J Musculoskelet Neuronal Interact 2010; 10(2):174-179

Original Article

Hylonome

Osteoprotegerin and nuclear factor-kappaB ligand are associated with leptin and adiponectin levels, in apparently healthy women

R. Tenta[1], D.B. Panagiotakos[1], E. Fragopoulou[1], T. Nomikos[1], C. Pitsavos[2], C. Chrysohoou[2], S. Antonopoulou[1], C. Stefanadis[2]

[1]Department of Nutrition Science - Dietetics, Harokopio University, Athens, Greece
[2]First Cardiology Clinic, School of Medicine, University of Athens, Athens, Greece

Abstract

Objectives: We investigated the relationship between the major bone turnover markers, i.e., Osteoprotegerin (OPG) and Receptor activator of nuclear factor-kappaB ligand (RANKL) and serum adipokines (leptin, adiponectin) levels in a sample of apparently healthy women. **Methods:** A random sample which consisted of 80 females (18-71 years) was studied. Elisa method was used to measure the OPG, RANKL and the leptin, adiponectin levels in females' serum. **Results:** OPG values were inversely correlated with leptin (*rho* = -0.38, *p* = 0.002) and positively correlated with age (*rho* = 0.27, *p*=0.01) and body mass index (*rho* = 0.29, *p*=0.009). RANKL values were inversely correlated with adiponectin (*rho* = -0.23, *p* = 0.06) and age (*rho* = -0.30, *p*=0.01). Additionally, OPG was higher in post- as compared to pre-menopausal women. Further data analysis adjusting for potential confounders revealed that the OPG/RANKL ratio was positively associated with adiponectin and inversely associated with leptin levels independent of the effect of age, body mass index and menopausal status. **Conclusions:** These results reveal that leptin circulating levels are inversely associated with serum OPG/RANKL ratio among healthy women.

Keywords: Opg, RANKL, Adipokines, Metabolism, Physiology

Introduction

The skeleton is a metabolically active organ that undergoes continuous remodeling throughout life. Bone mass in the skeleton is dependent on the coordinated activities of bone-forming osteoblasts and bone-resorbing osteoclasts. Remodeling of bone is important not only for maintaining bone mass, but also to repair microdamage and for mineral homeostasis[1,2].

Identification of the osteoclastogenesis inducer, the receptor activator of nuclear factor-kappaB ligand (RANKL), its cognate receptor RANK, and its decoy receptor osteoprotegerin (OPG), has contributed enormously to the dramatic advance in our understanding of the molecular mechanisms involved in osteoclast differentiation and activity. RANKL, which expresses on the surface of osteoblast/stromal cells and activated T cells, binds to RANK on the osteoclastic precursors or mature osteoclasts, and promotes osteoclastogenesis and bone resorption. While OPG, which is expressed by osteoblasts/stromal cells, strongly inhibits bone resorption, by binding to its ligand RANKL and thereby blocks the interaction between RANKL and RANK. A large body of research has shown that the molecular cross-talk between RANKL-RANK-OPG and other ligand-receptor systems fine-tunes bone homeostasis in normal physiology and disease[3,4].

A number of cytokines and hormones exert their effects on bone metabolism by regulating the OPG/RANKL ratio in the bone marrow microenvironment.

The cytokine-like hormone leptin, which is secreted by adipocytes, is an important candidate molecule linking changes in body composition with bone formation and bone resorption[5,6].

Adiponectin is a recently described and highly promising adipocyte-produced hormone that correlates negatively with

The authors have no conflict of interest. The ATTICA Study is funded by research grants from the Hellenic Society of Cardiology (grant – 1, 2002).

Corresponding author: Roxane Tenta, Harokopio University, 70 El. Venizelou Str., 176 71 Athens, Greece
E-mail: rtenta@hua.gr

Edited by: M. Bliziotes
Accepted 29 March 2010

obesity in general and central adiposity in particular. Evidence, reported so far, suggests that adiponectin possesses anti-hyperglycemic, anti-atherogenic, and anti-inflammatory properties[7]. In addition, adiponectin and its receptors have recently been found to be produced by human bone-forming cells, suggesting that adiponectin may be a hormone linking bone and fat metabolism[8].

Therefore, in this work we investigated the possible relationship between two important and highly interesting bone markers (i.e., OPG, RANKL), which are found implicated in various physiological processes, and serum adipokines (i.e., leptin, adiponectin) levels in a sample of apparently healthy females.

Materials and Methods

Study's sample

The working sample of this project consisted of 80 females (39±12 years, range 18-71) that were randomly selected from the ATTICA's study database. During 2001-2002, the ATTICA study enrolled 1528 women and 1514 men from the Attica region, Greece[9]. The sampling was random (based on local registries), and stratified by age and sex according to the age-sex distribution of the general population (census 2001). Participants had no history of cardiovascular disease or any other atherosclerotic disease, as well as chronic viral infections. Moreover, participants did not have cold or flu, acute respiratory infection, dental problems or any type of surgery in the past week. All women interviewed by trained personnel (cardiologists, general practitioners, dieticians and nurses) who used a standard questionnaire. The study was approved by the Medical Research Ethics Committee of First Cardiology Clinic, School of Medicine, University of Athens and was carried out in accordance with the Declaration of Helsinki (1989) of the World Medical Association.

Clinical and biochemical characteristics

Fasting blood samples were collected from 08.00 to 10:00 hours. The biochemical evaluation was carried out in the same laboratory that followed the criteria of the World Health Organization Reference Laboratories. ELISA method was used for the quantitative determination of human OPG and human ampli-sRANKL, in duplicate in serum samples of the participants by the Biomedica Gruppe immunoassay kits (Biomedica Medizinprodukte GmbH & Co KG, Wien, Austria). Adiponectin and leptin were measured by ELISA method in duplicate serum samples of the participants by immunoassay kit (R & D Systems Inc., Minneapolis, Minessota). Any use of drugs known to affect adiponectin levels, including fibrates and thiazolidinediones (PPAR-α and PPAR-γ antagonists, respectively), as well as renin-angiotensin system blocking agents, was included in our analysis. Height, weight were recorded and body mass index (weight in Kg/height in m^2) was calculated. Obesity was defined as body mass index >29.9 kg/m^2. Following standard definitions, hypertension was defined as systolic / diastolic arterial blood pressure >140/90 mmHg or the use of antihypertensive treatment, hypercholesterolemia was defined as total serum cholesterol >200 mg/dL or the use of lipid lowering agents and diabetes mellitus was defined as fasting glucose >125 mg/dL or the use of special medication. Finally, menopausal status and estrogen use was recorded in all participants.

Socio-demographic, dietary and lifestyle variables

Current smokers were defined as those who smoked at least one cigarette per day, former smokers were defined as those who had stopped smoking for at least one year, and the rest of the participants were defined as non-current smokers. For the ascertainment of physical activity status the International Physical Activity Questionnaire was used (IPAQ)[10], as an index of weekly energy expenditure, using frequency (times per week), duration (in minutes per time) and intensity of sports or other habits related to physical activity (in expended calories per time). Participants who did not report any physical activities were defined as physically inactive (sedentary lifestyle). Based on the FFQ all participants were also asked their usual average frequency of consumption of alcohol and coffee. Alcohol consumption was measured in wineglasses (100 ml) and quantified by ethanol intake (grams per drink). For the analysis all reported types of coffee (instant, brewed coffee, «Greek» type, «cappuccino» or filtered) were adjusted for one cup of 150 ml coffee and concentration 28 mg of caffeine. We also recorded, and included in the analysis as dummy variables, the consumption of decaffeinated coffee, tea and caffeine containing drinks (like cola) or chocolate consumption. The aforementioned variables have been associated with bone metabolism in previous studies[11,12].

Statistical analysis

Continuous variables are presented as mean values±standard deviation. Categorical variables are presented as frequencies. Associations between categorical variables were tested by the calculation of chi-squared test. Correlations between OPG, RANKL, OPG/RANKL ratio and the other continuous variables (i.e., age, BMI) were tested using the Spearman's *rho* correlation coefficient. Multiple linear regression models were applied to test the association between OPG, RANKL, OPG/RANKL ratio (dependent outcomes) and adiponectin, leptin levels (independent covariates), after controlling for several potential confounders. RANKL and OPG/RANKL ratio levels were log-transformed because of their skewed distribution. The variance inflation factor (VIF) was calculated to test for co-linearity between the independent variables (i.e., values <4 indicate no co-linearity). Standardized residuals were used to test model's goodness-of-fit. Normality was tested using the Kolmogorov-Smirnov criterion. All reported *P*-values are based on two-sided tests and compared to a significance level of 5%. SPSS 14 (SPSS Inc., Chicago, Il, USA) software was used for all the statistical calculations.

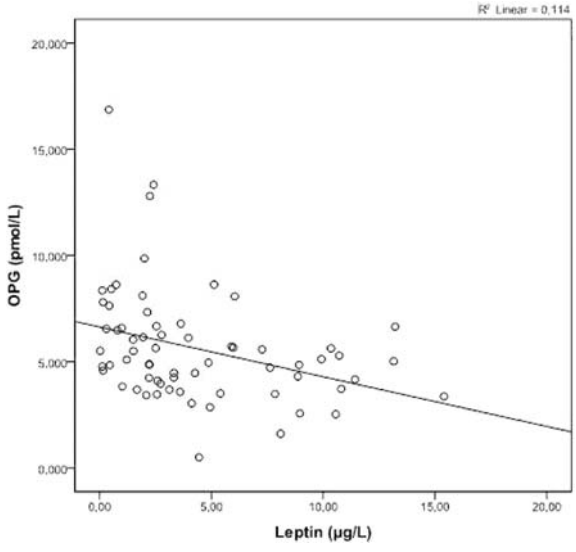

Figure 1. Scatter plots between OPG and leptin levels among apparently healthy women.

Age (in years)	39±12; 40
Post-menopausal status, %	14
Body mass index (kg/m²)	24.3±5.0; 23.5
Obesity, %	15
Hypertension, %	16
Hypercholesterolemia, %	33
Diabetes mellitus, %	2
Smoking, %	45
Physical inactivity, %	59
Alcohol drinking (gr. ethanol/day)	5.7±12.3; 1.7
Coffee drinking (ml/day)	85±81; 50
Tea drinking (ml/day)	75±50; 40
Adiponectin (μg/ml)	4.7±1.9; 4.6
Leptin (μg/L)	4.6±3.3; 3.7
Receptor activator of nuclear factor-κB ligand (pmol/L)	0.49±0.65; 0.29
Osteoprotegerin (pmol/L)	5.6±2.5; 5.1
OPG/RANKL ratio	27.5±27.8; 18.9

Table 1. Characteristics of the participants (n=80). Data are expressed as mean ± standard deviation; median values for the continuous variables and relative frequencies for the categorical variables. Receptor activator of nuclear factor-κB ligand=RANKL; Osteoprotegerin=OPG.

Results

In Table 1 basic descriptive characteristics of the participants are presented.

Unadjusted data analysis showed that serum OPG values were inversely correlated with leptin (*rho* = -0.38, p=0.002) (Figure 1) and positively correlated with age (*rho* = 0.27, p=0.01) and body mass index (*rho* = 0.29, p=0.009) while no association was observed with adiponectin (p=0.1). Additionally, OPG was higher in post-compared to pre-menopausal women (6.5±3.2 vs. 5.1±2.3 pmol/L, p=0.04), while no association was observed between OPG concentrations and physical activity status (p=0.47), smoking habits (p=0.36), history of hypertension (p=0.20), diabetes (p=0.99), and hypercholesterolemia (p=0.66). OPG was not correlated with RANKL concentrations in our sample (p=0.57). Furthermore, RANKL values were inversely correlated with adiponectin (*rho* = -0.23, p=0.06) and age (*rho* = -0.30, p=0.01), while no correlation was observed with leptin (p=0.62) and body mass index (p=0.188). RANKL was similar in both post- and pre-menopausal women (0.43±0.32 vs. 0.53±0.74 pmol/L, p=0.71). The unadjusted data analysis showed no correlation between the OPG/RANKL ratio and leptin (p=0.24) or adiponectin levels (p=0.38). Moreover, the OPG/RANKL ratio was positively correlated with age (*rho* = 0.42, p<0.001) and body mass index (*rho* = 0.26, p=0.03). Furthermore, OPG/RANKL ratio was similar in post- compared to pre-menopausal women (38±38 vs. 26±28, p=0.35), while no association was observed between OPG/RANKL ratio and physical activity status (p=0.47), smoking habits (p=0.36), history of hypertension (p=0.20), diabetes (p=0.99), and hypercholesterolemia (p=0.66).

However, residual confounding may exist. Therefore, data

	b±SE	p
Model for OPG		
Age (years)	0.004±0.028	0.89
Menopause (yes vs. no)	-1.74±1.00	0.09
Adiponectin (μg/ml)	-0.07±0.14	0.61
Leptin (μg/L)	-0.25±0.08	0.003
Body mass index (per 1 kg/m²)	0.13±0.07	0.06
Model for log{RANKL}		
Age (years)	-0.04±0.01	0.006
Menopause (yes vs. no)	-1.11±0.47	0.02
Adiponectin (μg/ml)	-0.11±0.07	0.12
Leptin (μg/L)	0.03±0.04	0.36
Body mass index (per 1 kg/m²)	-0.04±0.03	0.22
Model for log{OPG/RANKL}		
Age (years)	0.04±0.01	0.007
Menopause (yes vs. no)	0.89±0.48	0.07
Adiponectin (μg/ml)	0.13±0.07	0.08
Leptin (μg/L)	-0.09±0.04	0.02
Body mass index (per 1 kg/m²)	0.08±0.03	0.01

Table 2. Multiple linear regression models that evaluated the association between OPG, log{RANKL}, and log{OPG/RANKL} ratio (dependent variables) and adiponectin, leptin levels (independent variables). OPG/RANKL ratio levels were log-transformed because of lack of normality. Variables also entered in the models but showed no effect on the investigated outcomes were smoking, alcohol, coffee and tea drinking. The VIF was for adiponectin and leptin ranged between 1.25-1.26 and 1.11-1.26 respectively, indicating no co-linearity.

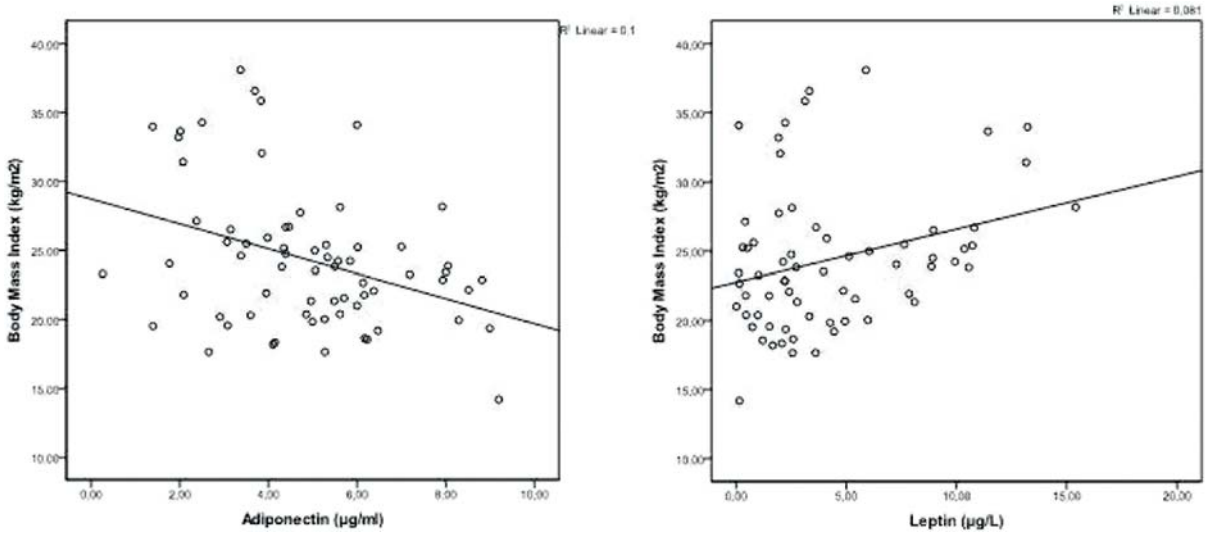

Figure 2. Scatter plots between Body Mass Index and adiponectin (left), leptin (right) levels among apparently healthy women.

analysis was further adjusted for age, menopausal status and body mass index of the participants, since these variables were correlated with OPG, and RANKL levels in the aforementioned analyses, and they have been suggested as determinants of adiponectin and leptin levels in previous studies[13-15]. The multi-adjusted analysis (Table 2) confirmed the previous findings. Specifically, adiponectin was positively associated with OPG/RANKL ratio, while leptin was inversely associated with OPG/RANKL ratio. The aforementioned relationships were independent of the effect of age, body mass index and menopausal status. Furthermore, the interaction terms between adiponectin, leptin levels and menopausal status on OPG/RANKL ratio were not significant (p=0.30, and p=0.68, respectively); suggesting that the effect of adiponectin and leptin levels on OPG/RANKL ratio was not altered by the menopausal status of the participants. It should be mentioned that the effects of adiponectin and leptin on the OPG/RANKL ratio levels were made more prominent after the introduction of BMI in the multi-adjusted model (Table 2, Figure 2). Variables also entered in the models but showed no effect on the investigated outcomes were smoking, alcohol, coffee and tea drinking.

When the analysis was stratified by menopausal status it was observed that leptin was inversely associated with OPG/RANKL ratio levels (b-coefficient±SE:-3.1±1.0, p=0.005), while adiponectin was positively associated with OPG/RANKL ratio (b-coefficient±SE: 6.8±1.9, p=0.001) only among pre-menopausal women (n=69). However, although the direction of the associations was similar, no significant relationships were observed among post-menopausal women (n=11).

Discussion

In this work an inverse association between OPG/RANKL ratio and serum leptin and a positive association with adiponectin levels among healthy women, was observed. This association was independent of age, body mass index, menopausal status and other lifestyle and clinical characteristics of the participants, which were considered as potential confounders in our analyses. Moreover, the latter finding was more evident among pre-menopausal women; however, the very small number of post-menopausal enrolled in this work does not allow us to conclude robust results. Because of the cross-sectional design of the study that cannot establish causal relations, but only generate research hypotheses for the associations observed, as well as the relatively small sample size, the presented findings should be generalized with conscious. However, despite the aforementioned consideration, the presented findings are of major importance in clinical research since they state a new hypothesis about the role of OPG, RANKL on adipokines metabolism (Figure 3).

Osteoprotegerin is a recently identified protein with an important role in bone remodeling which acts as a decoy receptor for RANKL; OPG is considered as a major regulator of bone metabolism through its effects on osteoclastogenesis, yet findings from previous studies of circulating OPG and commonly measured bone indices in humans have been conflicting. Nevertheless, higher OPG concentrations may indicate greater skeletal strength in women, possibly through reducing bone loss[16]. Uemura et al have shown a positive correlation between OPG and age in postmenopausal women, in a study with similar sample size[13]. Our findings show that OPG values as well as the ratio OPG/RANKL positively correlate with age, whereas RANKL inversely correlates with age. Nevertheless, the relationship between OPG and age is lost when menopausal status was taken into account.

Moreover, our experiments demonstrate that OPG values and the OPG/RANKL ratio correlate negatively with leptin. Much effort has been dedicated, in the last few years, to the

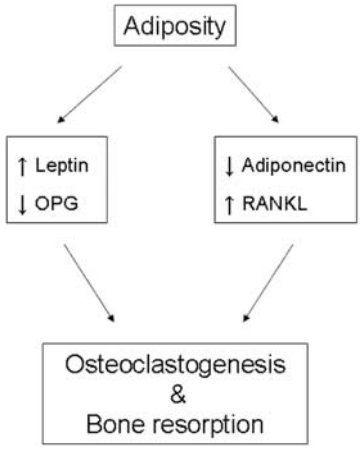

Figure 3. Schematical illustration of the relationship between body fat and bone metabolism.

relationship between leptin and bone. This interest stems from the knowledge that body weight is a major determinant of bone density. *In vitro* and animal studies as well as human cross-sectional studies about the role of leptin in bone metabolism are controversial[17]. The overall effect of leptin on bone results from a balance between negative central effects and positive direct peripheral effects. Recent studies support the notion of opposite effects of leptin on bone metabolism being dependent of a threshold that is triggered by leptin serum concentration[18]. In our study, both OPG values and the OPG/RANKL ratio correlate negatively with leptin and this may be a defense mechanism against bone loss, probably in a similar way that OPG levels are considered to act as a defense mechanism against atherosclerotic progression[19].

In previous studies involving premenopausal and postmenopausal healthy women it was demonstrated that serum leptin levels were negatively correlated with BMD (bone mineral density), whereas adiponectin did not seem to exert any effect on bone mass[20]. In other studies, serum adiponectin negatively correlated with BMD, and more significantly in postmenopausal women[21]. In addition, Luo et al. showed that adiponectin increased osteoclast formation indirectly through stimulating RANKL and inhibiting OPG production in osteoblasts, suggesting that adiponectin indirectly induces osteoclasts formation[22]. Moreover, Gannage-Yared et al, did not find any correlation between adiponectin and OPG levels, when they compared obese and non-obese young individuals[23].

In contrast, other studies indicated that adiponectin exerts an activity to increase bone mass by suppressing osteoclastogenesis and by activating osteoblastogenesis[24,25].

The discovery of the unique role of the OPG/RANKL/RANK signaling pathway in the process of osteoclastogenesis has led to the targeting of this pathway as a novel therapeutic approach in the management of osteoporosis[26,27]. In our study, the OPG/RANKL ratio levels correlate positively with adiponectin, independently of the effect of age, body mass index and menopausal status. This finding is very important, as there is, up to our knowledge, no other literature regarding the relationship between adiponectin levels and both of these bone markers in studies in human samples.

Finally, it should be discussed that the effects of adiponectin and leptin on the OPG/RANKL ratio levels were made more prominent after the introduction of BMI in the multi-adjusted model. An inverse relation between body mass index (BMI) and serum adiponectin levels as well as a positive relationship between BMI and serum leptin levels have been established in several studies[28-30]. In our study the above relationships were also confirmed (Figure 2). Therefore, the implication of BMI in bone metabolism should be taken into account and further investigated.

We tried to elucidate the influence of leptin and of adiponectin on bone tissue in a sample of 80 pre- and postmenopausal (healthy-considered) women. Although we should keep in mind that our sample number is not big enough to make statements, we would like to highlight a new finding about the role of adipokines on OPG, RANKL on metabolism. More specifically, we demonstrated that in the group of women that we studied, leptin correlates preferentially with OPG, while adiponectin correlates preferentially with RANKL, leading therefore to a differential modulation of the OPG/RANKL ratio from both adipokines. Nevertheless, more effort is still needed in order to fully elucidate and understand the interplay between hormones and bone metabolism.

Conclusion

The association between hormone secretion and markers of bone metabolism is of increasing scientific interest because more organs and tissues are affected directly or indirectly than we could initially predict. Pharmacological manipulation of the signaling pathways activated by adipokines (leptin, adiponectin) may have significant potential for the treatment and prevention of bone loss. Therefore, further research should be focused on the cooperation of OPG/RANKL/RANK system with other signal pathways and the interactions among bone remodelling and endocrinology system. Given that this time period is dynamic for cardiovascular disease, obesity and osteoporosis risk, these data underscore the need for additional prospective studies.

Acknowledgements

The authors would like to thank all the participants of the Study, and the field investigators of "ATTICA" study: John Skoumas, Natasa Katinioti, Spiros Vellas, Constantina Masoura for the physical examination, Efi Tsetsekou and Charambos Papageorgiou for the psychological evaluation, Manolis Kambaxis and Konstantina Palliou for the nutritional evaluation, as well as the laboratory team: Marina Toutouza (biochemical analysis), Carmen Vassiliadou (genetic analysis), Chryssoula Tselika (biochemical evaluation), Sia Poulopoulou (biochemical evaluation) and Maria Toutouza (database management).

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