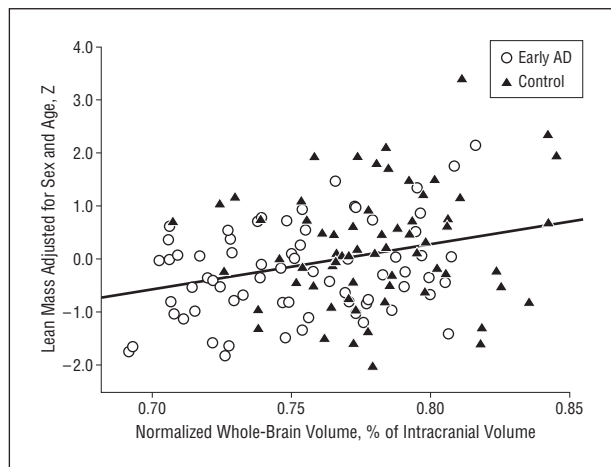
Figure. Relationship between lean mass and whole-brain volume. Whole-brain volume is positively associated (β=.20; $P<.001$) with lean mass in participants with early Alzheimer disease (AD) and controls without dementia. Whole-brain volume is normalized to account for differences in head size and provide an estimate of brain atrophy. For illustrative purposes in the figure, lean mass was adjusted for sex and age and presented in standardized units [Z]. This positive association was not different across the Alzheimer disease and control groups and was independent of age, sex, dementia severity, inflammation, insulin, and glucose measures.

tein, activities of daily living, physical performance, depressive symptoms, and apolipoprotein E4 status were not related to lean mass. Thus, additional analyses included further examination of the clinical and functional significance of body composition in AD in relation to brain volume, cognition, and the covariates of insulin and physical activity level.

BODY COMPOSITION AND COGNITIVE PERFORMANCE

Both indices of cognitive performance (global cognitive performance and MMSE) were related to lean mass (Table 3). Cognitive performance was not related to other measures of body composition (BMI, total body fat, and percentage of body fat). As our global cognitive performance measure is a composite measure of a variety of cognitive tests, we next assessed the relationship of lean mass with performance on component cognitive subtests. Lean mass was associated with performance on the Logical Memory I (β=.12; $P=.007$), Logical Memory II (β=.09; $P=.04$), Trail Making A (β=−.09; $P=.05$), Trail Making B (β=−.11; $P=.01$), Category Fluency (β=.09; $P=.05$), Block Design (β=.13; $P=.005$), and Digit Span Forward (β=.10; $P=.03$) tests. There were no dementia status × cognitive performance interactions in predicting lean mass, suggesting that the relationship between lean mass and cognition is similar in participants with AD and those without dementia. Controlling for dementia status, however, resulted in attenuation of these results, suggesting that group differences in both cognition and lean mass may be responsible for the results.

BODY COMPOSITION AND BRAIN STRUCTURE

Regression analyses identified a relationship between WBV and lean mass (Figure). This relationship was driven primarily by a relationship between WMV and lean mass (β=.19; $P<.001$). In contrast, GMV was unrelated to lean mass. The association of WBV and WMV with lean mass was unchanged after controlling for additional covariates of dementia status, physical activity, global cognition, and insulin AUC. There were no dementia status × WBV or sex × WBV interactions, suggesting that the positive relationship between WBV and body composition was similar in participants with AD vs controls and men vs women.

Whole-brain volume was not related to total body fat (β=.14; $P=.21$) or percentage of body fat (β=.01; $P=.89$) but was modestly associated with BMI (β=.20; $P=.05$), with higher BMI associated with higher brain volume (ie, less brain atrophy). Although BMI is a proxy measure for adiposity ($r=0.55$; $P<.001$), it also reflects lean mass ($r=0.28$; $P=.001$), and thus the modest relationship between BMI and WBV appears to be largely driven by the observed lean mass–WBV relationship.

OVERALL MODEL

We next examined an overall model that included all variables of interest (WBV, global cognition) and covariates (age, sex, dementia status, physical activity, and insulin levels) to assess which variables were most strongly related to lean mass. Age, sex, and dementia status (AD vs control) were forced into the model (step 1), with all covariates assessed in step 2 using a stepwise model of inclusion ($F=3.94$; $P<.05$ to retain). In this model, WBV (β=.12; $P=.04$), insulin (3-hour AUC; β=.10; $P=.02$), and physical activity level (β=.11; $P=.02$) were each independently associated with lean mass. When WMV and GMV were used rather than WBV, WMV, but not GMV, was retained (β=.17; $P<.001$) with insulin (β=.09; $P=.05$) and physical activity (β=.12; $P=.009$).

COMMENT

Our findings are consistent with prior studies indicating that alterations in body composition are apparent in

the earliest clinical stages of AD[2-4] and extends these findings by suggesting that AD-related alterations in body composition may be predominantly related to loss of lean mass (ie, sarcopenia). This is consistent with at least one large epidemiological study that found an association between cognitive impairment and reduced muscle mass in women without dementia.[25] Although the cross-sectional, case-control study design limits our ability to infer causal relationships, our data suggest that sarcopenia may be accelerated in the earliest stages of AD.

Our findings also suggest that lean mass may be a more sensitive measure to relate body composition to cognitive outcomes and dementia than measures of adiposity. Lean mass was reduced in individuals with AD compared with controls and was associated with brain volume and cognition; total body fat, however, was not related to dementia status, brain volume, or cognition. Although we observed a modest relationship between the nonspecific adiposity measure BMI and brain volume, this relationship was primarily driven by lean mass, as only lean mass, and not fat mass, was associated with WBV. Thus, our data highlight the importance of assessing specific measures of body composition and suggest the hypothesis that loss of lean mass may underlie previously described relationships of nonspecific measures of body composition (ie, BMI) with cognitive decline and dementia.[9,26,27]

We observed a direct correlation between WBV (an estimate of brain atrophy) and lean mass, suggesting that brain atrophy and loss of muscle mass may co-occur. Brain atrophy is considered a neuroimaging measure reflective of AD pathology.[28] Thus, our data are consistent with other studies suggesting that brain pathology may contribute to decline in body composition,[11] perhaps by disrupting central nervous system regulation of energy metabolism and food intake.[29] While AD and neurodegeneration predominantly affect gray matter, we find it particularly interesting that we observed a strong relationship between lean mass and WMV rather than GMV, and this relationship was similar in participants without dementia and those with AD, suggesting that mechanisms other than AD processes may underlie these relationships.

Sarcopenia in normal aging is most strongly associated with age-related reductions in physical activity.[30] In our cohort, individuals with early AD had reduced physical activity levels compared with the cohort without dementia. Additionally, lower physical activity was associated with less lean mass, suggesting that behavioral changes associated with AD may result in loss of lean mass. Alternatively, physical activity itself may attenuate the structural and functional brain and body changes associated with AD and aging. This is biologically plausible given accumulating animal and human evidence linking exercise and physical fitness with brain health.[12,31-33] Even after controlling for physical activity levels, however, lean mass remained independently associated with brain volume, suggesting that the decline in physical activity observed in aging and AD is unlikely to fully explain our results.

An alternative explanation for our observations is that AD and sarcopenia share common underlying mechanisms. Alzheimer disease is associated with systemic anabolic and inflammatory abnormalities that are also implicated in sarcopenia.[34-37] Although our measures of anabolic and inflammatory processes are limited in this study, we observed an independent relationship between lean mass and insulin, a well-known anabolic hormone[38] that may have neurotrophic[39] and neuroprotective[40] properties. We previously reported that insulin levels are associated with cognition and brain volume in early AD and, as in this study, the association was stronger for white matter than gray.[13] Interestingly, insulin signaling preferentially affects the development of white matter structures,[41] which, taken with our prior results, suggests that insulin signaling may play a role in maintaining cerebral white matter. Thus, our observation that WMV, lean mass, and insulin levels are interrelated suggests that reduced anabolic support to both the muscle and brain may be a potential mechanism underlying the observed relationships.

The current study is limited by its cross-sectional design, and further longitudinal and interventional studies will be necessary to more precisely define the nature and mechanisms of body composition changes in AD. Although clinical methods are imperfect in predicting AD pathology, we used sensitive[18] and validated[17] methods for diagnosing the earliest stages of AD. Additionally, participants were a convenience sample, which limits generalizability and may have introduced sampling bias that could affect the results. The relatively small sample size (n=140) could limit the power to resolve group differences or important interactions for marginal effects and thus increase the chance of type II error. Additionally, potentially important dietary factors were not measured. Nevertheless, our data suggest that loss of lean mass may be accelerated in AD, perhaps as a direct or indirect consequence of AD pathophysiology or through shared mechanisms common to both AD and sarcopenia.

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