Comparison of Single Agent and Combination Therapy of Alendronate and Tibolone in Postmenopausal Osteoporosis

POSTMENOPOZAL OSTEOPOROZDA ALENDRONAT VE TİBOLONUN TEK BAŞINA VE KOMBİNE KULLANIMLARININ KIYASLANMASI

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Abstract

Objective: Aim of this study was to compare the effect of tibolone (T), alendronate (A) and T + A treatment on bone mineral density (BMD) and bone remodelling markers in postmenopausal women with osteoporosis.

Material and Methods: 60 women having osteoporosis were enrolled to the study. The patients were divided into 3 groups. Alendronate 10 mg/day was given to the first, tibolone (T) 2.5 mg/day was given to the second, T + A were given to the third group for a year. 1500 mg/day calcium supplementation were given to all groups. BMD and bone remodelling markers were measured before and after the treatment.

Results: There was statistically significant increase in BMD in T + A group than the other two. If T and A groups compared, only A was found to be superior than T. Bone remodelling markers were found to be decreased significantly in all groups. Decrease in these markers was most significant in T + A group.

Conclusion: T + A is an effective treatment regimen in patients with postmenopausal osteoporosis. Only T or only A treatment can be second choice. In older postmenopausal patients with slower bone turnover and in women with gastrointestinal disorders, only T can be ordered. The economic state of the patient and the country, the effectiveness of the treatment must be considered during planning of treatment regimen.

Key Words: Alendronate, tibolone, bone mineral density, postmenopausal osteoporosis

Özet

Amaç: Postmenopozal osteoporozu olan kadınlarda tek başına tibolon (T), alendronat (A) ile T+A tedavisinin kemik mineral yoğunluğu (KMD) ve kemik turnover belirteçleri üzerindeki etkilerinin kıyaslanması.

Gereç ve Yöntemler: Çalışmaya alınan 60 osteoporozlu kadın 3 gruba ayrıldı. Bir yıl boyunca 1. gruba alendronat 10 mg/gün, 2. gruba tibolon 2.5 mg/gün (T), 3. gruba T + A verildi. Tüm gruplara 1500 mg/gün kalsiyum verildi. Tedavi öncesi ve sonrası KMD ve kemik turnover belirteçleri ölçüldü.

Bulgular: KMD, T + A alan grupta diğer gruplara göre anlamlı derecede yüksekti. Tek başına A alanlarda T alanlara göre KMD'de daha fazla artış tespit edildi. Kemik turnover belirteçleri en çok T + A grubu olmak üzere bütün gruplarda anlamlı derecede düşüş gösterdi.

Sonuç: Postmenopozal osteoporozlu hastalarda T + A etkili bir tedavi rejimidir. Tek başına A veya T ikinci seçenek olarak düşünülebilir. Kemik turnoveri yavaşlamış ileri yaşta hastalarda, gastrointestinal hastalığı olanlarda T tek başına verilebilir. Tedavi planlanırken hem hastanın hem ülkenin ekonomik durumu ve tedavinin etkinliği göz önünde bulundurulmalıdır.

Anahtar Kelimeler: Alendronat, tibolon, kemik mineral yoğunluğu, postmenopozal osteoporoz

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Osteoporosis is a disease which is characterised by low bone density, damage in microstructure of bone and as a result increase in fractures.[1,2] It is a public health problem of growing importance. Most important complication of osteoporosis is fractures. Osteoporotic fractures are seen mostly in vertebraes (11-15%), femur neck (6-9%), distal radius (2-5%), proximal humerus (8%) and pelvis (2-3%).[1,3,4] Vertebral fractures worsens quality of life. Femoral fractures cause 12-60% mortality and more than 60% morbidity in patients over 50 years. There is persistent debility in 50% of the patients.

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Dual-energy X-ray absorptiometry (DEXA) is a method used with very high sensitivity in diagnosis and follow up of osteoporosis.[5] It is accepted as optimal method to examine bone density of regional skeletal system or total bone density.[6] DEXA determines both cortical and trabecular bone density as g/cm^2.

Today there are many agents used in the treatment of osteoporosis. Hormon replacement therapy (HRT) is important in both prevention and treatment of osteoporosis. Estrogens were shown to increase serum calcitonin and active vitamin D levels.[7,8] They are effective on both osteoclasts and osteoblasts. They directly inhibit lysosomal activities of osteoclasts and prevent resorption. They regulate cytokines which stimulates osteoclasts (IL 1-B, IL 6, IL 1 alpha, IL 11). Their effects on osteoblasts are indirect and at the post receptor level. Estrogens increase production of transforming growth factor beta. This factor stimulates osteoblastic activity. For these reasons HRT is accepted as gold standard in prevention and treatment of postmenopausal osteoporosis.[7,8] Today HRT mainly consists of continuous estrogen-progesteron, cyclic estrogen-progesteron and tibolone (T) therapy.[9]

Another agent used very frequently in treatment of osteoporosis alone or with HRT is bisphosphonates. Bisphosphonates are analogues of pyrophosphates in bone structure. Bisphosphonates inhibit bone resorption powerfully both in vivo and in vitro conditions. They bind hydroxyapatite crystals with high affinity. Also they decrease resorption ability of osteoclasts.[10]

Alendronate (A) is a compound from aminobisphosphonate group. Resorption inhibition power of A is 1000 times higher than etidronate.[11] The dose of etidronate that inhibits bone resorption is very near to the dose which causes demineralisation. But dose of A that causes demineralisation is 6000 times higher than the therapeutic dose. For this reason the dose used for treatment of osteoporosis does not have side effect of osteomalasia.[12]

It was shown that if A was combined with T, it increased BMD more than simply A or T.[13-15] In this study we compared the effect of T + A combination on BMD in postmenopausal osteoporosis with only A and only T.

Material and Methods

This study was done on postmenopausal patients in Selçuk University Faculty of Medicine Department of Obstetric and Gynecology. It's a cohort clinical study. BMD of women over the age of 45 and postmenopausal for minimum 2 years were examined with DEXA method.

BMD measurement was done with Hologic QDR- 4500C. BMD of patients lower than 2.5 SD of normal value was accepted as having osteoporosis and taken into the study.

In order to eliminate secondary causes of osteoporosis, all patients underwent physical examination. Secondary causes of osteoporosis like hyperthyroidism, hyperparathyroidism, hiperprolactinemia, malignancy were excluded. Patients smoking, drinking alcohol, using steroid, anti-epileptics and taking heparin treatment foralong time were excluded from the study. Patients who underwent gastric or intestinal surgery before and/or having any systemic disease also excluded from the study. All patients selected among women with adequate mobilisation. Ethics committee approval was obtained for the study. Written informed consent was obtained from all subjects.

Sixty patients that were enrolled to the study were randomly divided in 3 groups. Alendronate 10 mg/day was given continuously to the 1st group. Patients advised about taking a tablet with enough water in the morning before breakfast, not eating and drinking anything for 2 hours before and after taking the medication, taking no other drugs and remaining upright for at least 30 min.

Patients in the 2nd group were given only T 2.5 mg/day.

Patients in the 3rd group were given T + A (10 mg/day A and 2.5 mg/day T)

These treatments were given for a year to all groups. 1500 mg/day calcium supplementation was given to the all groups. Before starting treatment, serum alkaline phosphatase (ALP), serum osteo-

calcin, deoxypyridinoline, calcium and phosphorus level in 24 hrs collected urine were measured in all patients.

Normal values of parameters used in the study are:

- Serum ALP level 64-316 U/L
- Urinary calcium (24 hours) 50-300 mg/day
- Urinary phosphorous (24 hours) 400-1300 mg/day
- Serum osteocalcin level 3.1-13.7 ng/mL
- Urinary deoxypyridinoline (24 hours) 3.0-7.4 nmol/mmol

Some biochemical markers and BMD were measured after a year and compared with the levels before treatment.

Statistical evaluation of results were done by SPSS for windows 10.0 programme. Data were summarised as mean ± SD and percent. Groups were compared using a one-way ANOVA and significance tested at the $p< 0.05$ value. Within group changes were evaluated by pair-wise Student's t-test, to examine whether the mean percent chances were significantly different from zero ($p< 0.05$).

Results

The 3 study groups were comparable at baseline with respect to demographic variables and baseline BMD and biochemical markers (Table 1, 2).

All patients in 3 groups were re-evaluated one year after beginning of treatment. When compared with pre-treatment values, lumbar BMD was increased 5.4% in A, 3.7% in T and 6.1% with T + A group. In femoral region BMD was increased 3.4% by A, 2.7% by T and 4.2% by T + A treatment. When these post treatment values compared with pre-treatment levels, statistically significant differences were detected ($p< 0.05$). These were shown in Graphic 1 and Graphic 2.

When groups were compared with each other, lumbar and femoral BMD of T + A group were significantly higher then only A and only T groups ($p< 0.05$). Also A group was found to be superior to T.

After one year treatment, blood osteocalcin, ALP, 24 hour urinary calcium, phosphorus and deoxypyridinoline levels were decreased 29%, 13%, 15%, 11%, 21% in A treatment, 25%, 10%,

Tablo 1. Baseline characteristics of groups.

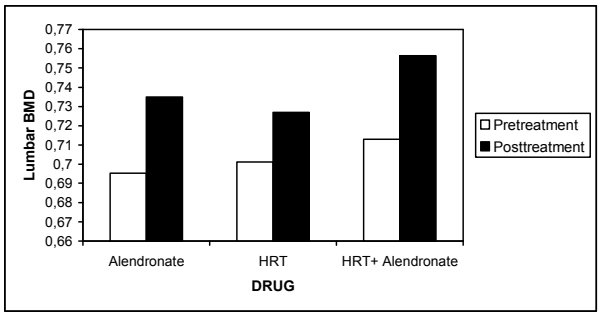
	Alendronate	Tibolone	Tibolone + Alendronate	Significance
Age (year)	49.1 ± 2.4	51.3 ± 4.8	51.1± 4.1	NS
Height (cm)	156.15 ± 5.3	157.45 ± 6.2	156.75 ± 7.8	NS
Weight (kg)	70.3 ± 11	70.2 ± 7.5	71 ± 11.6	NS
Post-menopausal period (year)	5.35 ± 2.8	5.40 ± 3.9	5.37 ± 4.3	NS

NS: Not significant ($p> 0.05$),
S: Significant ($p< 0.05$).

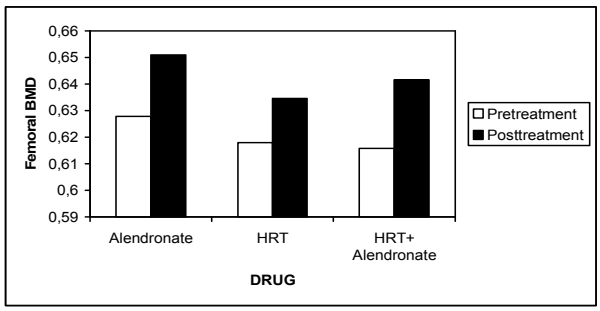
Tablo 2. Mean pre-treatment / post-treatment BMD values and biochemical marker levels.

	A		T		T + A	
	Pre	Post	Pre	Post	Pre	Post
Lumbar BMD	0.6953	0.7349	0.7011	0.7270	0.7130	0.7564
Femoral BMD	0.6279	0.6510	0.6180	0.6346	0.6158	0.6416
Osteocalcin	8.65 ± 2.3	6.14 ± 2.1	8.59 ± 3.4	6.4 ± 2.1	8.49 ± 2.1	5.6 ± 1.4
Deoxypyridinolin	11.73 ± 1.4	9.27 ± 1.2	11.8 ± 2.6	9.7 ± 1.3	11.68 ± 2.4	8.29 ± 2.5
Urinary Ca (24 h)	176 ± 68	150 ± 78	174 ± 64	154 ± 59	171 ± 58	138 ± 61
Urinary P (24 h)	738 ± 256	657 ± 149	729 ± 218	670 ± 152	728 ± 129	604 ± 192
ALP	174.3 ± 48	151 ± 45	175.3 ± 56	157.5 ± 47	176 ± 55	137 ± 25

Pre: Pretreatment, Post: Posttreatment.



Graphic 1. Pretreatment and posttreatment lumbar BMD values.



Graphic 2. Pretreatment and posttreatment femoral BMD values.

11%, 8%, 17% in T group and 34%, 22%, 19%, 17%, 29% T + A group respectively. When compared with pre-treatment levels, all post-treatment levels were significantly lower ($p< 0.05$). When all three groups were compared for biochemical markers no statistically significant difference was found between A and T groups ($p> 0.05$). When T + A group compared with the other two, statistically significant fall in all biochemical markers were seen in T + A group ($p< 0.05$). Mean pre-post treatment lumbar-femoral BMD and biochemical markers were seen in Table 2.

Cost of one year treatment calculated as:

Alendronate treatment: 579 USD

Tibolon: 314 USD

Alendronate + Tibolon: 893 USD.

If groups were compared with each other for cost of treatment statistically significant difference was found between them ($p<0,05$).

Discussion

Osteoporosis is seen in 40 percent of females over 50 years of age. It is very important pathology and is the cause of morbidity and mortality due to fractures.[16] In this study mean age of women with osteoporosis was 50 years, mean postmenopausal period was 5.3 years. In a meeting done in South California it was claimed that women shorter than 160 cm in height and lower than 50 kg in weight have higher risk for osteoporosis.[17] In this study mean height of women was 156 cm, mean weight was 70.5 kg.

There are many treatment regimens for osteoporosis. Especially HRT is important among them. Warming et al. conducted a study in which Levonorgestrel and 17 beta-estradiol were given transdermally for the prevention of postmenopausal osteoporosis. BMD at the lumbar spine, hip and total body increased by 8, 6 and 3% ($p< 0.001$) respectively, in the hormone groups versus placebo.[18] Wu Y et al. performed a comperative study on 2 different dosages of conjugated equine estrogen (CEE) continuously combined with medroxyprogesterone (MPA) in prevention of postmenopausal osteoporosis. BMD at the lumbar spine, hip and total body increased by 7, 4 and 3%, respectively, in all hormone groups versus placebo (all $p< 0.001$). Both 0.625 mg and 0.3 mg daily of CEE continuously combined with domestic MPA are effective in preventing postmenopausal osteoporosis. The former has more stronger effect than the latter.[19] Bone et al. reported that, only HRT increased BMD 6% in lumbar and 4.4% in femoral region.[13] Tiras et al. showed significant increase in lumbar BMD but no important change in femoral region.[14] Wimalawansa et al. conducted a similar study and found 7.3% increase in lumbar and 4.8% increase in femoral BMD.[15] In this study one year T increased BMD 3.7% and 2.7% in lumbar and femoral region respectively.

The other agent intensively used in treatment of postmenopausal osteoporosis is another bisphosphonate compound; alendronate. Although HRT increases BMD significantly, this is not as much as alendronate. At least a year treatment with alendronate progressively increases BMD.[20] Standard treatment regimen is 10 mg/day continuous and 70 mg once a week usage.

In the study of Pols et al., one year A treatment was given to the women with postmenopausal osteoporosis. After treatment BMD of lumbar and femoral regions were evaluated. 4.9% increase in lumbar, 2.4% in femoral neck, 3.6% in intertrochanteric region and 3% in total hip BMD were found.[21] Bone et al. performed a similar study, 2 year A treatment resulted in 6% increase in lumbar, 4% increase in femoral BMD.[22] In this study, one year continuous A treatment resulted in 5.4% increase in lumbar, 3.4% in femoral BMD.

Combination treatment was found to be superior to single agent treatment. HRT + A combination was found to be more effective on BMD increase than only A or HRT.[13-15] In the study of Bone et al., only A treatment increased BMD 6% in lumbar, 4% in femoral region. Only HRT resulted in 6% increase in lumbar and 3.4% in femoral region. But HRT + A caused 8.3% in lumbar, 4.7% increase in femoral region.[13] A similar study done by Wimalawansa et al. and only A caused 6.8%-1.2%, only HRT 6.8%-4%, HRT + A 10.9% and 7.3% increase in lumbar and femoral BMD respectively.[15]

In this study one year A treatment increased lumbar BMD 5.4% and femoral BMD 3.4%. One year T resulted in 3.7% and 2.7% increase in lumbar and femoral BMD. On the other hand T + A caused 6.6% and 4.2% increase in lumbar and femoral BMD respectively.

There are many biochemical markers used for follow up of osteoporosis. Among these most frequently used and easily measured one is serum ALP level. Because only half of the serum ALP is originated from bone, it's not very sensitive in follow up of osteoporosis.[23,24] Another important biochemical marker used to show bone formation is serum osteocalcin levels. Due to high turnover in postmenopausal period its level increases. Deoxypyridinoline level in 24 hour collected urine is also important marker of bone resorption. Urinary levels decrease with treatment. Bettica et al. examined the effect of continuous A treatment on biochemical markers. After 3 months treatment, significantly decrease in serum osteocalcin and urinary deoxypyridinoline level were detected.[25] In a similiar study done by Delmas et al., HRT significantly decreased osteocalcin and other biochemical markers.[26] Raun et al. detected 20% decrease serum osteocalcin levels when compared to pretreatment levels by 1 year alendronate treatment.[27] Also it was shown that HRT + A combination significantly decreases biochemical markers then single agent.[13,14] In this study serum ALP, osteocalcin and urinary deoxypyridinoline levels were declined 13-29-21% in A, 10-25-17% in T and 22-34-29% T + A groups respectively.

24 hours urinary calcium and phosphor levels increase in postmenopausal patients due to bone resorption. These levels turn to the normal range after treatment. One year treatment with A resulted in significantly decrease in urinary calcium and phosphor levels in the first 3-6 months.[28] Weisinger et al. showed 30% decrease in 24 hours urinary calcium levels after a year 10 mg/day A treatment.[29] In this study 24 hour urinary calcium and phosphor levels decrease 15-11% in A, 11-8% in T and 19-17% in T+A group.

Cost of treatment regimens were calculated by Marie et al. and yearly cost of continuous alendronate treatment were found 650 USD.[30] In our study, one year treatment costs and mean increase in lumbar and femoral BMD calculated as:

Continuous alendronate treatment: 579 USD-5.4-3.4%

Tibolone treatment: 314 USD-3.7-2.7%

Tibolone+Alendronate: 893 USD-6.1-4.2%

When one year treatment costs and BMD values were compared, very important differences were found between A, T and T + A regimens.

Conclusion

As a result T + A treatment increases BMD more than only A or T. Serum and urinary bone turnover markers were decreased significantly in all regimens. But this decrease is more significant in combination group.

HRT + A treatment can be the first choice in patients with postmenopausal osteoporosis. Only HRT and only A treatment can be second choice. In older postmenopausal patients with slower bone

turnover and in women with gastrointestinal disorders, only HRT can be ordered. Also economic state of the patient and the country, the effectiveness of the treatment must be considered during planning of treatment regimen.

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