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The cause-effect relationship between bone loss and Alzheimer's disease using statistical modeling

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ABSTRACT

Background: Animal studies provide strong evidence that the CNS directly regulates bone remodeling through the actions of the hypothalamus via two distinct pathways, the neural (mediated by leptin) arm and neurohumoral (mediated by neurohormones and growth factors) arm. The impact of AD on central regulatory mechanisms of bone mass is not known.

Objectives: To test a model that assesses the relationship between hypothalamic atrophy and bone loss in Alzheimer's disease (AD) and potential mediation through neural (leptin) and neurohumoral (insulin-like growth factor –1, IGF-1) mechanisms.

Hypotheses: AD-related hypothalamic structural change alters neural and neurohumoral regulatory systems of bone remodeling and contributes to bone loss in early AD.

Design: A secondary data analysis of data obtained in a two-year longitudinal study with path analysis and longitudinal mediation modeling.

Participants: The data were collected as a part of the University of Kansas Brain Aging Project, a two-year observational study of 71 older adults with early stage AD and 69 non-demented controls.

Measurements: Demographic characteristics and measures of bone density, body composition, and hypothalamic volume, serum levels of leptin, growth hormone, and IGF-1 were collected.

Results: Hypothalamic atrophy and bone loss were observed in AD group and were associated. Data modeling suggests that bone loss may precede measurable changes in the brain. Leptin increased over two years in AD and the increase in leptin was associated with hypothalamic atrophy. However, changes in leptin or IGF-1 levels did not mediate the relationship between hypothalamic atrophy and bone loss.

Conclusions: This study extends previous findings by suggesting that bone loss in AD may be related to neurodegenerative changes (atrophy) in the hypothalamus. Further studies are needed to explore the role of brain atrophy and mediating mechanisms in bone loss. Further exploring temporal relationship between bone loss and AD may have an important diagnostic value.

Introduction

Alzheimer's disease (AD) and bone loss are among the most common conditions associated with aging. Low bone mineral density (BMD) and increased rates of bone loss are associated with cognitive decline and a higher risk of developing AD [1–3]. Individuals with all stages of AD have lower bone density and an increased incidence of fractures [4–6]. Some evidence suggests that bone loss may occur years before the onset of cognitive AD manifestations [2,3,7]. Although AD and bone loss share many common risk factors and exacerbating mechanisms [8], whether alterations in these factors are a cause or a consequence of AD remains unclear [9].

Animal studies provide strong evidence that the central nervous system (CNS) directly regulates bone remodeling through the hypothalamus via two distinct pathways, the neural and neurohumoral arms [10–12]. Briefly, the neural arm involves hypothalamic control of bone remodeling through increased sympathetic nervous system output mediated by leptin. The neurohumoral arm involves hypothalamic control of the anterior pituitary hormones, such as growth hormone (GH) and insulin-like growth factor-1 (IGF-1) [13]. The evidence of AD-related dysfunction in both the neurohumoral and neural arms is abundant [14–17]. The association between leptin levels and BMD in

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humans however, range from negative [18–20] or no association [21,22] to positive relationships [23,24].

We previously demonstrated that low bone density in early-stage AD was associated with lower volumes of the hypothalamus [25]. We then proposed a hypothesis that AD-related hypothalamic structural change alters neural and neurohumoral regulatory systems of bone remodeling and contributes to bone loss in early AD. The purpose of the present study was to test the hypothesis stated above and further extend previous observations by assessing the roles of leptin and GH-IGF-1 in mediating relationship between hypothalamic structural changes and bone loss in AD. We used statistical modeling to explore hypothetical cause-effect relationships between bone loss and hypothalamic regulation in a two-year longitudinal study of individuals with early AD and older controls without AD.

Materials and methods

Study participants and demographics

Data for this study were collected through the University of Kansas Brain Aging Project, a case-control, 2-year longitudinal study assessing the role of lifestyle factors in brain aging. The presence and severity of AD were determined by the Clinical Dementia Rating (CDR) and CDR sum of boxes score [26]. Seventy-one patients with early-stage AD (CDR 0.5, n = 57 and CDR 1.0, n = 14) and 69 non-demented elderly control participants (CDR 0) were enrolled in the Brain Aging Project. We excluded individuals with unstable diagnosis from baseline to follow up (N = 4 reverters, N = 9 converters) and unknown dementia status at baseline. Baseline clinical and demographic characteristics of these individuals, exclusion criteria, and detailed clinical, bone density, body composition, neuroimaging, and blood sample assessment methodology have been reported previously [27] and can be found in *Supplementary Text S1*.

Statistical analysis

Statistical analyses were conducted using SPSS (PASW statists 22, SPSS Inc., Chicago, IL) and Mplus [28]. Continuous variables were summarized as means ± standard deviation (SD), and categorical variables were summarized by ratio. Independent samples t-tests and Mann-Whitney *U* test were used for analyzing group differences in continuous variables, and chi-square statistics were used for categorical data. Paired *t*-test, repeated measures ANOVA or Wilcoxon Signed Rank exact test for two-related samples (longitudinal), two-tailed, were used to test change in variables over two years as deemed appropriate. Pearson and Spearman correlations were used to investigate the univariate relationships between variables. Analyses were conducted separately for individuals with and without AD.

Path analyses and hypothetical causal modeling

The development of the models of effects of neurodegeneration on central control of bone remodeling via neural and neurohumoral hypothalamic regulatory arms was informed by animal studies confirming such biological regulatory mechanisms [11], evidence of hypothalamic structural damage and dysfunction in AD, and our prior observations of an association between hypothalamic volume and bone density. The first hypothetical model we tested used change scores (difference between baseline and follow-up scores) and tested direct effects of hypothalamic atrophy on bone loss and indirect effects mediated by changes leptin and GH-IGF-1. Indirect effects were calculated via bootstrapping estimation. The causal *a priori* theoretical assumptions (what causes what) are shown in the path diagrams by arrows (Fig. 1).

Because several different models can be fit equally well to the same covariance matrix [29] and the selection of the direction of hypothetical causation can be arbitrary, we also tested an alternative hypothesis, that changes in BMD precede changes in hypothalamic volume. We used an improved application of the "half-longitudinal" mediation model, adjusting for baseline values when estimating follow up outcomes, to explore the direction of causal association [30]. We tested the autocorrelations for each variable with itself between baseline and follow up and the cross lags between variables from baseline to follow up. Correlations between the variables at baseline and follow up were estimated. Given the longitudinal mediation, we included baseline values for a more accurate estimate of change processes assuming autoregressive effects [31]. The significance level for change over time and correlation analyses was set as two-tailed $p \leq 0.05$; all variables related to the proposed hypothesis that correlated with bone loss at $p < 0.10$ were included in exploratory predictive modeling and path analysis; and the root mean square error of approximation (RMSEA) was set at < 0.05.

Results

Sample characteristics and changes over time

BMD and bone loss

The baseline and follow-up characteristics for participants in the study are presented in Table 1. There was no difference in age and gender distribution between the groups at baseline and follow up. BMD declined from baseline in both groups ($p < 0.05$) with greater bone loss in AD compared to the non-demented controls in total body (2.10% in AD vs. 0.95% in non-demented, $p = 0.03$).

Changes in body composition

Groups were similar at baseline in BMI, percent body fat, and waist-to-hip circumference ratio. Over two years however, the AD group had a slight increase in the percent body fat (34.9 ± 11.1 vs. 34.0 ± 10.4 at baseline, $p < 0.05$) and waist-to-hip circumference ratio (0.91 ± 0.07 vs. 0.87 ± 0.08 at baseline, $p < 0.001$) while no change was found in non-demented controls.

Hormone levels

There was no difference between the groups at baseline in measures of serum leptin, total IGF-1, and GH. Levels of IGF-1 declined slightly over two years in both AD and non-demented with no difference between groups. Leptin levels in the control group remained unchanged over two years (13.1 ± 10.3 ng/ml at baseline vs. 13.3 ± 10.0 ng/ml at follow-up, $p = 0.84$). In the AD group leptin levels increased significantly (14.9 ± 11.5 ng/ml vs. 21.9 ± 19.8 ng/ml at follow-up, $p < 0.001$).

Decline in physical activity in both groups

The average baseline level of physical activity of the control group was comparable to that reported for community dwelling elderly persons in the US (PASE score = 130.7 ± 55.5).[32] Baseline habitual physical activity level was lower in AD (102.8 ± 76.5p = 0.02) than in non-demented. Both groups declined over two years and with a greater decline in physical activity in AD vs. non-demented ($p = 0.07$).

Whole brain and hypothalamic atrophy

As expected, whole brain atrophy rate was higher in AD (2.2% vs. 1.2% in non-demented per year, $p < 0.001$). Hypothalamic volumes were smaller in AD group at baseline (0.65 ± 0. 10 cm^3 vs. 0.72 ± 0.12 cm^3 in non-demented, $p = 0.001$), consistent with previously reported results [33], and at follow-up (0.54 ± 0. 08 cm^3 in AD vs. 0.58 ± 0.08 cm^3 in non-demented, $p = 0.006$).

Predictors of bone loss

We correlated changes in total body BMD with baseline measures of vitamin D, demographic characteristics, baseline levels of physical

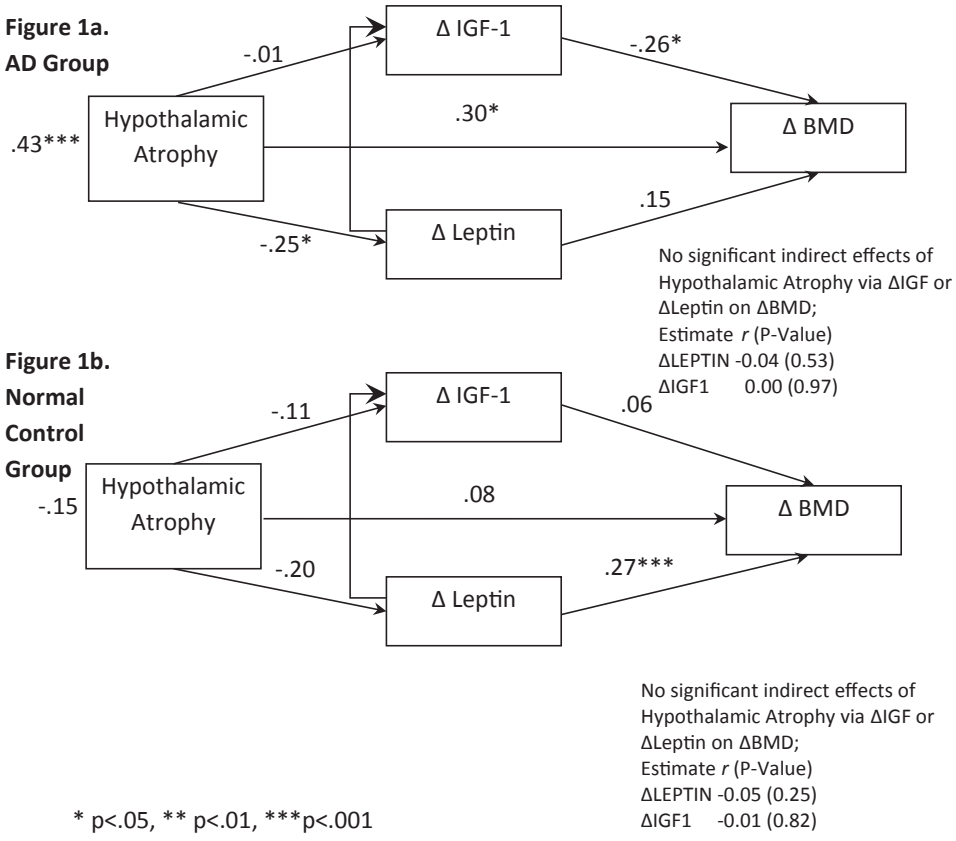

Fig. 1. Hypothetical model #1 of the relationship between hypothalamic volume change and bone loss in the AD group (1a) and non-demented controls (1b); BMD – bone mineral density; IGF-1 – insulin-like growth factor 1; the arrows indicate the direction of hypothetical causation; β coefficients displayed along the arrows. Hypothalamic atrophy – Δ Hypothalamic volume.

activity, two-year change in physical activity, adiposity, whole brain atrophy, and hypothalamic atrophy. As expected, in the non-demented group, decline in the total body BMD was related to decline in physical activity ($\beta = 0.23$, $p = 0.09$), age ($\beta = -0.31$, $p = 0.02$) and female gender ($\beta = -0.32$, $p = 0.02$), together explaining 28% of total variance in bone loss. In the AD group, decline in the total body BMD was associated with lower baseline vitamin D level ($\beta = -0.41$, $p = 0.02$) and hypothalamic atrophy ($\beta = 0.30$, $p = 0.06$), which together explained 23.1% of total variance in bone loss (Table 2).

Next, all variables related to the proposed hypothesis that correlated with bone loss ($p < 0.10$) were included in further analysis. No relationship was observed between baseline GH levels and bone density or bone loss or mediating variables (leptin and IGF-1); therefore, GH was not included in further analyses. Due to significant correlation between leptin and body fat, we corrected the levels of leptin for total fat mass and used the level of leptin in pkg/ml per gram of fat [34,35].

Path analysis

Hypothetical model #1

Based on the correlation matrix and the theoretical reasoning that the hypothalamic volume change over two years caused bone loss via changes in the central hypothalamic mediators and unknown mechanisms not tested in the study, we arbitrarily set the model #1 as follows: hypothalamic atrophy (Δ hypothalamic volume) on ΔBMD via the separate pathways of ΔIGF-1 and ΔLeptin. In this model, we simultaneously tested the direct effects of hypothalamic volume on ΔBMD and indirect effects of hypothalamic atrophy on ΔBMD via the separate pathways of ΔIGF-1 and Δleptin.

For the AD group (Fig. 1a), we found significant direct effects of

Table 1
Sample characteristics at baseline and change over two years.

	Baseline		Change over time (Δ, baseline minus follow-up)		p-value	
	Non-demented (n = 64)	Early AD (n = 58)	Non-demented (n = 63)	Early AD (n = 58)	baseline	Δ
Age, y	73.8 ± 6.8	75.4 ± 6.3			ns	
Gender, F/M	34/30	33/25			ns	
Vitamin D, ng/ml	27.5 ± 8.0	24.1 ± 8.7	–	–	*	–
MMSE	29.4 ± 0.8	26.2 ± 3.1	0.3 ± 1.1	3.6 ± 5.4	***	***
Growth Hormone, ng/ml	0.90 ± 0.94	0.85 ± 1.14	–	–	ns	–
Insulin-like Growth Factor –1, ng/ml	118.9 ± 49.7	116.9 ± 44.3	35.7 ± 33.5	30.3 ± 30.9	ns	ns
Leptin, ng/ml	12.6 ± 10.0	14. 8 ± 11.4	−0.2 ± 6.0	−7.3 ± 11.8	ns	*
BMI, kg/m^2	26.2 ± 3.8	25.8 ± 3.8	0.4 ± 1.3	−0.8 ± 1.8	ns	ns
Body Fat, %	33.6 ± 8.8	34.0 ± 10.4	0.04 ± 2.3	−1.1 ± 4.3	ns	*
Waste/hip Circumference	0.87 ± 0.10	0.87 ± 0.08	−0.2 ± 0.08	−0.3 ± 0.06	ns	*
Total Bone Density, g/cm^2	1.16 ± 0.11	1.12 ± 0.12	0.01 ± 0.03	0.02 ± 0.03	t	*
%	–	–	−0.95 ± 2.7%	−2.1 ± 3.1%	–	*

Data represent means ± SD unless otherwise stated; AD – Alzheimer's disease; MMSE – Mini Mental State Exam; BMI – body mass index; $^{*}P \leq 0.05$; $^{**}P \leq 0.001$; $^{***}P \leq 0.0001$; ns – not significant.

Table 2
Univariate correlates of bone density at baseline and percent change in bone density from baseline.

	BMI	Lean Mass	Fat Mass	25OHD	Leptin	HGH	IGF-1	HV
ND BMD	0.26*	0.70***	0.15	0.18	−0.25**	−0.21	0.31*	0.01
AD BMD	0.32*	0.64***	0.08	0.12	−0.07	−0.05	0.13	0.25**
	ΔBMI	ΔLean Mass	ΔF at Mass	Baseline 25OHD	ΔLeptin	Baseline HGH	ΔIGF-1	ΔHV
ΔND BMD	−0.09	−0.12	−0.11	−0.10	−0.23	−0.18	0.007	−0.01
ΔAD BMD	−0.004	−0.08	−0.02	0.33*	−0.08	−0.2	0.22	−0.29**

ND non-demented; BMD – total body bone mineral density; AD – Alzheimer's disease; BMI – body mass index (kg/m^2); Fat and lean masses in kg; 25OHD- serum levels of vitamin D; HGH – human growth hormone; IGF-1 – total serum insulin-like growth factor 1; HV – hypothalamic volume in cm^3; *P ≤ 0.05; **P < 0.01; ***P ≤ 0.0001, Δ – for all but BMD = absolute change over two years.

hypothalamic atrophy on bone loss. ΔLeptin was not a significant predictor of ΔBMD but it was independently related with ΔIGF-1 and hypothalamic atrophy. No significant indirect effects were found. Hypothalamic volume loss significantly predicted increased leptin levels, though it was unrelated to ΔIGF-1. The correlation between ΔLeptin and ΔIGF-1 was significant ($r = 0.43$, $p < 0.05$).

For the normal-control group, (Fig. 1b), we found significant direct effects of ΔLeptin on ΔBMD, but none of the other variables was a significant predictor. No significant indirect effects were found. Hypothalamic atrophy did not significantly predict changes in IGF-1, Leptin or BMD.

Hypothetical model #2

Since in the AD group ΔLeptin did not have a direct effect on ΔBMD but it was independently related with ΔIGF-1 and hypothalamic atrophy, we tested an alternative biologically plausible model that examined the potential role of changes in leptin and IGF-1 on bone loss (Fig. 2). As ΔLeptin was a non-significant predictor of bone loss in the demented group, we adjusted the model by removing the direct path from ΔLeptin to ΔBMD, but allowed for an indirect effect of ΔLeptin via either hypothalamic atrophy or ΔIGF-1. Hypothalamic atrophy continued to have direct effects on ΔBMD and predicted ΔLeptin (−0.23, 0.02). The indirect effect of hypothalamic atrophy on ΔBMD via a complete ΔLeptin – ΔIGF-1 path did not reach significance (0.2, p = 0.16). ΔLeptin was positively and significantly associated with ΔIGF-1 (0.41, < 0.001). Furthermore, the indirect effect of ΔLeptin – ΔIGF-1 path on ΔBMD reached statistical significance (−0.08, 0.05). The model demonstrated good fit for the data in the AD group (X2(df) = 7(6); CFI = 1.0; RMSEA < 0.001). This model did not fit the data and was not relevant in the normal control group.

Longitudinal mediation analysis

We next explored other potential causal directions of relationships between change in hypothalamic volume, leptin, IGF-1, and bone density across two time points two years apart using longitudinal mediation analysis separately for the AD and normal-control groups. We specifically did not restrict the direction of the effects among variable in this analysis.

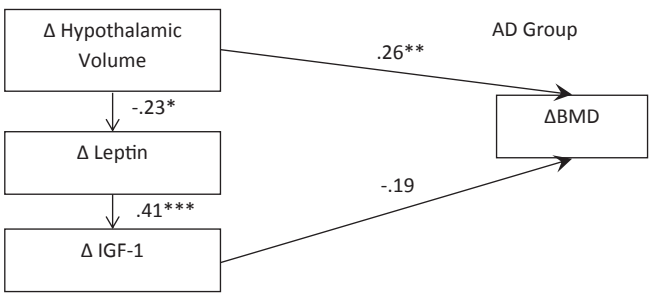

Fig. 2. Alternative hypothetical model #2 of the relationship between hypothalamic volume change and bone loss in the AD group; BMD – bone mineral density; IGF-1 – insulin-like growth factor 1; the arrows indicate the direction of hypothetical causation; β coefficients displayed along the arrows. *p < 0.05, **p < 0.01, ***p < 0.001.

Contradictory to initial hypothetical effect direction, we found a strong direct effect of baseline BMD on follow up hypothalamic volume (β = 0.50, p < 0.001) in AD and a modest effect in non-demented (β = 0.27, p < 0.05); i.e., low baseline BMD predicted lower hypothalamic volume at follow-up. Baseline hypothalamic volume, leptin, and IGF did not predict follow-up hypothalamic volume. Though BMD predicted increased leptin levels (β = −0.21, p = 0.01) in AD, this did not mediate the relationship between BMD and hypothalamic volume. Baseline BMD was not related to follow-up IGF-1 in either group. Fit indices suggest this model fit the data well (X^2(df) = 7/7, CFI = 1.00; RMSEA = 0.00).

Discussion

In our previous work, we demonstrated a relationship between low BMD and low hypothalamic volumes in the earliest clinical stages of AD [5]. Here, we reported that bone loss and hypothalamic atrophy are observed in AD in a longitudinal study. We further tested a hypothesis that neurodegenerative changes in AD may influence bone mass via alteration in central regulatory mechanisms of bone remodeling. In this exploratory longitudinal study with a smaller number of participants, we observed: 1) moderate association between hypothalamic atrophy and bone loss in the expected direction that, however failed to achieve the threshold value for p ≤ 0.05, possibly due to a small sample size and 2) more atrophy in the hypothalamus was associated with increase in leptin over two years in the AD group. However, we failed to find any evidence of a complete indirect mediation between hypothalamic structural changes and bone loss through leptin or IGF-1 in either group.

Genetic and pharmacological manipulations in animal models suggest the importance of central regulation of bone homeostasis through hypothalamic control via both neural pathways and hypothalamo-pituitary hormonal mechanisms [11,36,37]. Consistent with previous evidence documenting leptin as bone catabolic factor, we observed the relationship between higher baseline leptin and lower baseline and follow-up bone density in the non-demented group. Leptin levels were not related to bone density or bone loss in the AD group. Based on our results we speculate that the patterns of the relationship among IGF-1, leptin, and bone density may differ in AD and non-demented aging.

This study suggests that bone loss in AD may be related to neurodegenerative changes (atrophy) in the hypothalamus with different mechanisms involved in bone loss in aging and AD. These changes may be related to a cascade of events including increase in peripheral levels of leptin. In our study, the peripheral leptin levels increased significantly in AD participants but not in non-demented controls over two years. This observation is in contrast with several other studies reporting an association between AD and lower levels of leptin [38–40]. Why increase in level of leptin over two years in early AD was observed

in our study remains unclear. Some studies suggest that this may be related to abnormal functioning of hypothalamus-regulated time-keeping and clock genes (e.g., nocturnin) that are found to be involved in shifting differentiation of mesenchymal stem cells towards adipogenesis in aging [41–44]. Additionally, reports on association between leptin levels and cognitive function or AD are highly contradictory and this association needs to be further explored [45,46]. Nevertheless, the model of independent neural and neurohumoral arms that contribute to bone loss in individuals with AD is perhaps oversimplified. The relationship between leptin and bone are far more complex than initially proposed in earlier animal experiments [47,48]. The co-dependent relationships among brain, bone, fat, and metabolism should be further investigated in normal and pathological conditions in humans and animal models to gain a better understanding of these interrelationships and to provide a basis for future clinical applications.

The causal assumption for hypothesis testing in this study was based on the theoretical reasoning and data from animal models. Since, however, AD participants were already diagnosed with mild AD and had lower BMD at the beginning of the study [5] the true epidemiological association between bone loss and AD remains an open question. The mediation analysis in our study demonstrated that low baseline BMD was predictive of lower hypothalamic volume at follow up in AD and to the lesser extent in non-demented. Several epidemiologic studies support the same observation, reporting that low bone density and accelerated bone loss are associated with higher risk for developing AD or cognitive decline later on [3,7,49]. It seems unlikely that low bone density causes AD. Our observations rather suggest that bone loss may precede clinical signs of dementia or brain structural changes in AD.

The initial hypothesis tested in this study implied an effect-cause type of association, where AD causes bone loss. Our path analysis modeling of change over two years suggests that an effect-cause type of association where AD causes bone loss is plausible although needs to be further tested and confirmed by other studies. Though structural changes in the hypothalamus were associated with bone loss, it is possible that functional changes in brain regulatory mechanism in preclinical stages of AD may have played initial causal role in decline in BMD. Alternatively, the effect-effect scenario cannot be ruled out. In this case, both bone loss and AD are the effects of some common underling cause. Recent studies in AD suggest that evident physical decline such as loss of body mass, sarcopenia, and functional decline precede cognitive and anatomical neuroimaging brain changes in AD. This evidence suggests the presence of systemic changes in clinically unrecognized stages of disease or a long-standing trait that predisposes one to developing bone loss and AD.

The results of our study should be interpreted with caution due to exploratory nature of the study and several marginally significant observations. Statistically modeled hypothetical causation may not be necessarily correct in a biological model and is most likely an oversimplification. The measures were taken at two time points two years apart, limiting the ability to draw causal inference from the analyses. Additionally, our conclusions were based on peripheral levels of leptin and IGF-1. Furthermore, a consideration should be given when interpreting our study results as we adjusted the levels of leptin by fat in calculating changes over time for inclusion in mediation and path analysis models. Our measures were taken once in the morning and did not assess differences in fluctuations of these hormones. Much variance in bone loss remained unexplained by potential involvement of central regulatory mechanisms within our model. Additional or alternative mechanisms such as change in sex hormones, actual activity of the sympathetic nervous system, detailed nutritional status, and effects of other local and systemic mediators may contribute to these relationships in the very early stages. A relatively small sample size may have resulted in several marginally significant observations and did not allow us to explore the effects of gender on observed relationships or test more complex mediations, including gender dimorphism in the circulating leptin levels; i.e., women have higher circulating leptin levels and lower bone density than men. Additionally, the study was conducted over two years, and longer periods may be needed in order to assess dementia progression and clinically significant bone loss.

Altogether, we are the first to explore the relationship between hypothalamic volume and bone loss in early AD. We conclude that it is conceivable that central regulatory leptin-dependent mechanisms of bone mass may be disturbed by neurodegeneration as evident by different patterns of the relationships between leptin and bone density in AD. However, detailed mechanisms of bone loss in AD and causal and temporal relationships between AD and bone loss need to be further investigated. Additionally, the relationship between low baseline BMD and lower hypothalamic volume at follow up suggests that bone loss may precede noticeable structural changes in the hypothalamus.

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Author contributions: All authors meet the criteria for authorship stated in the Uniform Requirements for Manuscripts Submitted to Biomedical Journals and agree with the presented findings. This work has not been published before nor is being considered for publication in another journal.

Sponsor's role: The sponsor was not involved in the study design, data analysis and interpretation or reporting of this work.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.mehy.2018.10.024.

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