The effect of antiresorptive treatment on osteopontin values in osteoporosis

Osteoporozda Antirezorptif Tedavinin Osteopontin Değerleri Üzerine Etkisi

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Abstract

Background: An association between increased OPN levels and lowered bone mineral density (BMD) with increased bone turnover markers was established. The aim of this study is to evaluate the levels of OPN in OP patients who receive antiresorptive treatment (ART).

Methods: Ninety female OP patients in the post-menopausal period for at least a year in the age range of 45 - 70 years and 80 healthy female volunteers were included in the study. OP patients were divided into 2 subgroups as ART-receiving (60 patients; bisphosphonate (15), calcitonin (15), raloxifene (15), strontium ranelate (15) and ART non-receiving (30 patients). Bone mineral density was analyzed using the dual energy X-ray absorptiometry method. The plasma OPN concentration was calculated using the enzyme-link immunosorbent assay method.

Results: OPN levels were significantly lower in antiresorptive-receiving OP patients compared to OP patients who did not receive ART and compared to the control group ($p<0.001$ and $p=0.008$ respectively). There was no meaningful difference in terms of the OPN values between the controls and OP patients who did not receive ART ($p>0.05$).

Conclusions: Lowered OPN levels in ART-receiving OP patients suggest that OPN could be used as a biomarker in ART follow-up in OP.

Keywords: Osteoporosis, bone mineral density, antiresorptive treatment, osteopontin.

Özet

Amaç: Yüksek osteopontin (OPN) seviyelerinin kemik rezorpsiyonu ile ilişkili olduğu bildirilmiştir. Osteoporozda (OP) anabolik etki amacıyla uygulanan parathormonun, OPN düzeylerinde düşmeye neden olduğu tespit edilmiştir. Bu çalışmanın amacı OP tedavisi için antirezorptif tedavi alan hastalarda OPN

düzeylerinin değerlendirilmesidir.

Materyal ve metot: Çalışmamıza, 45-70 yaş arası, en az bir yıldır menopoza girmiş, OP tanısı alan 90 kadın hasta ve 80 sağlıklı kadın gönüllü dahil edildi. OP hastaları antirezorptif kullanan (60 hasta;15 bifosfonat, 15 kalsitonin, 15 raloksifen, 15 strontium ranelate kullanan hasta) ve kullanmayanlar (30 hasta) olmak üzere iki gruba ayrıldı. Hastalara KMY ölçümü, DEXA (Dual Enerji X-Ray Absorbsiyometri) yöntemi ile yapıldı. Plazma OPN konsantrasyonu enzyme-link immunosorbent assay (ELISA) methodu kullanılarak hesaplandı.

Bulgular: Antirezorptif kullanan OP grubunda OPN düzeyleri, antirezorptif almayan OP grubuna ve OP olmayan sağlıklı kontrol grubuna göre istatistiksel olarak anlamlı düzeyde daha düşüktü (sırasıyla $p<0.001$ ve $p=0.008$). OP olmayan sağlıklı kontrollerle ilaç kullanmayan OP grubunun OPN değerleri arasında istatistiksel olarak anlamlı bir fark yoktu ($p>0.05$).

Sonuç: Sonuçlarımızın, antirezorptif tedavinin OPN seviyelerinde düşmeye neden olduğunu göstermesi, bize OPN'nin, antirezorptif tedavinin takibinde bir biomarker olarak kullanılabileceğini düşündürdü.

Anahtar kelimeler : Osteoporoz, Kemik mineral dansitesi, antiresoptif tedavi

Introduction

Osteoporosis (OP) is a skeletal degenerative disease causing increased bone fragility and risk of fracture due to decrease in bone mass and deterioration in bone microarchitecture (1-3). Prevention of fractures, increase of bone mineral density (BMD), improvement of symptoms caused by the disease and improvement in life quality are targeted by OP treatment. Drugs that decrease bone resorption show their effects by lessening the inequilibrium between bone resorption and bone formation. Bisphosphonates, calcitonins, selective estrogen receptor modalities (SERM) and hormone replacement therapies (HRT) are currently the main antiresorptive treatment (ART) options (4-6).

Osteopontin (OPN) is a phosphoglycoprotein compound which was first identified in the extracellular matrix of the bone (7). OPN has a role in cell adhesion and chemotaxis of osteoclasts during bone resorption. Additionally, OPN was also reported to have roles in both resorption and formation during the bone re-modelling process (7). OPN release was reported to be controlled by parathormone (8). Additionally, it has been suggested that OPN is involved in urinary stone formation, cardiovascular diseases, tumorigenesis and metastasis (9-11).

An association between increased OPN levels and lowered bone mineral density (BMD) with increased bone turnover markers was determined (12,13). It was determined that low-dose and intermittent application of parathormone onto the bone in order to create an anabolic effect decreases OPN levels (14). However, the effect on OPN levels in patients receiving ART is unknown.

The aim of this study is to compare the OPN levels between ART-receiving OP patients and patients who were diagnosed as OP but not receiving any kind of treatment, and also with healthy volunteers in the same age group. By this means, a better understanding of the effect of ART and the contribution that OPN makes on bone metabolism in OP patients is intended.

Materials and Method

Ninety female OP patients in the post-menopausal period for at least one year in the age range 45 to 70 who were admitted to the Physical Medicine and/or

Rehabilitation & Orthopedics clinics of the University of Gaziantep between June 2012 and January 2013 were included in the study along with 80 healthy female volunteers. The Control group was composed of healthy volunteers who were examined for osteoporosis. Ethical approval was granted by the local Ethical Committee in concordance with the declaration of Helsinki. All patients and volunteers were informed of the study and written consent obtained. OP patients (n=90) were divided into 2 subgroups: (a) at least 3 months receiving therapy for OP (n=60) and (b) patients who had not yet started treatment (n=30). The treatment group was composed of 4 equal subgroups comprising 15 patients each according to the administered treatment (bisphosphonate, calcitonin, raloxifene, and strontium ranelate respectively). Calcium and vitamin D consumption of the patients was also recorded.

Age, height, weight, duration of menopause, pregnancy counts and exercise habits for each patient were recorded. Those with a duration of ART for less than 3 months or those who received a different antiresorptive drug before ART, those having a history of immobilization, usage of drugs with the potential of affecting bone metabolism (steroids, diuretics, heparin, anticonvulsants, antacids, thyroxin, etc.), those suffering a disease (hyperthyroidism, hyperparathyroidism, malabsorption, chronic kidney and liver disease, inflammatory rheumatoid disease, osteomalasia or vitamin D deficiency, etc.) were excluded from the study as were smokers and drinkers.

OP diagnosis was made by using clinical evaluation, lateral lumbar graphs, evaluation of the BMD of the lumbar vertebra and femoral neck, and laboratory findings. BMD determination was performed by using the dual energy X-ray absorptiometry (DEXA) method (Hologic, QDR-4500 Elite, USA) from lumbar vertebrae (L2-L4) antero-posterior and from left femoral neck. Patients with the hip or total lumbar T-score -2.5 or below were diagnosed as OP according to World Health Organization criteria.[10]

Blood samples were taken in the morning and again when volunteers and patients were hungry. All blood samples were stored in appropriate conditions during the study and all samples analyzed at the same time in order to eliminate sample calibration errors. In the enzyme-link immunosorbent assay (ELISA) method, the plasma OPN concentrations were quantified by using a specific enzyme immunoassay kit (eBioscience, San Diego, USA) according to the recommendations of the manufacturer. The detection limit was 0.26 ng/ml.

Statistical Analysis

The SPSS (Statistical Package for Social Sciences) for Windows 15.0 software was used for statistical analysis. One-way ANOVA was used for comparison of the quantitative data between groups. For binary comparison, the Tukey significance difference test was used in order to determine deviation between groups. For inter-group comparison of the data outside of the normal distribution, the Mann-Whitney U and Kruskal-Wallis tests were used. Results of a 95% confidence interval and $p < 0.05$ were considered significant.

Results

There were no meaningful differences in terms of age, body mass index (BMI), menopause duration and average vitamin D levels between OP patient groups and controls ($p>0.05$). However, average daily calcium and cholecalciferol intake values were markedly higher in the ART group when compared to healthy controls and non-treated patients ($p=0.027$ & $p=0.032$, respectively) (Table 1).

There were meaningful differences in terms of the OPN levels among groups ($p<0.001$). The average OPN level of the ART group was significantly lower than the controls and non-treated patients ($p<0.001$ and $p=0.004$, respectively). With the control group, average OPN level was higher than in non-treated patients. However, this difference was not significant ($p>0.05$) (Table 2, Figure 1A-C).

There were meaningful differences in terms of lumbar spine and hip BMD between groups. BMD values for controls were markedly higher compared to ART-receiving and non-receiving patients ($p<0.05$). However, there were no significant differences between treatment receiving and non-treatment receiving patients. ($p>0.05$) (Table 2).

There were significant differences in terms of lumbar and hip T and Z scores ($p<0.05$). In the control group, lumbar T and Z scores were higher compared to the ART-receiving and non-receiving patients ($p<0.05$). For the non-medication-receiving OP patients, the average T and Z scores were higher than the ART-receiving group. While the difference in terms of the Z score was significant ($p<0.05$), the difference in terms of the T score was insignificant ($p>0.05$) (Table 2).

After comparison of the different subgroups of ART-receiving patients and non-treated patients in terms of OPN levels, it was determined that levels of OPN in bisphosphonate, raloxifene and calcitonin were markedly lower ($p<0.001$). There was no meaningful difference in the strontium ranelate group ($p>0.05$); the lowest OPN level was in the raloxifene group while the highest value was in the strontium group (Table 3, Figure D).

Discussion

In this study, it is shown that there are no differences in terms of serum OPN levels in controls and non-receiving ART OP patients while levels of OPN were lower in ART-receiving patients. Additionally, it is shown that OPN levels were significantly lower in OP patients who receive any one of the following treatments: bisphosphonate, raloxifene, and calcitonin compared to those who do not receive any treatment. Conversely, there was no meaningful difference in terms of the OPN levels between strontium ranelate-receiving patients and controls.

Rapid loss of bone in women during the postmenopausal period is mostly related to decreased estrogen levels. Age and low BMI are other important risk factors for postmenopausal OP patients (15). Estrogen levels were not evaluated in our study and there were no significant differences regarding age and BMI between groups.

Antiresorptive agents used in OP treatment slow down remodelling speed and increase bone mineral content by allowing more time for mineralization (16,17). There is strong evidence for BMD being a good predictor of the risk of fractures during time without treatment. However, it has been reported in most studies that response to ART and a decrease in the risk of fractures cannot be completely attributed to BMD changes (18-21). However, evaluation of changes in bone metabolism markers was reported to be more important in the determination of improvement in fracture risk (22,23). Although BMD values of ART-receiving patients before and after treatment were not compared in our study, there were no marked differences in terms of lumbar and hip T scores between ART-receiving and non-ART-receiving OP patients.

According to the results of various experimental studies on mice, groups with OPN insufficiency were shown to be more resistant against bone loss and risk

of fractures induced by ovariectomy or age. Moreover, a positive correlation between age or low BMI and OPN levels was determined (24-28). A positive correlation between OPN levels and age and bone resorption markers in postmenopausal women was reported, along with negative correlations between OPN levels and various parameters, including height, weight, hip BMD and T-scores (12). However, also reported were no significant associations between these parameters and OPN levels in the premenopausal women (of childbearing age) group. In addition, OPN levels were reported to be markedly higher in postmenopausal women with OP, compared to healthy controls (12,13). Differing from previous studies, OPN levels of women who were not diagnosed as OP (average total lumbar and hip T scores: -1.6±1.2 and -1.2±1.4, respectively) were higher compared to those who were diagnosed as OP and not receiving ART in our study. It is known that OPN is produced by both osteoblasts and osteoclasts and is involved in both resorption and formation in the remodelling process (7). In this context, it is probable that osteoblastic activity and formation-related OPN are lower in the OP stage compared to the osteopenic and normal stages. This could offer an explanation for lower-than-average OPN in OP patients compared to non-diagnosed OP patients. Therefore, separate evaluation of patients whose lumber-hip T-scores were osteoporotic, osteopenic, and in the normal range, could be a more suitable approach.

In animal models of OPN insufficiency, early vascularization and a delay in matrix organization and late remodelling stages of callus were determined in fracture healing suggesting that OPN is required in normal fracture healing (29). To our knowledge, ideal OPN levels needed to preserve BMD or prevent OP and original microarchitectural structure or resupply them has not yet been established.

It was determined that low-dose and intermittent application of parathormone onto the bone in order to create an anabolic effect decreases OPN levels and suggests that OPN could be used as a biomarker regarding early treatment response in OP (14). In our study, the determination of markedly lower OPN levels in ART-receiving OP patients compared to patients who were not receiving treatment and the control group was important. At this point, ART might also have a lowering effect on OPN levels as in anabolic effective parathormone treatment. Bisphosphonates, SERMs, and calcitonin are widespread agents used for inhibiting bone resorption in OP (30,31). Strontium ranelate is a bone resorption-suppressing and bone formation stimulating double-effect agent which, in turn, produces production-oriented equilibrium in bone cycle (32). We believe that lowered OPN levels in ART-receiving patients (with the exception of strontium ranelate), is related to the appearance of the antiresorptive effect. If the involvement of OPN in resorption by stimulating osteoclast activity and also in formation was taken into consideration (7,33,34), we believe that strontium helps OPN in maintaining the equilibrium in a manner that increases bone formation but not stimulating extreme bone resorption at the same time.

The salient results of our study in which OPN levels were compared for the first time in ART-receiving, non-ART-receiving OP patients and controls are: 1) OP is not a factor which changes OPN levels by itself 2) Bisphosphonate, raloxifene, and calcitonin markedly lower OPN levels in OP patients 3) Strontium ranelate does not produce a significant change in terms of OPN levels in OP patients

compared to healthy controls.

Lack of evaluation of the OPN levels of patients before and after ART, unequal durations of ART for each patient, lack of classification of the bisphosphonates in the study and lack of evaluation of bone turnover markers were the limitations of this study.

A better understanding of how ART options used in OP treatment act on OPN levels could help us to use OPN as a treatment follow-up marker in ART. To this end, larger prospective studies involving different demographical and clinical parameters are required.

Conflict of Interest: The authors declare that they have no conflict of interest.

Table 1. Demographical properties and some parameters affecting bone metabolism of the patients and controls.

	Group I, Healthy controls (n=80)	Group II, ART receiving OP patients (n=60)	Group III, OP patients who do not receive treatment (n=30)	P value
Age	61.4 ± 8.2	62.8 ± 5.2	62.0 ± 5.7	>0.05
BMI(kg/m²)	25.33±3.44	26.24±4.12	25.77±3.52	>0.05
Menopause duration (years)	14.74±7.44	15.11±3.1	14.82±4.22	>0.05
Vitamin D levels (nmol/L)	22.24±9.12	21.84±8.36	22.80±7.52	>0.05
Daily vitamin D intake (IU/day)	190.5±17.3	388.4±14.3*†	224.4±14.7	**0.032**
Daily calcium intake (mg/day)	282.8±19.2	580.7±15.5*†	362.5±19.1	**0.027**

*BMI=Body mass index. Values were shown as average ± SD (standart deviation). One way ANOVA test and Tukey HDS test was used. p<0.05 is stati stically meaningful. *p<0.05=group I versus group II, †p<0.05= group II versus group III.*

Table 2. Comparison of OPN levels and BMD within groups.

	OPN (ng/ml)	Lomber spine BMD(g/cm²)	Lomber spine T score	Lomber spine Z score	Total hip BMD(g/cm²)	Total hip T score	Total hip Z score
Group I, Healthy controls	49.7 ± 0.22	1.12±0.1	- 1.6±1.1	-0.3±0.3	1.24±0.2	-1.2±1.3	-0.2±0.4
Group II, ART receiving OP patients	22.6 ± 0.21	0.88±0.4	- 2.9±0.7	-0.9±0.8	0.91±0.7	-2.5±1.2	-0.8±0.7
Group III, OP patients who do not receive treatment	40.2 ± 3.03	0.92±0.3	-2.7±0.6	-0.7±0.6	0.95±0.6	-2.4±0.9	-0.6±1.3
P_1	***< 0.001***	***< 0.034***	***< 0.027***	***< 0.009***	***< 0.042***	***< 0.023***	***< 0.013***
P_2	***< 0.001***	***< 0.021***	***< 0.012***	***< 0.001***	***< 0.023***	***< 0.021***	***<0.001***
P_3	*> 0.05*	***< 0.024***	***< 0.022***	***< 0.019***	***< 0.036***	***< 0.024***	***< 0.012***
P_4	***< 0.004***	*> 0.05*	*> 0.05*	***< 0.044***	*> 0.05*	*> 0.05*	***< 0.032***

p_1=Comparison of groups I, II and III, p_2= group I versus group II, p_3= group I versus group III, p_4= group II versus group III. Values were shown as average ± SD (standart deviation). Kruskal-Wallis test, One way ANOVA test, and Tukey HDS test was used. p<0.05 is statistically meaningful.

Table 3. Comparison of ART receiving patients' OPN levels within group.

Antiresorptive treatment	Patient count (n)	OPN (ng/ml)	P
Biphosphonate	15	17.6±11.8	**<0.001**
Strontium ranelate	15	36.5±17.4	0.233
SERM	15	13.6±8.8	**<0.001**
Calcitonin	15	15.6±11.7	**<0.001**
No drug use	30	40.2 ± 3.03	

Values were shown as average ± SD (standart deviation).Mann -Whitney U test was used for statis tics. p<0.05 is statistically meaningful.

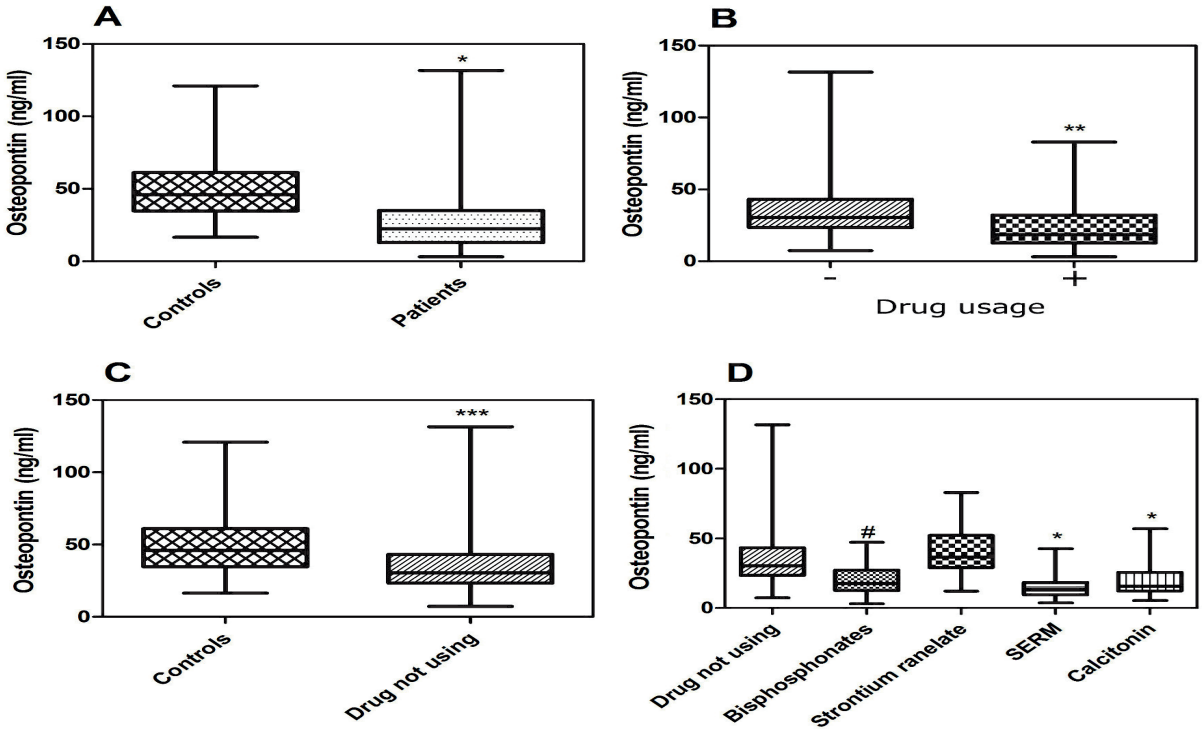

Figure 1. OPN levels in OP patients and controls. A) Comparison of OPN levels between OP patients and controls. OPN levels were lower in patients regardless of whether they receive ART or not (*p<0.0001). B) Comparison of OPN levels between ART receiving and non-receiving OP patients. OPN levels were lower in patients who receive ART (**p=0.0005). C) Comparison of OPN levels between non-receiving ART OP patients and controls. OPN levels were similar (***p>0.05). D) Comparison of the OPN levels in ART-receiving patient subgroups and patients who do not receive treatment. For bisphosphonate (#p=0.003), SERM (*p<0.0001), and calcitonin (*p<0.0001) there was a significant decrease while there was no change in strontium ranelate (p>0.05).

Yazarlarla ilgili bildirilmesi gereken konular (Conflict of interest statement) : Yok (None)

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