Journal of Health, Medicine and Nursing
ISSN 2422-8419 An International Peer-reviewed Journal
Vol.80, 2020

The Role of Bone Turnover Markers in the Follow up of the Treatment of Osteoporosis

Nazife Yasemin Ardicoglu Akisin[1*] Aylin Aker Ayrı[2]
1.TOBB Economy and Technology University, Department of Biochemistry
2.Medikal Park Hospital, Department of Gynecology

Acknowledgement: We would like to express our gratitude to Prof.Dr.B. Adam who served as the supervisor of the thesis from which this study was adapted.

Abstract
Although bone mineral density (BMD) measurement is the common method for the diagnosis of postmenopausal osteoporosis (PMO, bone turnover markers have been proposed as good indicators for monitoring the efficiency of antiresorptive treatment. We aim to evaluate course of bone turnover markers in the follow-up of treatment osteoporosis and compare the results of these markers with bone mineral densities. 47 postmenopausal patients were included in this study. The age average of the patients was 59.1±7.6 (48-81). Patients were divided into 5 groups depending on the type of the treatment: Calcium and vitamin D (8 patients); calcium, vitamin D and risendronate (10 patients); calcium, vitamin D and alendronate (10 patients); calcium, vitamin D and hormone replacement therapy (tibolone) (9 patients) and calcium, vitamin D and calcitonine (10 patients). Samples were taken from each group, prior to treatment and in the third and sixth months of the treatment. Bone mineral density measurements were carried out before the treatment and in the sixth month. The basal concentrations of bone turnover markers [serum Type I collagen C-telopeptide (CTX), N-mid-Osteocalcin (OC) and urinary deoxypridinoline (Dpd)] and Interleukin-1β (IL-1β) were compared to the values in the third and sixth month of the therapy and also to BMD.OC, CTX and Dpd are good markers for the evaluation the effectiveness antiresorptive therapy. The changes in CTX and OC seems to be reflect the changes in bone mass in the early period. However, the changes in Dpd levels come out later. HRT (tibolone) and biphosphonates especially risendronate are thought to be effective therapeutic approaches, because a significant decrease in bone turnover markers and an improvement in BMD – especially in lombar vertebra - were observed in the follow up of treatment. A good correlation found between the changes in levels of CTX and Dpd and changes in BMD during treatment, which suggest that these two markers would be useful for monitoring response to antiresorptive therapy.

Keywords: Postmenopausal osteoporosis, bone turnover markers, serum Type I collagen C-telopeptide, N-mid-Osteocalcin, urinary deoxypridinoline, Interleukin-1β
DOI: 10.7176/JHMN/80-14
Publication date: September 30th 2020

1. Introduction

PMO is a disease characterised by low bone mineral denisty and microarchitecural impairment -as result of reduction in circulating estrogen causing an accelerated bone turnover and resorption- which lead to bone fragility and an increase risk of fractures. It is a very serious health problem leading to significant morbidity, disability, mortality and decreased quality of life (1,2). Bone mineral density (BMD) measurement is the most common method used for the diagnosis and the follow-up of the treament of osteoporosis (3). However, changes in BMD measured by densitometry are not detected until the bone loss is great, therefore it would be useful to have dynamic tests that could reflect the changes earlier (4). In recent years, for the evaluation of efficiency of the treatment of osteoporosis, bone formation and resorption markers are being used. With these markers, earlier information can be obtained when compared to bone mineral density measurement, so that they may be used to detect patients who do not respond to therapy (5,6). The magnitude and the timing of reduction (within weeks) in the levels of bone turnover markers are thought to be their advantage when compared to BMD measurements by which slower changes and smaller magnitude are obtained (7).

Antiresorptive agents (biphoshonates and calcitonin), hormone replacement therapy (ERT-tibolone) and calcitriol (1,25 dihydroxyvitamin D) with calcium supplementation are the most widely used treatments in PMO. Biphosphonates directly reduce the bone turnover by inbiting the activity of osteoclasts (3,8) . Randomized placebo-controlled studies with alendronate and risendronate show their effect on inducing the gain of BMD, reducing the increased rates of bone turnover and decreasing the risk of fractures (2,9,10). In previous studies, it was shown that calcitriol increases bone mass not only at lumbar spine but also at femoral neck (11,12). Another common therapeutic approach, calcitonin stimulates the increase in bone mass and also decreases in bone resorption markers and OC levels (13,14). Tibolone, synthetic estrogenic, prosgestagenic and androgenic steroid, reduces bone resorption by decelerating bone turnover (15). Recent studies have revealed that tibolone is

effective in incerasing the bone mass and that was proved by the increase in BMD measurement and decrease in bone turnover markers (16,17).

In this study, we aim to show that the bone turnover markers are as reliable as BMD measurement in the follow-up of the treatment of PMO and reflect the changes in bone mass earlier and also, to select the earliest marker that can reflect the changes in BMD.

2. Patients and Methods

2.1.Subjects

Forty-seven postmenopausal women [aged 48-81 (59.1±7.6)] who were admitted to Fatih University Faculty of Medicine Department of Obstetrics and Gynecology were taken in this study. Osteoporosis was confirmed with BMD measurement.

The patients were in menopause for 5 years and diagnosis of osteoporosis was made according to the criteria declared by World Health Organisation. None of the patients had used medication neither for osteoporosis nor effecting bone mass and none had a disease that effects bone metabolism or cause secondary osteoporosis.

All patients were given Ca 1500 mg, D vitamini 400 IÜ daily. They were divided into 5 groups depending on the type of the treatment: only calcium and vitamin D (8 patients); calcium, vitamin D and risendronate (10 patients); calcium, vitamin D and alendronate (10 patients); calcium, vitamin D and hormone replacement therapy (tibolon) (9 patients) and calcium, vitamin D and calcitonine (10 patients). Blood and urine samples were taken from each group, prior to treatment and in the third and sixth months of the treatment. Bone mineral density measurements were carried out before the treatment and in the sixth month.

2.2 Assays

The blood and urine specimens were immediately santrifuged, seperated and stored at -20^{o}C till analysis. Serum calcium (Ca), phosphorus (P), creatinine (Crea), alkaline phosphatase (ALP) levels and urinary calcium and creatinine levels were measured by Hitachi 912 (Roche Diagnostics Co., Mannheim, Germany) autoanalyzer. The creatinine clearance is calculated according to the formula. Serum IL-1β and urinary DPD (Pyrilinks-D) levels were measured by IMMULITE One Analyzer (DPC Diagnostic Products Co., CA, USA) using chemiluminescent immunoassay. Serum CTX (β-crossLabs) ve N-mid OC levels were measured by Roche Elecsys 2010 Analyzer (Roche Diagnostics Co., Mannheim,Germany) using electrochemiluminescent immunossay. All the analysis were made in single run after and calibration of the assay was controlled by spesific control seras. The inter-assay and intra-assay coefficients of variation (%CV) are shown in the Table 1.

Table 1. The inter-assay and intra-assay %CV for the parameters

Tests	***İntra assay***		***İnter assay***	
	Mean	***% CV***	***Mean***	***%CV***
Serum Ca (mg/dl	8.48	0.9	8.38	1.5
Serum Crea (mg/dl)	1.54	0.9	1.54	2.1
Serum P (mg/dl)	1.38	0.9	1.91	1.4
Serum ALP (U/L)	458	0.5	357	2.2
Urinary Crea (mg/24 h)	23.97	0.8	24.44	2.1
Urinary Ca (mg/24h)	14.28	0.8	13.96	1.2
Serum CTX (ng/ml)	0.08	4.6	0.08	4.7
Serum OC (ng/ml)	6.95	0.7	7.04	1.6
Serum IL-1β (pg/ml)	39	2.8	13	7.7
Urinary DPD (nM DPD/mM crea)	30	15	30	20

2.3.Bone Mineral Density

BMD of lumbar vertebra (L2-L4), femur neck and Ward's triangle were measured by dual energy X-ray absorptiometry (Lunar Radiation Corporation) at the beginning and in the sixth month of the treatment.

2.4.Statistics

The sattistical analysis was performed with SPSS for Windows 9.0 software programme. One-way analysis of variance (ANOVA) and Banferroni test were used to compare the changes between groups for normally distributed variables and Kruskall-Wallis analysis of variance for the non- normally distributed variables. To compare the changes due to time with in the groups, ANOVA for the normally distributed variables and Paired t ve Wilcoxon test were used. Pearson correlation analysis method was used for the correlation analysis. Results were given as mean ± SD. Statistical significance was assumed with $p<0.05$.

3. Results

The groups were well matched in age, the age of menopause and menarche ??, BMI (Body Mass Index), smoking and creatinine clearance (Table 2). During the follow-up no fractures or side effects occured.

Table 2. Demographic characteristics of the patients

	Group I (n=8)	Group II (n=10)	Group III (n=10)	Group IV (n=9)	Group V (n=10)
Age	58.3±2.9	60.8±8.3	61.1±7.6	55.5±8.0	59.5±9.2
Age of menarche	13.1±1.1	13.9±1.1	13.1±1.9	13.3±1.0	12.9±1.1
Age of menopause	45.1±4.8	48.2±3.1	46. ±4.3	48.1±5.5	47.6±4.1
BMI (kg/m^2)	23.0±1.0	24.7±3.1	26.0±7.1	26.5±3.9	26.2±4.4
Smoking	4 (%50)	2 (%20)	5 (%50)	2 (%22)	2 (%20)

Lombar vertebra, femur neck, Ward's triangle BMD values of the groups were compared with eachother (Table 3).

Table 3. Baseline and sixth month BMD values

	Lombar Vertebra		*Femur Neck*		*Ward's Triangle*	
	Baseline	**6. month**	**Baseline**	**6. month**	**Baseline**	**6. month**
Group I (n=8)	–3.35 (-3.33±0.16)	–2.77* (-2.75±0.22)	–2.13 (-2.15±0.2)	–1.96* (-1.94±0.2)	-2.83 (-2.80±0.9)	-2.51 * (-2.50±0.12)
Group II (n=10)	–2.18 (-2.13±0.65)	–1.40 * (-1.50±0.87)	–1.21 (-1.12±0.59)	–1.40 (-1.40±0.5)	-1.71 (-2.00±1.2)	-1.92 (-2.05±0.8)
Group III (n=10)	–2.18 (-2.21±1.00)	–1.64* (-1.53±0.8)	–1.76 (-1.52±0.7)	–1.46* (-1.33±0.8)	-2.64 (-2.95±0.97)	-2.13 * (-2.60±1.30)
***Group IV* (n=9)**	–1.64 (-1.73±1.02)	–1.20* (-1.70±1.0)	–1.43 (-1.22±0.5)	–1.21 (-0.90±0.66)	-2.38 (-2.50±0.3)	-2.01 (-2.20±0.6)
Group V (n=10)	–2.78 (-2.55±0.67)	–1.93* (-2.02±0.8)	–1.45 (-1.14±1.0)	–1.35 (-1.05±1.1)	–1.45 (-1.14±1.0)	-1.73 (-1.50±1.2)

* Significant difference in sixth month compared to baseline ($p < 0.05$)

The increase in lombar vertebra, femur neck ve Ward's triangle scores in the sixth month were significantly different for the group I and III when compared to baseline values ($p<0.05$). For the groups II, IV and V significant difference was seen only in lomber vertebra scores ($p<0.05$).

During the siz month follow up, the changes in bone turnover parameters in time and in and between the groups are shown in Figure1 and Table 4.

Figure 1. The changes in bone turnover parameters in time

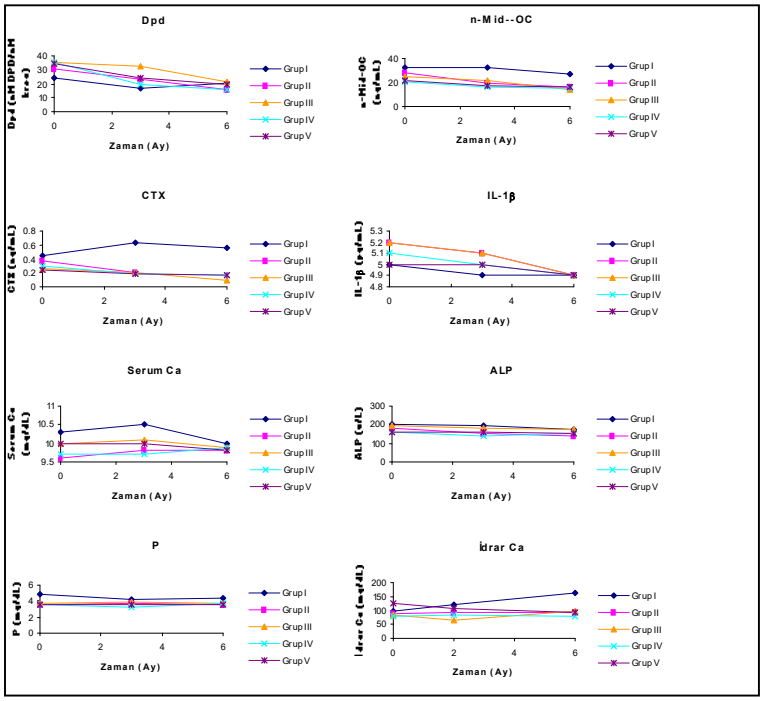

Table 4. The changes in bone turnover parameters in time and in end between groups

	OC [1]			CTX [2]		
	Baseline	**3rd month**	**6th month**	**Baseline**	**3rd month**	**6th month**
Group I	32.6±4.3	32.6±6.2$^{*\,b}$	27.2±5.16^{*c}	0.45±0.22	0.63±0.12*	0.56±0.48^{c}
Group II	28.5±12.2^{1a}	19.8±9.2^{b}	15.8±7.6^{c}	0.37±0.37^{2a}	0.2±0.18	0.06±0.06^{c}
Group III	24.8±11.9	21.1±10.1	14.4±5.4^{c}	0.26±0.19	0.20±0.17*	0.1±0.07^{c}
Group IV	21.0±5.8^{a}	16.6±5.6	14.7±6.5^{c}	0.29±0.19^{a}	0.18±0.12	0.16±0.10^{c}
Group V	21.3±14.0	17.3±9.9	16.7±11.5	0.24±0.12	0.19±0.13	0.17±0.15

	Dpd [1]			IL-1β		
	Baseline	**3rd month**	**6th month**	**Baseline**	**3rd month**	**6th month**
Group I	24.1±3.2^{a}	17.0±2.50*	20.4±14.3	5.07±0.1	4.96±0.11	4.90±0.9^{c}
Group II	30.6±12.9	23.2±10.9^{b}	15.7±6.28^{c}	5.23±0.2^{a}	5.10±0.13^{b}	4.90±1.13^{c}
Group III	35.3±18.8	33.1±15.2^{*b}	21.3±10.5^{c}	5.22±0.2	5.10±0.13^{b}	4.95±0.11^{c}
Group IV	35.6±28.9^{a}	19.4±11.9	15.7±6.35^{c}	5.1±0.1a	5.04±0.15^{b}	4.90±0.14
Group V	34.6±20.1^{a}	24.0±9.6^{b}	20.03±6.8	5.02±0.8	5.01±0.09^{b}	4.94±0.18

	sCa			sP		
	Baseline	**3rd month**	**6th month**	**Baseline**	**3rd month**	**6th month**
Group I	10.36±0.24*	10.55±0.2^{*b}	10.05±0.20	4.81±0.34*	4.25±0.53*	4.36±0.31*
Group II	9.65±0.59*	9.8±0.43*	9.86±0.50	3.69±0.52	3.67±0.45	3.59±0.55*
Group III	10.05±0.65	10.16±0.44	9.95±0.43	3.79±0.55	3.85±0.57	3.74±0.57
Group IV	9.75±0.37	9.76±0.61*	9.97±0.73	3.54±0.67	3.25±0.43^{*b}	3.68±0.40
Group V	10.08±0.44	10.05±0.66	9.87±0.63	3.63±0.46	3.62±0.44	3.57±0.41*

	ALP			uCa		
	Baseline	**3rd month**	**6th month**	**Baseline**	**3rd month**	**6th month**
Group I	205.6±10.1^{a}	193.0±4.03^{b}	174±15.3^{c}	96.71±73.8^{a}	119.9±19^{b}	161.1±88^{c}
Group II	180.8±46.9	153.0±51.4^{a}	139.1±47^{b}	89.01±36.4^{c}	91.24±33.7	90.70±54.2
Group III	198.5±55.1	182.0±41.4	171.0±52.1	84.1±67.0	64.88±61.0	96.45±69.0
Group IV	158.5±26.8^{a}	141.4±16.7	155.3±21.8	80.47±55.1	84.58±45.7	79.38±50.4
Group V	163.4±31.9	160.9±34.0	153.8±33.8	124.6±100.	108.5±53.5	95.06±66.6

* : significantly different compared to other groups ($p<0.05$)
^{a} : significant difference between baseline and 3rd month
^{b} : significant difference between 3rd month and 6th month
^{c} : significant difference between baseline and 6th month
^{1} : borderline difference due to time and treatment groups
^{2} : significant difference due to time and treatment groups ($p<0.01$)

Baseline OC levels were found similiar between the groups when we compare the five treatment groups. However, in group I the elevation in the 3rd and 6th month found different when compared to other groups ($p<0.05$). Dpd levels were found significantly lower in 3rd month in group I ($p<0.05$) and significantly higher in group III ($p<0.05$). For serum Ca levels, baseline values were significantly higher in group I and lower values in group II and 3rd month values were found significantly higher in group I and lower in group II and IV ($p<0.05$). Serum baseline P levels were found only different in group I ($p<0.05$). In the 3rd month, the elevation in group I and the fall in group IV and in the sixth month the elevation in group I and fall in group II and V were found significant ($p<0.05$). CTX, IL-1β, ALP and urinary Ca levels show no difference in groups.

When we compare the parameters in group I due to time, OC levels decrease in the 6th month when compared to baseline and 3rd month ($p<0.01$). Only significant decrease in CTX levels was seen in between 3rd and 6th month ($p<0.01$). Dpd levels were found to decrease in 3rd month ($p<0.01$) and IL-1β levels were found significantly different between the baseline and sixth month ($p<0.05$). Significant decrease was seen in 6th month when compared to 3rd in serum ca levels ($p<0.05$). The decrease in all ALP and urinary Ca levels were significant ($p<0.05$), but no difference was observed in P levels.

For the parameters in group II, OC levels in the 3rd month compared to baseline and in the sixth month compared to 3rd were found significantly lower ($p<0.01$,$p<0.05$). CTX levels were lower in 3rd and 6th month compared to baseline ($p<0.05$). Dpd levels in the 6th month were lower than the baseline and the 3rd

month($p<0.05$). The decrease in IL-β and ALP levels were found significant although they were in normal range ($p<0.05$). No significant difference were noted for urinary Ca and serum P levels.

OC and CTX were foun lower only in the 6th month compared to baseline($p<0.05$) in the group III. The difference in Dpd and IL-1β levels were detected in the 6th month when compared to baseline and 3rd month($p<0.01$, $p<0.05$). No significant difference were noted for serum and urinary Ca, serum P and ALP levels.

We found significant decrease in OC, CTX and Dpd levels in the 3rd and 6th month in group IV when compared to baseline ($p<0.05$), however the difference between the 3rd and the 6th month was insignificant. The significant decrease were seen between the 3rd and the 6th month for IL-1β levels ($p<0.01$), in the 3rd month for ALP levels ($p<0.05$) and in the 6th month for P levels ($p<0.05$).

In group V, Dpd levels were significantly lower in 3rd month than baseline and in 6th month than 3rd month ($p<0.05$) and IL-1β levels decrese in the 6th month compared to 3rd month ($p<0.05$).

When we evaluate the results depending on the comparison either between the groups or due to time, we found that the difference for OC ($p= 0.68$) and Dpd ($p=0.71$) were at/in? borderline, for CTX it is significant ($p<0.01$), and for IL-1β, serum Ca, ALP, P ve urinary Ca it is insignificant.

BMD scores seems to correlate with OC, IL-1β, Dpd and P levels at the beginning of the treatment and with OC, CTX and Ddp levels in the 6th month. A correlation was observed between OC and CTX levels not only at the beginning but also in the 6th month.

4. Discussion

Osteoporosis is a common health problem for the postmenopausal women. In recent years, researchers aim to find new bone spesific parameters that will facilitate the early diagnosis and the follow-up of osteoporosis.

Osteoporosis is diagnosed by BMD measurement. It was shown that increased bone turnover is correlated with bone loss. Bone loss can be evaluated by bone turnover markers because, the bone mass is determined by bone turnover (18,19). These markers are used to give information about the BMD in an early period than BMD measurement (20,21)

Osteoclastic bone markers [Tartarate resistant acid fosphatase (TRAP), Hyroxyproline (Hyp), Pridinoline (Pyd), Deoxypiridinoline (Dpd), Type I collagen N-telopeptide (NTX), Type I collagen C-telopeptide (CTX)] reflect the bone resorption and formation markers derived from osteoblasts [Osteocalcin (OC), alkaline phosphatase (ALP), type I collagen propeptides) inform us about the future bone loss (20,22,23). In 60-70% of women with early postmenopausal osteoporosis , TRAP,OC, urinary Ca, Hyp and Dpd show bone loss (18,19). Chaki et al. noted that bone spesific ALP, CTX, NTX, OC, Pyd, Dpd can be used to predict future BMD in postmenopausal women (24).

Calcitonin is commonly used in the osteoporosis treatment (25,26). In short-term and long-term placebo controlled studies calcitonin was denoted to be an effective treatment (26,27).

In two previous studies, treatment with tibolone increased BMD and decreased OC and CTX levels and this deceleration in markers are found to be inversely proportional to BMD (28,29). It was also revealed that serum CTX levels reflect the bone loss and future fracture risk (30). Rymer et al. showed that tibolone increased vertebra and femoral neck BMD and cause a decrease in OC and ALP levels in three different long term studies (26,32,32). Also, some other studies support these results and verify the efficiency of tibolone on BMD (17,33-35). Parviainen et al., Christagau et al. and Bjarnason et al noted that tibolone significantly decreases Dpd, CTX and OC levels (36-38).

In their placebo controlled long-term study Greenspan et al. concluded that CTX and NTX predict long-term changes in vertebral BMD in women receiving alendronate (39). Combined treatment with biphosphonates and HRT had a favorable effect on BMD and also decrease bone spesific ALP, NTX, CTX, Dpd levels (40-42). Also, OC levels well correlate with the improvement in BMD made by combined treatment with calcitonin and HRT and can be used in the follow-up of treatment (13,14,43,44). And also by calcitonin therapy while the BMD increases, CTX levels decreases (45). However, there are adverse results of studies about calcitonin in which no change in OC levels were observed (46,47).

In this study, a bone formation marker – OC, two resorption markers – CTX and Dpd- and a cytokine -IL-1β- which thought to have effect on bone turnover were analysed and the suitable marker/markers that can reflect future KMD and that can be used to evaluate the efficiency of treatment are aim to be investigated.

Just about all the parameters analysed start to decrease in the first three months. However, in risendronate and tibolone groups the decrease were significant. The decrease in OC, CTX and Dpd levels in the 6th month correlate with the KMD scores.

It is known that the antiresorptive treatment given inhibits bone resorption and indirectly effects on bone formation. In our study, CTX and OC decreases in four groups except the calcitonin group. Also, in tibolone and risendronate group the decreased revealed earlier (in the 3rd month). OC and CTX levels were in correlation

during the six months period. The decrease in Dpd levels found insignificant only in the group which was given only Ca and vitamin D. Other groups had shown signifiant decrease in the 6th month, also, this descending began in the 3rd month in tibolone group. No statistical difference was found between CTX and OC levels in evaluating the effectiveness of treatment or reflecting the future bone status.

Estrogen defficiency has the major role in postmenopausal osteoporosis. Recent studies direct us to a fact that, estrogen stimulates the secretion of local factors that effect bone remodeling and in the absence of estrogen this mechanism is impaired (48). IL-1β is one of these factors that stimulates the differentiation and activation of osteoclasts. IL-1β is inreased in some cases with estrogen deficiency except menopause and this supports the modulator effect of estrogen on cytokines (49-52). IL-1β levels were significantly higher in women with potmenopausal osteoporosis compared to healthy ones and also found inversely proportional to the BMD (53,54). Also, studies with different results exist. In these studies no difference was observed in IL-1β levels in postmenopausal period and no correlation was detected with BMD (55,56).

In our study, the IL-1β levels were decreased in risendronate in the 3rd month, but significant difference was detected in other groups in the 6th month. No correlation between IL-1β levels and BMD were observed. This prevensts IL-1β to be the marker.

Only the change in CTX levels between groups and due to time is significant. The significance for OC and Dpd is in/at?? borderline. The changes in IL-1β, serum Ca, ALP, P and urinary Ca levels are insignificant.

Lombar vertebra BMD scores were significantly elevated in all treatment groups. The increase in femur neck and Ward's triangle scores are increased in Ca and vitamin D group and in risendronate group. The correlation between the BMD and OC and CTX were significant in the 6th month.

We concluded that, CTX and OC are the suitable markers for the follow-up of the treatment of postmenopausal osteoporosis. The changes in their levels also give information about the future-period bone mineral density. Considering the decrease in these parameters and the increase in the bone mineral density, the most appropriate treatments were determined as tibolone and risendronate and with these treatments, improvement in bone mineral density became most evident in lomber vertebra.

References

Osteoporoz , Atik Şahap, Ankara 1998, Meteksan A.Ş.

Shchimmer RC, Bauss F, Effect of daily and intermittent use of ibandronate on bone mass and bone turnover in postmenopausal osteoporosis: A review of three phase II studies, Clinical Therapeutics 25(1):19-34,2002

Body JJ, Gaich GA, Scheele WH, Kulkarni P, Miller PD, Peretz A, Dore RK, A randomized double-blind trial to compare the efficacy of teriparatide [recombinant human parathyroid hormone (1-3)] with alendronate in postmenopausal women with osteoporosis, J Endocrinol Metab 87(10):4528-4535.

De Leo V, Ditto A, la Marca A, Lanzetta D, Massafra C, Morgante G, Bone mineral density and biochemical markers of bone turnover in peri- and postmenopausal women, Calcif Tissue Int 66:263-7,2000

Chapurlat RD,Cummings SR, Does follow-up of osteoporotic women treated with antiresorptibe therapies improve effectiveness? Osteoporos Int 13:738-44,2002.

Delmas PD, Eastell R, Garnero P, Seibel MJ, Stephan J. The use of biochemical markers of bone turnover in osteoporosis. Osteoporos Int,Suppl 6:S2-17,2000

Riggs BL. Are biochemical markers for the bone turnover clinically useful for the monitoring therapy in individual osteoporotic patients? Bone 26:551-2,2000.

Russel RG, Rogers MJ, Biphosphonates from the laboratory to the clinic and back again, Bone,25:97-106,1999.

Harris ST, Eriksen EF, Davidson M et al. Effect of combined risedronate and hormon replacement therapies on bone mineral density in postmenopausal women, J Clin Endocrinol Metab, 86:5,1890-7,2001

Reginster JY, Deroisy R, Dougados M, Juspin I, Colette J, Roux C, Prevention of early postmenopausal bone loss by strontium ranelate: The randomized, two year, double-masked, dose ranging, placebo-controlled PREVOS Trial, Osteoporos Int 13:925-31,2002

Sairenen S, Karkkainen M, Tahtela R, Laitinen K, Makela P et al. Bone mass and markers of bone and calcium metabolism in postmenopausal women treated with 1,25-dihydroxyvitamin D (Calcitriol) for four years, Calcif Tissue Int 67:122-7,2000

Ooms ME, Roos JC, Bezemer PD, van der Vijgh WJ et al. Prevention of bone loss by vitamin D supplementation in elderley women: a randomized double blind trial, J Clin Endocrinol Metab 80:1052-8,1995

Kraenzlin ME, Seibel MJ, Trechsel U et al. The effect of intranasal salmon calcitonin on postmenopausal bone turnover as assessed by biochemical markers: evidence of maximal effect after 8 weeks of continous treatment. Calcif Tissue Int, 58:216-20, 1996

Bütün B, Tuncer T, Akyokuş A ve ark. Primer osteoporozlu hastalarda çeşitli tedavi şekillerinin serum osteokalsin düzeyi üzerine etkisi. Romatol Tıb Rehab, 5:16-21, 1994

Yılmaz H, Ceran F, Şaşak G ve ark. Osteoporozun medikal tedavisi Dirim Aylık Tıp Dergisi, 77(6):6-12,2002
Rymer J, Robinson J, Fogelman I, Ten years of treatment with tibolone 2.5 mg daily: effects on bone mass in postmenopausal women, Climacteric, 5(4):390-8,2002
Gallagher JC, Baylink DJ, Freeman R, Prevention of bone loss with tibolone in postmenopausal women: results of two randomized, double-blind, placebo-controlled, dose-finding studies, J Clin Endocrinol Metab, 86(10):4717-26,2001
Christiansen C, Riis BJ, Rodboro P, Prediction of rapid bone loss in postmenopausal women, Lancet,1:1105,1987
Christiansen C, Riis BJ, Rodboro P, Screening procedure for women at risk of developing postmenopausal osteoporosis, Osteoporos Int, 1:35,1990
Cosman F, Nieves J, Wilkinson C et al. Bone density change and biochemical indices of skeletal turnover, Calcif Tissue Int, 58:236,1996
Reeve J, Pearson J, Mitchell A et al. Evolution of spinal bone loss and biochemical markers of bone remodeling after menopause in normal women, Calcif Tissue Int, 57:105, 1995
Mole PA, Walkinshaw MH, Robins SP, Can urinary pyridinium crosslinks and urinary estrogens predict bone mass and rate of bone loss after menopause? Eur J Clin Invest,22:767,1992
Mole PA, Walkinshaw MH, Robins SP, Can urinary pyridinium crosslinks and urinary estrogens predict bone mass and rate of bone loss after menopause? Eur J Clin Invest,22:767,1992
Chaki O, Yoshikata I, Kikuchi R et al. The predictive value of biochemical markers of bone turnover for bone mineral density in postmenopausal Japanese women, J Bone Miner Res, 15:8,1537-44,2000
Aloia JF, Miele G, Culleton J et al. Treatmant of osteoporosis with salmon calcitonin- clinical experience with 100 patients. Adv Ther, 8:36-47, 1991
Reginster JY, Meurmans L, Deroisy L et al. A 5-year controlled randomized study of prevention of postmenopausal trabecular bone loss with nasal salmon calcitonin and calcium. Eur J Clin Invest, 24: 565-9,1994
Gruber HE, Ivey JL, Baylink DJ et al. Longterm calcitonin therapy in postmenopausal osteoporosis. Metab Clin Exp, 33:295-303, 1984
Roux C, Pelissier C, Fechtenbaum J, Randomized, double masked, 2-year comparison of tibolone with 17 beta-estradiol and norethhidrone acetate in preventing postmenopausal bone loss, Osteoporos Int, 13(3):241-8,2002
Chailurkit L, Ongphiphadhanakul B, Piaseu N, Saetung S, Rajatanavin R, Biochemical markers of bone turnover and response of bone mineral density to intervention im early postmenopausal women : An experience in a clinical laboratory, Clin Chem, 46:6,1083-88,2001
Garnero P, Borel O, Delmas PD, Evaluation of a fully automated serum assay for C-terminal cross-linking telopeptide of type I collagen in osteoporosis, Clin Chem, 47:4, 694-702,2001
Rymer J, Robinson J, Fogelman I, Effects of 8 years treatment with tibolone 2.5 mg daily on postmenopausal bone loss, Osteroporos Int, 12(6):478-83,2001
Rymer J, Chapman MG, Fogelman I, Effects of tibolone on postmenopausal bone loss, Osteoporos Int, 4(6):314-9,1994
Milner M, Harrison RF, Gilligan E, Bone density changes during two years treatment with tibolone or conjugated estrogens and norgestrel, compared with untreated contols in postmenopausal women, Menopause, 7(5):327-33,2000
Beardsworth SA, Kearny CE, Purdle DW, Prevention of postmenopausal bone loss at lumbar spine and upper femur with tibolone: a two-year ransomised contolled trial, Br J Obstet Gynaecol, 106(7):678-83,1999
Lippuner K, Haenggi W, Birkhauser MH, Prevention of postmenopausal bone loss using tibolone or conventional peroral or transdermal hormone replacement therapy with 17beta-estradiol and dydrogesterone, J Bone Miner Res, 12(5):806-12,1997
Parviainen MT, Jaaskelainen K, Kroger H, Urinary bone resorption markers in monitoring treatment of symptomatic osteoporosis, Clin Chim Acta, 279(1-2):145-54,1999
Christagau S, Rosenquist C, Alexandersen P, Clinical evaluation of the serum CrossLabs One Step ELISA, a new assay measuring the serum concentration of bone-derived degradation products of type I collagen C-telopeptides, Clin Chem, 44(11):2290-300,1998
Bjarnason NH, Bjarnason K, Haabo J, Tibolone: prevention of bone loss in late postmenopausal women, J Clin Endocrinol Metab, 81(7):2419-22,1996
Greenspan S, Rosen HN, Parker RA, Early changes in serum N-telopeptide and C-telopeptide cross-linked collajen type I predict long-term response to alendronate therapy in elderly women, J Clin Endocrinol Metab, 85:10,3537-40,2000.
Harris ST, Eriksen EF, Davidson M et al. Effect of combined risedronate and hormon replacement therapies on bone mineral density in postmenopausal women, J Clin Endocrinol Metab, 86:5,1890-7,2001

Christgau S, Bitsch- Jensen O, Bjarnason H et al. Serum crossLabs for monitoring the response in individuals undergoing antiresorptive therapy, Bone, 26:5,505-11, 2000

Johnell O, Schele WH, Lu Y et al. Additive effects of raloxifene and alendronate on bone density and biochemical markers of bone remodeling in postmenopausal women with osteoporosis, J Clin Endocrinol Metab, 87:3,985-92,2002

De Leo V, Ditto A, la Marca A, Lanzetta D, Massafra C, Morgante G, Bone mineral density and biochemical markers of bone turnover in peri- and postmenopausal women, calcif Tissue Int, 66,263-7,2000

Johansen JS, Riis BJ, Delmas PD, Christiansen C, Plasma BGP: an indicator of spontaneous bone loss of the effect of oestrogen treatment in postmenopausal women, European Journal of Clinical Investigation 18,191-95,1988

Sairanen S, Karkkainen M, Tahtela R et al. Bone mass and markers of bone tuırnover and calcium metabolism in postmenopausal women treated with 1,25-Dihydroxyvitamin D (Calcitriol) in four years, Calcif Tissue Int, 67,122-7,2000

Gonelli S, Cepollaro C, Montomoli M et al. Treatment of postmenopausal osteoporosis w.th recombinant human growth hormon and salmon calcitonin: a placebo controlled study. Clin Endocrinol, 46:55-61, 1997

Kollerup G, Hermann AP, Brixen K et al. Effects of salmon calcitonin suppositories on bone mass and turnover in established osteoporosis. Calcif Tissue Int, 54:12-5, 1994

Horowitz M, Cytokines and estrogen in bone: Anti-osteoporotic effects. Science, 260:626-27, 1993

Hgasen AK, Nordsletten L. Aasen AO, et al. There is no difference in spontaneus and 17-beta estradiol induced interleukin-1 beta release by peripheral blood mononuclear cells from non-osteoporotic women with different rates or early postmenopausal bone loss. J Clin Endocrinol Metab. 80(80): 2480-4, 1995

Pacifici R. Estrogen, cytokines and pathogenesis of postmenopausal osteoporosis. J Bone Miner Res, 11: 1043-51, 1998

Manolagas SC, Jilka RL. Bone marrow, cytokines and bone remodeling. N Engl J Med, 332: 305-11, 1995

Pacifici R. Estrogen, cytokines and pathogenesis of postmenopausal osteoporosis – the second decade. Endocrinology, 139(6): 2659-61, 1998

Zheng SX, Vrindts Y, Lopez M et al. Increase in cytokine production (IL-1β, IL-6, TNF-α but not IFN-γ,GM-CSFor LIF) by stimulated whole blood cells in postmenopausal osteoporosis, Maturitas, 26, 63-71,1997

Pacifici R, Rifas L, Teitelbaum S et al. Spontaneous release of interleukin-1 from human whole blood monocytes reflects bone formation in idiopathic osteoporosis. Proc Natl Acad Sci USA, 84: 4616-20, 1987

Khosla S, Peterson JM, Egan K et al. Circulating cytokine levels in osteoporotic and normal women. J Clin Endocrinol Metab, 79: 707-11, 1994

Mc Kane WR, Khosla S, Peterson JM et al. İrculating levels of cytokines that modulate bone resorption: effects of age and menopause in women. J Bone Miner Res, 9: 1313-18, 1994