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Adiponectin and bone mass density: The InCHIANTI study

Nicola Napoli^{a,b}, Claudio Pedone^{c,*}, Paolo Pozzilli^a, Fulvio Lauretani^d, Luigi Ferrucci^e, and Raffaele Antonelli Incalzi^{c,f}

^aDivision of Endocrinology and Diabetes, Università Campus Bio-Medico di Roma, Italy

^bDivision of Bone and Mineral Diseases, Washington University in St Louis, St Louis, MO, USA

^cCentro per la Salute dell'Anziano, Area di Geriatria Università Campus Bio-Medico di Roma, Italy

^dTuscany Region Health Agency, Florence, Italy

^eLongitudinal Studies Section, Clinical Research Branch, National Institute on Aging, National Institutes of Health, Baltimore, MD, USA

^fFondazione San Raffaele - Cittadella della Carità, Taranto, Italy

Abstract

Introduction—Adiponectin serum concentration has been reported to be inversely correlated with bone mineral density (BMD) in humans. The data on this issue, however, are biased by small study sample size and lack of controlling for body composition.

Methods—We used data from the third follow-up of the InCHIANTI study, which included measurements of BMD using quantitative CT of the tibia and of body composition using bioimpedance. Serum adiponectin was measured using radioimmunoassay. We excluded participants with diabetes, hyperthyroidism, using hormone replacement or corticosteroid therapy. We evaluated the correlation of adiponectin with total, trabecular, and cortical BMD using Pearson's coefficient, and linear regression models to estimate the association between adiponectin and BMD controlling for potential confounders (age, body mass index, alcohol intake, fat mass, smoking).

Results—Our sample was made up of 320 men (mean age: 67 years, SD: 15.8, range: 29–97 years) and 271 postmenopausal women (mean age: 76 years, SD: 8.2, range: 42–97 years). In men, serum adiponectin was not independently associated with BMD. In women, after correction for potential confounders, adiponectin was associated with total ($\beta = -0.626$, $P < 0.001$), trabecular ($\beta = -0.696$, $P < 0.001$), and cortical ($\beta = -1.076$, $P = 0.001$) BMD.

Conclusion—Our results show that adiponectin is inversely associated with bone mass in women. Further studies are needed to confirm these findings prospectively and then to clarify the explanatory mechanisms.

Keywords

Adiponectin; Bone mass; pQCT

*Corresponding author: Centro per la Salute dell'Anziano, Area di Geriatria, Università Campus Biomedico, Via Alvaro del Portillo, 21 00128 Roma, Italy. c.pedone@unicampus.it (C. Pedone).

Introduction

Obesity is associated with higher bone mineral density (BMD), most likely because of increased mechanical loading [1,2]; other factors that may mediate the association between obesity and BMD include hyperinsulinism and enhanced aromatization of androgen to estrogen [2,3]. However, in the last years, the discovery of adipocyte-dependent hormonal factors has opened new research perspectives on alternative mechanisms of interaction between bone and fat [2,4,5]. Leptin, in particular, has been the object of very elegant animal studies showing that leptin-deficient mice have higher BMD: leptin has a direct effect on osteoblasts and bone marrow stromal cells but is also part of a very complex mechanism that regulates bone mass through a hypothalamic relay, using two neural mediators, the sympathetic tone and CART, both acting on the osteoblasts [6,7]. Discovered a few years ago, adiponectin is another adipokine almost exclusively secreted by adipocytes that has potent functions in several tissues [8,9]. In fact, its receptors (AdipoR1 and AdipoR2) are expressed in muscle, liver, pancreas, and bone [10,11]. Experimental data show that adiponectin knockout mice are insulin-resistant with a gene-dose effect and that this condition was reverted by adiponectin administration [12].

In humans, adiponectin is negatively associated to obesity, and low levels are described in patients affected by diabetes or myocardial infarction [13–15]. Adiponectin is structurally similar to tumor necrosis factor alpha (TNF- α) and receptor activator for nuclear factor κ ligand (RANKL), a potent regulators of osteoclastogenesis [16]. In vitro studies on the effect of adiponectin on bone cells yielded contradictory results. The majority of available data, however, suggest that adiponectin has an anabolic effect on osteoblasts and inhibits osteoclastogenesis, likely independently of RANKL and osteoprotegerin [12,17]. These actions would be expected to result in a positive effect of adiponectin on bone mass in vivo. In contrast, animal studies have found that adiponectin knockout (AdKO) mice have increased both bone mass and trabecular number and lower bone fragility [12]. Accordingly, several clinical studies have shown a negative correlation between adiponectin and BMD in both males and females independently of confounding factors [18–22]. However, these studies were generally small and did not take into account body composition. Being adiponectin serum levels inversely related to fat mass (FM) [18,23], the relationship between adiponectin and BMD should be evaluated taking into account body weight and proportion of fat mass. Finally, to our knowledge, most of these studies used DEXA measurement, which does not allow to distinguish trabecular from cortical compartment and, then, site-specific effects, if any, of adiponectin. The only study estimating BMD using quantitative computed tomography (QCT), a method able to differentiate trabecular from cortical bone, was limited by the small sample size (mostly affected by diabetes) and by the wide range of age [18]. Moreover, only vertebral measurement was reported, without information on the cortical compartment [18].

We conducted this study to investigate the relationship between serum adiponectin concentration and the BMD of the trabecular and cortical compartment in a large cohort of Italian healthy subjects. Women and men were analyzed separately to evaluate the selective effect of adiponectin on BMD for each sex.

Methods

Study population

We used data from the InCHIANTI study, which was designed to investigate the factors contributing to the decline of mobility in older persons [24]. The participants in the study were randomly selected from the populations of two town areas in the Chianti region: Greve in Chianti and Bagno a Ripoli. The Italian National Institute of Research and Care on Aging ethical committee ratified the study protocol. Participants received an extensive description of the study and signed an informed participation consent that included permission to conduct analyses on the biological specimens collected and stored. For those unable to fully consent because of cognitive or physical problems, surrogate consent was also obtained from a close relative. The eligible participants were interviewed at their homes by trained study researchers using a structured questionnaire aimed at investigating their health status, their physical and cognitive performance, and other factors possibly related to loss of independence in late life. The interview was followed by a physical examination at the study clinic. Participants were followed up with evaluations at 3 and 6 years. Data on body composition were collected only at the 6 years of assessment, and therefore, we used only data coming from this evaluation.

At 6 years, 797 participants were reassessed and had BMD and adiponectin measurements. We excluded women who had not entered menopause ($n = 64$), participants with diabetes ($n = 81$) and hyperthyroidism ($n = 9$), and those on hormone replacement ($n = 52$) or corticosteroid ($n = 17$) therapy. The final sample size was 591.

Estimation of bone mass density

Bone mass density was estimated using peripheral quantitative computed tomography (pQCT) using a XCT 2000 device (Stratec Medizin-technik, Pforzheim, Germany). The precision error of the XCT2000 is below 1% for volumetric trabecular and cortical density and between 1% and 3% for composite geometry parameters [25]. The tibiotalar joint was identified using a pQCT longitudinal scout and used as an anatomic marker for the identification of measurements sites. Standard (2.5 mm thickness) transverse scans were obtained at 4% and 38% of tibial length to measure trabecular and cortical bone density, respectively. The cross-sectional images obtained by pQCT were analyzed using BonAlyse software (BonAlyse Oy, Jyväskylä, Finland) that automatically identifies cortical and trabecular bone and assesses its density. Areas with density values $>710 \text{ mg/cm}^3$ were considered as cortical bone [26], whereas areas with density between 180 and 710 mg/cm^3 were considered as trabecular bone. Both technical and statistical procedures intended to minimize the partial volume effect, i.e., the measurement as cortical bone of voxels including both cortical bone and surrounding tissues, were previously described in detail [27,28]. Tibial volumetric density measured using high-resolution pQCT has been shown to be associated with number and severity of vertebral fractures [29].

Biochemistry

Serum adiponectin concentration was measured using RIA assay (Human Adiponectin RIA Kit; LINCO Research, Inc, MO, USA), and the measure unit was expressed in nanograms

per milliliter. For adiponectin, the MDC was 1 ng/ml in a 100- μ l sample, and the intra-assay CV was less than 7% and interassay CV was less than 10%. All cytokine assays were done in duplicate and were repeated if the second measure was $>10\%$ or $<10\%$ compared to the first. The average of the two measures was used in the analyses.

Estimation of body composition

Body composition was estimated using an impedance plethysmograph that emitted 800- μ A, 50-kHz alternating currents (BIA-101, RJL/Akern System, Clinton Township, MI). Standard electrodes were placed on the right hand and foot, and measurements were made with the patients in the supine position following the tetrapolar method.

Analytic approach

All analyses were performed separately in men and women. We used descriptive statistics to evaluate the main characteristics of participants, and Pearson's correlation coefficients to evaluate the relationship of adiponectin with anthropometric variables (weight, BMI, fat mass) and BMD. We used linear regression models to quantify the association between adiponectin and BMD of different bone compartments adjusting for potential confounders: age, BMI, fat mass, smoking, and alcohol intake. Fat mass was expressed as percent of total body weight, while smoking exposure was quantified using pack-years calculated as no. cigarettes smoked per day/20 $\times$ number of year of smoking. Alcohol intake was evaluated using the EPIC questionnaire [30] implemented in the InCHIANTI protocol.

All analyses were performed using SAS V9 for Windows (SAS Inc., Cary, NC).

Results

Our sample was made up of 320 men (mean age: 67 years, SD: 15.8, range: 29–97 years) and 271 women (mean age: 76 years, SD: 8.2, range: 42–97 years). The main characteristics of participants are reported in Table 1. As expected, women had more fat mass compared to men, less smoking exposure, lower alcohol intake, and higher serum levels of adiponectin.

In men, adiponectin was negatively correlated with weight and BMI (Table 2), as well as with total (Pearson's $r = -0.118$, $P = 0.035$) and cortical (Pearson's $r = -0.171$, $P = 0.002$) BMD (Fig. 1). No correlation was found with FM. After correction for age, smoking, BMI, alcohol, and FM, serum adiponectin was not associated with BMD. Of the potential risk factors, age was negatively associated with BMD regardless of the compartment taken into account, smoking was negatively associated with total and trabecular BMD, BMI was positively associated with total BMD only, and FM was negatively associated with cortical BMD (Table 3).

In women, adiponectin was negatively correlated with all anthropometric measures (Table 2), with total BMD (Pearson's $r = -0.316$, $P < 0.001$) and with both trabecular ($r = -0.281$, $P < 0.001$) and cortical ($r = -0.272$, $P < 0.001$) BMD (Fig. 1). After correction for potential confounders, adiponectin was still associated with total ($\beta = -0.626$, $P < 0.001$), trabecular ($\beta = -0.696$, $P < 0.001$), and cortical ($\beta = -1.076$, $P = 0.001$) BMD. Of the other potential risk factors, age was negatively associated with BMD regardless of the compartment taken into

account and BMI was positively associated with total and trabecular BMD. Smoking and FM were not found to be associated with BMD (Table 3).

To investigate whether the different relationship between adiponectin and BMD in men and women was actually due to a gender effect, we evaluated in a linear regression model including all the participants and having the same set of explanatory variables the interaction between gender and adiponectin. For both trabecular and cortical BMD, the interaction term was statistically significant ($\beta = -0.971$, $P < 0.001$ for trabecular BMD and $\beta = -1.041$, $P < 0.001$ for cortical BMD).

Discussion

To our knowledge, this is the first large study investigating the effects of adiponectin on trabecular and cortical compartments of bone separately. We have found that adiponectin levels are inversely associated with total, cortical, and trabecular BMD in women, after correction for recognized determinants of BMD as well as for FM, an important inverse correlate of serum adiponectin. In men, we found no association between adiponectin and BMD.

Clinical results relative to the effect of adiponectin on BMD have been conflicting: some studies have reported an inverse association between serum adiponectin and BMD [18,21], while others failed to detect any relationship in middle-aged men or women [31–34]. Among the most robust studies, that by Richards on 1735 nondiabetic women found a strong negative correlation with BMD in postmenopausal women but not in the premenopausal ones, demonstrating the importance of menopausal status [19]. Similar results were recently described by Michaëlsson et al. [21] in a large cohort of elderly subjects and by Araneta et al. [35]. An inverse, but not statistically significant relationship was described also from Gonnelli, who studied elderly men coming from the same area of Italy of our study [34]. Thus, our data obtained by pQCT confirm previous results in postmenopausal women. Furthermore, the exclusion of important confounders such as diabetes mellitus and use of hormone replacement therapy and corticosteroids guarantees for the reliability of present results. Likely more important, the inverse correlation between adiponectin and BMD in women persists even after taking into account the positive effect of FM per se, as a primary component of body weight. Finally, pQCT allowed us to avoid the influence of body and bone size on measurements, another limitation of DEXA. Indeed, DEXA cannot differentiate cortical from trabecular bone, and DEXA measurement can be altered by bone size (it is averaged on a two-dimensional projection of the bone) and by the composition of the soft tissue surrounding the bone [36].

Our findings might have practical implications. Indeed, the density of cortical bone largely outweighs that of trabecular bone as a determinant of the elastic modulus of bone, the physical dimension which explains most of the resistance to mechanical stress and risk of fracture [37,38]. Even in the vertebrae, which are primarily made by trabecular bone, the cortical bone bears up to 75% of the axial load [39]. Accordingly, identifying factors that affect cortical bone metabolism might pave the way to new therapeutic interventions. Thus, the finding that adiponectin seems to exert comparable effects on cortical and trabecular

bone not merely expands our knowledge of how adipose tissue regulates bone turn over, rather it points at the modulation of the adiponectin receptor as a potential mechanism for improving the elastic modulus. The metabolic implications of such a perspective also seem worthy of consideration, given that adiponectin affects insulin resistance and atherogenesis [2,13,40].

We found significantly lower adiponectin serum levels in men, likely due to the physiological postmenopausal adiponectin increase in women: animal models show that estrogen can suppress adiponectin secretion in mice and cultured adipocytes [41]. In humans, adiponectin is negatively correlated with estrogen levels, and postmenopausal women using estrogen replacement therapy have lower adiponectin than nonusers [42]. On the other hand, testosterone is known to suppress adiponectin secretion [43]. Being the male climacterium a much more gradual phenomenon than menopause and our male subjects younger than females, it is not surprising that adiponectin was lower in males.

The fact that the effect of adiponectin on bone was only evident in women likely reflects the greater average contribution of FM to total weight in females and, at variance with males, the further age-related FM increase in older females [44]. This divergent behaviour is clearly evident when comparing BMI and FM of genders: the average BMI was slightly higher in females (27.8 kg/m² vs. 26.8 kg/m² in men), but FM was greater by 31.6%. Adiponectin, however, has already been shown to have different effects in men and women, although evidences pertaining to BMD are conflicting. At variance from our study, for example, in the Rancho Bernardo study, it has been shown that adiponectin was inversely associated with BMD in both men and women, but it was associated with vertebral fractures in men only [35]. Another study also showed an inverse correlation between adiponectin and BMD in both sexes, but the association with fractures was evident in women only [21]. Both these studies used DeXA to evaluate BMD, and the discrepancy with our results might be due to the different technique used. It should be noted that the studies cited have not formally investigated the presence of an interaction between adiponectin and gender with respect to BMD, while in our sample we found a significant interaction with respect to both trabecular and cortical BMD. However, the aim of this study was not to examine sex differences in the relationship between adiponectin and BMD.

The mechanism through which adiponectin regulates bone physiology has not been yet fully elucidated. Luo et al. [45] reported that adiponectin not only enhances human osteoblast proliferation and differentiation but also promotes osteoclast formation; in contrast, Yamaguchi et al. [46] reported an inhibition of osteoclasts. Treatment of mice with adenovirus expressing adiponectin resulted in increased trabecular bone mass and decreased number of osteoclasts and levels of plasma N-telopeptide [17]. However, in another experimental model, AdKO presented in general higher trabecular BMD compared to the controls, but these results varied with age, being significant at 14 weeks [12]. Thus, it cannot be excluded that also in humans effect of adiponectin on bone varies with age. On the other hand, Shinoda et al. [16] did not find abnormalities in the bone in transgenic mice overexpressing adiponectin: histological analyses of the proximal tibiae of these mice at 8 weeks of age revealed no difference in bone volume (BV/TV), bone formation, or bone

resorption parameters. Thus, these contrasting results do not provide a conceptual basis for interpreting our findings.

This study is limited by its cross-sectional nature that prevents us from defining the inverse relationship between adiponectin and BMD in women as causal. Furthermore, although we attempted to minimize methodological errors in the measurement of cortical apparent vBMD, partial volume effects cannot be excluded. Cortical bone mass in the appendicular skeleton is influenced by the thickness of the cortex and may not represent the real material density of the bone. According to Hangartner and Gilsanz [47], the material density of appendicular bone can be measured accurately and without partial volume errors by CT if the cortical thickness is greater than 2–2.5 mm. Above this threshold, a number of pixels contain only bone, and CT measurement is directly related to the linear attenuation coefficient of the mineral content. However, voxel size of 0.5 mm was used, and a value of Ch.Th lower than 3.3 mm was present in less than 10% of participants. Thus, we assumed that partial volume error was limited in this study. Third, the hypothesis that adiponectin partly affected bone through its vascular effects could not be tested [40]. Indeed, no measure of atherosclerotic burden such as the intima-media thickness was available at the time of the 6-year InCHIANTI assessment to correct the adiponectin BMD. Finally, we were unable to dose the different isoforms of adiponectin that may have different metabolic activity [48].

In conclusion, our results demonstrate that adiponectin is inversely correlated with bone mass in females. Further studies are needed to confirm these findings prospectively and then to clarify the explanatory mechanisms.

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Fig. 1.
Simple regression analysis between adiponectin and bone parameters.

Table 1

Characteristics of participants.

	Men (<i>n</i>=320)	Women (<i>n</i>=271)
	Mean (SD)	Mean (SD)
Age (years)	67.2 (15.8)	75.6 (8.3)
Body mass index (kg/m ²)	26.8 (3.4)	27.8 (4.5)
Fat mass (%)	24.2 (5.1)	35.4 (6.8)
Years since menopause	-	26.5 (9.9)
Smoking (pack-years)	19.8 (21.5)	2.9 (7.7)
Alcohol intake (g/day)	21 (19.3)	6 (8.5)
Total BMD (mg/cm ³)	283.1 (50.1)	219.0 (46.2)
Trabecular BMD (mg/cm ³)	215.2 (45.8)	176.0 (45.6)
Cortical BMD (mg/cm ³)	1069.5 (55.0)	1021.9 (68.7)
Serum alkaline phosphatase concentration (U/L)	109.8 (73.6)	133.1 (80.5)
Adiponectin (μg/mL)	19.0 (11.2)	27.4 (13.8)

Table 2

Correlation coefficients of adiponectin with body composition and bone mineral density.

	Men (<i>n</i>=320)	Women (<i>n</i>=271)
	Pearson's <i>r</i> (P value)	Pearson's <i>r</i> (P value)
Weight	−0.174 (0.002)	−0.213 (<0.001)
Body mass index	−0.135 (0.017)	−0.204 (<0.001)
Fat mass (%)	0.081 (0.163)	−0.152 (0.017)
Serum alkaline phosphatase concentration (U/L)	−0.038 (0.501)	−0.020 (0.736)
Waist-to-hip ratio	−0.053 (0.345)	−0.117 (0.055)
Total BMD (mg/cm ³)	−0.118 (0.035)	−0.316 (<0.001)
Trabecular BMD (mg/cm ³)	−0.087 (0.123)	−0.281 (<0.001)
Cortical BMD (mg/cm ³)	−0.171 (0.002)	−0.272 (<0.001)

Table 3

Association between adiponectin and bone mineral density adjusted for potential confounders.

	Men (<i>n</i> = 320)	Women (<i>n</i> = 271)
	<i>β</i> (<i>P</i> value)	<i>β</i> (<i>P</i> value)
<i>Total bone mineral density</i>		
Age	−1.247 (< 0.001)	−2.222 (<0.001)
Smoking (pack-years)	−0.413 (0.001)	−0.208 (0.555)
Body mass index	2.046 (0.067)	4.339 (0.001)
Fat mass (%)	19.119 (0.805)	−93.526 (0.276)
Alcohol intake	0.176 (0.180)	0.563 (0.064)
Waist-to-hip ratio	19.914 (0.737)	−84.450 (0.065)
Serum adiponectin concentration	−0.364 (0.134)	−0.659 (0.001)
<i>Trabecular bone mineral density</i>		
Age	−0.86544 (<0.001)	−1.673 (<0.001)
Smoking (pack-years)	−0.36368 (0.002)	−0.112 (0.763)
Body mass index	0.8554 (0.4078)	3.177 (0.024)
Fat mass (%)	28.79969 (0.6883)	−91.052 (0.314)
Alcohol intake	−0.03422 (0.7789)	0.284 (0.375)
Waist-to-hip ratio	43.9000 (0.4254)	−56.294 (0.242)
Serum adiponectin concentration	−0.3334 (0.1389)	−0.718 (<0.001)
<i>Cortical bone mineral density</i>		
Age	−0.666 (0.001)	−2.142 (<0.001)
Smoking (pack-years)	−0.248 (0.0941)	−0.662 (0.268)
Body mass index	−1.125 (0.394)	2.460 (0.278)
Fat mass (%)	−169.656 (0.064)	−98.886 (0.497)
Alcohol intake	−0.125 (0.421)	0.534 (0.293)
Waist-to-hip ratio	−54.679 (0.439)	−119.294(0.124)
Serum adiponectin concentration	−0.462 (0.108)	−1.122 (<0.001)