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The Effects of Adiponectin and Leptin on Changes in Bone Mineral Density

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Abstract

Introduction—Adiponectin and leptin are hormones secreted by adipose cells that may impact bone mineral density (BMD). Few studies have evaluated the longitudinal association of leptin and adiponectin levels with rates of BMD change.

Methods—Hip and whole body areal BMD (aBMD) were measured 5 times using dual energy x-ray absorptiometry (DXA) over 10 years. Trabecular lumbar spine volumetric BMD (vBMD) was measured using quantitative computed topography (QCT) at baseline and year 6 in the Pittsburgh cohort only. Random slope and intercept models were used to account for within person correlation as a result of repeated measures of hip and whole body aBMD. Linear regression was used to model changes in spine trabecular vBMD.

Results—Among women, the annualized rate of hip aBMD loss in the highest tertile of adiponectin was −0.67% (95% CI: −0.77, −0.58) compared to −0.43% (95% CI: −0.51, −0.35)] in the lowest tertile (p trend=0.019) after adjusting for age, race, BMI, diabetes, baseline hip aBMD, and weight change. In men, hip aBMD loss was greatest in the high adiponectin group (tertile 3), however this association was not significant, p trend=0.148. After adjusting for weight change in women, the association between higher leptin and lower hip aBMD loss was attenuated and no longer significant, p trend=0.134. Leptin and adiponectin levels were not associated with whole body aBMD or trabecular lumbar spine vBMD loss.

Conclusions—Adiponectin was associated with increased hip aBMD loss in women only; supporting evidence that adiponectin may have an important role in bone health.

Keywords

leptin; adiponectin; bone loss; hip aBMD; whole body aBMD; trabecular lumbar spine vBMD

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Introduction

Leptin is secreted by adipose cells and has been shown to be highly correlated with body fat mass[1], involved in fat metabolism, and appetite control.[2] At high levels it may increase the likelihood of insulin resistance, or metabolic syndrome[3]. Leptin may also modulate bone formation in humans by enhancing differentiation of bone marrow stromal cells into osteoblasts, and by inhibiting generation of osteoclasts.[4,5] In vivo studies of mice have supported some of these findings by showing an increase in BMD after leptin administration.[6,7] Positive effects on BMD were also observed after administration of leptin prevented the fall in plasma osteocalcin observed during a 24-hour and 5-day starvation study in male mice.[6] Hamrick et al. found that leptin treatment induced loss of bone marrow adipocytes and increased bone formation in leptin-deficient ob/ob mice.[7] Conversely, Ducy et al. identified leptin as a potent inhibitor of bone formation among leptin deficient and leptin receptor-deficient mice[8]. Population-based cross-sectional[9–14] and longitudinal studies[15,16] have produced conflicting results.

Adiponectin, another adipocyte derived hormone regulates insulin sensitivity and has anti-inflammatory properties.[17,18] At low levels it has been shown to be associated with various comorbidities including diabetes, myocardial infarction (MI), and atherosclerosis.[19–21] Unlike leptin, adiponectin levels are lower among obese individuals.[22] Adiponectin and its receptorsare expressed in human osteoblasts, suggesting that adiponectin may be a hormone linking bone and fat metabolism.[23] However, adiponectin may have negative effects on bone by stimulating the receptor activator of nuclear factor-κB ligand (RANKL) pathway and inhibiting the production of the decoy receptor for RANKL, osteoprotegerin.[24] Population-based cross-sectional[25–28] and prospective [15,29,30] studies showed differing associations.

Limitations of these past longitudinal studies include small sample sizes, short follow-up time, inadequate or no adjustment for potential confounders, and failure to evaluate change in BMD. The aim of this report is to test the hypothesis that lower baseline serum leptin levels and higher adiponectin levels will be associated with greater hip and whole body areal BMD (aBMD) loss in older women and men over 10 years. Another aim is to determine if leptin and adiponectin levels are associated with trabecular lumbar spine volumetric BMD (vBMD) loss over 6 years.

Methods

Study Population

This Health Aging and Body Composition (Health ABC) study at baseline (1997–1998) consists of 3,075 participants, aged 70–79, from two field centers, Pittsburgh, PA and Memphis, TN. Among women and men enrolled, 46% and 37% were blacks, respectively. To be eligible to participate in Health ABC, subjects had to report no difficulty walking at least 1/4 mile and or climbing a flight of stairs. Participants were identified from a random sample of white Medicare beneficiaries and all age-eligible black community residents in designated ZIP code areas surrounding Pittsburgh and Memphis. Exclusion criteria included reported difficulty performing basic activities of daily living, obvious cognitive impairment, inability to communicate with the interviewer, intention of moving within 3 years, or participation in a trial involving a lifestyle intervention. The institutional review board (IRB) at each center approved the study protocol, and written informed consent was obtained from all the participants.

Leptin and Adiponectin

Specimens were obtained by venipuncture in the morning after an overnight fast, processed, aliquoted into cryovials, frozen at −70°C, and subsequently shipped to the Health ABC Core

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Laboratory at the University of Vermont. Baseline leptin (n=3020) concentrations were measured in duplicate using the Sensitive Human Leptin radioimmunoassy (RIA) Kit (product number SHL-81K) from Linco Research, Inc. (St. Charles, MO). The assay is a competitive RIA in which the concentration of leptin is determined by competition with 125I-Human Leptin. The intra-assay CV is 3.7–7.5% and the inter-assay CV is 3.2–8.9%. Total circulating levels of baseline adiponectin (N=3044) were measured in duplicate by RIA (Linco Research, St. Charles, MO) with an intra-assay coefficient of variation of 1.8–3.6%.

Hip and Whole Body aBMD

Hip and whole body aBMD (g/cm^2) were measured using DXA (QDR 4500A; software version 9.03; Hologic, Bedford, MA, USA). DXA quality assurance procedures were conducted at both study sites and monitored by the study Coordinating Center, ensuring scanner reliability and identical scan protocols. An anthropometric spine phantom was scanned daily, and a hip phantom was scanned once per week to assess longitudinal performance of the scanners. These measurements were taken at baseline, year 3, year 5 or 6, year 8, and year 10.

Trabecular Lumbar Spine vBMD

Trabecular lumbar spine vBMD (mg/cm^3) was assessed using central Quantitative Computed Tomography (QCT) (General Electric 9800 Advantage, 80 kVp/140 mAs, 10-mm slice thickness; GE Medical Systems, Milwaukee, WI). QCT images were acquired at the level of the L3 vertebra to obtain trabecular vBMD. The change in trabecular vBMD was calculated by taking the difference between year 6 (2002–2003) and baseline (1997–1998) trabecular vBMD. QCT scans were limited to 815 participants in the Pittsburgh cohort.

Potential confounders

Demographic variables included self-report of age, race, (black or white), sex, site, and education (<HS, HS graduate, or post secondary). Whole body DXA was also used to measure total lean body mass (kg) and body fat (kg). Weight was measured on a standard balance beam scale to the nearest 0.1 kg, and height was measured by a stadiometer to the nearest 0.1 cm. BMI (kg/m^2) was calculated by using the formula weight (kg)/height^2(m^2). Annual weight change (through year 10) was estimated as the weight difference from baseline to the most recent re-assessment divided by the respective time. Lifestyle factors included self-report of smoking (never, current, or former), and alcohol consumption (no consumption in last year, <1 drink per week, 1–7 drinks per week, or >1 drink per day). To assess supplementary intake for vitamin D and calcium, and non-steroidal anti-inflammatory drug (NSAID) use, participants were asked to bring all prescription and over the counter medications, which were coded based on the Iowa Drug Information System.[31] To estimate dietary intake of calcium and vitamin D, participants completed a 108-item interviewer-administered FFQ (Block Dietary Data Systems, Berkeley, CA). Physical activity (kcal/week) was determined using the caloric expenditure in the past week for self-reported walking, climbing stairs, and exercise.[32] Diabetes was defined using fasting glucose (≥126 mg/dl), self-report, or hypoglycemic medication use. Similarly, subjects were classified as having hypertension through measurement of blood pressure (systolic ≥140 or diastolic ≥90), self-report or antihypertensive medication use. Other medical conditions were determined by asking respondents if they have ever been told by a doctor that they had a specific diagnosis of MI and history of fracture after age 45.

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Statistical Analysis

All statistical analyses were performed using the Statistical Analysis System (SAS, version 9.1; SAS Institute, Cary, NC). Two-sample t-tests (Wilcoxon rank-sum test for non-parametric measures) and chi-square tests of independence were used to evaluate mean and proportion differences by sex. Leptin and adiponectin means differed in women and men and this difference could not be explained by BMI. Therefore, sex-specific tertiles were used in the analysis (Table 2). For normally distributed variables a test of linear trend was performed by treating leptin or adiponectin tertiles as continuous. The Cochran-Armitage test for trend was used for dichotomous variables. For non-parametric variables with more than 2 groups the Jonckheere-Terpstra test of trend was performed.

Linear mixed-effects models were used to account for repeated measures of hip and whole body aBMD. Participants were excluded from hip or whole body aBMD analyses if they lacked a baseline measurement or had only one measurement during the study. Linear mixed-effects models included a random intercept for each subject and a random slope for time to account for within person correlation. Regression coefficients were estimated for the interaction between time and all the independent variables in the model. We estimated the average change in hip and whole body aBMD annually by leptin and adiponectin tertiles. Annual trabecular lumbar spine vBMD change was assessed using multiple linear regression. Leptin or adiponectin levels in the high or medium tertiles were compared to the low tertile with respect to BMD change. Tests of trend across adipokine tertiles were used to evaluate dose-response relationships with BMD change. Backward elimination procedure was used with covariates age, race, BMI, and the exposure of interest forced in all the multivariable models. Weight change was added in the final model to determine if this factor better explained our associations. Multi-collinearity was evaluated using the variance inflation factor (VIF). Covariates were excluded from the multivariate models for VIF ≥10.

Results

Table 1 shows baseline characteristics by sex. Women had significantly higher serum leptin (21.4 vs. 7.9 ng/ml) and adiponectin levels (13.3 vs. 9.5 μg/ml) than men, $p<0.001$. Women were also younger, had higher BMI, and total body fat, lower weight change and total lean mass, more likely to never smoke or consume alcohol, had lower dietary vitamin D or calcium intake, lower prevalence of diabetes and MI. Men had higher hip (0.97 g/cm^2 vs. 0.91 g/cm^2) and whole body aBMD (1.17 g/cm^2 vs. 1.01 g/cm^2) than women, $p<0.001$.

Baseline characteristics by leptin and adiponectin sex-specific tertiles are summarized in table 2. Greater serum leptin levels were significantly (p trend<0.05) associated with higher BMI, no consumption of alcohol in past year, diabetes, hypertension, and higher hip and whole body aBMD in both men and women. Among women only, increasing leptin tertiles were significantly associated with lower age, higher weight change, <HS education, supplementary calcium intake, lower dietary and supplementary vitamin D intake, lower physical activity, lower history of fracture prevalence, and higher NSAID use. In women, these associations were also significant for adiponectin, but the direction of these associations was reversed with the exception of NSAID use.

Multivariate Analysis for Hip aBMD Change

Table 3 shows the repeated measures longitudinal association of serum leptin and adiponectin with rates of hip aBMD change. Among women, the annualized rate of hip aBMD loss in the highest tertile of adiponectin was −0.67% (95% CI: −0.77, −0.58) compared to −0.43% (95% CI: −0.51, −0.35)] in the lowest tertile (p trend=0.019) after adjusting for age, race, BMI, diabetes, baseline hip aBMD, and weight change. The

association of higher leptin with lower aBMD loss among women was significant (p trend=0.023) in the base model. However, additional adjustment for weight change resulted in a null finding (p trend=0.134). Among men, the association of leptin and hip aBMD loss was substantially attenuated after adjusting for baseline BMI (p trend=0.440). The association between adiponectin and hip aBMD loss in men was not significant in the unadjusted (p trend=0.439) and multivariate (p trend=0.148) regression models.

Multivariate Analysis for Whole Body aBMD Change

Table 4 shows the effects of serum leptin and adiponectin on rates of whole body aBMD loss. Among women, the annualized rate of whole body aBMD loss in the highest tertile of leptin was −0.25% (95% CI: −0.32, −0.19) compared to −0.39% (95% CI: −0.46, −0.32)] in the lowest tertile (p trend=0.020) after adjusting for age, race, and BMI. Additional adjustment for site, NSAID use, lean mass, and baseline whole body aBMD attenuated this association to non-significance (p trend=0.146). In men, the association of leptin with whole body aBMD change was mostly explained by BMI and baseline whole body aBMD. Leptin or adiponectin levels in the high or medium tertiles compared to the low tertile did not differ significantly by whole body aBMD change in all models.

Multivariate Analysis for Trabecular Lumbar Spine vBMD Change

Table 5 shows the six year longitudinal association between leptin and adiponectin tertiles and trabecular lumbar spine vBMD. In the base model, annual trabecular vBMD rates increased [0.52% (95% CI: −0.45, 1.48)] among women in the highest tertile of leptin and decreased in the medium [−0.04% (95% CI: −0.80, 0.73)] and low tertiles [−0.95% (95% CI: −1.91, −0.02)]; however no significant trend (p trend=0.059) was observed. In the base model adjusted for weight change, annual trabecular vBMD loss among men was highest [−1.33% (95% CI: −1.92, −0.74)] in the top adiponectin tertile compared to the medium [−0.38% (95% CI: −0.93, 0.17)] and low groups [−0.62% (95% CI: −1.15, −0.09)], p for trend=0.095. In all models, trabecular vBMD change did not differ by leptin or adiponectin tertiles.

Discussion

To our knowledge this is the largest and most comprehensive study to evaluate the associations of baseline serum leptin and adiponectin with rates of BMD change. In women, higher adiponectin levels predicted greater hip aBMD loss independent of age, race, BMI, diabetes, baseline BMD, and weight change. The effect of leptin on hip aBMD loss in women was largely explained by weight change. Among men, neither leptin nor adiponectin were associated with rates of hip aBMD change. Leptin and adiponectin levels were not associated with whole body aBMD or trabecular lumbar spine vBMD change.

Higher adiponectin levels were associated with greater hip aBMD loss in women, but not men. There have been several cross-sectional studies that have reported that adiponectin is inversely associated with BMD.[27,28,33]. Three prospective studies found an inverse association between adiponectin and BMD.[15,29,30] The study in Estonia reported that higher adiponectin was associated with higher lumbar spine aBMD loss.[15] However, their study did not control for measures of adiposity. The Swedish longitudinal study reported that higher adiponectin (measured on average 12 years before BMD) was associated with lower aBMD of lumbar spine, proximal femur, and whole body in older men and women.[29] However, this study did not adjust for BMI or body composition measures and failed to assess longitudinal change in BMD over time. Finally the Rancho Bernardo Study found that an inverse association between adiponectin (measured on average 4 years before BMD) and femoral neck, total hip, and radial aBMD in women and men.[16] However, adiponectin was not

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associated with bone change in the Rancho Bernardo Study at any of these sites in men or women.

A recent study showed that recombinant adiponectin induced RANKL and inhibited OPG mRNA expression in human osteoblasts in a dose and time dependent manner leading to osteoclast formation.[24] The observation that the rate of bone loss was higher with greater levels of adiponectin may reflect greater osteoclast activation and bone resorption. Population based longitudinal studies evaluating the association of adiponectin and markers of bone turnover are needed.

We found no association between leptin and changes in hip, whole body, and trabecular lumbar spine BMD. After adjusting for weight change, the association between leptin and hip aBMD change was no longer significant in women. Also, the association between leptin and whole body aBMD (in women) change was confounded by site, NSAID use, lean mass, and baseline whole body aBMD. In men, the association of leptin with hip and whole body aBMD change was largely explained by BMI. Prior cross-sectional reports have shown that leptin is positively associated with BMD[11,13,33–35]. Few studies have assessed the association between leptin and BMD longitudinally.[15,16] The twelve month prospective study in Estonia among 35 women mean age 69.7 years, reported that higher leptin was correlated with lower loss of whole body aBMD.[15] However, this study did not adjust for measures of adiposity. The Rancho Bernardo Study found that leptin (measured on average 4 years before the BMD measurement) predicted higher femoral neck, total hip, lumbar spine, and radial aBMD in women but not men. However, consistent with our findings, they failed to find an association between leptin and hip aBMD change over 4 years.

We previously reported a roughly two-fold risk in incident fractures among men in the top tertile for adiponectin.[36] Thus, it is unclear why the association of adiponectin with hip aBMD change was confined to women. The annual rate of hip aBMD loss in men was approximately 0.15 percentage points higher in the top quartile of adiponectin compared to the medium and low tertiles; however there was no statistical trend or difference by groups. Adiponectin was 40% higher in women compared to men, despite greater body fat in women. However, it is uncertain if sex differences in adiponectin account for these differential associations. Consistent with our findings, a previous study in mice showed that there was a stronger inverse correlation for adiponectin and bone mass in female mice compared to male mice.[37] The association between adiponectin and bone may be influenced by sex hormones.[30] Future prospective studies that control for sex hormones are needed.

Strengths of this study include a large sample size, reliable ascertainment of exposures and outcomes, adjustment for many potential confounders, long follow-up period, and multiple time points for assessment of hip and whole body aBMD data. Nevertheless, our study has several limitations. We measured leptin and adiponectin at baseline only and could not account for changes in over time. Also, trabecular lumbar spine vBMD was only measured in the Pittsburgh cohort and at two time points; thus power is potentially an issue in this particular analysis. In addition, survival bias may impact our findings because healthier individuals with higher baseline BMD are more likely to have to have a repeat BMD measurement.[38] However, there were no significant differences in baseline leptin or adiponectin among participants who died or remained alive, and among those that did or did not return for a follow-up. Finally, we adjusted for many covariates, but lacked sufficient data to adjust for insulin (a hormone associated with leptin and adiponectin) and bone markers (i.e., osteocalcin, PINP, or CTX) which are related to BMD and body weight.

In summary, in a large cohort of older adults, higher adiponectin was associated with greater annual hip aBMD loss in women only; supporting evidence that adiponectin may have an

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important role in bone health. Identification of potential mediators in the causal pathway may better explain these findings.

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Table 1

Characteristics among older women and men

	Women (N=1584)	Men (N=1491)	P-value
Leptin (ng/ml), mean (SD)	21.4 ± 14.7	7.9 ± 6.9	<0.001
Adiponectin (μg/ml), mean (SD)	13.3 ± 7.4	9.5 ± 5.6	<0.001
Age (years), mean (SD)	73.5 ± 2.9	73.8 ± 2.9	0.013
BMI (kg/m^2), mean (SD)	27.7 ± 5.5	27.1 ± 4.0	<0.001
Weight change (kg), mean (SD)	−0.37 ± 1.74	−0.40 ± 1.94	<0.001
Total fat mass (kg), mean (SD)	29.2 ± 9.3	24.2 ± 7.2	<0.001
Total lean mass (kg), mean (SD)	41.3 ± 6.2	57.1 ± 7.3	<0.001
White, %	53.9	63.2	<0.001
Education, %			<0.001
<HS	23.2	27.3	
HS graduate	39.5	25.5	
Post secondary	37.3	47.2	
Memphis, %	50.1	50.4	0.885
Smoking, %			<0.001
Never	57.2	29.4	
Current	9.9	10.8	
Former	32.9	59.8	
Alcohol, %			<0.001
No consumption in last year	57.7	42.6	
< 1 per week	21.9	19.6	
1–7 per week	16.9	26.2	
>1 per day	3.5	11.6	
Dietary calcium (mg/day), mean (SD)	753.2 ± 363.6	817.3 ± 428.9	<0.001
Supplementary calcium, %	28.4	7.2	<0.001
Dietary vitamin D (IU/day), mean (SD)	192.6 ± 131.1	225.9 ± 147.5	<0.001
Supplementary vitamin D, %	13.4	3.4	<0.001
Physical activity (kcal/week), median (IQR)	298.5 (26.7–920.4)	688.0 (165.1–1832.1)	<0.001
History of fracture after age 45, %	27.4	16.1	<0.001
Diabetes, %	16.3	22.0	<0.001

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	Women (N=1584)	Men (N=1491)	P-value
Hypertension, %	77.6	74.0	0.020
MI, %	17.9	22.4	0.051
NSAID use, %	25.2	18.4	<0.001
Hip aBMD (g/cm^2)	0.81 ± 0.15	0.97 ± 0.15	<0.001
Whole body BMD (g/cm^2)	1.01 ± 0.11	1.17 ± 0.12	<0.001

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Table 2

Characteristics by leptin and adiponectin tertiles in older women and men

	Leptin				Adiponectin			
	Low	**Middle**	**High**	**P Trend**	**Low**	**Middle**	**High**	**P Trend**
Women	N=518	N=517	N=517		N=562	N=501	N=505	
Leptin (ng/ml)	0.3–12.4	12.5–24.1	24.2–99.3	<0.001	-	-	-	
Adiponectin (μg/ml)	-	-	-		1.0–9.0	10.0–15.0	16.0–49.0	<0.001
Age (years), mean (SD)	73.8 ± 3.0	73.5 ± 2.8	73.2 ± 2.8	0.001	73.1 ± 2.8	73.4 ± 2.8	74.1 ± 2.9	<0.001
BMI (kg/m^2), mean (SD)	23.7 ± 3.9	27.4 ± 4.0	31.8 ± 5.0	<0.001	30.1 ± 5.4	27.5 ± 5.1	25.3 ± 4.8	<0.001
Weight change (kg), mean (SD)	−0.22 ± 1.39	−0.30 ± 1.67	−0.56 ± 2.07	0.002	−0.40 ± 1.50	−0.31 ± 1.35	−0.38 ± 2.25	0.780
Total fat mass (kg), mean (SD)	22.1 ± 6.7	28.6 ± 6.1	36.7 ± 8.4	<0.001	32.5 ± 9.3	29.3 ± 8.8	25.4 ± 8.3	<0.001
Total lean mass (kg), mean (SD)	38.3 ± 5.0	40.9 ± 5.7	44.6 ± 6.0	<0.001	44.1 ± 6.3	40.8 ± 5.8	38.7 ± 5.1	<0.001
White, %	68.0	55.3	39.1	<0.001	29.9	61.9	72.9	<0.001
Education, %				<0.001				<0.001
<HS	18.0	21.8	29.6		33.1	17.7	17.8	
HS graduate	40.1	42.2	37.4		37.2	42.8	38.8	
Post secondary	41.9	37.0	33.0		29.7	39.6	43.4	
Memphis, %	47.7	46.8	56.1	0.007	48.0	49.7	52.9	0.117
Smoking, %				0.136				0.007
Never	58.7	54.9	57.7		53.0	58.0	61.1	
Current	13.5	11.0	5.2		10.9	8.8	9.9	
Former	27.8	34.0	37.1		36.1	33.2	29.0	
Alcohol, %				0.002				<0.001
No consumption in last year	54.3	55.9	62.6		65.1	54.2	52.8	
< 1 per week	21.9	22.8	21.1		20.8	22.8	22.2	
1–7 per week	19.7	16.6	14.5		11.2	20.0	20.2	
>1 per day	4.1	4.7	1.8		2.9	3.0	4.8	
Dietary calcium (mg/day), mean (SD)	788.1 ± 375.0	732.7 ± 357.2	743.9 ± 358.7	0.065	764.5 ± 388.6	729.2 ± 345.2	764.5 ± 352.9	0.970
Supplementary calcium, %	37.7	26.4	21.1	<0.001	20.4	30.5	35.1	<0.001
Dietary vitamin D (IU/day), mean (SD)	212.8 ± 140.2	178.3 ± 123.5	186.7 ± 127.4	0.002	192.9 ± 134.4	184.9 ± 122.7	199.7 ± 135.2	0.450
Supplementary vitamin D, %	18.7	12.0	8.7	<0.001	9.8	12.6	17.3	<0.001

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	Leptin				Adiponectin			
	Low	**Middle**	**High**	**P Trend**	**Low**	**Middle**	**High**	**P Trend**
Physical activity (kcal/week), median (IQR)	425 (55–1040)	289 (47–895)	213 (5–788)	<0.001	207 (8–793)	343 (42–1025)	371 (70–898)	0.001
History of fracture after age 45, %	30.9	27.3	24.0	0.013	20.7	27.7	34.5	<0.001
Diabetes, %	10.7	16.0	21.9	<0.001	30.1	10.7	6.3	<0.001
Hypertension, %	72.0	78.1	82.2	<0.001	84.3	76.5	71.3	<0.001
MI, %	8.3	8.3	6.6	0.299	7.8	9.0	6.7	0.529
NSAID use, %	21.0	26.0	27.9	0.011	23.6	24.5	27.6	0.140
Hip aBMD (g/cm^2)	0.75 ± 0.14	0.80 ± 0.13	0.88 ± 0.14	<0.001	0.87 ± 0.14	0.80 ± 0.14	0.75 ± 0.14	<0.001
Whole body BMD (g/cm^2)	0.99 ± 0.11	1.00 ± 0.11	1.04 ± 0.11	<0.001	1.05 ± 0.11	1.01 ± 0.11	0.98 ± 0.11	<0.001
Men	N=488	N=491	N=489		N=519	N=452	N=505	
Leptin (ng/ml)	0.1–4.3	4.4–8.4	8.5–60.3	<0.001	-	-	-	
Adiponectin (μg/ml)	-	-	-		1.0–6.0	7.0–10.0	11.0–53.0	
Age (years), mean (SD)	73.8 ± 2.9	73.7 ± 2.8	73.7 ± 2.9	0.307	73.4 ± 2.8	73.7 ± 2.9	74.1 ± 2.9	<0.001
BMI (kg/m^2), mean (SD)	24.2 ± 2.8	27.1 ± 3.0	29.9 ± 3.8	<0.001	28.1 ± 3.7	27.1 ± 3.9	26.0 ± 4.0	<0.001
Weight change (kg), mean (SD)	−0.33 ± 2.18	−0.36 ± 1.67	−0.51 ± 1.94	0.163	−0.43 ± 1.81	−0.38 ± 2.18	−0.37 ± 1.84	0.615
Total fat mass (kg), mean (SD)	18.2 ± 4.4	24.4 ± 4.8	29.8 ± 6.9	<0.001	25.2 ± 6.8	24.6 ± 7.0	22.7 ± 7.5	<0.001
Total lean mass (kg), mean (SD)	54.2 ± 6.3	57.3 ± 6.9	59.7 ± 7.7	<0.001	58.8 ± 7.4	57.3 ± 7.2	55.1 ± 6.9	<0.001
White, %	63.3	68.0	57.9	0.078	49.3	64.8	76.2	<0.001
Education, %				0.248				0.033
<HS	30.0	26.1	26.0		30.1	24.6	26.7	
HS graduate	24.6	25.9	26.0		27.8	24.8	24.0	
Post secondary	45.4	48.0	48.0		42.1	50.6	49.3	
Memphis, %	46.5	52.3	52.8	0.049	48.9	48.0	53.9	0.117
Smoking, %				0.023				0.174
Never	31.1	27.8	29.9		29.7	33.0	25.8	
Current	16.0	8.6	7.5		10.4	11.7	10.3	
Former	52.9	63.6	62.6		58.9	55.3	63.8	
Alcohol, %				0.051				<0.001
No consumption in last year	39.0	43.4	45.4		47.1	41.1	39.3	
< 1 per week	19.7	20.1	19.2		21.7	20.7	16.4	
1–7 per week	29.1	25.8	23.5		22.3	25.3	30.9	

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	Leptin				Adiponectin			
	Low	**Middle**	**High**	**P Trend**	**Low**	**Middle**	**High**	**P Trend**
>1 per day	12.2	10.7	11.9		8.9	12.9	13.4	
Dietary calcium (mg/day), mean (SD)	824.4 ± 431.3	807.5 ± 416.9	820.0 ± 440.5	0.878	802.1 ± 441.3	822.4 ± 445.1	828.0 ± 401.8	0.355
Supplementary calcium, %	7.6	6.7	7.4	0.887	5.6	7.8	8.3	0.089
Dietary vitamin D (IU/day), mean (SD)	225.8 ± 151.6	221.7 ± 138.7	230.8 ± 152.9	0.630	222.7 ± 153.4	221.6 ± 146.2	232.2 ± 142.2	0.330
Supplementary vitamin D, %	2.5	3.3	4.5	0.080	2.5	3.6	4.2	0.142
Physical activity (kcal/week), median (IQR)	766 (189–1977)	657 (121–1840)	647 (178–1715)	0.279	579 (148–1539)	794 (172–2003)	761 (178–1944)	0.070
History of fracture after age 45, %	17.2	14.9	16.0	0.591	16.6	14.9	16.6	0.983
Diabetes, %	15.2	22.0	28.9	<0.001	35.0	19.4	11.2	<0.001
Hypertension, %	72.3	70.5	78.9	0.019	76.5	75.0	70.9	0.041
MI, %	16.8	12.5	17.6	0.715	16.6	16.6	13.7	0.211
NSAID use, %	17.7	18.3	19.1	0.583	16.7	17.8	20.8	0.094
Hip aBMD (g/cm^2)	0.93 ± 0.15	0.97 ± 0.14	1.02 ± 0.15	<0.001	1.02 ± 0.15	0.98 ± 0.14	0.92 ± 0.15	<0.001
Whole body BMD (g/cm^2)	1.17 ± 0.12	1.17 ± 0.12	1.18 ± 0.12	0.026	1.20 ± 0.12	1.18 ± 0.12	1.15 ± 0.12	<0.001

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Table 3

The association between sex-specific tertiles of leptin/adiponectin and hip aBMD change[a] using linear mixed-effects regression models

	Leptin				Adiponectin			
	Low (ref)	**Middle**	**High**	**P Trend**	**Low (ref)**	**Middle**	**High**	**P Trend**
Women								
Unadjusted	−0.52 (−0.60, −0.44)	−0.43 (−0.51, −0.34)	−0.60 (−0.69, −0.51)	0.983	−0.50 (−0.57, −0.42)	−0.47 (−0.56, −0.39)	−0.57 (−0.66, −0.48)	0.886
Age adjusted	−0.51 (−0.59, −0.44)	−0.43 (−0.51, −0.34)	−0.62 (−0.71, −0.53)	0.758	−0.51 (−0.59, −0.44)	−0.49 (−0.57, −0.49)	−0.55 (−0.65, −0.46)	0.518
Age and race adjusted	−0.57 (−0.65, −0.49)	−0.44 (−0.53, −0.36)	−0.57 (−0.66, −0.48)	0.178	−0.43 (−0.51, −0.36)	−0.55 (−0.61, −0.44)	−0.65 (−0.74, −0.55)*	0.043
Age race and BMI adjusted	−0.61 (−0.70, −0.52)	−0.45 (−0.53, −0.36)	−0.52 (−0.63, −0.42)	0.021	−0.42 (−0.50, −0.34)	−0.53 (−0.61, −0.44)	−0.66 (−0.76, −0.57)*	0.015
Base model†	−0.62 (−0.71, −0.53)	−0.45 (0.53, −0.36)	−0.53 (−0.64, −0.43)	0.023	−0.41 (−0.50, −0.33)	−0.53 (−0.62, −0.44)	−0.70 (−0.80, −0.59)*	0.005
Base model† + weight change	−0.60 (−0.70, −0.51)	−0.46 (−0.55, −0.37)	−0.57 (−0.68, −0.46)	0.134	−0.43 (−0.51, −0.35)	−0.56 (−0.64, −0.47)	−0.67 (−0.77, −0.58)*	0.019
Men								
Unadjusted	−0.61 (−0.68, −0.53)	−0.54 (−0.62, −0.46)	−0.56 (0.65, −0.48)	0.089	−0.55 (−0.62, −0.48)	−0.51 (−0.59, −0.43)	−0.66 (−0.74, −0.57)	0.439
Age adjusted	−0.61 (−0.68, −0.53)	−0.55 (−0.62, −0.47)	−0.57 (−0.65, −0.49)	0.101	−0.56 (−0.64, −0.49)	−0.51 (−0.59, −0.43)	−0.65 (−0.73, −0.56)	0.234
Age and race adjusted	−0.61 (−0.69, −0.54)	−0.56 (−0.63, −0.48)	−0.56 (−0.65, −0.48)	0.064	−0.54 (−0.61, −0.46)	−0.53 (−0.61, −0.45)	−0.68 (−0.77, −0.60)	0.149
Age race and BMI adjusted	−0.59 (−0.67, −0.50)	−0.56 (−0.63, −0.48)	−0.59 (−0.68, −0.50)	0.440	−0.54 (−0.62, −0.47)	−0.53 (−0.61, −0.45)	−0.67 (−0.76, −0.58)	0.278
Base model‡	−0.56 (−0.65, −0.46)	−0.58 (−0.66, −0.49)	−0.67 (−0.78, −0.57)	0.490	−0.55 (−0.63, −0.47)	−0.55 (−0.64, −0.47)	−0.71 (−0.80, −0.62)	0.147
Base model‡ + weight change	−0.60 (−0.69, −0.51)	−0.58 (−0.66, −0.50)	−0.60 (−0.70, −0.51)	0.427	−0.55 (−0.63, −0.47)	−0.54 (−0.63, −0.47)	−0.70 (−0.79, −0.61)	0.148

[a] Mean annualized % change in aBMD (95% CI);

* $p<0.05$ for comparison of high and medium tertiles with low (ref) tertile

† Adjusted for age, age*time, race, race*time, BMI, BMI*time, diabetes*time, and baseline hip aBMD

‡ Adjusted for age, age*time, race, race*time, BMI, BMI*time, physical activity, lean mass*time, total fat*time, and baseline hip aBMD

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Table 4

The association between sex-specific tertiles of leptin/adiponectin and whole body aBMD change[a] using linear mixed-effects regression models

	Leptin				Adiponectin			
	Low (ref)	**Middle**	**High**	**P Trend**	**Low (ref)**	**Middle**	**High**	**P Trend**
Women								
Unadjusted	−0.35 (−0.41, −0.29)	−0.27 (−0.33, −0.21)	−0.29 (−0.35, −0.23)	0.345	−0.31 (−0.37, −0.25)	−0.31 (−0.34, −0.27)	−0.25 (−0.31, −0.20)	0.394
Age adjusted	−0.35 (−0.41, −0.29)	−0.27 (−0.33, −0.22)	−0.30 (−0.35, −0.23)	0.366	−0.31 (−0.37, −0.25)	−0.31 (−0.34, −0.27)	−0.26 (−0.31, −0.19)	0.355
Age and race adjusted	−0.37 (−0.43, −0.21)	−0.28 (−0.34, −0.22)	−0.27 (−0.33, −0.21)	0.073	−0.28 (−0.34, −0.22)	−0.31 (−0.34, −0.38)	−0.28 (−0.35, −0.22)	0.636
Age race and BMI adjusted	−0.39 (−0.46, −0.32)	−0.28 (−0.34, −0.22)	−0.25 (−0.32, −0.19)	0.020	−0.27 (−0.34, −0.21)	−0.31 (−0.34, −0.28)	−0.29 (−0.35, −0.22)	0.539
Base model[†]	−0.37 (−0.44, −0.30)	−0.28 (0.34, −0.22)	−0.28 (−0.34, −0.21)	0.146	−0.27 (−0.33, −0.20)	−0.37 (−0.43, −0.31)	−0.30 (−0.36, −0.23)	0.369
Base model[†] + weight change	−0.37 (−0.44, −0.30)	−0.28 (−0.34, −0.22)	−0.28 (−0.36, −0.22)	0.145	−0.27 (−0.33, −0.21)	−0.37 (−0.43, −0.31)	−0.30 (−0.36, −0.23)	0.368
Men								
Unadjusted	−0.43 (−0.49, −0.37)	−0.36 (−0.42, −0.30)	−0.36 (−0.42, −0.29)	0.110	−0.38 (−0.44, −0.32)	−0.39 (−0.45, −0.33)	−0.39 (−0.45, −0.33)	0.833
Age adjusted	−0.43 (−0.49, −0.37)	−0.36 (−0.42, −0.30)	−0.36 (−0.42, −0.30)	0.119	−0.38 (−0.44, −0.31)	−0.39 (−0.45, −0.33)	−0.39 (−0.45, −0.33)	0.999
Age and race adjusted	−0.44 (−0.50, −0.37)	−0.37 (−0.43, −0.31)	−0.35 (−0.41, −0.29)	0.082	−0.40 (−0.46, −0.34)	−0.40 (−0.46, −0.34)	−0.37 (−0.43, −0.31)	0.374
Age race and BMI adjusted	−0.42 (−0.49, −0.35)	−0.37 (−0.43, −0.31)	−0.37 (−0.40, −0.30)	0.446	−0.39 (−0.45, −0.33)	−0.40 (−0.46, −0.34)	−0.38 (−0.44, −0.32)	0.602
Base model[‡]	−0.39 (−0.46, −0.32)	−0.37 (−0.43, −0.31)	−0.40 (−0.47, −0.33)	0.800	−0.37 (−0.43, −0.31)	−0.40 (−0.46, −0.34)	−0.41 (−0.47, −0.34)	0.595
Base model[‡] + weight change	−0.39 (−0.46, −0.32)	−0.37 (−0.43, −0.31)	−0.40 (−0.47, −0.33)	0.802	−0.37 (−0.43, −0.31)	−0.40 (−0.46, −0.34)	−0.41 (−0.47, −0.34)	0.593

[a] Mean annualized % change in aBMD (95% CI)

[†] Adjusted for age, age*time, race, race*time, BMI, BMI*time, site, site*time, NSAID use*time, lean mass*time, and baseline whole body aBMD

[‡] Adjusted for age, age*time, race, race*time, BMI, BMI*time, education*time, time, site, site*time, time*physical activity, lean mass*time, and baseline hip aBMD

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Table 5

The association between sex-specific tertiles of leptin/adiponectin and trabecular lumbar spine vBMD change[a] using linear regression models

	Leptin				Adiponectin			
	Low (ref)	**Middle**	**High**	**P Trend**	**Low (ref)**	**Middle**	**High**	**P Trend**
Women								
Unadjusted	−0.67 (−1.52, 0.19)	0.11 (−0.66, 0.88)	0.07 (−0.78, 0.92)	0.233	0.43 (−0.37, 1.23)	−0.65 (−1.44, 0.14)	−0.24 (−1.10, 0.63)	0.238
Age adjusted	−0.66 (−1.51, 0.20)	0.11 (−0.66, 0.88)	0.06 (−0.79, 0.91)	0.248	0.41 (−0.40, 1.22)	−0.64 (−1.43, 0.15)	−0.22 (−1.09, 0.65)	0.276
Age and race adjusted	−0.57 (−1.46, 0.31)	0.09 (−0.68, 0.86)	−0.01 (−0.86, 0.86)	0.241	0.32 (−0.52, 1.17)	−0.63 (−1.43, 0.16)	−0.13 (−1.04, 0.78)	0.365
Age, race, and BMI adjusted	−0.91 (−1.88, 0.06)	0.06 (−0.71, 0.83)	0.36 (−0.61, 1.34)	0.112	0.40 (−0.46, 1.26)	−0.66 (−1.45, 0.14)	−0.19 (−1.11, 0.72)	0.335
Base model[†]	−0.95 (−1.91, 0.02)	−0.04 (−0.80, 0.73)	0.52 (−0.45, 1.48)	0.059	0.44 (−0.41, 1.29)	−0.67 (−1.46, 0.11)	−0.23 (−1.14, 0.68)	0.269
Base model[†] + weight change	−0.84 (−1.80, 0.12)	−0.14 (−0.90, 0.63)	0.53 (−0.43, 1.49)	0.081	0.40 (−0.44, 1.24)	−0.67 (−1.45, 0.11)	−0.17 (−1.08, 0.73)	0.353
Men								
Unadjusted	−0.90 (−1.45, −0.36)	−0.98 (−1.53, −0.42)	−0.37 (−0.93, 0.20)	0.186	−0.63 (−1.16, −0.11)	−0.38 (−0.94, 0.17)	−1.31 (−1.89, −0.73)	0.112
Age adjusted	−0.88 (−1.43, −0.34)	−1.01 (−1.55, −0.44)	−0.37 (−0.93, 0.20)	0.200	−0.65 (−1.18, −0.13)	−0.39 (−0.94, 0.17)	−1.28 (−1.86, −0.70)	0.145
Age and race adjusted	−0.89 (−1.43, −0.34)	−1.01 (−1.56, −0.44)	−0.36 (−0.92, 0.21)	0.296	−0.62 (−1.16, −0.09)	−0.39 (−0.95, 0.16)	−1.31 (−1.90, −0.72)	0.201
Age race and BMI adjusted	−0.61 (−1.23, 0.01)	−1.00 (−1.56, −0.45)	−0.66 (−1.31, −0.01)	0.914	−0.69 (−1.23, −0.16)	−0.38 (−0.93, 0.17)	−1.23 (−1.82, −0.64)	0.324
Base model[‡]	−0.60 (−1.21, 0.02)	−0.98 (−1.53, −0.43)	−0.69 (−1.34, −0.05)	0.815	−0.62 (−1.15, −0.09)	−0.40 (−0.94, 0.15)	−1.31 (−1.90, −0.72)	0.115
Base model[‡] + weight change	−0.59 (−1.20, 0.03)	−0.99 (−1.54, −0.44)	−0.70 (−1.35, −0.06)	0.761	−0.62 (−1.15, −0.09)	−0.38 (−0.93, 0.17)	−1.33 (−1.92, −0.74)	0.095

[a] Mean annualized % change in aBMD (95% CI)

[†] Adjusted for age, race, BMI, supplementary calcium, and baseline trabecular vBMD

[‡] Adjusted for age, race, BMI, diabetes, and baseline trabecular vBMD