Published in final edited form as:

J Alzheimers Dis. 2009 January 1; 18(4): 777–785. doi:10.3233/JAD-2009-1185.

Bone Density and Brain Atrophy in Early Alzheimer Disease

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Abstract

Studies suggest a link between bone loss and Alzheimer's disease. To examine bone mineral density (BMD) in early Alzheimer's disease (AD) and its relationship to brain structure and cognition we evaluated 71 patients with early stage AD (Clinical Dementia Rating (CDR) 0.5 and 1) and 69 non-demented elderly control participants (CDR 0). Measures included whole body BMD by dual energy x-ray absorptiometry (DXA) and normalized whole brain volumes computed from structural MRI scans. Cognition was assessed with a standard neuropsychological test battery. Mean BMD was lower in the early AD group (1.11 ± 0.13) compared to the non-demented control group (1.16 ± 0.12 , $p=0.02$), independent of age, sex, habitual physical activity, smoking, depression, estrogen replacement, and apolipoprotein E4 carrier status. In the early AD group, BMD was related to whole brain volume ($b=0.18$, $p=0.03$). BMD was also associated with cognitive performance, primarily in tests of memory (logical memory [$b=0.15$, $p=0.04$], delayed logical memory [$b=0.16$, $p=0.02$], and the selective reminding task, free recall [$b=0.18$, $p=0.009$]). Bone mineral density is reduced in the earliest clinical stages of AD and associated with brain atrophy and memory decline, suggesting that central mechanisms may contribute to bone loss in early Alzheimer's disease.

Keywords

bone mineral density; brain atrophy; Alzheimer's; memory; hypothalamus

INTRODUCTION

The prevalence of Alzheimer's disease (AD) is rising dramatically as the population ages and is now among the leading causes of death in older people[1]. While cognitive decline is a clinical hallmark of AD, changes in physical health are also apparent during the course of AD and include increasing frailty, lower aerobic capacity, weight loss and gait and motor dysfunction[2–5].

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Author contributions: Conception and design: Natalia Loskutova, Jeffrey M. Burns. Acquisition of data, analysis and interpretation of data: Natalia Loskutova, Robyn Honea, Eric D. Vidoni, William M. Brooks, Jeffrey M. Burns. Drafting the manuscript: Natalia Loskutova, Jeffrey M. Burns. Revising the manuscript critically for important intellectual content: Robyn Honea, Eric D. Vidoni, William M. Brooks. Final approval of the manuscript to be published: all authors.

Conflict of Interest: The authors and co-authors have no relevant conflict of interests.

Bone health is an important issue in AD given a higher risk of falls and increased incidence of fractures in individuals with AD compared to cognitively healthy older adults. Additionally, individuals with AD have poorer recovery[6–8] and higher mortality rates[9] after suffering a hip fracture. While several studies in women suggest that low bone mineral density (BMD) is associated with higher risk of developing AD[10] and cognitive decline[11,12], there is little data on bone health in individuals with AD. In a study of women, BMD was reduced in AD compared to cognitively normal females of similar age, with decreasing BMD in the most severely demented[13], suggesting that bone loss may be accelerated in AD. Although this evidence suggests a link between AD and BMD[14] little is known about how early in the disease bone loss might occur and whether bone loss is observed in men with AD.

Multiple factors have been postulated to explain the association between bone loss and cognitive decline in women, including estrogen exposure, apolipoprotein E4, depression and lifestyle factors such as physical activity, nutritional, dietary, and environmental factors. Accumulating evidence also suggests that the central nervous system directly regulates bone health through actions primarily orchestrated by the hypothalamus[15–17], a structure affected early in the AD process[18,19]. However, no studies have evaluated bone health in relation to cognition and brain structure. The purpose of this study was to compare bone health in the earliest clinical stages of AD with non-demented aging and to determine whether BMD is associated with cognitive performance and brain atrophy, which is used as a marker of neurodegeneration. We hypothesized that bone density would be lower in early AD and that reduced BMD would be associated with brain atrophy and cognitive decline. Understanding the association of bone loss and AD, in the context of other BMD-modifying factors, may provide strategies for developing effective prevention and treatment of osteoporosis and could ease the burden associated with bone fractures in AD.

MATERIALS AND METHODS

Sample and recruitment

71 patients with early-stage AD (Clinical Dementia Rating (CDR) 0.5, n=57 and CDR 1.0, n=14) and 69 non-demented elderly control participants (CDR 0) were enrolled in the University of Kansas Brain Aging Project. Participants were recruited from a referral based memory clinic and by media appeals. Signed institutionally-approved informed consent was obtained prior to enrollment from all participants or their legal representatives and the informants who know the participants well and served as the collateral source. Participants with a history of neurologic disease other than AD, diabetes mellitus, ischemic heart disease, schizophrenia, major depression, contraindications to MRI, and a history of alcohol abuse were excluded from the study. Clinical assessment methodology and clinical and neurological characteristics of the study participants have been presented previously[2].

Whole body bone mineral density

Dual energy x-ray absorptiometry (DXA) (Prodigy fan-beam densitometer, Lunar Corp., GE Medical Systems, Madison, WI) was used to determine total skeleton BMD. We used whole body BMD as a measure of global bone health. Whole body BMD gives a comprehensive view of the whole skeleton[20] and is mostly determined by cortical bone[21]. Cortical bone porosity and decline in mechanical properties are reported in aging[22] and associated with fractures. Cortical bone density decline is found to be more specific than trabecular BMD for the older population and may play an important role in bone fragility in elderly[23,24].

Magnetic resonance imaging

Structural MRI data were obtained at the Hoglund Brain Imaging Center with a 3.0 T Allegra MR scanner (Siemens Medical Solutions, Erlangen, Germany). T1 weighted magnetization

prepared rapid gradient echo (MP-RAGE) sequence ($1 \times 1 \times 1 \text{ mm}^3$ voxels; TR = 2500ms, TE = 4.38ms, TI = 1100ms, FOV $256 \times 256 \text{ cm}^2$ with 18% oversample, flip angle 8 degrees) was performed for high resolution structural analysis. We used FMRIB Software Library (FSL; www.fmrib.ox.ac.uk/fsl) for computing whole brain volume. Each image was preprocessed and skull-stripped with Brain Extraction Tool (BET). Next, images were normalized by registration to the Montreal Neuroimaging Institute (MNI) average 152 template and then segmented into white, gray matter and CSF with FMRIB's Automated Segmentation Tool. Since brain volumes differ between sexes, brain volumes were normalized to intracranial volume for each participant summing white and gray matter volumes and presented as percent of intracranial volume (% ICV). Image processing was conducted with Laboratory of Neuroimaging Pipeline (University of California, Los Angeles, www.pipeline.loni.ucla.edu). Normalized brain volumes were not related to sex ($r=0.09$, $p=0.3$). Normalized brain volume was used as a sensitive marker of brain atrophy[25].

Neuropsychological assessment

We administered a psychometric battery consisting of standard measures of memory (WMS-R Logical Memory I and II[26], Free and Cued Selective Reminding Task [27]), language (Boston Naming Test–15 item[28]), working memory (WMS III Digit Span Forwards and Backwards[26] WAIS Letter-number sequencing[29]), executive function (Trailmaking A and B[30], Verbal Fluency [animals, fruits and vegetables][31], and Stroop Color-Word Test [32]), and visuospatial ability (WAIS Block Design[29]) as reported previously[2]. We created a composite measure of global cognition by first, converting individual test scores for each participant to z-scores using a reference sample of non-demented older adults ($n=83$) and then computing the mean of all z-scores for each participant. Mini-Mental State Examination (MMSE) was administered as a standard measure of global cognition[33].

Other potential modifiers

Habitual physical activity level was assessed using the Physical Activity Scale for the Elderly (PASE) [34]. The PASE scores were collected from the study participants and their collateral sources. The modified Physical Performance Test (PPT) was administered as a physical frailty assessment[2]. Geriatric Depression Scale (GDS) was administered to study participants and their collateral source to assess depressive signs[35]. Apolipoprotein E (ApoE) genotypes were obtained using restriction enzyme isotyping[36]. Self-reported tobacco history was collected along with demographic characteristics for each participant. Tobacco use for those with a present or past history of smoking was calculated in Pack Years. Participants were divided into three groups (never smoked, smoked more than 100 cigarettes previously but not in last 30 days, currently smoking) for statistical analysis. DXA was used to assess fat mass and percent body fat of the participants dressed in a hospital gown. Body weight in kg and height in cm were recorded and body mass index (BMI, kg/m^2) was calculated for each study participant. Total cholesterol, triglycerides, high-density (HDL) and low-density (LDL) lipoproteins levels were assessed in fasting venous blood samples as described previously [37].

Self-reported medication use was collected from the collateral source by a nurse clinician. Hormone-replacement therapy (HRT) medications (estrogen, testosterone and selective estrogen receptor modulators), thyroid hormone replacement, bisphosphonates, beta-blockers, vitamin D and calcium were considered as bone affecting. The total number of participants in each group that reported use of medications with primary or potential effects on bone health for two or more weeks prior to the study enrollment was recorded.

Statistical analyses

Statistical analyses were conducted using SPSS 16.0 software package (SPSS Inc., Chicago, Ill). Continuous variables were summarized as means $\pm$ standard deviation (SD) and categorical

variables were summarized by percent. Independent samples t-tests were used for analyzing group differences in continuous variables and chi-square statistics were used for categorical data. The general linear model was used for assessing effects of dementia and additional potential modifiers (habitual physical activity (PASE), signs of depression (GDS), frailty (PPT), genetic component (ApoE4), use of bone affecting medications and tobacco history) on BMD, with age and sex included as primary covariates. We added an interaction term to examine whether the association of BMD and dementia was modified by sex (dementia*sex). An association of BMD with age was assessed with Pearson r coefficient of correlation. An association of BMD with past or present history of smoking (Pack Years) was assessed by partial correlation controlled for age and sex. We used a stepwise linear regression model to examine: 1) the association of BMD with whole brain volume, first controlling for age and sex followed by additional models assessing the effect of other covariates on the relationship between BMD and whole brain volume, and 2) the association of BMD with cognitive measures, controlling for age and sex and the effect of the potential modifiers on this association. Assumptions for linearity, normality, equal variance and homoscedasticity of errors were examined and adequately met. Statistical significance was tested at $\alpha=0.05$.

RESULTS

Sample description

Demographic and clinical characteristics of the participants in the non-demented ($n=69$) and early AD groups ($n=71$) are summarized in Table 1. Early AD and non-demented groups were similar in age (mean age 74.1 ± 6.8 years) and sex distributions. Average BMI, percent body fat, and serum levels of total cholesterol, triglycerides, HDL and LDL did not differ between groups. As expected, participants in the early AD group had mild global cognitive impairment, lower level of habitual physical activity (PASE), higher frailty scores (PPT) and more depressive signs (GDS). Participants with early AD were more likely to carry the ApoE4 allele than controls. Brain atrophy was evident in the early AD group. The early AD group had significantly smaller mean normalized whole brain volume than the non-demented group. Whole brain volume was significantly associated with MMSE score ($r=0.42$, $p<0.001$), our composite measure of global cognition ($r=0.47$, $p<0.001$), and dementia severity (CDR Box score, $r=-0.44$, $p<0.001$) after controlling for age and sex.

The groups did not differ in the use of medications with primary or potential bone affecting qualities. Table 2 shows the percentage of participants reporting prolonged use of hormone replacement medications, bisphosphonates, thyroid hormone replacement, beta-blockers, vitamin D, and calcium supplements in each group.

Bone mineral density and dementia status

Mean whole body BMD was lower in the early AD group (1.11 ± 0.13) compared to the non-demented control group (1.16 ± 0.12 , $p=0.02$). As expected, BMD decreased with age ($r=-0.21$, $p=0.01$) and was lower in females (1.08 ± 0.10) than in males (1.21 ± 0.12 , $p<0.001$).

We next used the general linear model to assess the role of dementia status on BMD while controlling for age, sex, and additional covariates. After controlling for age and sex, individuals with AD had lower BMD than non-demented individuals ($b1=-0.04$, $p=0.03$). There was no interaction between dementia status and sex (dementia*sex, $p=0.71$) suggesting that AD-related BMD differences were similar in men and women (Figure 1).

Bone mineral density and additional modifiers

Additional modifiers (physical activity (PASE), frailty (PPT), signs of depression (GDS), genetic makeup (ApoE4) and use of bone affecting medications) were not related to BMD.

There were no significant effects of smoking history on BMD ($p=0.46$) after controlling for age and sex and no dementia*smoking history interaction ($p=0.75$). There was no association between Pack Years and whole body BMD after controlling for age and sex in participants who are currently smoking and used to smoke in either early AD or non-demented groups.

Bone mineral density and whole brain volume

We specifically tested the hypothesis that brain atrophy was associated with BMD. First, we examined the association of BMD with whole brain volume in the entire cohort using stepwise linear regression analysis with age and sex as covariates. Higher BMD was associated with larger brain volumes, i.e. less brain atrophy ($b=0.18$, $p=0.03$). Age and sex accounted for 28.1% of the variance with whole brain volume explaining an additional 7.6% of the variance.

Given that group differences in brain volume and BMD may explain this relationship we next examined the association of brain volume with BMD in the early AD and non-demented groups separately. A scatterplot of whole brain volume and age- and sex-adjusted BMD is presented in Figure 2. In early AD, whole brain volume was associated with BMD ($b=0.3$, $p=0.004$), explaining 8.8% of variance of BMD after controlling for age (non-significant) and sex ($b=0.53$, $p<0.001$, 26.2 % of variance of BMD explained). In the non-demented group, whole brain volume was not associated with BMD after controlling for age and sex.

Because bone health can be modified by multiple factors, we repeated a series of regression analyses to examine the influence of potential modifiers on the observed BMD - whole brain volume relationship. All models controlled for age and sex. Potential modifying factors such as habitual physical activity (PASE), frailty (PPT), depressive signs (GDS), Apolipoprotein E4 allele status (ApoE4 carriers vs. non-carriers), use of bone affecting medications and smoking history were each added to the linear regression model, but none attenuated the bone density-whole brain volume relationship.

Bone mineral density and cognitive performance

In the entire cohort, BMD was not associated with our composite measure of global cognition or MMSE performance. BMD was positively associated with performance on logical memory ($b=0.15$, $p=0.04$), delayed logical memory ($b=0.16$, $p=0.02$), and the selective reminding task ($b=0.18$, $p=0.009$) after controlling for age and sex. Addition of any of the potential modifying factors to the regression model did not attenuate the bone-density-cognitive performance relationship. Within-group analyses were conducted next to minimize the effect of group differences in BMD and cognitive performance. In the early AD group, BMD remained associated with logical memory ($b=0.25$, $p=0.01$), delayed logical memory ($b=0.27$, $p=0.009$), and the selective reminding task ($b=0.25$, $p=0.02$). Measures of dementia severity (CDR and CDR box score) were not related to BMD. In non-demented participants, BMD was not associated with performance on any cognitive measures.

DISCUSSION

The results of the study suggest that BMD is reduced in the earliest clinical stages of AD in both men and women. Additionally, BMD was related to whole brain volume and memory performance in AD, with higher BMD associated with higher whole brain volume (less brain atrophy) and better memory performance. These results suggest that AD-related brain changes may affect bone remodeling or that bone loss and AD may share common biological mechanisms.

There is evidence that major factors contributing to bone loss are associated with AD though it remains unclear whether alterations in these factors are a cause or a consequence of AD.

BMD has been viewed as a proxy for cumulative estrogen exposure in women and the BMD-cognition relationship has been interpreted as evidence for a link between estrogen and cognition[12]. Although we did not specifically measure estrogen levels, our observation of reduced BMD in men with AD and more recent clinical trial evidence of an increased risk of dementia in estrogen users suggests alternative mechanisms may be responsible for the link between bone loss and AD[38].

Some epidemiological studies suggest dietary factors may play a role in AD risk[39,40]. Though, the role of dietary protein and fat in bone health is still a matter of debate, animal [41] and human[42–44] studies show that adequate energy and protein provision is essential for preservation of skeletal health in elderly. Decreased food intake and changes in dietary patterns may occur in AD[45,46] and could potentially explain lower bone density in the AD group[47]. In addition to dietary deficiencies in microelements and nutrients, disturbances in microelement metabolism and exposure to high concentrations of some minerals are associated with both low bone mass[48] and AD[49]. High levels of trace elements in the brains of AD patients are associated with oxidative damage[50], a potential etiologic mechanism of AD.

Although, diet was not assessed in the study participants[51], our early AD cohort was similar in BMI and percent body fat indicating that AD participants were not underweight [52]. Serum levels of total cholesterol, triglycerides, HDL and LDL in the early AD group did not differ from non-demented controls, indirectly suggesting that their global nutritional status was similar to the non-demented older adults[53,54].

The ApoE4 allele has also been associated with bone loss [55,56]. Our analyses were unchanged when controlling for ApoE4 carrier status suggesting that ApoE4 does not mediate this relationship, consistent with the findings of other studies[57,58]. Our data raise the possibility that the relationship between bone loss and ApoE4 in other studies of non-demented older women may have been driven by the likelihood of a higher prevalence of unrecognized, preclinical AD in the ApoE4 cohort.

Physical activity is an important modulator of bone mass, though its effect on bone mass may be attenuated in older adults[59]. Our early AD cohort demonstrated significant reductions in levels of habitual physical activity and thus it is possible that AD-related behavioral changes may exacerbate age-related bone loss. Habitual physical activity level, however, was not associated with BMD and controlling for physical activity did not modify AD-related BMD differences or the relationship between BMD and brain volume. Smoking is another major lifestyle risk factor for osteoporosis and appears to have negative effects on bone mass at the major sites of osteoporotic fractures[60,61]. In our cohort, however, whole body BMD was not associated with smoking and controlling for smoking did not attenuate the relationship between brain atrophy and BMD in AD. We examined additional factors that may influence bone mass such as physical frailty[62,63], depressive signs[64,65], and hormone-replacement therapy including vitamin D and calcium supplement intake and we found no evidence that they influenced bone loss in the early stages of AD.

Another possible explanation of the current results is that AD-related neurodegenerative brain changes may directly affect central control of bone remodeling. Atrophy of the limbic system, including the hypothalamus, is prominent in AD[18]. The hypothalamus is a central regulator of a number of homeostatic metabolic processes including a major role in regulating bone mass [17]. Our results demonstrate the independent association of BMD with whole brain volume in early AD and suggest that neurodegenerative changes may influence bone mass in AD. Future studies should assess regional brain atrophy, including the limbic system, to examine the hypothesis that neurodegeneration may contribute to loss of bone mass in AD.

Limitations of the study include the cross-sectional design that reduces our ability to infer causal relationships among variables. Further longitudinal and interventional studies are necessary to establish cause and effect. Additionally, the sample size limits the power to fully examine the influence of covariates on BMD. We did not examine peripheral factors related to bone health including estrogen, calcium, and vitamin D serum levels, all of which have been linked to AD although we did take into account participant use of such therapies. Given that our study participants are a convenience sample, it remains possible that our results may be influenced by sampling bias. Additionally, our AD sample was confined to the earliest clinical stages of AD, with most of the demented subjects (80.3%) were in the very mild (CDR 0.5) stage, comparable to mild cognitive impairment. Although this very early AD group is one of the strengths of the study, it limits the range of dementia severity and may have reduced our power to resolve a relationship between BMD and dementia severity and other variables. Nevertheless, to our knowledge, this is the first study to suggest that bone loss is apparent in men and women in the earliest clinical stages of AD and that bone mineral density is related to brain structure and cognitive performance.

Acknowledgments

Sponsor's role: The sponsors played no role in the study design, collection, analysis and interpretation of data and preparation and submission of the manuscript.

Funding Sources: This study was supported by grants R03AG026374 and R21AG029615 from the National Institute of Aging, K23NS058252 from the National Institute on Neurological Disorders and Stroke and by generous support from the University of Kansas Endowment Association. The University of Kansas General Clinical Research Center (M01RR023940) provided essential space, expertise, and nursing support. The Hoglund Brain Imaging Center is supported by grant C76 HF00201 and Dr. Brooks was also supported by R01 NS039123 and R21 AG026482, R21 HD050534, R01 DK080090, and P20 RR015563.

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Figure 1. Bone Mineral Density in Non-demented and Early AD Groups
Bone mineral density is reduced in males and females in the early stages of Alzheimer's disease (AD).

Figure 2. Relationship between Whole Brain Volume and Whole Body Bone Mineral Density in the Non-demented and Early AD Groups

Larger normalized whole brain volumes (less brain atrophy) are associated with higher whole body bone mineral density. Open circles represent non-demented participants (CDR 0) and filled circles represent participants with early stages of AD (CDR 0.5 and 1).

Table 1

Sample Characteristics

	Non-demented (n=69)	Early AD (n=71)	p-value
Age (years)	73.3 (6.9)	74.9 (6.6)	0.173
Education (years)	16.5 (2.7)	15.3 (3.4)	0.015
Females, n (%)	40 (58)	41 (57.7)	0.94
Bone mineral density (g/cm ²)	1.156 (0.12)	1.112 (0.13)	0.02
Whole brain volume (% ICV)	78.0 (2.8)	75.3 (3.3)	<0.001
BMI (kg/m ²)	25.7 (3.6)	25.0 (5.1)	0.24
Body fat (%)	36.7 (9.0)	36.6 (9.9)	0.95
Serum cholesterol (mg/dL)	182.8 (34.3)	188.7 (37.4)	0.33
Serum triglycerides(mg/dL)	111.3 (53.4)	120.1 (61.5)	0.37
HDL(mg/dL)	55.0 (13.1)	54.0 (13.4)	0.69
LDL(mg/dL)	105.5 (25.7)	111.6 (30.2)	0.21
MMSE	29.4 (0.8)	26.1 (3.5)	<0.001
ApoE4 carriers, n(%)	19 (27.9)	39 (58.2)	<0.001
Geriatric Depression Scale	0.83 (0.95)	1.72 (1.57)	<0.001
Physical activity (PASE)	125.27 (63.6)	98.00 (56.3)	<0.001
Frailty (PPT)	30.45 (3.4)	27.59 (3.8)	<0.001

All data represent means (SD), unless otherwise noted. AD- Alzheimer's disease; % ICV represents percent of intracranial volume; BMI- body mass index; HDL- high-density lipoproteins; LDL- low-density lipoproteins; MMSE- Mini-Mental State Examination; ApoE4- Apolipoprotein E; PASE- Physical Activity Scale for the Elderly; PPT- Physical Performance Test

Table 2

Current Medications

Medications	Non-demented (n=69)	Early AD (n=71)	p-value
Beta-blockers, n (%)	3 (4.3%)	9 (12.7%)	0.08
Thyroid hormone replacement, n (%)	12 (17.4%)	9 (12.9%)	0.44
Hormone replacement therapy, n (%)	9 (13%)	7 (9.9%)	0.55
Bisphosphonates, n (%)	12 (17.4%)	14 (19.7%)	0.72
Vitamin D, n (%)	29 (42%)	19 (26.8%)	0.06
Calcium, n (%)	34 (49.3%)	28 (39.4%)	0.16

All data represent number (%) of participants in each group. AD- Alzheimer's disease.