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Reduced Limbic and Hypothalamic Volumes Correlate with Bone Density in Early Alzheimer's Disease

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Abstract

Accelerated bone loss is associated with Alzheimer's disease (AD). Although the central nervous system plays a direct role in regulating bone mass, primarily through the actions of the hypothalamus, there is little work investigating the possible role of neurodegeneration in bone loss. In this cross-sectional study, we examined the association between bone mineral density (BMD) and neuroimaging markers of neurodegeneration (i.e., global and regional measures of brain volume) in early AD and non-demented aging. Fifty-five non-demented and 63 early AD participants underwent standard neurological and neuropsychological assessment, structural MRI scanning, and dual energy x-ray absorptiometry. In early AD, voxel-based morphometry analyses demonstrated that low BMD was associated with low volume in limbic grey matter (GM) including the hypothalamus, cingulate, and parahippocampal gyri and in the left superior temporal gyrus and left inferior parietal cortex. No relationship between BMD and regional GM volume was found in non-demented controls. The hypothesis-driven region of interest analysis further isolating the hypothalamus demonstrated a positive relationship between BMD and hypothalamic volume after controlling for age and gender in the early AD group but not in non-demented controls. These results demonstrate that lower BMD is associated with lower hypothalamic volume in early AD, suggesting that central mechanisms of bone remodeling may be disrupted by neurodegeneration.

Keywords

Alzheimer's disease; bone density; hypothalamus; voxel-based morphometry

INTRODUCTION

Epidemiologic projections indicate that the incidence of Alzheimer's disease (AD) will increase dramatically in the coming decades due largely to the demographics of the disease and our aging population. Associated cognitive and physical decline greatly contributes to disability in older adults and places considerable burden on the health system, patients, and caregivers. Bone health is an important issue in AD given that AD patients are at higher risk than cognitively healthy adults for osteoporosis, falls, bone fractures, and poor post-fracture outcomes [1,2]. Bone mineral density (BMD) is a strong predictor of bone fractures and

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accounts for 60–70% of bone strength [3]. We have previously demonstrated that BMD is reduced in both men and women in the earliest clinical stages of AD compared to non-demented older adults independent of habitual physical activity, smoking, depression, estrogen replacement, and apolipoprotein E4 carrier status. Moreover, low BMD was independently associated with lower whole brain volume and memory deficits, suggesting that degeneration of the central nervous system (CNS) may play a role in bone loss [4]. However, it is unknown whether bone loss is related to volume loss in specific regions of the brain, such as the hypothalamus.

Bone mass is maintained locally by the balance between bone resorption by osteoclasts and bone formation by osteoblasts. Multiple factors modulate this servo system and perturbations of this system can result in bone loss. The most important and well-studied regulators of bone health are calcium and vitamin D availability, sex steroids, and mechanical usage. Recent work, however, indicates that the CNS directly regulates bone remodeling through the actions of the hypothalamus through two distinct pathways, the neurohumoral and neural arms [5,6]. Briefly, the neurohumoral arm involves hypothalamic control of the anterior pituitary hormones, such as growth hormone (GH), thyroid stimulating hormone (TSH), and follicle-stimulating hormone (FSH) (see [7] for a full review). GH executes its anabolic action on bone through insulin-like growth factor 1 (IGF-1). TSH and FSH receptors are present in bone cells and receptor activation stimulates bone resorption. The neural arm involves hypothalamic control of bone remodeling through sympathetic nervous system (SNS) output. SNS output from the leptin-ergic/peptidergic neurons in the ventral hypothalamus directly regulates bone remodeling through activation of beta-2 adreno-receptors on the osteoblasts, resulting in reduced bone formation [8]. There is evidence that sympathetic output from the hypothalamus via the neural arm may be more important than actions of sex steroids in the regulation of bone remodeling [9,10].

Clinical, neuropathological, and neuroimaging data together suggest that the hypothalamus is affected in AD and undergoes neuronal loss [11], profound plaque and tangle formation [12, 13], and overall atrophy [14]. However, there have been no studies to investigate whether neurodegeneration of CNS and the hypothalamus, specifically, is associated with bone loss. We hypothesized that atrophy of the hypothalamus and loss of hypothalamic neurons associated with AD may be one of the mechanisms of accelerated bone loss in AD. Thus, the aim of this cross-sectional study was to examine the underlying neural substrate of an association between BMD and brain volume and establish specific correlations of regional grey matter (GM) with bone loss in early AD and non-demented aging using voxel-based morphometry (VBM) analysis.

MATERIALS AND METHODS

Sample and recruitment

71 patients with early-stage AD (Clinical Dementia Rating (CDR) 0.5 ($n = 57$) and CDR 1 ($n = 14$)) and 69 non-demented elderly control participants (CDR 0) were enrolled in the University of Kansas Brain Aging Project. Of these, 16 non-demented and 6 early AD participants were excluded for excessive head motion. The final sample included 63 patients with early-stage AD (CDR 0.5, ($n = 49$) and CDR 1 ($n = 14$)) and 55 non-demented elderly control participants (CDR 0). Participants were recruited from a referral based memory clinic and by media appeals. All participants had standard neurological and neuropsychological assessment, structural MRI scanning and dual energy x-ray absorptiometry. Mini-Mental State Examination (MMSE) was administered as a standard measure of global cognition [15]. The absence or presence and severity of AD were determined by a standard clinical evaluation that included the CDR [16]. Detailed clinical assessment methodology and clinical and neurological characteristics of the study participants have been presented previously [17]. Participants with

a history of neurologic disease other than AD, diabetes mellitus, ischemic heart disease, schizophrenia, major depression, alcohol abuse, contraindications to MRI, and use of antipsychotic and other investigational medications were excluded from the study. Signed institutionally approved informed consent was obtained prior to enrollment from all participants or their legal representatives.

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, mostly determined by cortical bone [18], as a measure of global bone health that gives a comprehensive view of the whole skeleton [19]. Cortical bone porosity and decline in mechanical properties are reported in aging [20] and associated with fractures. Cortical bone density decline is found to be more specific than trabecular BMD loss for the older population and may play an important role in bone fragility in elderly [21,22].

Magnetic resonance imaging and voxel-based morphometry

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 = 2500 ms, TE = 4.38 ms, TI = 1100 ms, FOV $256 \times 256 \text{ cm}^2$ with 18% oversample, flip angle 8 degrees) were collected and processed for VBM analysis. Every scan was examined for image artifacts and gross anatomical abnormalities. Sixteen non-demented and six demented subjects were excluded for movement artifact or inhomogeneity that distorted brain matter. We used MRIcro[®] software to reconstruct raw Di-com images. Data analysis for 55 non-demented and 63 AD subjects was performed using the VBM5 tool-box (<http://dbm.neuro.uni-jena.de>), an extension of the SPM5 algorithms (Wellcome Department of Cognitive Neurology, London, UK) running under MATLAB 7.1 (The MathWorks, Natick, MA, USA) on Linux. The VBM5 toolbox extends and enhances the unified segmentation approach implemented in SPM5 [23] by using a generative model that integrates tissue classification, image registration, and MRI inhomogeneity bias correction. The approach allows for more accurate classification of brain tissues in presence of excess atrophy or abnormal morphology [24,25]. Images were then modulated and saved using affine registration plus non-linear spatial normalization [24], resulting in final tissue maps of GM, white matter (WM), and cerebrospinal fluid (CSF) and smoothed with a 10 mm FWHM Gaussian kernel before statistical analysis. Additionally, for each study participant total GM, WM, CSF, and whole brain volumes (GM plus WM) in cm^3 were computed using the normalized tissue maps of each study participant. Finally, total hypothalamic volumes in cm^3 were derived from small volume correction (SVC) analysis in VBM.

Statistical analyses

Statistical analyses were conducted using SPSS (Version 16, 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. Effect size for total hypothalamic volume was computed using G*Power3 free software [26]. Partial correlations controlling for age and gender were used to examine an association between BMD, CDR score, MMSE, and brain volumes. Statistical significance was tested at $\alpha = 0.05$.

Imaging statistics

To analyze brain images in SPM5, we used a linear regression model with independence between subject groups, unequal variance, no grand mean scaling, and centered covariates on the overall mean. We used absolute threshold masking set at 0.10 to restrict each analysis to one tissue type. First, the relationship of BMD to brain volume was assessed across all voxels within each group using multiple regression analysis, with age and gender as confounding variables. The relationship between BMD and regional GM was considered significant at $p < 0.001$ uncorrected. We then examined the relationship of BMD with hypothalamic volumes using the small volume corrections (SVCs). The bilateral hypothalami were derived from the Wake Forest University Pickatlas (<http://www.fmri.wfubmc.edu>) [27]. These hypothalamic volumes of interest (VOIs) were pre-selected based on our hypothesis that the hypothalamic control of bone remodeling is affected in AD [7]. To correct for multiple comparisons in SVC analyses, results were considered significant at $p < 0.05$ FWE. The hypothalamic volumes were extracted for each participant from the previous automated step and used for visualization purposes in graphic representations and secondary correlation analyses within AD group. All analyses were covaried for age and gender. The x , y , z coordinates of the areas of significant correlation were obtained from the analyses and reported with reference to the Montreal Neurological Institute (MNI) standard space within SPM5 after conversion to the standard space of Talaraich and Tournoux using custom software [28].

RESULTS

Sample description

Demographic and clinical characteristics of the participants in the non-demented ($n = 55$) and early AD groups ($n = 63$) are summarized in Table 1. Early AD and non-demented groups were similar in age (mean age 73.9 ± 6.4 years) and gender distribution. As expected, participants with AD had mild deficits in global cognition (MMSE 26.1 ± 3.7 vs. 29.5 ± 0.7 in non-demented, $p < 0.001$). The groups did not differ in the use of anti-osteoporotic medications and vitamin D and calcium supplements as has been reported in details previously [4].

As we previously reported in a larger group of these participants [4], 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 , $p = 0.03$). As expected, BMD decreased with age ($r = -0.22$, $p = 0.02$) and was lower in females (1.08 ± 0.10) than in males (1.21 ± 0.12 , $p < 0.001$). The early AD group had smaller mean normalized whole brain ($p < 0.001$) and GM volumes ($p < 0.001$) than the non-demented group. WM volumes did not differ between groups ($p = 0.42$).

Bone density and brain structure

We first assessed the relationship of BMD with regional brain volumes on a global level (across the entire GM) followed by SVC analyses confined to the hypothalamus using VBM neuroimaging analyses. Given the group differences in brain volume and BMD, we assessed the non-demented and early AD groups separately to avoid correlations driven by these group differences. All analyses were controlled for age and gender.

In the early AD group, analysis of regional GM volume adjusted for age and gender showed that BMD was significantly associated with large clusters of GM areas in the left superior temporal gyrus and left inferior parietal cortex, with the peak voxels in the left inferior parietal lobule (BA 40), and in the limbic GM with peaks in the cingulate, parahippocampal gyri, and the hypothalamus (Fig. 1). All clusters for the voxel-wise analyses ($k > 100$, $Z > 3.4$ and p uncorrected < 0.001) are presented in Table 2. There were no significant inverse correlations between BMD and regional GM volumes. We did not observe any significant relationship between BMD and GM volume of any area in the non-demented group.

Bone density and hypothalamic volume

We specifically tested the hypothesis that hypothalamic volume was associated with BMD. The hypothesis-driven SVC isolating the hypothalamus demonstrated a significant positive relationship between BMD and the hypothalamus after controlling for age and gender in the early AD group (Fig. 2). The significant cluster for each result was extracted using the VOI function in SPM5 and the mean volume per cluster for each individual was used to plot the results for visualization purposes.

Secondary analyses of the hypothalamic volumes derived for each individual demonstrated a difference between groups ($p < 0.001$, effect size $d = 0.61$) with lower volumes in AD ($0.57\text{cm}^3 \pm 0.10$) compared to non-demented controls ($0.65\text{ cm}^3 \pm 0.12$). We did not observe any relationship between BMD and hypothalamic volume in the non-demented group ($r = 0.15$; $p = 0.3$; Fig. 3). Total hypothalamic volume was associated with BMD ($r = 0.34$, $p = 0.007$) in AD. The magnitude of this association was moderate in the CDR 0.5 sub-group (very mild AD; $r = 0.33$, $p = 0.03$) and larger in the CDR 1 sub-group (mild AD; $r = 0.59$, $p = 0.04$) of AD patients (Fig. 4). There was, however, not a significant CDR * hypothalamic volume interaction ($p = 0.38$) for AD participants perhaps related to the small CDR 1 sample size ($n = 14$).

DISCUSSION

In our previous work, we demonstrated a relationship between BMD and lower whole brain volume in the earliest clinical stages of AD and proposed a hypothesis that neurodegenerative changes may influence bone mass in AD via alteration in the central regulatory mechanism of bone remodeling controlled by the hypothalamus [4]. This study extends the prior study by identifying specific regional relationships between BMD and grey matter volume, including the hypothalamus, that are present in early AD but not non-demented controls.

Our data suggest that hypothalamic volume is reduced in individuals in the early clinical stages of AD compared to non-demented older adults, consistent with prior studies demonstrating lower hypothalamic volume in AD [14]. Furthermore, by using VBM neuroimaging analyses, we have demonstrated that hypothalamic volume is associated with whole body BMD, with lower hypothalamic volumes correlated with reduced BMD in the AD group. Additionally, we have demonstrated that lower grey matter volume in other areas predominantly affected in AD correlates with BMD reductions. These data suggest that AD-related neurodegeneration, in particular affecting the hypothalamus, may disrupt central mechanisms regulating bone mass and contribute to bone loss in early AD.

Brain atrophy in AD

The hypothalamus, a part of the limbic system, has extensive connections within the brain and modulates a variety of regulatory processes including appetite, energy expenditure, sleep and wakefulness, and stress responses, all of which are disturbed in AD [29,30]. Additionally, the hypothalamus plays a role in memory through connections with the hippocampal formation. Brain atrophy, a sensitive marker of neurodegeneration, progresses in a relatively stereotypical fashion through the course of AD, beginning in the limbic system (i.e., the posterior cingulate and the hippocampus), progressing to the temporal-parietal cortices followed by the frontal lobes and late in the disease the occipital lobe and sensorimotor cortices [31]. Evidence of AD-related limbic atrophy in the hypothalamus is limited but has been reported using manual tracing of the structure [14]. We used automated VBM-based volume computation to assess hypothalamic volume and found evidence of hypothalamic volume loss in AD with a similar effect size as that previously reported. Thus, although our hypothalamic volumes were slightly larger than the previous manual tracing studies [14], our results using automated estimation of

the hypothalamic volume corroborate previously reported findings of smaller hypothalami in AD, suggesting that atrophy is present in the hypothalamus in AD.

Bone density and brain structure

Our results demonstrate that BMD is associated with hypothalamic volume in AD, with smaller hypothalamic volumes associated with lower BMD independent of age and gender. This relationship was observed in AD participants only and not in non-demented controls, suggesting the relationship of BMD with hypothalamic volume may be AD-specific. Our findings of associations between BMD and lower GM volumes of the parietal and temporal cortices and limbic system, areas of the brain that are preferentially affected in the early stages of the disease [32], further suggests this relationship is specific to AD. These findings extend prior observations associating BMD with cognitive decline [33] and an increased risk of AD [34, 35]. We interpret these findings as suggesting either the presence of a pathological mechanism common to both bone loss and limbic atrophy or that hypothalamic atrophy in AD may contribute to bone loss via alterations in central regulatory mechanisms of bone remodeling.

Pathological changes occur in the hypothalamus in AD and include profound neuronal loss [11], abundant AD plaques and tau tangles [12], and overall volume loss [14]. AD is associated with clinical symptoms referable to hypothalamic dysfunction including sleep and circadian rhythm disturbances [36], alterations in appetite and energy expenditure, and body wasting [37,38]. Thus, it is plausible that hypothalamic damage could result in clinically evident bone loss, given the central role the hypothalamus plays in regulating bone mass. The hypothalamus regulates bone mass through both a direct neural pathway and through the neurohumoral arm [6]. Although, this study does not assess direct measures of hypothalamic dysfunction, there is abundant evidence of AD-related dysfunction in both the neurohumoral and neural arms. Dysfunction of the hypothalamo-pituitary axis and activity of the SNS are reported in AD. For instance, GH levels [39] are reduced in AD while interestingly a number of other hypothalamic factors are increased in AD, including corticotropin-releasing hormone (CRH) [40], cortisol [41,42], FSH [43,44], and TSH [45]. Additionally, several studies demonstrate evidence of increased sympathetic activity [46] including increased brain noradrenergic activity and elevated serum and cerebrospinal fluid levels of norepinephrine [47–49]. Why increased activity has been observed in some aspects of the hypothalamic-pituitary axis in AD remains unclear but may be related to disturbed negative feedback [50] while increased SNS activity may be related to overcompensation of remaining noradrenergic neurons in response to profound noradrenergic neuronal loss [51]. Thus, further study should examine if hypothalamic structural change in AD alters neurohumoral systemic mediators of bone remodeling such as the pro-resorption factors (cortisol, FSH, and TSH, and sympathetic output) and bone formation factors (GH).

Additionally, common factors, such as vitamin D deficiency, have been linked to both AD [52–54] and bone loss [55–57]. Recent discovery of vitamin D receptors in rodent [58] and human hypothalamus [59] indicates that vitamin D may affect hypothalamic function or serve as central neuroactive substance. The possibility that vitamin D deficiency contributes to AD pathology, hypothalamic dysfunction and subsequent bone loss should be explored in the future studies.

It is important to recognize that the cross-sectional design of the study limits our ability to examine temporal development and cause-effect relationship between BMD and regional brain volumes. Additionally, the role of AD severity in this relationship should be more precisely defined in future studies. In addition, given that our study participants are a convenience sample, it remains possible that our results may be influenced by sampling bias. Our data suggest that the association between BMD and total hypothalamic volume may be accentuated in more advanced AD, with a larger relationship observed in more advanced AD (CDR 1 vs.

CDR 0.5). Although, our very early AD group is one of the strengths of the study, the relatively narrow range of dementia severity limits our ability to examine bone loss-regional brain volume relationship in more advanced stages of AD.

In conclusion, to our knowledge, this is the first study to demonstrate that lower BMD is associated with lower hypothalamic volume in early AD, suggesting that central mechanisms may contribute to AD-related bone loss. Bone loss in AD is an increasingly important clinical problem that may thus require different treatment approaches and preventive strategies as central mechanisms of bone remodeling may be disrupted by neurodegeneration.

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Fig. 1.

Areas in yellow indicate regions where grey matter volume correlates with bone mineral density in AD participants. Identified regions include the left superior temporal gyrus, left inferior parietal cortex (peak voxels in the left inferior parietal lobule [BA 40]), and limbic GM (peaks in the cingulate, parahippocampal gyri, and the hypothalamus). Analyses were controlled for age and sex and reported as significant at $p < 0.001$ uncorrected (see Table 2). The coronal image is presented in neurological orientation (left is left).

Fig. 2. Small volume correction analyses confined to the hypothalamus demonstrate a significant positive correlation between whole body bone mineral density and the hypothalamic volume after controlling for age and gender ($p < 0.05$ FWE) in the early AD group. The coronal image is presented in neurological orientation (left is left).

Fig. 3. Insignificant relationship between whole body bone mineral density and total volume of the hypothalamus ($b_0=0.79$, $b_1=-1.2$, $p=0.3$) in non-demented group.

Fig. 4.

Positive relationship between whole body bone mineral density and total volume of the hypothalamus ($b_0 = -1.93$, $b_1 = 3.4$, $p = 0.007$) in the early AD group (clinical dementia rating (CDR) 0.5 (filled circles) and CDR 1.0 (open circles)).

Table 1

Sample characteristics

	ND (n = 55)	AD (n = 63)	p-value
Age (years)	73.2 (6.3)	74.4 (6.5)	0.30
Females (n)	32	39	0.68
MMSE	29.5 (0.7)	26.1 (3.7)	< 0.001
BMD (g/cm ²)	1.16 (0.12)	1.11 (0.13)	0.03
WBV (cm ³)	945.6 (87.2)	861.4 (93.6)	< 0.001
GMV (% of ICV)	43.0 (2.1)	40.7 (2.4)	< 0.001
WMV (% of ICV)	34.8 (1.8)	34.5 (2.3)	0.42
Total Hypothalamic volume (cm ³)	0.65 (0.12)	0.57 (0.10)	< 0.001

MMSE: Mini-Mental State Examination; BMD: whole body bone mineral density; WBV: normalized whole brain volume in cm³; ICV: total intracranial volume; GMD: grey matter volume; WMV: white matter volume.

Table 2

Positive correlations between BMD and gray matter volume in the participants with AD with adjustment for age and gender

Cluster	K	Anatomical region	Talairach region	Talairach coordinates in MNI space			Z	P Value	
				x	y	z		FWE	uncor
1	17864	Parietal	L Inferior Parietal lobule, BA,40	-60	-47	22	4.74	0.03	< 0.001
		Temporal	L Superior temporal gyrus	-43	11	-15		0.11	< 0.001
2	3750	Limbic	L Precuneus Posterior Cingulate, BA23	-5	-57	12	4.0	0.42	< 0.001
3	2222	Limbic	L Parahippocampal Gyrus, BA 34	-12	1	-20	4.31	0.16	< 0.001
4	1509	Subcortical	Hypothalamus	-1	3	-15	4.11	0.30	< 0.001
		Limbic	R Cingulate Gyrus	2	-1	42	3.54	0.90	< 0.001
		Limbic	L Cingulate Gyrus, BA 32	-5	6	43	3.49	0.93	< 0.001
5	390	Frontal	R Medial Frontal Gyrus, BA 9	8	27	34	3.48	0.94	< 0.001
		Occipital	L Middle occipital gyrus	-49	-69	-15	3.45	0.95	< 0.001
6	143	Limbic	R Parahippocampal/Fusiform	22	-44	-13	3.43	0.96	< 0.001

Only clusters for the voxel-wise analysis with $k > 100$, $Z > 3.4$ and p uncorrected < 0.001 uncorrected are listed; K: cluster size; L: left; R: right; BA: Brodmann area; MNI: Montreal Neurological Institute; FEW: Family-Wise Error; uncor: uncorrected p value.