Treatments of patients with postmenopausal osteoporosis: a comparative study

A Aslan1*, S Sargin2, A Özmeric3, Ş Yağcı4

Abstract
Introduction
The aim of this paper is to compare the effects of six different therapy protocols via vertebral and femoral T scores and bone mineral density values in postmenopausal women with osteoporosis.

Materials and Methods
One hundred and forty-four women who applied to our outpatient clinics between 2009 and 2012 in the cities of Kastamonu and Afyonkarahisar, in Turkey, were included in this study. All patients were separated into six groups according to the treatment modality they had taken: alendronate, ibandronate, risedronate, calcitonin, strontium ranelate and raloxifene. Results of 144 patients who were treated with the six treatment modalities regularly for 2 years were evaluated. Bone mineral density values and T scores were measured by the dual energy X-ray absorptiometry method.

Results
In the alendronate group, a significant improvement in L1-L4 bone mineral density values and T scores were observed. In other treatment groups, moderate improvements in lumbal and femoral bone mineral density values and T scores were observed, but no significant evidence for beneficial effects of these therapies was proved.

Conclusion
The effects of alendronate on vertebral bone mineral density values and T scores were statistically significant in pharmacological treatment of osteoporosis. But the other drugs showed partial improvement on vertebral and hip bone mineral density values and T scores.

Introduction
Osteoporosis (OP) is a multi-factorial systemic metabolic disease characterised by reduction in bone mineral density (BMD) and increased risk of bone fractures. Genetic, environmental, hormonal and dietary factors play the main role in the aetiology. The incidence of OP was reported as 12.9%-19.6% in normal population with two current and comprehensive studies. Moreover, OP rates among postmenopausal Caucasian women were also reported as 30% in the literature. Osteoporotic bone fractures increase the mortality and morbidity of the disease and may also cause significantly increased costs in all socioeconomic expenses. Dual energy X-ray absorptiometry (DXA), used in the diagnosis and follow-up of OP, is an accurate, widely used, highly sensitive and non-invasive method in detecting BMD. According to the World Health Organisation (WHO), a standard deviation in BMD of –2.5 or more below than the young adults’ scores in the same society is called OP. This definition is a quantitative aspect depending on T scores in OP. DXA measurements and T scores are used to calculate OP in vertebra and hip regions.

Material and Methods
This work conforms to the values laid down in the Declaration of Helsinki (1964). The protocol of this study has been approved by the relevant ethical committee related to our institution in which it was performed. All authors gave full informed consent to participate in this study.

One hundred and sixty-one women who were administered to our outpatient clinics between 2009 and 2012 in the cities of Kastamonu and Afyonkarahisar, in Turkey, were included in this study. However, the results of a total of 144 out of 161 women were evaluated. The inclusion criteria are all patients were older than 70 years.
50 years of age and they all permitted approvals. Exclusion criteria are secondary OP-related diseases such as metabolic, endocrinological, neuropsychiatric and malignant diseases\textsuperscript{11}, consumption of alcohol, tobacco or long-time steroid usage (more than 3 months and 5 mg) and carrying vertebral or femoral prosthesis were exclusion reasons. In addition, for 17 patients who completed the study, the results were excluded from evaluation for various reasons: six of these patients have not been regularly checked and 11 patients have developed several side effect or complications. Adverse effects were noted in Table 1 according to the groups.

**Bone mineral density scanning**

Bone density measurements were done in all women by using Lunar–DPX IQ or in other devices via converting the results to Lunar parameters\textsuperscript{12}. The most appropriate positioning in vertebral (ant-post. L2–L4) and femoral (total and neck) scanning’s, maintenance and calibration of the device were carried out according to International Society for Clinical Densitometry (ISCD)\textsuperscript{9} and the Turkish Society of Nuclear Medicine\textsuperscript{13} recommendations. After noting the age, weight, height and gender, patients underwent DXA scanning. OP was diagnosed according to T scores based on WHO parameters\textsuperscript{7}\textsuperscript{9},\textsuperscript{13}. Patients’ preferences (pills, spray and effervescent), accompanied diseases (bisphosphonate intolerance in gastritis–ulcer and calcitonin side effects in painful osteoporotic vertebra fractures), IRS of social security institution and clinicians’ choices were all considered when deciding therapy. However, only IRS criteria were taken into account in the management of diagnostic and therapeutic procedures.

After evaluating the results of 144 patients they were separated into six groups according to the treatment modalities. One of the following treatment modalities were carried out in all patients for 2 years:
- 1-Alendronate 70 mg/week ($n = 22$), 2-ibandronate 150 mg/month ($n = 26$), 3-risedronate 35 mg/week or 150 mg/month ($n = 26$), 4-calcitonin 200 IU/day ($n = 24$), 5-strontium 2 g/day ($n = 25$), 6-raloxifene 60 mg/day ($n = 21$). Also, all patients took supplemental treatment with 1000 mg calcium and 880 IU vitamin D3 (Ca–D3).

Patients were asked to come for periodic examinations once a month and any increase or decrease in complaints was noted. Detailed physical examinations were also carried out. Results of 144 patients who used six treatment modalities regularly for 2 years were evaluated. BMD values and T scores were measured by the DXA method.

**Statistical analysis**

BMD values before the treatment and 2 years after the treatment were analysed statistically. Data of these six groups were compared by using one-way analysis of variance according to quantitative parameters such as age, BMD values and T scores. Pre-treatment and follow-up BMD values were also compared by using paired $t$ test to assess the beneficial effects of therapy in each group. All data were defined as mean ± standard deviation terminologically.

**Results**

Demographical characteristics of 144 patients (age, weight, height and body mass index (BMI) are shown in Table 2. No statistically significant differences between the groups were found ($P > 0.05$). Pre- and post-treatment T scores and BMD values of lumbar and femoral regions in all groups were shown in Table 3.

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**Table 1** Adverse effects according to the groups

<table>
<thead>
<tr>
<th>Bisphosphonates intolerance (one case)</th>
<th>Ibandronate</th>
<th>Alendronate</th>
<th>Calcitonin</th>
<th>Strontium</th>
<th>Risedronate</th>
<th>Raloxifene</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bisphosphonates tolerance (two cases) used irregularly of Ca–D3 (one case)</td>
<td>Hypocalcaemia/tetany (one case) used irregularly of Ca–D3 (one case)</td>
<td>Ischaemic cardiac disease (one case)</td>
<td>Bisphosphonates intolerance (one case)</td>
<td>Cholecystitis (one case) used irregularly of Ca–D3 (two cases)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Table 2** Demographic data of patients (age, length, weight and body mass index and comparison according to groups

<table>
<thead>
<tr>
<th>Age (mean ± SS)</th>
<th>Length (mean ± SS)</th>
<th>Weight (mean ± SS)</th>
<th>BMI (mean ± SS)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ibandronate</td>
<td>Alendronate</td>
<td>Calcitonin</td>
<td>Strontium</td>
</tr>
<tr>
<td>70 ± 9.56</td>
<td>68 ± 5.56</td>
<td>67.5 ± 9.48</td>
<td>68.9 ± 8.7</td>
</tr>
<tr>
<td>152.4 ± 9.5</td>
<td>151.2 ± 6.1</td>
<td>153.5 ± 8.1</td>
<td>145.4 ± 30.8</td>
</tr>
<tr>
<td>61.6 ± 12.8</td>
<td>60.3 ± 14.5</td>
<td>59.6 ± 11.7</td>
<td>58.5 ± 16.1</td>
</tr>
<tr>
<td>26.5 ± 5.09</td>
<td>26.5 ± 6.75</td>
<td>25.1 ± 3.73</td>
<td>26.6 ± 4.87</td>
</tr>
</tbody>
</table>

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In the alendronate group, a significant improvement in L1–L4 BMD values and T scores were observed. Only a minor improvement in total femoral BMDs values and T scores after 2-year-therapy were observed, and these findings were not found to be statistically meaningful. In the other treatment groups, although a mild improvement in lumbar and femoral BMDs values and T scores were observed, no significant evidences for beneficial effects of these therapies were shown. On the other hand, adverse effects were noted in Table 1 according to the groups.

Discussion
OP is the most common bone disease, which is characterised by low bone mass, low BMD and deterioration of the bone’s basic structure. These changes cause an increase in the fragility and fracture risk of the bone. Classic triad is composed of morbidity, mortality and cost. On account of OP and osteoporotic fractures, the mortality and cost. On account of age, low BMD and history of fracture. Preventing from fractures is the main aim in the treatment1–8.

Some drugs are used to reduce the fracture risk. For medical treatment of OP, the most commonly used agents are bisphosphonates such as alendronate, risedronate, ibandronate and raloxifene, which are selective oestrogen receptor modulators, stronntium ranelate, calcitomin, denosumab and parathyroid hormone10–18. At the same time, the potential side effects such as hypocalcemia, nephropathy, gas- tropathy and osteonecrosis of these drugs should be considered.

In the present time, a completely reliable, effective and commonly accepted treatment modality is not defined yet19. On the other hand, BMD that is determined by DXA is important for diagnosis of the OP. BMD must be ordered to begin the treatment, to stop the treatment, to restart the treatment and to evaluate the risk of fracture. A treatment option should be chosen for the patients who have a T score < −2.5 or who have a new fracture. The treatment has to be carried on even the patients’ T score > −2.5 and till the patients have no risk factors14–23. In this retrospective study, we evaluated 144 postmenopausal patients who had OP due to WHO criterions. T scores, which were evaluated by DXA, were taken into account. We commented on the efficiency of six different drug protocols (alendronate, ibandronate, risedronate, calcitomin, stronntium and raloxifene) which were followed up 2 years by vertebral and hip BMD and T scores.

Any bone-loss-preventing medication is much more preferred in postmenopausal OP, because the low bone density is the most important risk factor. Bisphosphonates are the most preferred and used drugs24. Although there are too many bisphosphonates, third-generation

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Table 3  Comparison of T score and bone mineral density T score according to the groups

<table>
<thead>
<tr>
<th></th>
<th>Ibandronate</th>
<th>Alendronate</th>
<th>Calciton</th>
<th>Strontium</th>
<th>Risedronate</th>
<th>Raloxifene</th>
</tr>
</thead>
<tbody>
<tr>
<td>VT</td>
<td>−2.95 ± 1.1</td>
<td>−3.17 ± 0.6</td>
<td>−2.68 ± 1.4</td>
<td>−2.59 ± 1.0</td>
<td>−3.02 ± 1.1</td>
<td>−2.44 ± 1.5</td>
</tr>
<tr>
<td>VT1</td>
<td>−2.87 ± 1.1</td>
<td>−2.29 ± 2.1</td>
<td>−2.27 ± 1.6</td>
<td>−2.19 ± 1.1</td>
<td>−2.60 ± 1.3</td>
<td>−2.28 ± 1.6</td>
</tr>
<tr>
<td>P value*</td>
<td>0.952</td>
<td>0.039</td>
<td>0.862</td>
<td>0.747</td>
<td>0.535</td>
<td>0.998</td>
</tr>
<tr>
<td>VBMD</td>
<td>0.770 ± 0.14</td>
<td>0.721 ± 0.05</td>
<td>0.811 ± 0.18</td>
<td>0.831 ± 0.12</td>
<td>0.758 ± 0.13</td>
<td>0.828 ± 0.18</td>
</tr>
<tr>
<td>VBMD1</td>
<td>0.794 ± 0.14</td>
<td>0.759 ± 0.10</td>
<td>0.866 ± 0.21</td>
<td>0.889 ± 0.14</td>
<td>0.813 ± 0.15</td>
<td>0.845 ± 0.18</td>
</tr>
<tr>
<td>P value*</td>
<td>0.930</td>
<td>0.041</td>
<td>0.759</td>
<td>0.802</td>
<td>0.719</td>
<td>0.719</td>
</tr>
<tr>
<td>Ft</td>
<td>−2.29 ± 1.1</td>
<td>−2.55 ± 1.0</td>
<td>−1.63 ± 1.0</td>
<td>−1.97 ± 1.0</td>
<td>−2.59 ± 1.1</td>
<td>−2.27 ± 1.0</td>
</tr>
<tr>
<td>Ft1</td>
<td>−1.98 ± 1.0</td>
<td>−2.34 ± 1.0</td>
<td>−1.51 ± 1.0</td>
<td>−1.59 ± 1.1</td>
<td>−2.47 ± 1.1</td>
<td>−1.92 ± 1.1</td>
</tr>
<tr>
<td>P value*</td>
<td>0.415</td>
<td>0.935</td>
<td>0.821</td>
<td>0.814</td>
<td>0.0868</td>
<td>0.783</td>
</tr>
<tr>
<td>FBMD</td>
<td>0.735 ± 0.14</td>
<td>0.691 ± 0.11</td>
<td>0.800 ± 0.12</td>
<td>0.778 ± 0.10</td>
<td>0.697 ± 0.14</td>
<td>0.792 ± 0.13</td>
</tr>
<tr>
<td>FBMD1</td>
<td>0.773 ± 0.12</td>
<td>0.703 ± 0.12</td>
<td>0.819 ± 0.13</td>
<td>0.829 ± 0.11</td>
<td>0.711 ± 0.13</td>
<td>0.793 ± 0.13</td>
</tr>
<tr>
<td>P value*</td>
<td>0.293</td>
<td>0.865</td>
<td>0.847</td>
<td>0.737</td>
<td>0.625</td>
<td>0.932</td>
</tr>
</tbody>
</table>

BMD, bone mineral density; VT, vertebral L1–L4 T score; VT1, 2-year follow-up vertebral L1–L4 T score; VBMD, vertebral bone mineral density; VBMD1, 2-year follow-up vertebral bone mineral density; FT, femoral total T score; FT1, 2-year follow-up, femoral total T score; FBMD, Femur bone mineral density; FBMD1, 2-year follow-up, Femur bone mineral density.

*Independent samples test.
bisphosphonates (neridronate, alendronate, olpadronate, risedronate, ibandronate) are commonly used in present time. The efficiency of bisphosphonates in postmenopausal women's osteoporotic treatment is proved in the literature. It consists of strontium ranelate, nalic acid and two stable strontium atoms (Sr2+). Sr2+ is a divalent caption and looks like Ca, owing to its anatomic and ionic features, and it helps to bone mineralisation.

The literature shows that strontium ranelate might be used in OP treatment effectively. Raloxifene, which belongs to the selective oestrogen receptor modulator group, is a benzo thiophene. It can be preferred for prevention in OP and OP treatment through the agency of its positive impact in BMD and serum lipids. It prevents postmenopausal bone loss and decreases the level of bone turnover’s arbiters in early postmenopausal women. As a result of multiple outcomes of raloxifene evaluation (MORE), it decreases the incidence of fracture in 30% of women who have a vertebral fracture and also it decreases the incidence of fracture in 50% of women who do not have a vertebral fracture. And according to MORE, raloxifene does not have any control over non-vertebral fractures. Calcitonin is a peptide synthesised by thyroid C cells. It represents directly the activity of osteoclasts, and in this wise it reduces the bone destruction. Minimum dose is 200 IU per diem for significant impact. Calcitonin is much more effective in cancellous bone. Some controlled studies have showed that it decreases the formation of new fractures in osteoporotic women. Also in the PROOF study, it is shown to decrease peripheral fractures rather than the vertebral fractures with a rate of 30%.

In our study, all groups were evaluated separately, and there was a significant statistical improvement in BMD values and T scores for the alendronate group. At the same time for all groups there was an improvement in vertebral and hip BMD values and T scores, although not statistically significant. If these patients did not get treatment, their BMD values and T scores would get worse. There are too many comparative studies about OP drugs in the literature. But we did not come across a study which compared six drugs.

Savaş et al. compared the results of the 1-year-treatments between oral alendronate (10 mg/day) and intranasal calcitonin (200 U/day) for OP in postmenopausal women. Alendronate caused better scores than calcitonin in the BMD scores after 1 year of treatment. Bone turnover was inhibited more with alendronate than with calcitonin. Aydeniz et al. compared the protocols of four treatment groups. Group A was calcitonin nasal spray 200 IU/day and 1000 mg/day calcium; Group B was alendronate 10 mg/day and 1000 mg/day calcium and Group C was etidronate disodium 400 mg/day/15 day, and after 2.5 months 0.50 mcg/day Vitamin D and 1000 mg/day calcium (four times of 3 months treatment cycles); Group D was nasal calcitonin 200 IU/day and vitamin D 0.50 mcg/day and 1000 mg/day calcium. After 1 year of treatment, BMD increased in all groups with no statistical significant difference between each other. They suggested that, the main factors for treatment selection, were reverse effects and cost effectiveness. Gürer et al. conducted a study to compare the treatment between raloxifene and calcitonin. While the increase in BMD of vertebral trabecular bone was statistically significant, it was not in BMD of the femoral cortical bone. But they did not find a statistically significant difference between groups. In another study of Gürer et al., they made a comparison between alendronate and raloxifene. The increase of lumbar BMD was statistically significant. There were no differences in the results of femur BMD both in the beginning and at the end of the treatment. At the same time there was no difference between groups for femur BMD.

In our study, increase of the vertebral BMD values and T scores, they were only significant in the alendronate group, after 2 years. These two values increased partially in the other groups, but these were not statistically significant. Another purpose of the treatment is to cease the negative progression of the BMD scores. No significant difference was determined about BMD between all groups. No drug complication was observed in our study. A meta-analysis result showed that alendronate decreases hip fracture by 55% in osteoporotic postmenopausal women. In this clinical observation, it was claimed that the decrease in vertebral fractures can only be seen 1 year after medical treatment. In another meta-analysis, it was shown that the protection from hip fractures begins 18 months after medical treatment. Preventing effect on hip fracture was statistically significant after 18 months for women who have or do not have vertebral fractures. This effect was prolonged for 36 months. In our study, we found the effect of alendronate over vertebra was efficient like other studies. We observed this effect was more in lumbar vertebra then femur.

Adequate calcium/vitamin D supplementation should be taken in combination with antiresorptive drugs in OP treatment. Postmenopausal OP treatment can be supported with calcium and/or vitamin D via current recommendations. The combination of vitamin D with calcium may be beneficial in terms of efficacy and, perhaps for optimising adherence. In cases of insufficient exposure to sunlight or OP, the recommended daily intake of vitamin D is 800–1000 IU. In postmenopausal women with a double-blind placebo-controlled study, the patients who received 800 IU vitamin D and 1200 IU vitamin D differed in terms of efficacy and, perhaps for optimising adherence.
mg calcium daily for 18 months, were proved to have femoral BMD increase by 2.7%. Various studies indicate that individuals with a low starting BMD level, may need a high dose (2000–4000 IU) of vitamin D to achieve desirable vitamin D levels. Furthermore, in the study of de Jong et al., it has been shown that virtually all patients with a hip fracture have low vitamin D plasma levels; substitution with 50,000 IU oral cholecalciferol daily for 7 days increases vitamin D plasma levels rapidly, safely and consistently. In our study, all patients received daily 1200 mg calcium and 800 IU of vitamin D3. In all groups, there was an improvement in the scores of BMD values compared with pre-treatment. This combination treatment may have an impact on our results.

These OP drugs have various side effects associated with several complications in the treatment process. For example, intolerance during treatment of oral bisphosphonates, hypocalcaemia and tetany in the treatment with calcitonin, increased ischaemic cardiac disease risk and cholecystitis are some of them. In our study, we have excluded the scores of the patients who had to cease treatment due to side effects. These are shown in Table 1.

Limitations of our study
Shortness of following time may be accepted as a limitation. And we use only the DXA results of BMD values and T scores to evaluate the efficiency of drugs. Although we did not use bone turnover markers and vitamin D levels, these are very useful for following the efficiency of drugs. In the current literature, some facts were observed about calcitonin that was associated with cancer and strontium that was associated with cardiac diseases. Because of these reasons, calcitonin and strontium were removed from the OP guidelines. It may seem a handicap for our study but when the years of this study were considered, it can be estimated that no strong data were apparent about side effects of this drug in that time; besides social insurance companies were affording that drug in terms of acceptance.

Conclusion
The effects of alendronate on vertebral BMD values and T scores are statistically significant in pharmacological treatment of OP. But the other drugs make partial improvement on vertebral and hip BMD values and T scores. While the clinicians decide the type of the treatment of OP, they must consider the side effects of the drugs, patient’s congruence, options of the personal treatment and another clinical specialty. At the same time, the clinicians must consider effectiveness and side effects of the treatment. After that there must be an equilibrium between benefits and risks of the treatment.

The comparison of six drugs in OP treatment is the original feature of our study. But it is obvious, that studies with multi-centric, long-term follow-ups may have more comprehensive effect about this subject.

Abbreviations list
BMD, bone mineral density; DXA, dual energy X-ray absorbiometry; IRS, insurance reimbursement system; MORE, multiple outcomes of ra-
loxifene evaluation; OP, osteoporosis; WHO, World Health Organisation.

Acknowledgement
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Research study


