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Sex Differences in the Association Between Adiponectin and BMD, Bone Loss, and Fractures: The Rancho Bernardo Study

Maria Rosario G. Araneta, Denise von Mühlen, and Elizabeth Barrett-Connor

ABSTRACT: We evaluated sex differences in the prospective association between adiponectin with BMD, bone loss, and fractures. Adiponectin, an adipose-derived protein with insulin-sensitizing properties, is also expressed in bone-forming cells. Conflicting results and sex differences in the adiponectin–BMD association have been reported in cross-sectional studies. Serum adiponectin was measured in fasting blood samples obtained in 1984–1987 in 447 postmenopausal women (mean age: 76 yr) and 484 men (mean age: 75 yr). Four years later, BMD was measured at the midshaft radius by single photon absorptiometry and at the femoral neck, total hip, and lumbar spine by DXA. In 1992–1996, axial BMD was remeasured in 261 women and 264 men. Multivariable analysis adjusted for age, weight, calcium intake, type 2 diabetes, alcohol intake, and exercise. Among women, adiponectin was inversely associated with BMD at the femoral neck ($\beta = -0.002$, $p = 0.007$), total hip ($\beta = -0.002$, $p = 0.009$), lumbar spine ($\beta = -0.003$, $p = 0.008$), and midshaft radius ($\beta = -0.002$, $p = 0.01$) after 4.4 yr and at the femoral neck and total hip 8.6 yr later. Among men, adiponectin was inversely associated with BMD at the femoral neck, ($\beta = -0.002$, $p = 0.03$), total hip ($\beta = -0.004$, $p < 0.001$), and midshaft radius ($\beta = -0.003$, $p < 0.001$) after 4.4 yr and at the hip 8.6 yr later. Adiponectin was not associated with 4-yr bone loss in either sex but was associated with vertebral fractures (adjusted OR: 1.13; 95% CI: 1.08–1.23; $p = 0.009$) among men only. Adiponectin was inversely associated with BMD; however, sex differences were observed by anatomical site and with regards to vertebral fractures.
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Address correspondence to: *Maria Rosario G. Araneta, PhD, Department of Family and Preventive Medicine, University of California San Diego, 9500 Gilman Drive, MC-0607, La Jolla, CA 92093-0607, USA, E-mail: haraneta@ucsd.edu*

INTRODUCTION

ADIPONECTIN, AN ADIPOSE-DERIVED protein, plays an important role in glucose homeostasis and has anti-inflammatory and anti-atherogenic effects.[1] Recent studies have suggested that adiponectin may be a novel determinant of BMD. Benner et al.[2] showed transcription, translation, and secretion of adiponectin and its receptors (AdipoR1 and AdipoR2) in bone-forming cells, suggesting that adiponectin may provide an important signal linking fat and body weight to BMD. Luo et al.[3] reported that adiponectin induces human osteoblast proliferation and differentiation; furthermore, adiponectin seems to stimulate the RANKL pathway to inhibit osteoprotegerin production in human osteoblasts, thus indirectly increasing osteoclastogenesis. However, epidemiological studies are limited to a few cross-sectional studies that have produced conflicting results. Studies among postmenopausal women are limited to a few reports where adiponectin was inversely related with BMD at the total hip, femoral neck, forearm, or lumbar spine,[4–7] but the association was inconsistent among perimenopausal women.[8–10] Among men, studies are limited to a few studies where adiponectin was inversely and independently associated with BMD[7,11] and correlated positively with bone turnover biochemical markers.[12] However, no association was observed between adiponectin with BMD at the lumbar spine or femoral neck among middle aged men in Korea[13] or among elderly men in Italy.[14] Similarly, a study in Mexico showed adiponectin was negatively associated with BMD at the spine among overweight men (BMI > 27 kg/m^2) but not in nonoverweight men.[15]

Prior studies have shown those with type 2 diabetes have elevated BMD but reduced adiponectin concentration compared with nondiabetics.[1,16] Adiponectin concentration is significantly higher among women compared with men[1] and increases after menopause.[17] However, sex differences in the association between adiponectin and BMD in older adults have been evaluated in just one longitudinal study.

Whereas some of the above studies suggest adiponectin may play a role in bone metabolism, the association between adiponectin and fracture risk has been evaluated in just two studies, with conflicting results. Although increasing levels of adiponectin was a negative determinant of BMD among elderly men in Sweden, it was not associated with fracture risk after a follow-up period of 15 yr.[11] However, adiponectin was associated with moderate or severe vertebral fractures in men with type 2 diabetes but not among postmenopausal women.[18]

The objectives of the study are to determine whether (1) adiponectin concentration is associated with BMD at the

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Department of Family and Preventive Medicine, University of California San Diego, La Jolla, California, USA.

midshaft radius, femoral neck, hip, and spine in older men and women after 4.4 and 8.6 yr, respectively, and (2) adiponectin is associated with bone loss and fractures.

MATERIALS AND METHODS

Data were obtained from the Rancho Bernardo study, a community-based longitudinal study begun in 1972.[19] Blood samples were obtained by venipuncture between 7.5 and 11 h after a requested 12-h fast in 1984–1987 and stored at −70°C within 4 h; serum was separated and frozen at −70°C until 2004 when the samples were thawed (for the second time) for measurement of adiponectin by radioimmunoassay (Linco, St. Louis, MO, USA). The sensitivity and the intra- and interassay CVs were 0.8 mg/liter, 6%, and 7%, respectively. Linco reports reproducible results for the adiponectin assay after two freeze-thaw cycles, and adiponectin levels did not vary by years of frozen sample storage or hour of sample collection.

Between 1988 and 1992, lifestyle habits were assessed using a standardized questionnaire, and a standardized medical interview was used to ascertain menopausal status. Medication use was elicited, including current estrogen, calcium supplement use, and bone-specific medication. Participants were asked to bring pills or prescriptions of prescribed and nonprescribed medications and nutritional supplements used within the month before each clinical visit; these medications and prescriptions were examined and recorded by a clinic nurse. A self-administered Harvard-Willett Diet Assessment Questionnaire was used to estimate dietary calcium intake. Total calcium intake was the sum of calcium intake from dietary and supplemental calcium. Menopausal status was ascertained through a self-administered questionnaire that included date of last menses and hysterectomy.

Height (cm) and weight (kg) were measured using a stadiometer and a regularly calibrated scale, respectively, in women wearing light clothing and no shoes. Body mass index (BMI) was calculated as weight (kg) divided by height (m^2). Waist was measured in centimeters at the natural bending point, and hip was measured at the iliac crest. Percent body fat, including total fat mass (kg) and total lean mass (kg), was assessed by bioelectrical impedance analysis using a body composition analyzer (Model 1990B; Valhalla Scientific, San Diego, CA, USA).

A 75-g oral glucose tolerance test was administered in the morning after a minimum 8-h fast; blood samples were obtained by venipuncture at 0 and 2 h. Type 2 diabetes was defined using the 1999 World Health Organization criteria: fasting plasma glucose level ≥126 mg/dl, 2-h postchallenge glucose level ≥200 mg/dl, a history of type 2 diabetes mellitus diagnosed by a physician, or treatment with an oral hypoglycemic agent or insulin.[20]

BMD was defined as total BMC (g) divided by the area (cm^2). Between 1988 and 1992, BMD was measured at the midshaft radius of the nondominant arm using single photon absorptiometry (model SP2B; Lunar). The midshaft radius was the mean of four scanned lines. Femoral neck, total hip, and lumbar spine were measured using DXA (QDR-1000; Hologic, Waltham, MA, USA). Femoral neck BMD was measured at the narrowest point of the femoral neck and perpendicular to the femoral midline. Total hip BMD was calculated as the total BMD of the greater trochanter, femoral neck, and intertrochanter regions. Spine BMD was measured in the anteroposterior view and was the mean of four lumbar vertebrae (L_1–L_4). All bone scans were administered by certified BMCD technologists. Approximately 4.1 yr later (in 1992–1996), axial BMD measurements were repeated using the same DXA machine. The machines were calibrated daily, with measurement precisions of ≤1% for the spine, ≤1.5% for the hip, and ≤5.0% for the radius.

Bone loss was defined as the change in BMD between the initial and second BMD measures, divided by the time interval (yr) between the two visits. Between 1992 and 1996, lateral vertebral radiographs of the thoracic and lumbar spine (T_7–L_4) were obtained and were read by a single radiologist specializing in skeletal deformities (Dr. David Sartoris, University of California, San Diego, CA, USA) who defined fracture status by using the qualitative and semiquantitative grading scheme for vertebral deformity.[21] Informed consent was obtained from all participants, and the study was approved by the UCSD Human Research Protections Program.

All analyses were conducted using SAS version 9.0 (Cary, NC, USA). Generalized linear regression was used to determine differences in adjusted mean values for continuous variables, whereas χ^2 was used to estimate differences for categorical variables. Pearson correlation coefficients were computed to examine correlations between anthropometric variables, adiponectin, and BMD. Adiponectin was stratified into equal quartiles to assess linear trends of BMD and anthropometric markers. Univariate analysis was used to identify covariates associated with BMD or adiponectin. Linear regression was performed to evaluate the association between adiponectin and BMD at the midshaft radius, femoral neck, total hip, and lumbar spine, while adjusting for covariates associated with BMD in univariate analysis, including age, weight, type 2 diabetes, calcium intake, alcohol intake, and smoking status. These regression models also adjusted for covariates that were associated with adiponectin, including type 2 diabetes, waist:hip ratio, and alcohol intake.

RESULTS

A total of 447 postmenopausal women and 484 men had adiponectin measurements in 1984–1987 and BMD measurement between 1988 and 1992. As shown in Table 1, compared with women, men were slightly younger, had higher BMI, weight, waist girth, and alcohol intake, but lower percent body fat, fat mass, calcium intake, and adiponectin concentration. Men had significantly higher mean BMD at all anatomical sites (Table 1). Men were also more likely to report exercise at least three times per week, to have ever smoked, and to use thiazides, and less likely to use thyroid hormones.

Adiponectin was positively and significantly correlated with age ($p < 0.001$) and was inversely and significantly

TABLE 1. Demographic, Anthropometric, Biochemical, and BMD Characteristics Among Postmenopausal Women and Older Men, Rancho Bernardo, California, 1988–1992

	Women (*n = 447*)	*Men* (*n = 484*)
Age (yr)	76.0 ± 8.4	74.8 ± 8.3*
Adiposity variables		
BMI (kg/m^2)	24.4 ± 3.8	25.8 ± 3.2*
Weight (kg)	61.4 ± 10.5	77.6 ± 11.3*
Waist (cm)	79.4 ± 10.2	94.1 ± 8.7*
Total body fat (%)	28.9 ± 5.9	19.9 ± 5.1*
Fat mass (kg)	18.2 ± 6.7	15.9 ± 6.4*
Dietary variables		
Total calcium (log)	2.90 ± 0.3	2.81 ± 0.2*
Alcohol intake (g/d)	7.99 ± 11.6	14.3 ± 17.2*
Biochemical markers		
Adiponectin (μg/ml)	16.28 ± 7.1	11.1 ± 5.8*
BMD (g/cm^2)		
Midshaft radius	0.558 ± 0.105	0.764 ± 0.104*
Femoral neck	0.609 ± 0.104	0.737 ± 0.130*
Total hip	0.745 ± 0.131	0.932 ± 0.154*
Lumbar spine	0.861 ± 0.168	1.068 ± 0.199*
Categorical variables	(%)	%
Exercise ≥3 times/week	62.0	76.9*
Smoking		
Never	53.4	31.5*
Prior smoker	38.1	60.4*
Current smoker	8.6	8.1*
Estrogen use		
Never	39.2	—
Prior use	45.9	—
Current use	15.0	—
Thyroid medication use	24.4	6.1*
Thiazide use	5.7	9.3*
Type 2 diabetes	13.9	13.2

* $p < 0.05$.

correlated with BMI, weight, waist circumference, waist hip ratio, total percent body fat, and fat mass in both men and women ($p < 0.0001$). Among men and women, Pearson correlation coefficients were highest between weight and BMD at all sites (the femoral neck, hip, spine, and midshaft radius ($p < 0.0001$). Adiponectin correlated highest with waist girth among women and with weight among men ($p < 0.0001$, data not shown).

As shown in Table 2, age increased with higher adiponectin quartiles, whereas BMI, weight, waist circumference, waist:hip ratio, percent body fat, and fat mass decreased significantly with increasing adiponectin quartile in both men and women (trend $p < 0.001$). Age- and weight-adjusted BMD showed that mean BMD decreased significantly at all anatomical sites with increasing adiponectin quartile (trend $p < 0.02$; Table 2) in women and at all sites except the lumbar spine among men (trend $p = 0.147$). Age- and waist-adjusted BMD showed similar results, although midshaft radius BMD did not decline with increasing adiponectin quartiles in women (trend $p = 0.083$; data not shown). Among men, age- and waist-adjusted BMD also showed that mean BMD decreased with increasing adiponectin quartile at all sites, except at the lumbar spine (trend $p = 0.213$, data not shown).

Regression analysis showed that, among postmenopausal women, adiponectin was inversely associated with BMD at all sites (Table 3). This association persisted after adjusting for age and either weight or waist ($p < 0.01$). Adiponectin remained associated with BMD at all sites in multivariable analysis that adjusted for age, weight, calcium intake, type 2 diabetes, alcohol intake, and exercise. These observations persisted when weight was replaced by either BMI, waist girth, or fat mass in the multivariable models. Thyroid medications and estrogen use have been shown to alter BMD in prior studies. Although neither estrogen nor thyroid medication use were associated with BMD in univariate analysis, further adjustment for both thyroid medication and estrogen use in the multivariate model showed the association between adiponectin and BMD at the four anatomical sites persisted (data not shown). The majority (85%) of these women were not taking estrogen, and the observations from multivariable regression persisted when the analysis was stratified and limited to non–estrogen users or restricted to the 66 estrogen users.

Among men, adiponectin was inversely and independently associated with BMD at the femoral neck, total hip, and midshaft radius, but not at the lumbar spine after adjusting for age, weight, calcium intake, type 2 diabetes, exercise, and alcohol intake (Table 3). These observations persisted when weight was replaced by other anthropometric markers.

BMD was measured again 4 yr later, between 1992 and 1996, among 261 women and 284 men, and was used to assess bone loss. As shown in Table 4, among women, mean BMD decreased by as much as 2.26% at the femoral neck and 3.6% at the total hip after a 4-yr period and decreased minimally at the spine (by 0.1%). Annual bone loss was 0.59% at the femoral neck, 0.91% at the hip, and 0.04% at the lumbar spine among women. Whereas men experienced less bone loss, after a 4-yr interval, BMD declined by 1.5% (or by −0.40% annually) at the femoral neck, by 1.99% (or by 0.54% annually) at the hip, and actually increased by 0.74% at the spine.

Baseline adiponectin was inversely associated with BMD measurement at the femoral neck and total hip 8.6 yr later in women, at the total hip in men, but not at the lumbar spine in men or women (Table 5) in a fully adjusted model. Adiponectin was not associated with bone loss during the collective 4-yr period or with annual bone loss at any site in either men or women (Table 5).

Information on incident fractures during the 1992–1996 visit was available for 251 of the 261 women with serial BMD measures. Of these, 19.1% had a vertebral fracture; however, adiponectin was not associated with vertebral fractures ($\beta = 0.003$, $p = 0.48$) in multivariable regression analysis that adjusted for age, weight, calcium intake, type 2 diabetes, alcohol intake, and exercise. A total of 20 women (8%) had at least two or more thoracic or lumbar fractures; however, the absence of an association with adiponectin persisted in multivariable analysis ($\beta = 0.004$, $p = 0.10$). Fracture data were available for 277 of the 284 men with serial BMD measures. Of these, 21 (7.6%) had at least one vertebral fracture. Among men, adiponectin

TABLE 2. Anthropometric and BMD Characteristics by Adiponectin Quartiles in Older Women and Men, Rancho Bernardo, 1998–1992

	Adiponectin quartiles				
	I	*II*	*III*	*IV*	*p (trend)*
Women	*n* = 108	*n* = 109	*n* = 112	*n* = 114	
Adiponectin (μg/ml)	1.4−10.9	11–15.3	15.4–20.4	≥20.5	
Age (yr)	73.0	75.9	77.1	77.9	<0.001
BMI (kg/m^2)	25.8	25.1	23.9	22.9	<0.001
Weight (kg)	65.5	63.0	59.9	57.4	<0.001
Waist (cm)	84.4	81.8	77.8	74.4	<0.001
Waist:hip ratio	0.83	0.81	0.79	0.76	<0.001
Total body fat (%)	30.9	30.0	28.2	26.7	<0.001
Fat mass (kg)	20.7	19.2	17.5	15.8	<0.001
Age- and weight-adjusted BMD (g/cm^2)					
Midshaft radius	0.570	0.561	0.564	0.538	0.018
Femoral neck	0.625	0.611	0.612	0.589	0.008
Total hip	0.769	0.739	0.751	0.720	0.006
Lumbar spine	0.900	0.854	0.862	0.830	0.004
Men	*n* = 117	*n* = 121	*n* = 120	*n* = 126	
Adiponectin (μg/ml)	1.6–6.7	6.8–9.8	9.9–13.8	≥13.9	
Age (yr)	72.7	73.3	74.9	78.3	<0.001
BMI (kg/m^2)	26.3	26.5	25.7	24.8	<0.001
Weight (kg)	78.9	79.8	77.4	74.5	<0.001
Waist (cm)	95.6	96.7	93.6	90.8	<0.001
Waist:hip ratio	0.93	0.93	0.92	0.90	<0.001
Total body fat (%)	20.4	21.2	19.3	18.9	<0.001
Fat mass (kg)	16.4	17.4	15.3	14.4	<0.001
Age- and weight-adjusted BMD (g/cm^2)					
Midshaft radius	0.775	0.781	0.768	0.736	0.001
Femoral neck	0.760	0.755	0.721	0.713	0.001
Total hip	0.966	0.953	0.917	0.895	0.001
Lumbar spine	1.081	1.086	1.057	1.052	0.147

(adjusted OR: 1.13, 95% CIs: 1.08–1.23, $p = 0.009$) was independently associated with vertebral fractures after adjusting for age, weight, calcium intake, type 2 diabetes, alcohol intake, and exercise. Men with baseline adiponectin levels >10 μg/ml had almost a 3-fold higher risk of vertebral fractures (adjusted OR: 2.98, 95% CI: 1.08–8.26, $p = 0.035$) compared with men with lower adiponectin levels. Nontraumatic nonvertebral fractures occurred in 11.1% of women, where fractures at the hip (3.8%) or wrist (3.8%) were the most common. However, adiponectin was not associated with nonvertebral fractures among women in multivariable analysis. Only one man (0.3%) had a nonvertebral fracture (at the hip).

DISCUSSION

In this cohort of postmenopausal women, adiponectin concentration was independently and inversely associated with BMD at the femoral neck, total hip, lumbar spine, and midshaft radius after 4.4 yr and at the femoral neck and total hip almost 9 yr later. However, adiponectin was not associated with bone loss or fractures among women. Among older men, adiponectin was also independently and inversely associated with BMD at the femoral neck, total hip, and midshaft radius, but not at the lumbar spine after 4.4 yr, and only with total hip BMD after 8.6 yr. Adiponectin was not associated with bone loss but was independently associated with a higher risk of vertebral fractures among older men. These associations were independent of age, weight, calcium intake, type 2 diabetes, alcohol, and exercise and persisted with further adjustment for thyroid medication or estrogen use (among women).

Our results were similar to a large population-based cohort in the United Kingdom, where adiponectin was inversely associated with BMD at the total hip, femoral neck, spine, and total forearm among postmenopausal women,[4] and consistent with reports by Lenchik et al. and Jurimae and Jurimae, where adiponectin was inversely and significantly associated with BMD at the total hip, distal radius,[10] and lumbar spine.[7,10] However, our findings differed from those of Kontogianni et al.,[8] where adiponectin was not associated with BMD at the lumbar spine in postmenopausal women. The differences might be explained by the differences in our study populations; our cohort of Rancho Bernardo women was 22 yr older, and as such, had higher adiponectin levels and lower BMD.

Our observations among older men are consistent with those of Lenchik et al.[7] and Peng et al.,[12] where adiponectin was inversely associated with BMD at the total hip and ultradistal radius. However, we did not observe an inverse association between adiponectin and lumbar spine, as reported by Oh et al.[13]and Gonelli et al.[14] Bone loss was minimal at the lumbar spine compared with the femoral neck or total hip among men and women, consistent

TABLE 3. Linear Regression Models of Adiponectin on BMD After 4.4 yr in Older Women and Men

	Femoral neck		*Total hip*		*Lumbar spine*		*Midshaft Radius*	
Adiponectin	*β*	*p*	*β*	*p*	*β*	*p*	*β*	*p*
Women								
Unadjusted	−0.0044	<0.001	−0.0058	<0.001	−0.0063	<0.001	−0.0047	<0.001
Age and weight adjusted	−0.0020	0.002	−0.0024	0.002	−0.0035	0.002	−0.0020	0.001
Age and waist adjusted	−0.0022	0.001	−0.0026	0.001	−0.0037	0.001	−0.0017	0.008
Fully adjusted model*	−0.0018	0.007	−0.0021	0.009	−0.0031	0.008	−0.0017	0.011
Men								
Unadjusted	−0.0053	<0.001	−0.0083	<0.001	−0.0052	<0.001	−0.0058	<0.001
Age and weight adjusted	−0.0030	0.003	−0.0048	0.005	−0.0037	0.019	−0.0003	<0.001
Age and waist adjusted	−0.0032	0.002	−0.0051	<0.001	−0.0010	0.014	−0.0032	<0.001
Fully adjusted model*	−0.0023	0.030	−0.0040	<0.001	−0.0027	0.108	−0.0028	<0.001

* Adjusted for age, weight, calcium intake, type 2 diabetes, alcohol, and exercise.

TABLE 4. Temporal Changes in BMD in Older Men and Women, 1988–1992 vs. 1992–1996

		BMD (g/cm²)			
	n	*1988–1992*	*1992–1996*	*Percent change*	*Annual change*
Women (*n* = 261)					
Femoral neck	251	0.6173	0.6033	−2.264	−0.5937
Total hip	251	0.7615	0.7354	−3.581	−0.9136
Lumbar spine	260	0.8701	0.8706	−0.096	−0.0397
Men (*n* = 284)					
Femoral neck	277	0.7529	0.7412	−1.539	−0.4043
Total hip	275	0.9591	0.9401	−1.991	−0.5365
Lumbar spine	282	1.0713	1.0798	0.740	0.2333

TABLE 5. Linear Regression Models of Adiponectin on Bone Loss and BMD

	Femoral neck		*Total hip*		*Lumbar spine*	
Adiponectin	*β*	*p*	*β*	*p*	*β*	*p*
Women						
BMD after 8.6 yr	−0.0020	0.016	−0.0023	0.025	−0.0025	0.099
Bone loss after 4 yr	−0.1073	0.069	−0.0855	0.162	−0.0523	0.303
Annual bone loss	−0.0222	0.165	−0.0155	0.378	−0.0094	0.496
Men						
BMD after 8.6 yr	−0.0029	0.058	−0.0064	<0.001	−0.0019	0.437
Bone loss after 4 yr	−0.0072	0.922	−0.0866	0.151	−0.0549	0.351
Annual bone loss	−0.0016	0.941	−0.0224	0.225	−0.0179	0.287

Adjusted for age, weight, calcium intake, type 2 diabetes, alcohol, and exercise.

with prior reports among older adults; the lumbar spine is primarily trabecular bone, whereas age-related bone loss seems to occur predominantly in the cortical bone. Lumbar spine BMD actually increased in our cohort of older men, but is likely confounded by osteoarthritic calcification, because osteophyte formation in the vertebral column typically develops with aging.

Almost all of the above studies were based on cross-sectional analyses where adiponectin and BMD measures were obtained during the same clinical visit, whereas our longitudinal design included BMD measures 4.4 and 8.6 yr after adiponectin measures. Our prospective study design might account for some of the differences in our observations compared with prior studies.

During the 4-yr interval, women experienced more bone loss annually compared with men, and bone loss was most prominent at the hip for both groups. However, adiponectin was not associated with bone loss in either sex at the femoral neck, total hip, or spine. Prior studies have reported rapid bone loss usually occurs between 40 and 55 yr of age,[22,23] whereas our participants had a mean age of 75 yr at the initial BMD measurement, and 79 yr when bone loss was evaluated. Their advanced age may account for the minimal bone loss.

Sex differences were also observed in the prevalence of vertebral fractures and was elevated in women compared with men; however, higher adiponectin concentration was associated with an elevated risk of vertebral fractures in men but not in women. Our observations are consistent with those of Japanese men and women with type 2 diabetes but contradict the absence of an association with fractures observed among elderly Swedish men.[18,11]

Consistent with other studies, adiponectin levels were ~50% higher among women compared with men; it is unclear if the sex differences in adiponectin levels accounts for the observed sex differences in the association between adiponectin with fractures and BMD after almost 9 yr. Analyses combining men and women showed no significant interaction between adiponectin and sex for BMD at any of the anatomical sites. Prior studies have suggested that the relationship between adiponectin and bone mass may be influenced by sex hormones. A recent study showed a stronger inhibitory effect of adiponectin overexpression on bone mass and strength in female mice compared with males.[24]

Prior studies have shown that adiponectin and its receptors are expressed in bone-forming cells.[2] Adiponectin induces human osteoblast proliferation and differentiation

and seems to stimulate the RANKL pathway to inhibit osteoprotegrin production in human osteoblasts, thus indirectly increasing osteoclastogenesis.[3] Ealey et al.[24] found that adiponectin transgenic mice had elevated circulating adiponectin, but lower BMC and decreased peak load, from compression testing of femur and lumbar vertebrae, compared with control mice of similar weight. They suggested that adiponectin inhibits the acquisition of bone mass in murine models, resulting in decreased biomechanical strength properties, which may enhance susceptibility to fractures. Furthermore, adiponectin may be the metabolic link that accounts, in part, for the relationship between obesity, BMD, and reduced susceptibility to fractures.[24]

This study has potential limitations, including the use of a single adiponectin assay; however, prior studies have shown that adiponectin levels have minimal diurnal variation. Furthermore, single measurements have been shown to accurately reflect levels over a 1-yr period.[25–27] It is unclear whether the long duration of freezing may have affected adiponectin levels; however, our observed adiponectin concentrations were similar to published values for older men and women of comparable body size.[5,14,28] The absence of an association with bone loss and fractures in women may reflect small sample sizes for participants with serial visits or the need for a longer follow-up period. Finally, findings from this white cohort may not be generalizable to other ethnic groups given the observed ethnic differences in adiponectin concentration.[29,30]

Our observations of an inverse association between adiponectin concentration with BMD among older men and women supports prior observations that adiponectin plays an important role in bone metabolism. Future studies are needed to evaluate the absence of an association between adiponectin with fractures in women.

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