Effect of Weekly Alendronate on Knee Symptoms in Patients with Osteoporosis and Knee Osteoarthritis Coexistence

Osteoporoz ve Diz Osteoartritinin Birlikte Bulunduğu Hastalarda Diz Semptomları Üzerine Haftalık Alendronatın Etkinliği

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Summary

Aim: The aim of this study was to examine the effect of alendronate 70 mg weekly on knee symptoms in elderly women with osteoporosis and knee OA coexistence.
Material and Methods: Elderly women who diagnosed as osteoporosis between 60-75 years old, underwent radiography of the knee if they reported symptoms of knee OA. Radiographs were read for Kellgren and Lawrence grade and individual features of OA. Osteoporotic patients with Knee OA treated with 70 mg alendronate once weekly for one year. Knee symptoms were assessed by interview before the treatment and 6 and 12 months after the treatment, and knee pain severity was evaluated using the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC), Lequense index, VAS at rest and at movement.
Results: Alendronate 70 mg once weekly use was associated with less severity of knee pain as assessed by WOMAC scores, Lequense index, VAS at rest and at movement at 6^{th} and 12^{th} month assessments.
Conclusion: This current study has shown that Alendronate 70 mg once weekly use was associated with less severity of knee symptoms in elderly women with osteoporosis and knee OA coexistence. Additional long-term randomised, placebo controlled clinical trials are needed to confirm this effect of weekly Alendronate. *(From the World of Osteoporosis 2010;16:17-21)*
Key words: Alendronate, osteoporosis, knee osteoarthritis

Özet

Amaç: Bu çalışmanın amacı, Osteoporoz ve diz osteoartritinin birlikte bulunduğu yaşlı kadınlarda diz semptomları üzerine haftalık alendronat 70 mg'ın etkinliğini araştırmak idi.
Gereç ve Yöntemler: Altmış-Yetmiş beş yaş arası osteoporoz tanısı alan yaşlı kadınlara, eğer diz semptomları bildirmişlerse, Kellgren-Lawrence evrelemesi ve diz osteoartritinin diğer bulguları için diz radyografisi çektirildi. 1 yıl süre ile, diz osteoartriti ve osteoporoz birlikteliği olan hastalar Alendronat 70 mg haftada bir gün ile tedavi edildiler. Hastalar diz semptomları için tedavi başlangıcında, 6. ayda ve 12. ayda WOMAC, Lequense index, istirahat ve harekette VAS skorları ile değerlendirildiler.
Bulgular: Alendronat 70 mg haftalık kullanımı, WOMAC skoru, Lequense index ve istirahatte ve harekette VAS skorları ile değerlendirilen diz semptomları şiddetinde 6. ve 12. aylarda anlamlı derecede azalma sağladı.
Sonuç: Bu çalışma, Alendronat 70 mg haftalık kullanımının, osteoporoz ve diz osteoartriti birlikteliği olan yaşlı kadınlarda, diz semptomlarını hafiflettiğini göstermektedir. Haftalık alendronatın bu etkisini değerlendirmek için, randomize, plasebo kontrollü çalışmalara ihtiyaç vardır. *(Osteoporoz Dünyasından 2010;16:17-21)*
Anahtar kelimeler: Alendronat, osteoporoz, diz osteoartriti

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Introduction

Knee Osteoarthritis is the most common form of joint disease which is characterized by degradation, loss of joint cartilage which results in pain and physical disability in the elderly (1). Osteoporosis is characterized by reduced bone mass and alteration in bone architecture, resulting in increased fracture risk. These fractures are a major cause of morbidity and mortality in the elderly (2). Osteoarthritis (OA) and osteoporosis (OP) are diseases of increasing incidence and prevalence with age. Although data from cross-sectional studies suggest that OA might be associated with less OP (3,4). Osteoarthritis does not seem to protect a patient from generalized primary osteoporosis. In a study the majority (74%) of the female hip OA patients were osteopenic or osteoporotic with signs of increased bone turnover (5). Patients with knee osteoarthritis (OA) generally complain of insidious throbbing arthralgias with activity. Although initially, resting relieves the pain, the patient eventually begins to suffer pain even at rest (6). A low BMD does not preclude osteoarthritic change in the knee, moreover Terauchi M et al found a low level of BMD was associated with varus deformity originating at the proximal tibia and a low BMD predisposes to trabecular microfractures and consequently increased stress on the articular cartilage (7). Osteoporosis is also common in the osteoarthritic arthroplasty population, with a prevalence at least equal to that in the general population. The prevalence of osteoporosis in osteoarthritic patients is 26%. 37% of these patients reported current treatment with biphosphonates (8). At the subchondral level of osteoarthritis, affected joints have decreased bone mineral content and quality. In addition, increased bone turnover has been observed at levels similar to those in patients with osteoporosis (9). Bisphosphonates are analogues of inorganic pyrophosphate and are inhibitors of bone resorption. Bisphosphonates may have disease-modifying effects in patients with knee OA. Clear trends towards improvement were observed by Spector et al in both joint structure and symptoms (pain, WOMAC scores) in patients with primary knee OA treated with biphosphonates (10). In a study, biphosphonates considered an adjunctive therapy in the pain management of RA patients (11).

Many derivatives have been developed for the treatment of enhanced bone resorption; several reports reveal that treatment with bisphosphonates is able to reduce the pain associated with different painful diseases (12).

This study examined and compared knee symptoms (WOMAC scores, Lequense index, VAS at rest and at movement) of patients with osteoporosis and knee osteoarthritis coexistence before and after six months, and one year of the treatment with weekly alendronate 70 mg.

Materials and Methods

Of the total 47 osteoporosis female patients referred for the first assessment, 7 did not meet the inclusion criteria and 2 subjects refused to participate; 38 female patients (age 60-75 years, ≥5 years since menopause), who admitted to rehab clinic and diagnosed as postmenopausal or senile osteoporosis with mean lumbar spine (L2-L4) BMD T-score < -2.5 and ≥-5.0 coexistence with knee OA according to the clinical and radiographic osteoarthritis criteria (all patients had Grade I, II to III knee osteoarthritis confirmed radiologically according to the Kellgren-Lawrence grading system) of the American College of Rheumatology and no other inflammatory diseases, were included the trial (Table 1).

Exclusion criteria included significant medical disease, hypersensitivity to bisphosphonates, contraindications for calcium or vitamin D therapy, renal impairment (GFR <30 ml/min), history of major upper gastrointestinal disease, any active disease known to influence bone metabolism, or recent treatment with drugs known to affect bone and cartilage (such as glucosamine-chondroitin)metabolism. All participants gave written informed consent.

The objective of the study was to test the effects of antiresorptive osteoporosis drug alendronate 70 mg weekly on symptoms of knee osteoarthritis with the prior hypothesis that biphosphonates may have disease modifying effects on knee osteoarthritis consequently would decrease the symptoms from initial of treatment.

The study was conducted in accordance with the principles of the Declaration of Helsinki or with the laws and regulations of the country concerned, whichever provided greater protection to the individual. The study protocol was also approved by the ethical board of our institution.

All patients received vitamin D 400 IU/day and elemental calcium 500 mg/day as dietary supplements throughout the study, irrespective of dietary intake. BMD was measured by a single DXA scan of the proximal femur and lumbar spine (mean BMD of at least two vertebrae [L2-L4]) at baseline.

This study was an open labelled, prospective study with a 1 year follow-up period. All patients received alendronate 70 mg weekly. All patients received also vitamin D 400 IU/day and elemental calcium 500 mg/day as

Table 1. Demographic properties of the patients

Number of patients included the study	38
Number of patients completed the study	31
Age (between 60-75 years)	67.3±6.3
Duration of knee osteoarthritis (year)	7.4±5.7
Distribution of KL radiologic grading (0/I/II/III/IV)	(0/5/22/11/0)
L2-L4 BMD, gm/cm^2	0.816±0.156

dietary supplements throughout the study, irrespective of dietary intake. The patients were allowed to use paracetamol (to a maximum of 3 gr daily) during the study period as considered appropriate by the physician. However, no paracetamol use was permitted for at least 48 hours before each clinical assessment. Patients were not allowed to use of NSAID's, opiades, slow-acting drugs such as glucosamine-chondroitin sulphate used to treat osteoarthritis.

Primary efficacy outcome was Western Ontario-McMaster University Osteo-Arthritis Index (WOMAC), Lequesne index and secondary outcome parameters included VAS at rest and at movement, global judgement. The clinical assessment was made by a study physician using the study parameters at baseline, at month 6, and at month 12.

Statistical analysis was performed using SPSS ver 13.0 statistical package. The efficacy parameters were statistically analysed using the values measured at baseline, at month 6, and at month 12. After the variance analysis in repeated measures, paired t-test was performed to compare differences at evaluation times of the study parameters. Statistical significance for comparisons was set at $p<0.05$.

Results

A total of 38 female osteoporosis patients (mean age of 67.3 (60-75) years) with knee osteoarthritis included the study. Kellgren-Lawrence distribution was 5 patients grade 1, 22 patients grade 2, 11 patients grade 3. The mean L2-L4 BMD was 0.816±0.156 gm/cm^2. The mean knee osteoarthritis duration of patients was 7.4±5.7 years. 31 patients completed the study. 7 patients dropped out the study (1 patient did not use the study drug regularly because of gastrointestinal complaints, 4 patients because of contact lacking, 1 patient died because of myocard infarctus, 1 patient because of glucosamine intake. Demographic data of the patients were given in the table 1 and reasons of dropping out the study in the Table 2.

31 female patients completed the study. While study parameters at 6th month and at the end of the study (12th month) compared with the initial parameters, patients showed a significant improvement in WOMAC scale, Lequesne index and significant reduction in the VAS score during standing and walking (Table 3, Figure 1). There was no statistically significant difference in WOMAC scale, Lequense index and VAS scores between 6. month and 12. month values (Table 3, Figure 1). There were no serious adverse effects reported.

Discussion

In this current study, we evaluated the symptom modifying effects of Alendronate in female osteoporotic patients with knee osteoarthritis. We found statistically significant improvements in knee symptoms of osteoporotic female patients at 6. and 12. months assessed by WOMAC scores, Lequense index, VAS at movement and at rest.

Knee OA has been considered a disease of the cartilage, but literature evidence suggests that subchrondral bone is also involved in the pathogenesis, in both disease initiation and progression. Increased local bone turnover, decreased bone mineral content and stiffness, and decreased trabecular numbers have been observed in knee OA subchondral bone structure compared with normal bone (13). A higher rate of subchondral bone turnover, as indicated by increased uptake of scintigraphic tracer in subarticular bone, is associated with more rapid progression of knee OA (14).

We suggest symptom modifying effect of alendronate on knee osteoarthritis in this current study due to improving periarticular bone changes of osteoarthritis. Drugs used to prevent or treat osteoporosis, including bisphosphonates, may influence the periarticular bone

Table 2. Reasons for dropping out of study of 7 patients

Reasons for dropping out	Number of patients	Time of drop-out
Drug adverse affect (GIS intolerability)	1	1 month
Lost to follow-up	4	6th month
Died due to myocard infarction	1	6th month
Glucosamine addition into the treatment	1	6th month

Table 3. Study parameters values of 31 patients who completed the study at baseline, at month 6, and at month 12

Parameters	Baseline (Mean±SD)	6. month (Mean±SD)	12. month (Mean±SD)
WOMAC	48.41±12.04	36.54±9.81 a	35.94±11.14 a,b
Lequesne index	12.96±4.74	9.86±4.38 c	9.88±3.76 c,d
Visual Analog Scale (VAS), (pain at movement) 100 mm	65.57±21.39	54.75±20.15 e	53.98±22.63 e,f
Visual Analog Scale (VAS), (pain at rest) 100 mm	46.08+11.31	33.19+13.31 e	32.07+12.42 e,f

a $p<0.05$, Comparison of WOMAC values at baseline versus at 6. and 12. months
b $p>0.05$, Comparison of WOMAC values at 6. month versus at 12. month
c $p<0.05$, Comparison of Lequesne index values at baseline versus at 6. and 12. months
d $p>0.05$, Comparison of Lequesne index values at 6. month versus at 12. month
e $p<0.05$, Comparison of VAS values (at movement and at rest) at baseline versus at 6. and 12. months
f $p>0.05$, Comparison of VAS values at (at movement and at rest) 6. month versus at 12. month

changes of OA and could, therefore, have an effect on the course of the disease, including the possibility of slowing its development and progression (15-17).

We found use of alendronate was associated with less severity of knee pain assessed by WOMAC scores and Lequense index. Carbone et al found that use of alendronate was associated with less severity of knee pain as assessed by WOMAC scores and significantly less subchondral bone attrition and bone marrow edema-like abnormalities in the knee as assessed by MRI, as compared with women who had not received this medication (18).

Spector TD et al observed in both joint structure and symptoms in patients with primary knee OA treated with risedronate. Risedronate 15 mg once daily (but not 5 mg once daily) significantly reduced markers of cartilage degradation and bone resorption. Both doses of risedronate were well tolerated in this study (10).

We also suggest that symptom modifying effects of alendronate in this study may be depend on anti-inflammatory and analgesic properties of it. The anti-inflammatory and analgesic properties of different bisphosphonates have been demonstrated in both animal and human studies. Biphosphonates offers an effective and convenient choice for the relief of bone pain in a wide variety of underlying bone conditions (19).

For example, in a study, biphosphonates considered an adjunctive therapy in the pain management of RA patients (11). Many derivatives have been developed for the treatment of enhanced bone resorption; several reports reveal that treatment with bisphosphonates is able to reduce the pain associated with different painful diseases (12).

The mechanisms of the analgesic properties of biphosphonates are unclear. They inhibit bone resorption by inhibiting osteoclast differentiation and activity, and they also display anti IL-1, IL-6, anti-TNF-α, anti NFkB properties (20). They also reduce inflammatory oedema and hyperalgesia in a rat model of persistent pain via reducing the levels of TNF-alpha, IL-1beta, and blocking the overexpression of substance P (SP) mRNA (21). One of the suggesting analgesic mechanism of BP may be inhibitory effect of which on the each level of P13-Akt-NFkappaB pathway (22). Because inhibition of NF-kappaB nuclear signalling in dorsal root ganglia reduces hyperalgesia in mice (23).

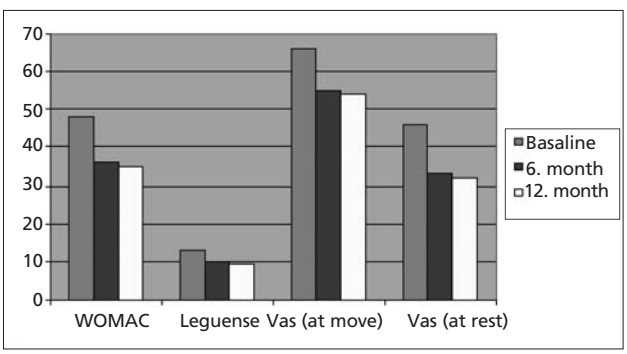

Figure 1. Changes in study parameters at 6. and 12. months

The biases of this study were a small number of patients, an open labelled study and the absence of a control group. So long-term randomised, placebo controlled clinical trials are needed to assess symptom modifying effects on knee osteoarthritis in osteoporotic female patients of weekly Alendronate.

Conclusion

In this current study, Alendronate 70 mg once weekly use was associated with less severity of knee pain as assessed by WOMAC scores, Lequense index, VAS at movement and at rest in patients with osteoporosis and knee osteoarthritis coexistence after six months, and one year of the treatment. Additional long-term randomised, placebo controlled clinical trials are needed to assess this effect of weekly Alendronate.

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