Influence of Adipokines and Ghrelin on Bone Mineral Density and Fracture Risk: A Systematic Review and Meta-Analysis

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Context: Adipokines (leptin, adiponectin, resistin, visfatin) and ghrelin may be implicated in bone metabolism.

Objective: The aim was to perform an overview of the influence of blood levels of adipokines or ghrelin on bone mineral density (BMD), osteoporotic status, and fracture risk in healthy men and women.

Data Sources: We reviewed Medline, Embase, and Cochrane databases up to March 2010 and abstracts of international meetings from 2008 to 2009.

Study Selection: Fifty-nine studies meeting the inclusion criteria (healthy men or women evaluated for both BMD or fracture risk and at least one adipokine and/or ghrelin levels) were analyzed in the systematic review of the 931 references found in the electronic databases.

Data Extraction: We used a predefined extraction sheet.

Data Synthesis: We performed meta-analyses using the method of the inverse of the variance estimated pooled correlations between adipokines/ghrelin and BMD. Inverse correlations between adiponectin levels and BMD were highlighted (pooled r from −0.14 to −0.4). Leptin is positively associated to BMD, especially in postmenopausal women (pooled r from 0.18 to 0.33). High levels of leptin were reported to be predictive of low risk of fractures, whereas high levels of adiponectin may be predictive of high risk of vertebral fractures in men only. No discriminative capacity of osteoporotic status was reported. We found no convincing data to support an association between resistin, visfatin, or ghrelin and BMD.

Conclusion: Adiponectin is the most relevant adipokine negatively associated with BMD, independent of gender and menopausal status. Inconsistent associations between adipokines and BMD are probably confounded by body composition, in particular fat mass parameters. **(*J Clin Endocrinol Metab* 96: 2703–2713, 2011)**

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Abbreviations: BMD, Bone mineral density; BMI, body mass index; CI, confidence interval; OR, odds ratio.

Adipose tissue may regulate bone metabolism and be involved in osteoporosis pathophysiology. Epidemiological data have established positive relationships between fat mass and bone mineral density (BMD). Obesity is protective against osteoporosis, whereas low body weight a major risk factor for fractures (1, 2). Fractures are inversely related to body mass index (BMI) in both men and women (3). BMI has a marked effect on 10-yr fracture risk probability evaluated in the FRAX algorithm (4). However, the effect of fat mass on bone remains unclear (5). Although abundant data suggest that adipose tissue protects the skeleton, recent studies provide evidence for an inverse relationship between bone and fat (6, 7). Moreover, a high prevalence (27.7%) of obesity was reported in postmenopausal women presenting a low-trauma fracture (8). Experimental data also support the links between adipose tissue and osteoporosis. An increase in bone marrow adiposity has been reported in osteoporotic patients (9). Adipocytes and osteoblasts share the same mesenchymal stem cell precursors and common hormonal and cytokine regulation factors (10, 11).

Multiple mechanisms seem associated with these links between bone and fat. In addition to the mechanical load supported by fat mass on the skeleton, adipose tissue is considered an endocrine organ. Besides estrogen synthesis in postmenopausal women, adipocytes produce adipokines: leptin, adiponectin, resistin, and visfatin (12, 13). Leptin, produced in bone marrow adipocytes and osteoblastic cells, regulates appetite and weight, osteoblast proliferation and differentiation *in vitro* (14–16), and osteoclasts (14, 17, 18). Its receptor is expressed in osteoblasts (14, 19). Leptin also affects bone through its actions on the central nervous system, in particular the hypothalamus (20, 21). Adiponectin, exclusively expressed by adipocytes, circulates in much higher concentrations than other adipocyte products. It is inversely related to visceral fat mass and BMI (22) and regulates metabolism and inflammatory pathways (23). It appears to exert a negative effect on bone mass (24, 25). Adiponectin receptors have been identified on both osteoblasts and osteoclasts (26, 27). Resistin has rarely been found to be expressed by adipocytes (28), but is expressed by bone marrow and peripheral mononuclear cells (29). It acts as an inflammatory cytokine in the atherogenic process. Visfatin is highly expressed in visceral fat and up-regulated in obesity and type 2 diabetes mellitus (30). Thus, in addition to the regulation of food intake and energy metabolism, adipokines seem to be implicated in the control of bone biology and remodeling.

Furthermore, ghrelin is a GH secretagogue synthesized predominantly in epithelial cells of the stomach. It has been reported to increase fat mass by stimulating appetite and reducing fat use. Serum ghrelin levels are inversely correlated with weight and fat mass in postmenopausal women (31). Because GH secretagogue receptors have been identified on osteoblastic bone cells, ghrelin may play a role in bone metabolism and mediate feeding effects on fat and bone (32, 33).

Thus, levels of adipokines and ghrelin may influence bone metabolism. The clinical relevance of plasma levels of adipokines or ghrelin, as a marker of bone health in healthy patients, remains unclear. The aim of this review was to obtain an overview of the influence of plasma levels of adipokines or ghrelin on BMD and fracture risk in healthy men and women.

Materials and Methods

Search strategy

The search was performed in electronic databases (Medline, Embase, Cochrane) and abstracts of international meetings held from 2008 to 2009 (the American Society for Bone and Mineral Research and The Endocrine Society). The electronic database search was last updated on March 30, 2010, and was conducted using the following keyword combinations: ((“Adipokines”{tw} OR “leptin”{tw} OR “adiponectin”{tw} OR “resistin”{tw} OR “visfatin”{tw} OR “Ghrelin”{tw}) AND (“Bone Density”{tw} OR “Osteoporosis”{tw} OR “Absorptiometry”{tw} OR “Fractures”{tw})). Articles were selected on the basis of the abstracts, before examining the full text. Articles not in English, German, French, or Spanish were excluded. The reviewers were not blinded to the journal, authors, or institution of the publications because this has been shown to be unnecessary (34).

Inclusion criteria

Articles were eligible if they reported the results of original transversal or longitudinal studies on the association of adipokines and/or ghrelin levels and BMD and/or fractures. Only studies including healthy men or women who were evaluated for both BMD or fracture risk and at least one serum adipokine and/or ghrelin levels assessment were selected. We excluded studies with patients aged less than 18 yr, patients with comorbidities or obesity, patients receiving metabolism medications (calcium and vitamin D excluded), and studies that focused on patients with high physical activities. The analysis focused on the BMD of lumbar spine, hip (femoral neck and total hip), distal and midshaft radius, and total body, measured by dual x-ray absorptiometry. BMD had to be expressed as a continuous variable in grams per square centimeter or T-score (*i.e.* SD compared with the mean value of BMD in a population of young adult women) or a categorical variable, such as osteoporosis defined by a T-score of −2.5 or below, osteopenia defined by a T-score between −2.5 and −1, and normal BMD defined by a T-score above −1. Vertebral and nonvertebral fractures were assessed on self-report or by spine radiographs.

Data extraction

Data extraction was performed by one reviewer (E.B.) on the full texts using a predefined extraction sheet available from the

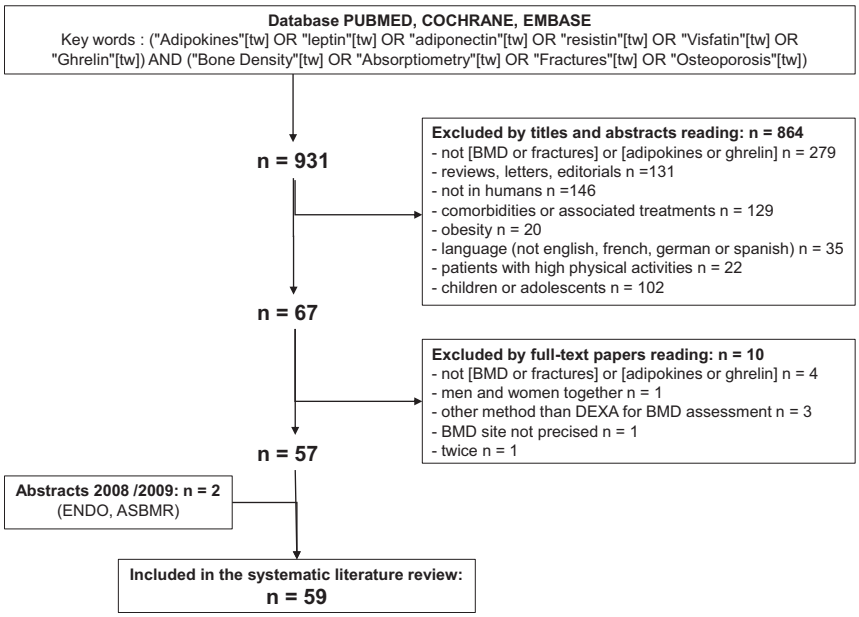

FIG. 1. Systematic literature search selection process (flow-chart).

authors. These data included patients' characteristics (mean age, gender, ethnicity), osteoporotic status, BMI, total percentage fat, total fat of participants, number of patients, adipokine or ghrelin assessment (dosage conditions, methods, units), BMD assessment (site, method, units), and fractures (site and method of diagnosis: self-report or radiographs). Mean data with measures of dispersion and correlations between adipokines/ghrelin levels and BMD with adjustment factors were collected (if available).

Quality assessment of studies

To assess the quality of publication, we examined patient inclusion criteria as well as the quality of the reporting. Articles were excluded if definitions of outcomes (BMD, osteoporotic status, or fractures) were unclear.

Statistical analysis

Data were recorded for each study as means ± SD or percentages. To accommodate differences in the ways in which adipokine levels were measured and reported in various studies, the absolute adipokine levels were converted into a common unit by calculating weighted-effect sizes. These sizes were derived by dividing the mean difference of adipokine levels in osteoporotic and nonosteoporotic groups of each study by its SD (standardized mean difference).

We performed two types of meta-analyses. For each, heterogeneity was tested with the Cochran Q statistic and measured with the I^2 statistics. A random-effect model was used to take into account within-study and between-study variance.

First, a meta-analysis of unadjusted correlations between adipokine or ghrelin levels and BMD was performed using the method of the inverse of the variance (a Fisher's z-transformation was applied on the correlation coefficients), according to gender and menopausal status, as it was planned *a priori*. The results were expressed in correlation coefficient r with 95% confidence intervals (CI) and *P* value (if <0.05, indicated statistical significance). This statistical analysis was performed with the software S-Plus 8.0 for Windows (Insightful Corp., Seattle, WA).

Second, when data were available, we performed a meta-analysis pooling the mean differences of hormone levels according to osteoporotic status. RevMan 5.0.18 software (Nordic Cochrane Centre, Copenhagen, Denmark) was used to calculate the pooled standardized mean difference for continuous outcomes (method of the inverse of the variance).

To examine the possibility of publication bias, we conducted funnel plots and quantified the bias using the Egger's test of the intercept. We also estimated the adjusted pooled correlations after imputing missing studies using Duval and Tweedie's trim and fill procedure. These analyses were performed in meta-analyses including at least 10 studies, using the Comprehensive Meta Analysis 2 computer program (CMA Biostat, Englewood, NJ).

Results

Selection and characteristics of included studies

The review process is summarized in Fig. 1. Using our search strategy, we found 931 citations, of which 864 were excluded by reading titles or abstracts. We excluded studies assessing patients with comorbidities: metabolic diseases (diabetes, obesity, gastric bypass, chronic renal disease), anorexia nervosa, inflammatory rheumatism (rheumatoid arthritis, spondyloarthropathy), endocrine diseases (Cushing's disease, acromegaly), and chronic obstructive pulmonary disease; animal studies; and studies focusing on athletic patients. Thus, 67 articles were full-text reviewed, and 57 of these met the inclusion criteria and had data available for at least one of the outcomes (35–91). Two recent abstracts from an international congress were also included (92, 93). Most of the studies were cross-sectional studies; only three provided longitudinal data (72, 74, 77), and eight compared adipokine levels according to osteoporosis status (41, 53, 66, 68, 73, 78, 90, 92). Pooling of studies for correlation analyses resulted in a combined sample size of 10,451 patients (1867 premenopausal women, 4213 postmenopausal women, and 4371 men) across 38 studies. The mean age of participants was 37 yr (range, 29.4–45.2) in premenopausal women, 65.3 yr (range, 49.9–77.7) in postmenopausal women, and 49.1 yr (range, 18.9–71.9) in men (data available for eight of 10, 26 of 29, and 13 of 16 studies, respectively). Ethnicity of participants was not reported in a majority of studies; 13 studies concerned Asiatic patients. Only seven

TABLE 1. Pooled correlations between adipokine/ghrelin and BMD according to gender and menopausal status using random-effect meta-analyses (35–70)

		Men							Premenopausal women		
Adipokine/ghrelin	BMD sites	Studies (Refs.)	No. of patients	*P* Cochran	I^2	Pooled r	95% CI	*P* value	Studies (Refs.)	No. of patients	*P* Cochran
Leptin	Lumbar spine	35–41	2005	<0.001	82	0.03	−0.1, 0.15	0.69	40, 42–48	968	0.45
	Total hip	39–41, 59	1030	0.17	40	0.14	0.06, 0.22	0.001	40, 42, 47	435	0.75
	Femoral neck	35–38, 41, 59	1885	<0.001	81	0.11	−0.01, 0.24	0.08	35, 45–48	631	0.09
	Total body	37, 39, 59, 62	1709	0.15	43	0.1	0.02, 0.17	0.01	42, 44–46, 48	635	0.86
Adiponectin	Lumbar spine	38, 39, 65–67	982	0.62	0	−0.18	−0.24, −0.12	<0.001	35, 46	298	0.11
	Total hip	39, 66, 67	810	0.08	61	−0.15	−0.26, −0.03	0.01	NA	NA	NA
	Femoral neck	38, 65, 66	309	0.15	47	−0.15	−0.3, 0.01	0.07	43, 46	298	0.32
	Total body	39, 66, 67	810	<0.001	96	−0.4	−0.66, −0.05	0.03	46	98	NA
Resistin	Lumbar spine	38, 39	312	0.1	64	−0.11	−0.31, 0.1	0.3	NA	NA	NA
Ghrelin	Lumbar spine	38, 66, 69, 70	821	0.56	0	−0.05	−0.12, 0.02	0.19	NA	NA	NA
	Total hip	66, 69, 70	741	0.006	80	0.05	−0.15, 0.25	0.6	NA	NA	NA
	Femoral neck	38, 66, 70	742	0.001	85	0.09	−0.14, 0.31	0.45	NA	NA	NA
	Total body	66, 69	216	0.34	0	0.13	−0.01, 0.26	0.06	NA	NA	NA

NA, Not applicable.

studies reported fracture data according to adipokine or ghrelin levels.

Influence of adipokine/ghrelin levels on BMD and osteoporotic status

Correlations between adipokine/ghrelin levels and BMD

We performed pooled correlations analyses on all studies according to gender and menopausal status (Table 1).

Leptin appeared positively correlated to BMD at all sites and with the higher pooled correlations in postmenopausal women (pooled r from 0.18 to 0.33). In premenopausal women, lower pooled correlations were highlighted only at lumbar spine (r = 0.08), total hip (r = 0.3), and total body BMD (r = 0.22). In men, correlations between leptin and BMD were found only at total hip (r = 0.14) and total body (r = 0.1) (35–64, 74, 87).

Consistent and inverse correlations were found between circulating adiponectin levels and BMD at lumbar spine, total hip, and total body in postmenopausal women and men (pooled r from −0.15 to −0.4) without differences between genders. In premenopausal women, data are much fewer, and negative correlations were identified only at the femoral neck (r = −0.14) and total body (r = −0.25) (35, 38, 39, 43, 46, 51, 52, 61, 65–68, 81).

No significant correlation was found between resistin or ghrelin and BMD at all sites (38, 39, 51, 66, 69, 70). One study reports the lack of correlations between visfatin and BMD, except for total hip BMD (r = 0.175; $P < 0.05$) (39).

Because adjusting adipokines for body weight or BMI commonly reverses the direction of the association found between adipokines and bone density (12), in Table 2 we reported data for both nonadjusted and adjusted correlations for fat mass, BMI, or body weight. Interestingly, the negative correlations between adiponectin and BMD remained significant even after adjusting for fat parameters, whereas the correlations between leptin and BMD rarely did.

We examined the year of publication as a potential source of heterogeneity in the three meta-analyses, including at least 10 studies (correlations between leptin and lumbar spine, femoral neck, and total body BMD in postmenopausal women). The year of publication was not found as a source of heterogeneity ($P = 0.33$, 1, and 0.58, respectively). We also examined the possibility of publication bias in these studies (Supplemental Fig. 1, published on The Endocrine Society's Journals Online web site at http://jcem.endojournals.org). We found no publication bias for the correlation between leptin and femoral neck or total body BMD. Concerning the correlation between leptin and lumbar spine BMD, although the Egger's test did not show any evidence for bias ($P = 0.16$), the funnel plot, first without and then with the imputed studies, suggests that smaller studies with lower correlation coefficients are missing, and this is confirmed after the imputation of missing studies (adjusted pooled correlation, 0.1; 95% CI, −0.02 to +0.22).

Association between adipokine/ghrelin levels and BMD

The association between adipokine or ghrelin levels and BMD values was evaluated in 28 reports using regression models (Supplemental Tables 1A and 1B) (35, 37–39, 42, 46, 48, 49, 51, 52, 58–62, 65, 67, 69, 70, 72, 74, 76, 78, 82, 87–89, 91).

In univariate analyses, a negative association between adiponectin and BMD was found in men and women, even after adjustment for specific body composition parameters, including BMI, and lifestyle habits (67, 72, 76). In multivariate analyses, five studies showed a negative association between adiponectin and lumbar spine BMD:

TABLE 1. Continued

Premenopausal women				Postmenopausal women							P value between groups
I^2	Pooled r	95% CI	P value	Studies (Refs.)	No. of patients	P Cochran	I^2	Pooled r	95% CI	P value	
0	0.08	0.1, 0.14	0.02	35, 36, 40, 44, 47–58	1678	<0.001	85	0.18	0.06, 0.3	0.005	0.19
0	0.3	0.21, 0.38	<0.001	40, 47, 55, 59–61	673	0.49	0	0.33	0.26, 0.4	<0.001	0.001
50	0.07	−0.05, 0.18	0.25	35, 36, 47–49, 51, 54–56, 58, 59, 61	1315	0.02	50	0.21	0.13, 0.28	<0.001	0.12
0	0.22	0.14, 0.29	<0.001	44, 48–52, 56, 58, 59, 61, 63, 64	993	<0.001	70	0.3	0.19, 0.41	<0.001	0.005
62	−0.11	−0.22, 0.01	0.07	51, 52, 67, 68	688	0.58	0	−0.17	−0.24, −0.1	<0.001	0.86
NA	NA	NA	NA	61, 67, 68	598	0.19	40	−0.22	−0.35, −0.09	0.001	0.4
0	−0.14	−0.25, −0.03	0.02	51, 61	124	0.04	76	−0.24	−0.58, 0.16	0.23	0.88
NA	−0.25	NA	<0.05	51, 52, 61, 67	619	0.02	70	−0.25	−0.42, −0.05	0.01	0.71
NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
NA	NA	NA	NA	51, 69, 70	581	0.19	39	−0.07	−0.21, 0.06	0.29	0.72
NA	NA	NA	NA	69, 70	493	0.7	0	−0.04	−0.12, 0.05	0.44	0.43
NA	NA	NA	NA	51, 70	540	0.22	35	−0.07	−0.2, 0.06	0.28	0.24
NA	NA	NA	NA	51, 69	129	0.42	0	−0.05	−0.04, 0.17	0.55	0.1

two studies in postmenopausal women ($\beta = -0.103$, $P = 0.048$; and $\beta = -0.005$, $P = 0.04$) (51, 89), two in premenopausal women ($\beta = -0.01$, $P = 0.043$; and $\beta = -0.283$, $P = 0.005$) (46, 52), and one in men ($\beta = -0.163$; $P = 0.025$) (39). For femoral neck BMD, one study found such negative association in postmenopausal women ($\beta = -0.445$; $P = 0.007$) (61), and one in premenopausal women ($\beta = -0.01$; $P = 0.002$) (46). Nevertheless, five other studies did not find such associations in lumbar spine or femoral neck in men (65), premenopausal women (78, 89), and postmenopausal women (51).

Results were much more discordant for leptin; in univariate analyses, we found positive and very weak associations with BMD in postmenopausal women, but no longer evident after adjustment for fat mass parameters in half of the reports (67, 88). In multivariable regression models, leptin was rarely identified as an independent predictor of BMD (two of five reports at lumbar spine, one of three at total hip), explaining in positive reports no more than 1 to 7% of the variability of BMD (49, 91). Moreover, when BMI or fat mass parameters were included in the model, most of the time leptin did not explain BMD variability any longer.

Concerning ghrelin, only two studies were available, and they did not show any association with BMD (51, 69), except in one report, and then only for total hip BMD in young women ($\beta = -0.31$; $P = 0.033$) (69).

Thus, the influence of plasma leptin, adiponectin, and ghrelin levels on BMD values would be very weak and mediated or confounded by the specific body composition parameters.

Adipokine/ghrelin levels and BMD variations

The ability of adipokine level to predict BMD variations was evaluated in three cohort studies (72, 74, 77).

Adiponectin was not associated with bone loss after 4 yr of follow-up at all bone sites in a cohort of 264 men and 261 postmenopausal women (72). In men, leptin would be associated with changes in forearm BMD at 4 yr, but not in total hip BMD (74). In another cohort of 35 postmenopausal women, significant associations with BMD variations at 12 months were reported for leptin (with femoral neck and total body BMD) and adiponectin (with lumbar spine BMD). In different predictive models with baseline variables explaining the variance in changes in BMD at 12 months, fat mass and leptin ($\beta = 0.001$) explained 10.2% of the decrease in femoral neck BMD, whereas the trunk fat/leg fat ratio and adiponectin ($\beta = -0.002$) explained 13.1% of the decrease in lumbar spine BMD ($P < 0.05$) (77).

Comparison of adipokine levels in patients according to osteoporosis status

Eight papers reported adipokine or ghrelin levels in patients according to their osteoporotic status (41, 53, 66, 68, 73, 78, 90, 92) (Table 3). No significant difference in leptin, adiponectin, or ghrelin levels was observed between osteoporotic and nonosteoporotic patients, except in one report. Pooled data for leptin in women showed a nonsignificant trend for lower levels of leptin in osteoporotic women (standardized mean difference osteoporotic *vs.* controls, −0.76; 95% CI, −1.68 to 0.16; $I^2 = 91\%$; $P = 0.11$; Supplemental Fig. 2).

Furthermore, another approach using the receiver operating characteristic analysis showed no capability of leptin to differentiate women with normal and decreased BMD (area under curve, 0.527 ± 0.029; 95% CI, 0.470–0.585) (79). To our knowledge, such analyses were not performed for other adipokines or ghrelin.

Adipokine/ghrelin levels and fracture risk

Leptin level and prevalent fractures

The association between leptin and prevalent vertebral fractures diagnosed on lateral spine radiograph was re-

TABLE 2. Studies reporting both nonadjusted and adjusted correlations for fat-related parameters (36, 38–40, 59, 61, 62, 65, 66)

	BMD site	First author, year (Ref.)	No. of patients	Without adjustment		Adjusted for fat-related parameters	
				r	*P* value	r	*P* value
Men							
Leptin	Lumbar spine	Thomas, 2001 (40)	343	−0.12	<0.05	−0.09[a]	NS
		Oh, 2005 (38)	80	−0.08	0.489	−0.24[b]	0.039
		Peng, 2008 (39)	232	0.13	NS	0.01[c]	NS
		Dennison, 2004 (36)	219	0.27	<0.001	0.10[d]	NS
	Total hip	Thomas, 2001 (40)	343	0.05	NS	−0.15[a]	<0.01
		Peng, 2008 (39)	232	0.13	NS	0.05[c]	NS
		Zoico, 2003 (59)	92	0.23	<0.05	0.13[a]	0.236
	Femoral neck	Zoico, 2003 (59)	92	0.25	<0.05	0.13[a]	0.21
		Dennison, 2004 (36)	219	0.30	<0.001	0.04[d]	NS
	Total body	Peng, 2008 (39)	232	−0.01	NS	−0.05[c]	NS
		Morberg, 2003 (62)	317	0.17	<0.05	−0.19[g]	<0.01
		Zoico, 2003 (59)	92	0.19	0.064	0.25[a]	<0.05
Adiponectin	Total hip	Peng, 2008 (39)	232	−0.26	<0.05	−0.14[c]	<0.05
	Femoral neck	Basurto, 2009 (65)	92	−0.24	<0.001	−0.09[e]	NS
	Total body	Peng, 2008 (39)	232	−0.21	<0.05	−0.15[c]	<0.05
Resistin	Lumbar spine	Oh, 2005 (38)	80	−0.24	0.05	−0.31[b]	0.011
		Peng, 2008 (39)	232	−0.02	NS	0.01[c]	NS
	Total hip	Peng, 2008 (39)	232	−0.08	NS	−0.04[c]	NS
	Total body	Peng, 2008 (39)	232	−0.05	NS	−0.09[c]	NS
Visfatin	Lumbar spine	Peng, 2008 (39)	232	0.08	NS	0.05[c]	NS
	Total hip	Peng, 2008 (39)	232	0.18	<0.05	0.14[c]	NS
	Total body	Peng, 2008 (39)	232	0.02	NS	0.01[c]	NS
Ghrelin	Femoral neck	Gonnelli, 2008 (66)	137	0.25	<0.01	0.20[f]	<0.05
Premenopausal women							
Leptin	Lumbar spine	Thomas, 2001 (40)	137	0.05	NS	−0.01[a]	NS
	Total hip	Thomas, 2001 (40)	137	0.31	<0.001	−0.04[a]	NS
Postmenopausal women							
Leptin	Lumbar spine	Thomas, 2001 (40)	165	0.25	<0.01	0.08[a]	NS
		Dennison, 2004 (36)	172	0.36	<0.001	0.14[d]	NS
	Total hip	Zoico, 2003 (59)	171	0.34	<0.001	0.15[a]	<0.05
		Thomas, 2001 (40)	165	0.44	<0.001	−0.01[a]	NS
	Femoral neck	Zoico, 2003 (59)	171	0.33	<0.001	0.16[a]	<0.05
		Dennison, 2004 (36)	172	0.35	<0.001	0.10[d]	NS
	Total body	Zoico, 2003 (59)	171	0.33	<0.001	0.30[a]	<0.001
Adiponectin	Total hip	Zoico, 2008 (61)	36	−0.46	<0.001	−0.36[a]	<0.05
	Femoral neck	Zoico, 2008 (61)	36	−0.45	<0.001	−0.36[a]	<0.05
	Total body	Zoico, 2008 (61)	36	−0.52	<0.001	−0.42[a]	<0.001

NS, Not significant.

Adjustment for fat-related parameters: [a] Fat mass; [b] age, BMI; [c] age, fat mass; [d] age, alcohol, tobacco, activities, calcium intake, osteoarthritis, BMI; [e] BMI; [f] age, BMI, calcium intake; [g] body weight.

ported in one study of 139 postmenopausal women (35.3% of the patients presenting vertebral fractures) (58). Plasma leptin levels, but not the percentage of fat mass, were significantly lower in women with vertebral fractures than without ($P < 0.05$). In a multiple logistic regression analysis, leptin contributed to the presence of vertebral fracture with an odds ratio (OR) of 0.642 (95% CI, 0.429–0.960; $P = 0.031$).

According to nonvertebral fractures, three observational studies in patients with hip fractures were available, but they lack a comparative group to assess the involvement of adipokines in peripheral fractures (60, 68, 86). However, one of these did not suggest any influence of serum leptin on hip fractures in 250 geriatric patients with current hip fracture: 40% of them were in the normal range, 40% had a decreased leptin level, and 20% had a higher leptin level (86). No data were available for ghrelin and other adipokines.

Leptin, adiponectin, and incident fractures

The association of adipokines and incident fractures was analyzed in three cohort studies (67, 72, 84).

In a follow-up of 8087 person-years reporting 28 vertebral and five nontraumatic hip fractures, a trend for an

TABLE 3. Results of comparisons between adipokines or ghrelin levels and osteoporotic status in eight studies (41, 53, 66, 68, 73, 78, 90, 92)

			Osteoporosis		Osteopenia		Normal BMD		
First author, year (Ref.)	Population	Adipokine or Ghrelin	No. of patients	Mean ± SD	No. of patients	Mean ± SD	No. of patients	Mean ± SD	*P* value
Odabasi, 2000 (53)	Postmenopausal women	Leptin	50	18.7 ± 1.78	NA	NA	30	22.35 ± 2.2	0.103
Yilmazi, 2005 (90)	Postmenopausal women	Leptin	36	17.03 ± 8.4	24	16 ± 7.84	30	16.55 ± 8.22	0.15
Breuil, 2008 (92)	Postmenopausal women	Leptin	20	3.71 ± 1.42	NA	NA	16	6.2 ± 2.7	0.002
Canhao, 2008 (73)	Women >50 yr	Leptin	24	24.76 ± 15.06	NA	NA	40	26.56 ± 14.57	NS
Kontogianni, 2004 (78)	Pre and postmenopausal women	Leptin	NA	NA	NA	NA	NA	NA	NS
Papadopoulou, 2004 (41)	Men	Leptin	44	12.7 ± 11.2	NA	NA	319	14.1 ± 12	NS
Canhao, 2008 (73)	Men	Leptin	10	9.72 ± 7.63	NA	NA	19	9.48 ± 7.13	NS
Kontogianni, 2004 (78)	Pre and postmenopausal women	Adiponectin	NA	NA	NA	NA	NA	NA	NS
Ozkurt, 2009 (68)	Postmenopausal women with hip fracture	Adiponectin	37	6.99 ± 0.5	NA	NA	68	6.33 ± 0.51	NS
Gonnelli, 2008 (66)	Men	Adiponectin	25	10.1 ± 5.3	65	10 ± 3.5	47	11.3 ± 3.8	NS
Gonnelli, 2008 (66)	Men	Ghrelin	25	757.5 ± 92.4	65	829 ± 113	47	853.6 ± 136.8	NS

NA, Not applicable; NS, not significant ($P > 0.05$).

inverse association between leptin level and fracture was observed, with a relative risk of 0.60 (95% CI, 0.34–1.06) per 1-SD increase of ln-transformed leptin in an age/gender-adjusted model ($P = 0.08$) and 0.64 (95% CI, 0.41–0.99) in a multivariate model adjusting for body weight and a variety of demographic and lifestyle variables ($P = 0.04$). High serum levels of leptin appeared predictive of a lower risk for nontraumatic fractures, independent of body weight (84).

In a 15-yr follow-up cohort of 507 men (age, 71 ± 0.6 yr), 314 patients (61.9%) were treated for fractures (67). No association between adiponectin levels and fractures was highlighted. The hazard ratio for fracture per 1 SD of adiponectin was 0.97 (95% CI, 0.86–1.10, after adjustment for age, weight, height, BMI, waist-to-hip ratio at enrollment, smoking status, physical activity, diabetes mellitus, and insulin resistance).

Finally, the Rancho Bernado Study also evaluated the association between adiponectin (blood sample in 1984–1987) and fractures (incident fractures during 1992–1996) (72). Vertebral fractures were assessed on lateral vertebral radiographs using the qualitative and semiquantitative grading scheme for vertebral deformity (Genant). Results differed according to gender. In men (n = 277), 21 vertebral fractures (7.6%) were reported. Adiponectin level was independently but weakly associated with vertebral fractures after adjusting for age, weight, calcium intake, type 2 diabetes, alcohol intake, and exercise (adjusted OR, 1.13; 95% CI, 1.08–1.23; $P = 0.009$). The association was higher in men with baseline adiponectin levels greater than 10 mg/ml compared with men with lower adiponectin levels (adjusted OR, 2.98; 95% CI, 1.08–8.26; $P = 0.035$). Nonvertebral fractures were not assessed. In postmenopausal women (n = 251), vertebral fractures were reported in 48 (19.1%) patients and nontraumatic, nonvertebral fractures in 28 (11.1%) patients. Adiponectin was not associated with vertebral ($\beta = 0.003$; $P = 0.48$) and nonvertebral fractures in linear multivariable regression analyses adjusted for age, weight, calcium intake, type 2 diabetes, alcohol intake, and exercise. The lack of association persisted if considering patients with two or more thoracic or lumbar fractures ($\beta = 0.004$; $P = 0.10$).

Discussion

We performed a systematic review of the literature, including 59 studies assessing the influence of adipokines or ghrelin on BMD and nontraumatic fractures in healthy men and women. Adiponectin would be the most relevant adipokine negatively associated to BMD and independently of gender, menopausal status, and fat mass parameters. Leptin appears positively correlated to BMD, in particular in postmenopausal women, but probably confounded with fat mass parameters. Adipokines and ghrelin fail to discriminate osteoporosis status. Concerning fracture risk, high levels of leptin would be predictive of low risk of fractures, unlike adiponectin, except maybe in men where high levels of adiponectin may be predictive of high risk of vertebral fractures. Data are lacking according to the value of adiponectin to predict unknown vertebral fractures. No convincing data support an association between resistin, visfatin, or ghrelin and BMD or fractures, although few data are available.

We found high heterogeneity between studies and no consistent difference in the levels of adipokines between nonosteoporotic and osteoporotic patients. To limit variability due to comorbidities or treatments, we voluntarily chose to focus our review on healthy patients, with exclusion of studies with patients receiving bone medication, excluding calcium, vitamin D, and hormone replacement

therapy. We found differences between gender and menopausal status only for the correlations between leptin and total hip and body BMD (Table 1). Identifying other variability and confounding factors was a crucial issue. The pooled data came from observational studies conducted in a variety of populations and ethnic groups. Ethnicity has not been assessable. Adjusting adipokine levels for body composition parameters or age would have been a sensible way of removing some confounding factors or some of the noise from the analyses (12, 94). However, we were unable to adjust the pooled correlations or to conduct subgroup analyses for age or BMI because of the lack of individual data in the original publications that reported age and BMI as mean ± SD. Indeed, as was previously discussed, results for the average patient cannot be applied to all patients (95).

Although fat mass may be a confounding factor, adipokines seem to have a proper role of in bone metabolism. These effects are probably both direct and indirect, in particular for leptin through its signaling in the brain (21). Plasma leptin levels, but not fat mass percentage, were significantly lower in women with vertebral fractures (58). Similarly, high levels of leptin appeared predictive of a lower risk for nontraumatic fractures, independent of body weight (84). Many other variables, such as estrogen levels, proinflammatory cytokines (96), and preanalytic variability of adipokine dosage (94, 97, 98) may interfere with adipokines and bone, but these data were not reported in the studies.

The relationship between fat and bone is complex. Many diseases with changes in fat metabolism, such as diabetes mellitus, Cushing's syndrome, and anorexia nervosa, have a severe impact on skeletal health. Despite having low visceral and sc fat depots, women with anorexia nervosa have elevated marrow fat mass, which is inversely associated with BMD. An inverse association between leptin and marrow fat was reported in these patients who exhibit premature conversion of hematopoietic to fat cells in the marrow of the peripheral skeleton (99, 100). Bone marrow adiposity is thus probably a main determinant of the links between adipocytes and bone metabolism. Plasma adipokine levels may imprecisely reflect the levels of adipokines in bone marrow fluids that constitute the bone microenvironment. Pino *et al.* (101) recently reported significant lower levels of leptin but also adiponectin in bone marrow supernatant fluids of osteoporotic patients compared with nonosteoporotic patients, with concentration different enough to discriminate the osteoporotic status. However, peripheral blood levels were not assessed in this study, and it is not possible to determine whether blood levels of adipokines are representative of the bone marrow fluid levels. In this hypothesis, higher levels of adiponectin would have been expected, according to the negative association between peripheral adiponectin and BMD. Reciprocal relationships between bone marrow adiposity and bone formation are currently under investigation for understanding osteoporosis pathophysiology. The increase in bone marrow adiposity of osteoporotic patients appears to be less an epiphenomenon in response to a decline in bone formation than one of the causes that alters bone metabolism itself (9). Thus, the influence of adipose tissue on bone may be related to mechanical but also metabolic effects that may differ according to fat distribution and the type of adipocytes (white or brown adipose tissue). Circulating adipokine levels, easily assessable, likely reflect the overall adipose tissue metabolism.

In conclusion, evidence from our meta-analyses shows that adipokines influence bone metabolism differently. Adiponectin displays the highest negative association with BMD, independent of fat mass or BMI. The relevance of serum adipokine levels to reflect bone marrow microenvironment and adiposity and its impact on osteoporosis outcome still need to be investigated in longitudinal studies.

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