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ORIGINAL PAPER

Circulating adiponectin represents a biomarker of the association between adiposity and bone mineral density

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Abstract An association exists between adiposity, insulin resistance, and osteoporosis; however, the mechanism of this relationship remains enigmatic. We aimed to determine whether the insulin resistance index (HOMA-IR), serum adiponectin, or leptin levels are associated with bone mineral density (BMD). A cross-sectional, observational study was designed. Eighty-four postmenopausal ambulant women [52.5 (50.0–58.0) years; body mass index (BMI): 29.4 (25.9–33.8) kg/m^2] referred for osteoporosis screening were enrolled. Anthropometric measures, fasting serum adiponectin and leptin levels, and the HOMA-IR were determined. The relationships between these variables and lumbar, hip, and forearm BMD measured by dual-energy X-ray absorptiometry (DXA) were analyzed. Considering all 84 participants, the HOMA-IR index was 1.82 (1.17–2.86), serum adiponectin was 13.25 (10.49–16.88) μg/ml, and serum leptin was 19.26 (14.94–24.90) ng/ml. BMI, waist circumference, and leptin positively correlated with hip and lumbar BMD, whereas adiponectin negatively correlated. Multivariate analysis confirmed an inverse relation between serum adiponectin level and femoral neck and lumbar BMD measurements. In total hip and forearm areas, there was no independent association of adipocytokines with BMD measurements. Instead, waist circumference was independently associated with BMD measurements. In conclusion, adiponectin may represent a biomarker in the relationship between visceral fat mass and BMD. However, this association is probably confounded by the specific body composition parameters (i.e., waist circumference, BMI) in postmenopausal women.

Keywords Adiposity · HOMA-IR index · Leptin · Adiponectin · Bone mineral density

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Introduction

Obesity is strongly correlated with increased bone mineral density (BMD) and reduced osteoporotic fractures [1, 2]. This association is explained partly by the mechanical loading effects of increased body weight [3, 4]; however, factors other than mechanical loading have been postulated to play a role, since this association also exists in non-weight bearing areas [3, 5]. Both fat and lean masses are important predictors of bone mass [6, 7], and adipose tissue-associated hormonal factors, such as estrogen [8, 9], leptin [10, 11], and adiponectin [12, 13] are suggested to take part in the link between fat mass and BMD [7].

Much attention has been focused on adiponectin and leptin, which are proteins secreted by the adipocytes. Leptin strongly correlates with obesity. On the contrary, low adiponectin levels correlate with obesity, particularly with central adiposity [14, 15]. In vitro studies have shown that cultured visceral adipocytes express and secrete adiponectin more actively than subcutaneous adipocytes [16]. Clinical data demonstrated that posterior subcutaneous abdominal

adipose tissue mass is the fat compartment that best predicts plasma adiponectin concentrations [17].

Although some studies suggest an independent association between circulating leptin levels and BMD in weight-bearing bone areas [18, 19], subsequent studies have cast doubt on this hypothesis [20]. The relationship between adiponectin and BMD has not been studied to the same degree, but the results are more consistent [12, 21].

During perimenopause, the adipose tissue becomes redistributed from the areas typical of gynoidal obesity, i.e., the regions of the thighs, buttocks and hips, to the abdominal region, while the total amount of adipose tissue is unchanged [22]. This results in visceral (central) obesity with its associated insulin resistance in postmenopausal women [23]. On the other hand, during the perimenopause, both the quantity and quality of bone decline rapidly [24]. Therefore, studying a population of non-geriatric postmenopausal women; i.e., a population with a tendency to a natural visceral adiposity; might provide valuable information about adipocytokines as well as insulin resistance, and their association with BMD. We aimed to investigate the potential role of the insulin resistance index, and serum adiponectin and leptin levels as biomarkers of adiposity in association with BMD measurements. To investigate this hypothesis, we studied a population of postmenopausal women in order to exclude possible confounding factors.

Subjects and methods

Subjects

A cross-sectional, single-center, observational study was designed. The study was conducted between October 01, 2006 and March 31, 2007. All the non-geriatric postmenopausal women (<65 years) referred for osteoporosis screening from the outpatient clinics of endocrinology, rheumatology, and general internal medicine at Hacettepe University Hospital were potential candidates for participating in the study. The eligible candidates had to be in menopause for at least 6 months, and their condition had to be confirmed by elevated follicle stimulating hormone (>40 U/l). Patients with secondary causes of osteoporosis (rheumatoid arthritis, hyperthyroidism, hypothyroidism, hyperparathyroidism, hypoparathyroidism, malabsorption, osteomalacia, congestive heart failure, hepatic failure, chronic kidney disease, immobilization, malignancy, history of pathologic fracture, chronic alcoholism, and obesity secondary to endocrine disorder) were excluded. Another exclusion criterion was the use of medications known to influence BMD or adipocytokine levels (heparin, antiepileptic drugs, regular or frequent use of non-steroidal anti-inflammatory drugs, selective serotonin reuptake inhibitors, nitric oxide pathway activators, bisphosphonates, selective estrogen-modulating agents, calcitonin, strontium, calcium supplements or vitamin D, statins, fibrates, long-term glucocorticoid therapy, diuretics, estrogens, thiazolidinediones, beta blockers, and thyroid or anti-thyroid medications). The third exclusion criterion was the presence of any risk factor for osteoporotic fractures (family history of osteoporotic fractures, low weight [less than 57 kg], and smoking). Lastly, patients with diabetes mellitus were also excluded. Thus, a group of non-diabetic, non-geriatric postmenopausal women with no risk factor for osteoporosis, other than menopause, was enrolled in the study. All the subjects signed an informed consent form that was approved by the Medical Ethics Committee of Hacettepe University, Ankara, Turkey.

Study design

Complete blood count, blood biochemistry, thyroid stimulating hormone (TSH), parathyroid hormone (PTH), and 25-hydroxy vitamin D levels were analyzed to exclude any subclinical diseases that can cause secondary osteoporosis. All the subjects were also asked to collect 24-h urine sample in order to determine creatinine clearance and daily calcium excretion. In order to rule out type-2 diabetes mellitus, all the participants were subjected to a 75-g oral glucose tolerance test (OGTT), in accordance with American Diabetes Association (ADA) suggestions. After an overnight fast, fasting plasma glucose, and 2-h postload glucose were determined. On admission to the outpatient clinic, anthropometrical parameters were measured in all the participants by the same investigator. In addition, a venous blood sample was taken in the morning after overnight fasting. BMD of the hip, spine, and forearm was measured by dual energy X-ray absorptiometry (DXA) (DXA, Hologic 2000, Hologic, Inc, Waltham, Massachusetts).

Phenotypic variables

Height was measured with anthropometer type Harpander, according to a standard technique. Weight was recorded using a medical electronic scale (Seca, Bradford, England) while the participants were wearing light-weight street clothing and no shoes. Body mass index (BMI) was calculated by dividing body weight (in kilograms) by the square of height (in meters). The waist circumference was measured with a flexible tape placed on a horizontal plane around the abdomen at the level of the iliac crest. The waist circumference was taken as a measure of visceral adiposity. This measure is agreed to correlate well with central obesity, and there is a strong evidence linking waist circumference with cardiovascular disease and the other metabolic syndrome components [25]. The values for waist

circumference as a measure of central obesity are ethnic-specific. Although there is no reported epidemiological study documenting normal ranges in Turkish women, European recommendations (waist circumference ≥80 cm points out to central obesity) could be available for research purposes [25]. BMD was determined at the hip (total and femoral neck), posterior–anterior spine (lumbar 1–4 vertebrae, L1–L4), and forearm (total radius). Coefficients of variation (CVs) for measured BMD values were <2%.

Blood analysis

A 15-ml blood sample was obtained from the antecubital vein in the morning (0830–0900) after overnight fasting. The plasma was separated and frozen at −80°C for later analysis. Serum adiponectin levels were measured in duplicate by radioimmunoassay (Linco Research, St. Charles, Missouri, USA); this assay uses I-125-labeled murine adiponectin as a tracer and a multi-species adiponectin rabbit antiserum for detection of adiponectin in human plasma, calibrated against recombinant human adiponectin standards. The lowest level of human adiponectin that can be detected by this assay is 1 ng/ml when using a 100-µl sample. This assay has intra-assay precision of 3.59% and interassay CVs of 9.25% at a concentration of 1.5 µg/ml, 6.21% and 6.90% at a concentration of 3.0 µg/ml, and 1.78% and 9.25% at a concentration of 7.5 µg/ml. Leptin concentrations were also measured in duplicate by leptin-coated-tube immunoradiometric assay (IRMA, Diagnostic System Laboratories, Texas, USA). This assay has intra- and interassay CVs of less than 5%. The insulin concentrations were determined in duplicate by standard radioimmunoassay (Linco Laboratories, Missouri, USA). Plasma glucose, HDL, LDL, and triglyceride were studied in the clinical chemistry of the department and were measured using a YSI 2700 biochemistry analyzer (Yellow Springs Instruments, Yellow Springs, Ohio). The homeostasis model assessment (HOMA), which is based on plasma levels of fasting glucose and insulin, has been widely validated and applied to quantifying insulin resistance [26]; therefore, insulin resistance was calculated using the HOMA-IR index: fasting plasma insulin (µIU/ml) × fasting plasma glucose (mmol/l)/22.5 [27]. PTH levels were determined by a chemiluminescent immunoassay (Immulite 2000 intact PTH, The Diagnostics Product Corporation, Los Angeles, California). 25-OH vit D levels were analyzed using a High performance liquid chromatography (HPLC) method.

Statistical analysis

Continuous variables were expressed as median and interquartile ranges 25 and 75 values. Pearson's correlation coefficients were computed to explore the relationship between BMD measurements (kg/m^2) and other measured continuous variables (e.g., leptin, adiponectin, and insulin levels). In order to evaluate other potential associations of BMD measurements, factors that were significant in this correlation analysis at the $P = 0.15$ level, and factors that had a plausible relationship with BMD measurements were introduced in a multiple linear regression model backward selection method. The variance inflation factors (VIFs) were checked for the final models.

For estimation of the significance of the model, analysis of variance (ANOVA) was calculated (F and P values are given). The model was considered to be significant with 95% confidence when $P < 0.05$ ($\alpha = 0.05$). In order to check the model assumptions, an examination of the pattern of the residuals was performed. Residuals that scattered randomly proved that the model was adequate.

SPSS software v.12.0 (SPSS, Chicago, IL) was used for all the statistical calculations.

Using the NCSS/PASS 2,000 program, a sample size power calculation indicated that 84 participants were sufficient to perform the study with a power of 99% and an alpha error of 5%. The graphics demonstrating the associations between adiponectin, leptin, and BMD values were drawn using the STATISTICA 6.0 program.

Results

Demographic characteristics and baseline laboratory values of the subjects

Characteristics and the laboratory values of the 84 postmenopausal women who participated in the study are given in Tables 1 and 2, respectively. Although the study population was relatively homogeneous in terms of age, BMI and waist circumference varied widely. The study

Table 1 Characteristics of the study population

Characteristic	Median (IQR 25–75)
Age (years)	52.5 (50.0–58.0)
Age at menopause onset (years)	48.0 (45.0–50.0)
Menopause duration (years)	4.5 (2.0–10.0)
BMI (kg/m^2)	29.4 (25.9–33.8)
Waist circumference (cm)	89.0 (78.5–99.5)
Femoral neck BMD (g/cm^2)	0.705 (0.630–0.774)
Total hip BMD (g/cm^2)	0.851 (0.782–0.926)
Lumbar spine BMD (g/cm^2)	0.889 (0.812–0.969)
Total forearm BMD (g/cm^2)	0.523 (0.474–0.565)

IQR interquartile range, *BMI* body mass index, *BMD* bone mineral density

Table 2 Laboratory values of the study population

Characteristic	Median (IQR 25–75)	Reference values of the laboratory
Fasting glucose (mmol/l)	5.17 (4.77–5.43)	3.9–5.6
Insulin (μIU/ml)	7.95 (4.79–11.57)	2–22
HOMA-IR index	1.82 (1.17–2.86)	
Adiponectin (μg/ml)	13.25 (10.49–16.88)	
Leptin (ng/ml)	19.26 (14.94–24.90)	
LDL (mg/dl)	126 (104–148.0)	<130 mg/dl
HDL (mg/dl)	56 (43–71)	35–60 mg/dl
Triglyceride (mg/dl)	110.5 (92.5–147.0)	<200 mg/dl
PTH (pg/ml)	56.65 (40.45–68.78)	9.5–75 pg/ml
25-OH Vit D (μg/l)	17.10 (13.93–23.70)	10–60 μg/l
Calcium excretion (mg/day)	112.0 (137.0–207.0)	100–300 mg/day
Serum calcium (mg/dl)	9.8 (9.5–10.0)	8.6–10.2 mg/dl
Serum phosphate (mg/dl)	4.1 (3.7–4.4)	2.3–4.7 mg/dl

IQR interquartile range, *LDL* low-density lipoprotein, *HDL* high-density lipoprotein, *PTH* parathyroid hormone, *HOMA-IR* homeostasis model assessment-insulin resistance

population was composed of 15 (17.9%) normal weight (BMI < 25 kg/m^2), 29 (34.5%) overweight (BMI ≥ 25 kg/m^2), and 40 (47.6%) obese (BMI ≥ 30 kg/m^2) subjects. Sixty-five (77.4%) of the participants were with increased waist circumference ($\geq$80 cm). The impaired glucose metabolism frequency was 36.9% [total 31 subjects; 18 with impaired fasting glucose (5.6–6.9 mmol/l), eight with impaired glucose tolerance (glucose level of 7.8–11 mmol/l at the second hour following the 75-g oral glucose loading) and five with both impaired fasting glucose and impaired glucose tolerance]. Twenty-nine (34.5%) of the participants were with HDL value of <50 mg/dl, and 19 (22.6%) had triglyceride levels of >150 mg/dl.

Bone mineral density measurements

Bone mineral density measurements are given in Table 1. In the study population, in accordance with the definition of the World Health Organization (WHO) [28], the frequency of osteoporosis was 29.8% in the femoral neck, 4.8% in the total hip, 15.5% in lumbar 1–4, and 14.3% in the total forearm. In the same order, the frequency of osteopenia was 52.4%, 51.2%, 51.2%, and 42.2%, respectively. Others had normal BMD measurements.

Correlations of adiponectin, leptin, and the homa-ir index

Serum adiponectin levels inversely correlated with waist circumference, whereas serum leptin levels strongly and positively correlated with BMI, waist circumference, fasting plasma glucose, and the HOMA-IR index. The HOMA-IR index correlated with BMI. Although it was not statistically significant, inverse relationships between adiponectin levels and both BMI ($r = -0.192$, $P = 0.08$) and leptin levels ($r = -0.198$, $P = 0.07$) were observed (Table 3).

Table 3 Pearson's correlation coefficients of adipocytokines, and HOMA-IR with metabolic parameters and indirect measurements of obesity

Variable	Adiponectin	Leptin	HOMA-IR
Age (years)	0.005	0.174	0.045
Menopause duration (years)	−0.140	0.123	0.047
BMI (kg/m^2)	−0.192	0.730[c]	0.253[a]
Waist circumference (cm)	−0.262[a]	0.591[c]	0.200
Fasting serum glucose (mmol/l)	−0.172	0.279[b]	0.360[c]
LDL (mg/dl)	0.055	0.084	0.093
HDL (mg/dl)	0.280[b]	−0.076	−0.020
Triglyceride (mg/dl)	−0.253[a]	−0.006	0.095
Adiponectin	–	−0.198	−0.152
Leptin	−0.198	–	0.232[a]
HOMA-IR	−0.152	0.232[a]	–

LDL low-density lipoprotein, *HDL* high density lipoprotein, *PTH* parathyroid hormone, *HOMA-IR* homeostasis model assessment-insulin resistance, *BMI* body mass index

[a] $P < 0.05$, [b] $P < 0.01$, [c] $P < 0.001$

Univariate analysis

Pearson's correlation coefficients documented a strong correlation between BMD measurements of the femoral neck, total hip, and lumbar spine, and BMI, waist circumference, leptin levels, and adiponectin levels. On the other hand, total forearm BMD measurements were negatively correlated with age and menopause duration (Table 4). The associations between BMD measurements and levels of adipocytokines are shown in Fig. 1. The relationship of adiponectin to BMD values was inverse in the femoral neck, total hip, and lumbar skeletal regions, while there was not a significant correlation in the forearm (total radius).

Table 4 Pearson's correlation coefficients of bone mineral density measurements, with anthropometric and laboratory measurements of the subjects

Variable	Femoral neck	Total hip	L1–L4	Total forearm
Age (years)	−0.095	−0.091	−0.057	−0.482[b]
Menopause duration (years)	−0.090	−0.088	−0.150	−0.534[c]
BMI (kg/m^2)	0.455[c]	0.433[c]	0.354[c]	0.076
Waist circumference (cm)	0.467[c]	0.481[c]	0.373[c]	−0.105
Fasting serum glucose (mmol/l)	0.294[b]	0.270[a]	0.217	−0.160
Insulin (μIU/ml)	0.035	0.045	0.139	−0.183
HOMA-IR	0.088	0.090	0.177	−0.184
Adiponectin (μg/ml)	−0.267[a]	−0.233[a]	−0.250[a]	0.233
Leptin (ng/ml)	0.275[a]	0.317[b]	0.289[b]	−0.085
PTH (pg/ml)	−0.078	−0.072	−0.033	−0.314[a]
25-OH Vit D (μg/l)	−0.069	−0.155	−0.012	0.250
LDL (mg/dl)	0.183	0.054	0.001	−0.059
HDL (mg/dl)	−0.253[a]	−0.143	−0.212	−0.070
Triglyceride (mg/dl)	0.143	0.041	0.202	−0.110

LDL low-density lipoprotein, *HDL* high density lipoprotein, *PTH* parathyroid hormone, *HOMA-IR* homeostasis model assessment-insulin resistance, *BMI* body mass index

[a] $P < 0.05$, [b] $P < 0.01$, [c] $P < 0.001$

Multivariate analysis

Separate regression models were introduced and the most plausible one with the highest R^2 is shown in Table 5. In this model, BMD measurement was the dependent variable, and adiponectin, leptin, and PTH levels, BMD, waist circumference, and menopause duration (in years) were the independent variables. Femoral neck BMD measurement positively correlated with BMI and inversely correlated with adiponectin and PTH levels. Total hip BMD measurement positively correlated with waist circumference and inversely correlated with PTH. Lumbar BMD positively correlated with BMI and negatively correlated with serum adiponectin level. Total forearm BMD positively correlated with BMI, whereas menopause duration and waist circumference inversely correlated with total radius BMD measurement. The VIF for all variables was <5 (Table 5).

Discussion

This study demonstrated that serum adiponectin level was inversely associated with BMD measurements of the femoral neck and lumbar spine, and that these associations were independent of confounding factors of adiposity measurements. However, in total hip and total forearm areas, instead of adipocytokines, waist circumference which correlated well with circulating adiponectin level was independently associated with BMD measurements. Although leptin positively correlated with BMD measurements; this was not an independent association at any site. On the other hand, biologic insulin resistance, measured as the HOMA-IR index, did not correlate with BMD measurements.

In our cohort of Turkish postmenopausal females, more than one-third of the study participants were with impaired glucose metabolism and with low value (<50 mg/dl) of HDL-C, while about one-fourth of them had triglyceride levels of >150 mg/dl. Moreover, about 80% of the subjects were either overweight or obese, and with increased waist circumference. The number of insulin receptors decreases with biological age, and this is often observed in perimenopausal women with visceral obesity. The decreased number of insulin receptors results in hyperinsulinemia and insulin resistance [23]. Adiponectin levels are reduced in association with insulin resistance. Visceral adiposity is an independent negative predictor of adiponectin [29]. Although our study population had a tendency toward visceral obesity, there was also a tendency for low BMD. For example, 82.2% of the subjects were either osteoporotic or osteopenic for femoral neck area. We think that this is a good cohort for testing our hypothesis.

A negative association between serum adiponectin level and BMD is known and has been demonstrated in many populations [12, 13, 30]. The association between leptin and BMD also has been well studied [31]. The largest data set comes from the Third United States National Health and Nutrition Examination Survey (1988–1994) in which 5,815 adults that underwent DXA of the proximal femur and

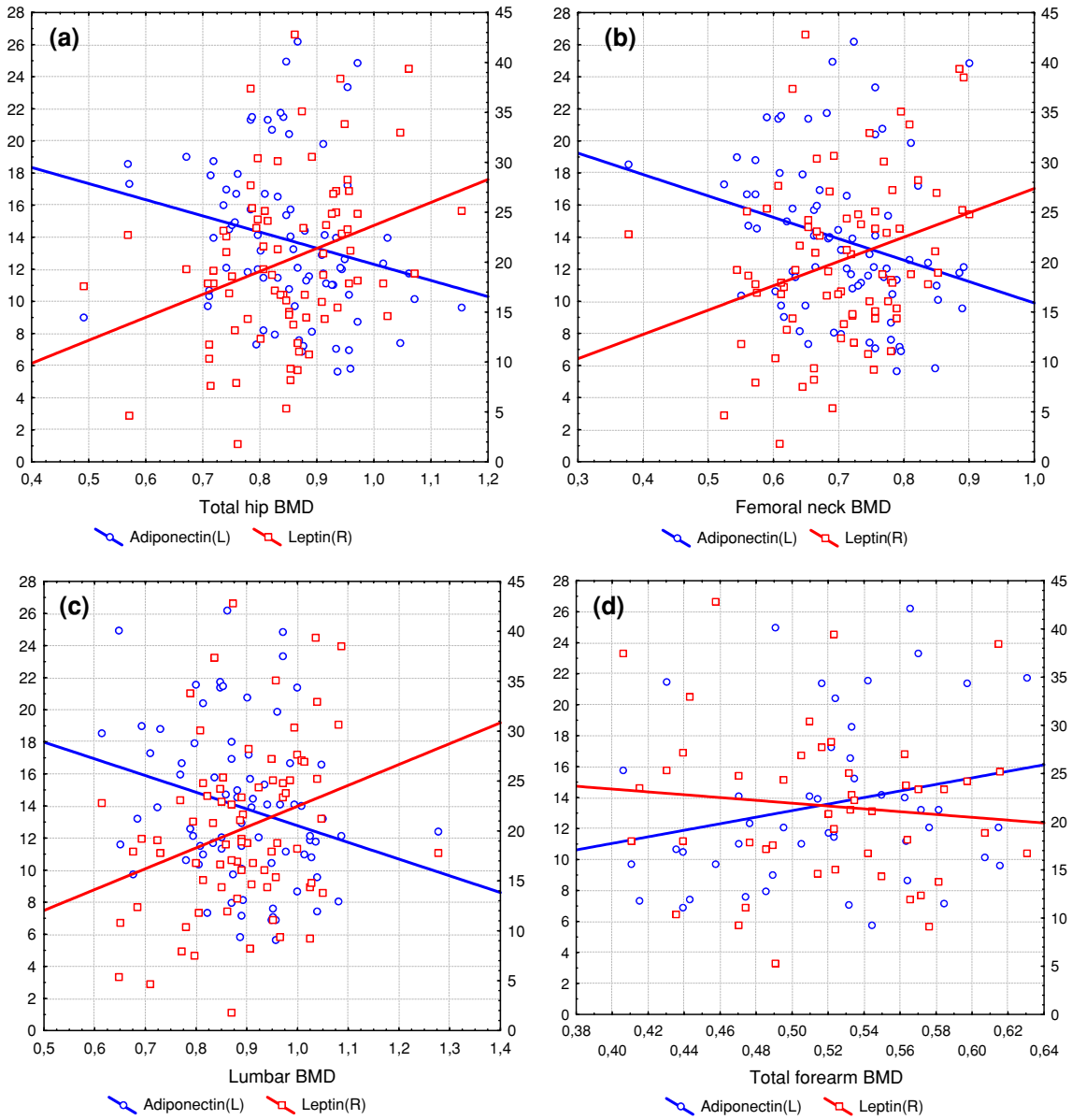

Fig. 1 The correlations between circulating adiponectin (dark line—round shape) and leptin (light line—square shape), and **a** total hip BMD, **b** femoral neck BMD, **c** lumbar BMD, **d** total forearm BMD. Note the positive correlation of leptin, and negative correlation of adiponectin in total hip, femoral neck, and lumbar areas. There is not a significant correlation between leptin either adiponectin and forearm BMD. (BMD: Bone mineral density)

measurement of fasting serum leptin were included [20]. In univariate analysis, proximal femur BMD increased with increasing leptin concentration in men, premenopausal women, and postmenopausal women; however, after adjusting for confounding factors, there was no association between leptin and BMD in premenopausal or postmenopausal women according to multivariate analysis. Our results are in accordance with these observations. On the other hand, studies with contradictory results also exist. For example, in one study conducted with postmenopausal women with normal average weight (BMI = 24 kg/m^2) [18], or in the other with a heterogeneous women population aged between 20 and 91 years [19], an association between leptin, and hip and lumbar spine BMD measurements were reported. Nevertheless, adiponectin was not studied in these two studies.

Taken as a whole, these observations as well as our findings suggest that adiponectin may be a mediator considering the effects of visceral fat on BMD, particularly in the postmenopausal period. Although leptin may be related to BMD in univariate analysis, there is a lack of this association in a model including both leptin and adiponectin. This might lead to the conclusion that adiponectin, instead of leptin, mediates the association between fat and

Table 5 Multivariate regression analysis (BMD as the dependent variable, and PTH, adiponectin, leptin, the HOMA-IR index, body mass index, waist circumference, and menopause duration as the independent variables)

Variable	β-coefficient	P	VIF
Femoral neck BMD ($R^2 = 0.277$; $F = 13.20$; $P < 0.001$)			
PTH	−0.234	0.028	1.14
Adiponectin	−0.211	0.041	1.10
Body mass index	0.511	<0.001	1.18
Total hip BMD ($R^2 = 0.302$; $F = 14.90$, $P < 0.001$)			
PTH	−0.271	0.014	1.14
Waist circumference	0.581	<0.001	1.14
Lumbar spine BMD ($R^2 = 0.207$; $F = 5.82$; $P < 0.001$)			
PTH	−0.187	0.097	1.09
Adiponectin	−0.205	0.042	1.14
Body mass index	0.468	0.004	1.14
Menopause duration	−0.223	0.062	1.05
Total forearm BMD ($R^2 = 0.258$; $F = 7.49$, $P < 0.001$)			
PTH	−0.211	0.093	1.13
Body mass index	0.493	0.005	2.09
Waist circumference	−0.343	0.042	2.18
Menopause duration	−0.521	<0.001	1.02

BMD bone mineral density, *PTH* parathyroid hormone, *VIF* variance inflation factor

BMD. This might be, at least in part, explained by different biochemical structures of these two adipocytokines. Leptin is a polypeptide containing 167 amino acids and circulates partially bound to plasma proteins [32]. Due to its biochemical configuration, it possibly cannot adhere to tissue easily. For example, it cannot cross blood–brain barrier, and enters the central nervous system via capillary junctions in the median eminence and by saturable receptor transport in the coroid plexus [33]. Adiponectin is a monomer protein of 247 amino acids; it accounts for 0.01% of total plasma protein, and circulates as a trimer, hexamer, or high molecular weight isoform [32]. It is proposed that adiponectin may adhere to the tissue, since it is detected in non-adipose tissues such as bone marrow and bone-forming cells [34].

In this study, independent association of adiponectin with areal BMD of femoral neck and lumbar vertebrae was found. However, this association was not observed in total hip and total forearm areas. Instead, waist circumference was associated with BMD of these two areas. Prior studies, with a few exceptions [12, 13], have not examined the association of forearm BMD with adiponectin levels. These two studies have found negative correlation between circulating adiponectin levels and forearm BMD measurements. Our study consisted of a postmenopausal group, while the aforementioned studies either investigated a wide age range (18–81 years old) women or a mixed women-and-men study population. The different study populations may partially explain the inconsistent findings of our results, since in postmenopausal women, no independent association between weight gain and forearm BMD was found [35]. Moreover, during perimenopausal period, in general, radius is metabolically less active compared to trabecular bone. Another possible explanation is that the influence of plasma adiponectin on BMD values is mediated or confounded by the specific body composition parameters (i.e., waist circumference, BMI, fat mass) in healthy postmenopausal women [36]. Adiponectin is both a marker of fat mass, and has a range of biological actions. It is likely that some of the relationship between adiponectin and BMD is due to this relationship with fat mass.

In our cohort, no correlation was observed between HOMA-IR index and BMD. To our knowledge, the English literature reveals only one study which directly evaluates the association between insulin resistance and BMD. This recently published article also reported no correlation of HOMA with BMD measurements, in multivariate analysis [36]. The results of the existing few studies investigating the association between insulin levels and BMD measurements have yielded contradictory results [10, 37]. Our results suggest that biological insulin resistance expressed as HOMA index is not associated with BMD measurements in postmenopausal women.

Some limitations of our study should be noted. First, the study population included only a special group of postmenopausal women; therefore, these results cannot be generalized to other populations, such as younger or elderly women, men, adolescents, or diabetic people. However, the design of the study eliminated other confounding factors affecting bone and adipocytokines metabolism, and this is an advantage. Second, although our study was designed to detect the relationships in the parameters analyzed, a population-based study with different ethnic groups would be more desirable. Third, the study population is relatively small, and the correlations modest. The study population is also quite selected, which has the potential to introduce a range of biases. In addition, the study population is reasonably close to the menopause. Factors that influence BMD will have been in operation over the duration of the participants' life. Given the changes in hormonal milieu that occur with the menopause, the measures of hormones at this time point do not necessarily reflect the factors that have influenced BMD over the long term. Therefore, we need to be careful in overinterpreting the data presented in this study. Fourth, we were unable to directly measure estradiol levels. Estrogens are the potent predictor of bone mass. Activity of androstendione conversion in fat tissue changes with age and duration of postmenopausal period. Visceral obesity increases the bioavailability of estradiol [38], and estradiol may be one of the mediators that

interacts both with fat tissue and bone. Therefore, it would have been better to include estradiol in the multivariate analysis as an important hormonal derivate of fat tissue in postmenopausal women. However, the study population is relatively homogenous in terms of age and all of the study participants were in menopause for at least 6 months. In addition, the menopause was confirmed in all of them with elevated FSH values (>40 U/l), which suggests the very low levels of circulating estradiol. Another limitation is that we used indirect measures of body composition (waist circumference, BMI, weight) to investigate the association between adiposity and body composition, mediated by adipose tissue associated hormonal factors. Although waist circumference is a measure agreed to correlate well with central obesity, direct measures such as fat mass and fat-free mass would have been interesting, if they could have been studied. Finally, taking into account the cross-sectional nature of the study, no inferences of causality could be made.

Conclusions

Adiponectin seems to play a role in the relationship between visceral fat mass and BMD. However, the association between adiponectin level and BMD is evident in weight-bearing areas (femoral neck and lumbar spine) with an inverse correlation, whereas there is not a clear association in metabolically less active cortical bone. This may suggest that the influence of circulating adiponectin on BMD values is probably confounded by the specific body composition parameters (i.e., waist circumference, BMI, fat mass) in postmenopausal women. Further prospective investigations in different population groups are needed to clarify these associations. Then, investigations to document the role of adiponectin manipulation in the treatment of osteoporosis in association with obesity and metabolic syndrome can be pursued.

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