Eklem Hastalıkları ve Cerrahisi
Joint Diseases and Related Surgery

Original Article / *Çalışma - Araştırma*

Eklem Hastalık Cerrahisi
2009;20(2):78-84

The relationship between serum adiponectin level and anthropometry, bone mass, osteoporotic fracture risk in postmenopausal women

Menopoz sonrası kadınlarda serum adiponektin ve antropometrinin kemik kütlesi ve osteoporotik kırık riski ile ilişkisi

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Objectives: The aim of the present study was to evaluate the possible correlation between bone mass and serum adiponectin levels, and the correlation between adiponectin levels and osteoporotic fracture risk in a prospective clinical trial.

Patients and methods: Postmenopausal non-diabetic 105 women (mean age 63.4±8.1; range 52 to 64 years) with hip fracture were evaluated. Of these 105 patients, 46 had trochanteric fractures, 24 had subtrochanteric fractures and 35 had femoral neck fractures. Anthropometric measurements were performed. Serum adiponectin level was measured by means of ELISA. Total bone mineral density and bone mineral content of lumbar spine and proximal femur were measured by dual-energy X-ray absorptiometry (DEXA).

Results: Lumbar bone mineral density and proximal femoral bone mineral density were not correlated with serum adiponectin levels. Serum adiponectin level was not found to have any significant effect on bone mass. Serum adiponectin levels were not significantly different between the patients with osteoporotic fractures and those with non-osteoporotic fractures.

Conclusion: Our study showed that serum adiponectin level is not associated with bone mass and osteoporotic fracture risk. Investigation of local adiponectin levels in bony tissue is needed to clarify the possible relation between adiponectin and bone mass, and risk of fractures associated with osteoporosis.

Key words: Adiponectin; anthropometry; bone mineral density; osteoporosis; DEXA.

Amaç: Bu çalışmada serum adiponektin düzeyi ile kemik kütlesi ve serum adiponektin düzeyi ile osteoporotik kırıklar arasındaki olası ilişki prospektif olarak araştırıldı.

Hastalar ve yöntemler: Kalça kırığı olan menopoz sonrası diyabetik olmayan 105 kadın hasta (ort. yaş 63.4±8.1; dağılım 52-64 yıl) prospektif olarak değerlendirildi. Hastaların 46'sı trokanterik, 24'ü subtrokanterik ve 35'i femoral boyun kırıklı idi. Antropometrik ölçümler yapıldı. Serum adiponektin düzeyi ELISA ile değerlendirildi. Lomber ve femoral kemik mineral yoğunluğu ve kemik mineral içeriği çift enerjili X-ışını soğurma cihazı (DEXA) ile ölçüldü.

Bulgular: Lomber ve femoral kemik mineral yoğunluğu serum adiponektin düzeyi ile ilişkili bulunmadı. Serum adiponektin düzeyinin kemik kütlesi üzerinde anlamlı bir etkisi saptanmadı. Osteoporotik kırıklı hastalarda ve osteoporozla ilişkisiz kırıklı hastalar arasında serum adiponektin düzeyleri yönünden anlamlı bir fark saptanmadı.

Sonuç: Bizim çalışmamızda serum adiponektin düzeyi ile kemik kütlesi ve osteoporotik kırık riski arasında klinik düzeyde bir ilişki bulunamamış olsa da kemik dokudaki lokal adiponektin düzeyinin incelendiği çalışmalar yapılarak bu olası ilişki daha net ortaya çıkarılabilir.

Anahtar sözcükler: Adiponektin; antropometri; kemik mineral yoğunluğu; osteoporoz; DEXA.

• *Received: July 2, 2008 Accepted: October 22, 2008*

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Osteoporosis related fractures might lead to diminished quality of life, disability and even death.[1-5] Determining and reducing future fractures associated with osteoporosis in high-risk populations could prevent morbidity and mortality.[2-5] Body weight is significantly correlated with increased bone mineral density (BMD), whereas there is an inverse association with postmenopausal bone loss and bone fracture as stated by the wider literature.[2] Both biomechanical and biochemical factors mediate this association. It is thought that increased body weight induces muscular mechanical loading and biochemical factors support the protective effects of high fat mass at non-weight bearing bone sites.[6] Such evidences as increased aromatization of androgen to estrogens in adipose tissue, decreased sex hormone binding globulin levels and high free sex steroids in obese women may illustrate the higher BMD.[7] Recently there is a new opinion that the newly identified hormones secreted from adipose tissue may be effective on the relationship between the fat mass and the bone mass. Adipocytokines like adiponectin may clarify the effects of fat mass on BMD.[8,9] Serum adiponectin levels decrease in obesity and obesity-related diseases.[10] The association between the bone mass and adiponectin levels is still controversial. There are few studies on the effects of adiponectin on bone metabolism. The published data are conflicting. Some authors presented an inverse association between adiponectin and BMD while others failed to find such a relationship.[8,9,11,12] We hypothesized that adiponectin may be used as a predictor for the rate of bone loss and fracture risk in postmenopausal women.

In this study, we aimed to investigate a possible correlation between bone mass and serum adiponectin levels, anthropometric parameters, and also the correlation between serum adiponectin levels and risk of osteoporosis-related fractures in non-diabetic postmenopausal women.

PATIENTS AND METHODS

We studied 105 non-diabetic postmenopausal women (mean age 63.4±8.1; range 52 to 64 years) selected from patients who attended our department with hip fracture. Of these 105 patients, 46 had trochanteric fractures, 24 had subtrochanteric fractures and 35 had femoral neck fractures. Seventy-one of these fractures occurred after simple falls and the remaining 34 fractures occurred due to high-energy traumas such as motor vehicle accidents or high-energy falls from a height. The investigational protocol described herein was approved by the Authors' Hospital Local Ethics Committee. Informed consent was obtained from all patients. The appropriate patients for the study criteria were included in the study consecutively, following an investigation of chronic disease and medical history in detail, physical examination, whole blood count, routine biochemical evaluation and measurement of several hormones such as insulin, estradiol, total testosterone, free testosterone, parathormone, cortisol, vitamin-D, thyroid stimulating hormone and follicle stimulating hormone. The patients included in this study were postmenopausal women with hip fracture. The mean duration of menopause was seven (5-14) years. Menopause was defined by absence of menses for more than six months and by elevated serum follicle-stimulating hormone (FSH) levels (FSH>40 U/l). Furthermore, we eliminated the patients who had rheumatic diseases, chronic hepatic and renal diseases, endocrinological diseases such as pituitary disease, hyperthyroidism or the patients receiving any treatment protocol that could effect the bone metabolism and bone turn-over, such as thiazid diuretics, β-Blockers, biphosphonates, calcitonin, calcium, vitamin-D, phenobarbital, heparin, thyroid hormone, glucocorticoid therapy, selective oestrogen receptor modulators and statins. In addition, smoker and drinking patients were excluded from the study. None of the patients was currently receiving drugs for osteoporosis. None of the patients was diabetic based on the ADA (American Diabetes Association) criteria.

Demographic and anthropometric characteristics for all participants were identified. All measurements were performed in lightly underweared, shoeless participants, while standing, by the same devices and unique observer, within three to five days after operation. Body weight was measured by a sensitive scale to the nearest 0.1 kg. Height was measured by a wall-mounted stadiometer to the nearest 0.5 cm. Body mass index (BMI) (weight/height^2, kg/m^2) was calculated. Patients whose BMI were ≥30 kg/m^2 were accepted as obese.

Bone mineral density values of the L_2-L_4 PA Spine, and the proximal femur (femoral neck and

intertrochanterik region) were obtained by dual-energy X-ray absorptiometry (DEXA) (Hologic-QDR 2000, MA, USA), within three to five days after operation. Bone mineral density values of the proximal femur were obtained from the unfractured side (left hip in 57 patients and right hip in 48 patients). Osteoporosis was defined as a T score lower than -2.5 in either the lumbar spine or the femoral neck according to WHO (World Health Organization) criteria. Bone mineral content of the same regions was measured by the same DEXA.

Serum adiponectin concentration was determined using a validated sandwich ELISA employing an adiponectin-spesific antibody by human adiponectin kit (catalog # EA 2500-5, lot # 411903). All serums were obtained from venous blood samples taken after 12 hours of fasting by centrifugating at 4500 rpm for ten minutes, and stored at -70 °C before assay.

Serum levels of insulin, estradiol, total testosterone, parathormone, cortisol, thyroid stimulating hormone (TSH) and FSH were measured using commercial chemiluminescence microparticle immune assay (CMIA) or electrochemiluminescence immune assay (ECLIA) as appropriate for the hormone. Serum levels of free testosterone measured using radioimmunassay (RIA) and the serum levels of 25 (OH) vitamine-D measured using high pressure liquid chomotography (HPLC). Cortisol and parathormone measurements were done using Elecsys, Roche; insulin, estradiols, total testosterone, TSH, FSH measurements were done using Architech 2000, Abbott, Illinois, USA; 25 (OH) vitamine-D measurements were done using Schimatzu, Koyoto, Japan. Serum levels of these hormones were within normal limits for the postmenapousal women in all patients. Serum values were between 7-18 μg/dl, 2-20.8 uIU/ml, 9.2-21.7 pg/ml, 0.09-0.88 ng/ml 0.3-3.01 pg/ml, 58-76 mIU/ml, 2-5.7 pmol/l, 0.07-3.72 uIU/ml and 20-80 mmol/lt for cortisol, insulin, estradiol, total testosterone, free-testosterone, follicle stimulating hormone, parathormone, thyroid stimulating hormone and 25 (OH) vitamin-D, consecutively.

Statistical analysis

Summary statistics were expressed as mean±SD. Correlation coefficients were calculated, properly to normality tests, to explore the relationship between BMD, BMC (lumber and proximal femur) and demographic, anthropometric values, serum adiponectin and other parameters. Student-t test and two-sample Mann-Whitney U-tests were used where appropriate to compare continuous variables of interest between normal and osteoporotic women. For categorical data χ^2 test was used for difference of distribution between groups. Multiple linear regression analysis was performed to investigate the effect of variables on bone mineral content of lumbar spine (LBMC), bone mineral content of proximal femur (FBMC), bone mineral density of the lumbar spine (LBMD), and bone mineral density of the proximal femur (FBMD). $P<0.05$ was considered to be statistically significant. All statistical analysis was performed using SPSS for Windows, version 11.5 (SPSS Inc, IL, USA).

RESULTS

Sixty-eight participants (64.7%) had normal bone density; thirty-seven participants (35.3%) had osteoporotic values. The mean LBMD, FBMD, LBMC and FBMC values were 0.85±0.16 g/cm^2, 0.76±0.14g/cm^2, 46.9±14.07 g, 28.75±8.05 g, respectively.

Meanings of anthropometric and demographic characteristics and serum adiponectin and other hormone levels of the study samples and also the BMD and the BMC values are presented in Table I. Both BMD and BMC values were significantly negatively related to age, significantly positively related to weight and BMI. Bone mineral density and BMC were not correlated with height and waist hip ratio. As shown in Table II, osteoporotic patients had lower weight and BMI values, longer duration of menopause; and also, they were older than the non-osteoporotic ones.

Serum adiponectin levels were significantly negatively correlated with weight ($r=-0.324$; $p<0.05$), BMI ($r=-0.339$; $p<0.05$). Serum adiponectin levels were significantly lower in obese subjects than non-obese ones, but were not different between subjects who had and did not have osteoporosis. The serum adiponectin levels were not related to BMD and BMC. Serum adiponectin levels were not different between the patients with osteoporotic fractures and the non-osteoporotic fractures.

In multiple linear regression analysis including age, BMI and adiponectin, both LBMC and FBMC

TABLE I

Characteristics of the subjects, correlation between LBMD, FBMD, LBMC, FBMC and other characteristics (n=105)

		LBMD	FBMD	LBMC	FBMC
	Mean±SD	r / *p*	r / *p*	r / *p*	r / *p*
Age (years)	63.4±8.1	-0.305 / <0.05	-0.398 / <0.01	-0.297 / <0.05	-0.302 / <0.01
Height (cm)	158.3±6.2	0.221 / NS	0.158 / NS	0.202 / NS	0.112 / NS
Weight (kg)	71.2±8.2	0.498 / <0.01	0.586 / <0.01	0.389 / <0.01	0.502 / <0.01
BMI (kg/m^2)	28.5±7.9	0.384 / <0.01	0.603 / <0.001	0.396 / <0.01	0.415 / <0.01
Adiponectin (μg/mL)	6.66±0.45	-0.118 / NS	-0.212 / NS	-0.195 / NS	-0.198 / NS

LBMD: Bone mineral density of the lumbar spine; FBMD: Bone mineral density of the proximal femur; LBMC: Bone mineral content of lumbar spine; FBMC: Bone Mineral content of proximal femur; NS: Non significant; BMI: Body Mass Index.

significantly related to age; in addition, BMI was related to FBMD (Table III).

DISCUSSION

Bone is a living tissue with a complex, continuous, coordinated cycle of resorption and formation of new bone. This turn-over is under the effect of biomechanical, biochemical, nutritional, systemic and local humoral factors.[1,2] Osteoporosis-related fractures increase morbidity and mortality in postmenopausal women.[1] Determining and preventing future fractures associated with osteoporosis in at-risk populations is one of the targets of the clinicians. Several radiological and hormonal investigations are being performedto estimate these kinds of fractures. In addition, biochemical markers are being investigated as the predictor of bone loss rate and associated fracture risk in postmenopausal women.[2,6]

Positive associations between fat mass and BMC are mediated by not only biomechanical but also biochemical factors.[6,8] This protective effect is the reason for the increased weight load, leading to mechanical stimulation. The observation of this protective effect not only at weight-bearing bone sites but also at non-weight-bearing bone sites suggests the possible contributing biochemical and hormonal agents.[6,8] The increased aromatisation of androgen to estrogene in adipose tissue, lowered sex hormone binding globulin levels with increased free sex steroids and bone formation induced by increased levels of circulating insulin in obesity may clarify the effects exerted by adipose tissue in the genesis of osteoporosis.[13] We believe that, new hormonal markers such as adiponectin may be used as predictors for the rate of bone loss and osteoporotic fracture risk in postmenopausal women. Determining and reducing

TABLE II

Characteristics of the subjects with normal and low bone mineral density score

	Normal BMD score (n=68)	Osteoporotic (n=37)	*p*
Age (years)	58.4±8.2	68.4±8.0	<0.001
Postmenopause duration (years)	19.3±12.1	21.4±13.8	<0.05
Weight (kg)	79.8±11.5	62.6±4.9	<0.001
BMI (kg/m^2)	31.2±5.9	25.5±9.9	<0.01
Adiponectin (μg/mL)	6.33±0.51	6.99±0.5	NS
LBMD (g/cm^2)	0.93±0.11	0.77±0.2	<0.001
FBMD (g/cm^2)	0.84±0.14	0.68±0.11	<0.001
LBMC	52.9±12.8	37±10.7	<0.001
FMBC	32.6±7.4	22.7±4.5	<0.001

LBMD: Bone mineral density of the lumbar spine; FBMD: Bone mineral density of the proximal femur; LBMC: Bone mineral content of lumbar spine; FBMC: Bone Mineral content of proximal femur; NS: Non significant; BMI: Body Mass Index.

TABLE III

Multiple linear regression analysis between LBMD, FBMD and variables (n=105)

	LBMD		FBMD	
	r	*p*	r	*p*
Age	-0.340	0.018	-0.369	<0.001
BMI	0.240	0.034	0.212	0.041
Adiponectin	-0.135	0.104	-0.090	0.341

LBMD: Bone mineral density of the lumbar spine; FBMD: Bone mineral density of the proximal femur; BMI: Body Mass Index.

future fractures associated with osteoporosis in high-risk populations could prevent morbidity and mortality. Clarification of the relationship between biochemical factors and the bone metabolism and fracture risk may be beneficial toprevent osteoporotic fractures. In this way, morbidity and mortality of the osteoporotic fractures may be prevented.

In the present study we aimed to investigate the possible role of the demographic features, anthropometric features, and serum adiponectin level on bone mass and bone metabolism, and to investigate if adiponectin could be used to determine osteoporotic fracture risk in postmenopausal women. We studied the dependence of the LBMD, FBMD, LBMC, and FBMC on the weight, height, body mass index and serum adiponectin level. Both BMD and BMC values were significantly negatively related to age, and significantly positively related to weight and BMI. Bone mineral density and BMC were not correlated with height and waist hip ratio. Serum adiponectin levels were significantly negatively correlated with weight, BMI. Serum adiponectin levels were significantly lower in obese subjects than in non-obese ones. Our outcomes supported the previous published data.

Recently some authors proposed that the adipocytokines secreted by adipose tissue may play a role in the bone metabolism and bone mass, besides the anthropometric and demographic characteristics.[8,9,12,14] Several characteristics of adiponectin suggest possible mechanisms on the regulation of bone metabolism. Adiponectin expresses prominent structural similarities to TNF-α family members, such as RANK-L and osteoprotegerin, two proteins involved in regulation of osteoclastogenesis.[15] Oshima et al.[16] reported that adiponectin induces osteoblastic differentiation and suppresses osteoclastogenesis. These experimental studies suggested that adiponectin may play a positive functional role in bone homeostasis. Nevertheless, the reflection of these mechanisms on individuals could not be absolutely exposed clinically, as is also shown in our study. In this study, we investigated the possible effects of adiponectin on bone metabolism and bone mass, and also osteoporotic fracture risk due to these factors. We could not find any correlation between serum adiponectin levels and bone mass; nor could we find any correlation between serum adiponectin levels and osteoporotic fracture risk. Serum adiponectin levels were not different between subjects who had and did not have osteoporosis. The serum adiponectin levels were not related to BMD and BMC. Serum adiponectin levels were not different between the patients with osteoporotic fractures and the non-osteoporotic fractures. In our study, we investigated the serum adiponectin levels but not local levels in bony tissue, which is one of the limitation of our study. We believe that real adiponectin levels in bony tissue may be camouflaged in venous circulation due to different factors such as obesity and insulin sensitivity. The effects and levels of local adiponectin in bony tissue may be different, more effective and important on bone mass and osteoporotic fracture risk.

In our study, we observed that serum adiponectin levels were negatively correlated with weight and BMI while there was no correlation between adiponectin levels and bone mass. The results of the limited number of studies about the effects of adiponectin on osteoporosis is controversial and contradictory. Lenchik et al.[9] reported a negative association between BMD and adiponectin levels in 80 adults, but most of the participants included in their study were diabetic and receiving hormone treatment, such as glucocorticoid, estrogene, and tiroid hormone, which possibly affected the BMD. In contrast, Kontogianni et al.[8] reported that there was no correlation between serum adiponectin levels and BMD in 25 premenopausal and 55 postmenopausal healthy participants. Huang et al.[11] reported that there was a negative correlation between serum adiponectin levels and BMD in simple correlation analysis but

no independent relationship in multivariete lineer regression analysis in 105 non-diabetic female adolescents. Jürimäe et al.[12] reported a negative association between serum adiponectin levels and BMD in a recently published study. The advantage of this study is that only postmenopausal non-diabetic women were included in the study to avoid the well known confounding factors such as hormonal diversities and the differences in body compositions and metabolisms between the premenopausal and postmenopausal women and also opposite sexes. In this study, we demonstrated that the serum adiponectin level is not related to BMD, BMC and facture risk. The reason why our finding is different from the previous reports suggesting association between serum adiponectin level and BMD is unclear at present. Therefore, further investigation regarding the biological roles of adiponectin in bone biology is still warranted.

Dual-energy X-ray absorptiometry of lumbar spine and proximal femur provides reproducible values at important sites of osteoporosis-associated fracture.[1] In the present study, BMD and BMC values of the all patients were evaluated by DEXA. Dual-energy X-ray absorptiometry measurements of BMD and BMC include both cortical and trabecular values and are influenced by body size and bone size. We believe that preferring DEXA which is cheap, useful and practical in clinical application, and a more reliable technique instead of three-dimensional techniques, like quantitative computed tomography (QCT), which are superior techniques for verifying the diagnosis of osteoporosis than DEXA, was another limitation of our study. On the other hand, dual DEXA is more widespread, cheaper and easily reached technique than QCT.

In conclusion, our study showed that increased weight and BMI are positively correlated with bone mass, but negatively correlated with serum adiponectin levels, and serum adiponectin level is not associated with bone mass and osteoporotic fracture risk. We believe that further research including more participants and investigation of local adiponectin levels in bony tissue are needed to clarify the possible relation between adiponectin and bone mass, and the risk of fractures associated with osteoporosis.

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