



## THIGH PAIN MIGHT BE A PRODRIMAL SYMPTOM OF ATYPICAL FRACTURE IN LONG TERM BIPHOSPHONATE USERS

### ABSTRACT

**Introduction:** Osteoporosis causes bones to lose their resilience, increases fragility and results in bone fracture even with minimal trauma during daily activities. We aimed to examine the patients who were treated for atypical fractures in terms of long-term bisphosphonate usage for the treatment of osteoporosis.

**Materials and Method:** A retrospective study was conducted on 21 patients who underwent surgery for an atypical femur fracture between years 2007-2013. Demographic data, history of bisphosphonate treatment, trauma type, patient complaints prior to fracture, fracture type and the type of treatment used for the fracture were assessed.

**Results:** The number of cases with atypical fractures was 21 and all of them had history of prolonged bisphosphonate use. The number of female patients was 19, and 2 patients were male, with an average age of 76.4 years. The number of patients with diaphyseal femur fractures was 17 and 4 patients had subtrochanteric femur fractures. Among the patients that have been using a bisphosphonate, alendronate (70 mg) was the most frequently used medication. The average length of bisphosphonate usage was 8.1 years and the average length of time that elapsed until a fracture occurred subsequent to the start of drug usage was 7.2 years. Prior to fracture, all of the patients had complaints of thigh pain that lasted on average for 8.5 months.

**Conclusion:** Bisphosphonates are one of the widely used agents used in the treatment of osteoporosis. Thigh pain in patients with prolonged bisphosphonate usage should alarm the physicians for possible atypical fracture in the future.

**Key Words:** Disphosphonate; Femoral Fracture; Osteoporosis.

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## UZUN DÖNEM BİFOSFONAT KULLANAN HASTALARDA UYLUK AĞRISI ATİPİK KIRIK HABERCİSİ OLABİLİR

### Öz

**Giriş:** Osteoporoz kemiklerin elastikiyetini azaltarak ve frajilitesini artırarak günlük aktiviteler sırasındaki minimal travmalarla bile kırık oluşmasına neden olur. Bu çalışmada atipik kırık nedeniyle tedavi edilen hastalarda uzun dönem bifosfonat kullanım öyküsü araştırıldı.

**Gereç ve Yöntem:** Atipik femur kırığı nedeniyle 2007-2013 yılları arasında opere olan 21 hasta demografik veriler, bifosfonat kullanım öyküsü, travma tipi, kırık öncesi semptomlar, kırık tipi ve kırık için uygulanan tedavi açısından incelendi.

**Bulgular:** Atipik kırıklı 21 hastanın tümünde uzun süreli bifosfonat kullanım öyküsü mevcuttu. İncelenen vakaların 19'u kadın, 2'si erkekti, yaş ortalamaları 76,4 olarak bulundu. Hastaların 17'sinde diafiz femur kırığı, 4'ünde subtrokanterik femur kırığı saptandı. En fazla (%33,3) kullanılan bifosfonatın 70 mg'lık alendronat olduğu saptandı. Ortalama bifosfonat kullanım süresi 8,1 yıl idi, ilaca başlanması ve kırık oluşumu arasında geçen süre ortalamasının 7,2 yıl olduğu gözlemlendi. Kırık oluşumundan önce tüm hastalarda ortalama 8,5 ay süren bir uyluk ağrısının olduğu saptandı.

**Sonuç:** Bifosfonatlar osteoporoz tedavisinde en sık kullanılan ilaçlardandır. Uzun süreli bifosfonat kullanımı olan hastalarda uyluk ağrısının varlığı muhtemel bir atipik kırığın habercisi olabilir.

**Anahtar Sözcükler:** Bifosfonat; Femur Kırığı; Osteoporoz.

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## INTRODUCTION

Osteoporosis, commonly seen in post-menopausal females and elderly adults, is defined as a systemic bone disease in which the risk of bone fractures increases as the bones weaken. The weakening of the bones increases fragility fractures during daily activities (1). Osteoporosis is responsible for 75% of bone fractures in the elderly, which may cause comorbidity and complex complications. The best approach in combating osteoporotic fractures is preventive strategies and medications. Drug treatment is based on bone metabolism and pathogenesis of the disease. Agents such as calcium, vitamin D and their metabolites, as well as oestrogen, calcitonin, and bisphosphonates prevent bone destruction, while parathyroid hormone, anabolic steroids, and sodium fluoride components increase bone formation (2).

Bisphosphonates have a wide range of therapeutic uses in osteoporosis, Paget disease and some syndromes related to the bone (3,4). These agents prevent bone resorption by inhibiting osteoclast functions and promoting osteoclast apoptosis. Alendronate was approved by the United States Food and Drug Administration (FDA) in 1995, for treating post-menopausal osteoporosis. Shortly thereafter, alendronate gained popularity and became one of the most frequently used agents for osteoporosis. However, side effects resulting from prolonged usage have been reported, including gastrointestinal effects such as dyspepsia, oesophageal cancer, mandibula osteonecrosis, atrial fibrillation, and atypical bone fractures (5-8).

An atypical femur fracture following a low energy trauma was first reported in 2005 related to prolonged alendronate usage (9). Following an increase in atypical fracture reports, the American Bone and Mineral Research Society studied the correlation between atypical fractures and bisphosphonate usage, and determined the major and minor criteria defining atypical fractures in 2009 (10) (Table 1). However, despite numerous studies, a clear correlation between prolonged usage of bisphosphonate and atypical fractures has not been fo-

und (11-14). In this study, we aimed to examine patients who have used bisphosphonate for a long period and were treated for atypical fractures.

## MATERIALS AND METHOD

A retrospective study was conducted on 21 patients who underwent surgery for an atypical fracture from 2007–2013, with a history of bisphosphonate use. We collected demographic information, bisphosphonate treatment duration, treatment type, trauma type, patient complaints prior to fracture, fracture type and the type of treatment used for the fracture.

## RESULTS

We evaluated 21 cases of atypical fracture that occurred due to prolonged bisphosphonate use. The number of female patients was 19, and 2 patients were male, with an average age of 76.4 years. The number of patients with diaphyseal femur fractures was 17 and 4 patients had subtrochanteric femur fractures (Figure 1). The type of bisphosphonate and the duration of usage are shown in Table 2. Among the patients who had been using a bisphosphonate, alendronate (70 mg) was the most frequently used medication. The average length of bisphosphonate usage was 8.1 years and the average length of time that elapsed until a fracture occurred subsequent to the start of drug usage was 7.2 years. Patients reported having used the drug continuously. The average age when a fracture occurred was 75.3 years. The number of patients who underwent surgery for the second time due to a femur fracture on the other side was 4, on an average 42 months after the initial surgery. Prior to fracture, all of the patients had complaints of thigh pain that lasted on average for 8.5 months. All of the fractures occurred after falling in the house, which caused minor trauma. An intramedullary nail was used to treat 20 patients, while one patient was treated conservatively. A

Table 1— Major and Minor Criteria of Atypical Fractures.

Major Criteria	Minor Criteria
Femur subtrochanteric or diaphyseal fracture	Cortical thickening
Transverse or oblique fracture	Periosteal reaction in the lateral cortex
Free of trauma or minimal trauma	Prior prolonged aching
Medial spike in complete fractures	Being bilateral or prolonged healing
Basic fracture	Drug related (bisphosphonates, steroids, PPI)



**Figure 1**— Atypical subtrochanteric femur fracture.

segmental fracture occurred in 3 patients during the operation due to femoral bowing and were treated accordingly.

## DISCUSSION

The incidence of osteoporotic fractures in the elderly has increased with prolonged life expectancy. Senile female and male osteoporosis patients over the age of 70 are affected at the same rate, with equal loss of trabecular and cortical bone. Both secondary hyperparathyroidism and decreased age-related osteoblast activity are responsible for bone loss. Additionally, cellular aging, decreased cellular response to cytokines and growth hormone, as well as decreased levels of insulin-li-

ke growth factor play a role in the pathophysiology of senile osteoporosis. Proximal femur, proximal tibia, pelvis and multiple compression vertebrae fractures are also common in this age group.

Post-menopausal osteoporosis occurs in post menopausal females and is characterised by oestrogen deficiency. Bone loss is greater in trabecular bone than in cortical bone and is thus more prevalent in the first 3-4 years after menopause. Post-menopausal bone loss primarily results from increased osteoclastic activity. The balance between construction and destruction is disrupted due to low oestrogen levels, increased cytokine stimulation of osteoclast activity and osteoblast apoptosis, while the normal bone mineral-matrix balance is unchanged. Moreover, calcium secretion into the urine increases, while parathyroid hormone and 1,25(OH)<sub>2</sub>D<sub>3</sub> levels fall. The most significant clinical finding is crush-collapse vertebrae, which results from low-energy trauma and distal radius fractures (15).

In recent years, the importance attached to drug development and quality of life has increased the opportunities for diagnosis and treatment of osteoporosis. Bisphosphonates are one of the agents used in treating and prophylactically preventing osteoporosis. These compounds strongly inhibit bone resorption, decrease osteoclast activity, and increase osteoclast apoptosis (16). Unlike other agents, the affinity of bisphosphonates for bone and their mechanism of action facilitate their binding to hydroxyapatite crystals. During the remodelling stage, they are re-released into the bloodstream and reconnect to the bone, which allows them to be active once more (17).

Black et al. reported an increase in clinically recognized vertebral fractures but no increase in nonvertebral fractures or morphometric vertebral fractures among patients discontinuing alendronate after 5 years of treatment (18). In our study, 17 of our patients had used alendronate for more than 5 years. Park-Wyllie et al. (12) observed that in 205466 females who

**Table 2**— Duration of Bisphosphonate Usage.

Drug (mg)	n	Duration (years)
Alendronate (70 mg)	7	8.1
Risedronate (35/75 mg)	3	6.3
Alendronate (70 mg)+Risedronate (35/75 mg)	5	10.2
Alendronate (70 mg)+Ibandronate (150 mg)	2	11.5
Alendronate (70 mg)+Risedronate (35/75 mg)+Ibandronate (150 mg)	2	12
Alendronate (70 mg)+Zoledronate (5 mg)	1	7
Risedronate (35/75 mg)+Zoledronate (5 mg)	1	9



had used bisphosphonate, 716 patients had a subtrochanteric and/or diaphyseal fracture. They categorized participants according to duration of treatment as long-term users (>5 years of therapy), intermediate users (3-5 years of therapy) and short-term users (100 days to 3 years). These exposure groups were compared with a reference group of transient (<100 days in total) users. They concluded that compared with transient bisphosphonate use, treatment for 5 years or longer was associated with an increased risk of subtrochanteric or femoral shaft fracture. However, they did not evaluate radiologically atypical fracture parameters. In our study, when fractures were classified according to the minor and major criteria, 21 cases were deemed as atypical fractures and the average length of bisphosphonate use was 8.1 years.

Atypical fractures are seen in patients with abnormal bone structure. In the elderly, fractures caused by a simple fall commonly occur in the trochanter region of the lower extremities (19). However, in patients who have used bisphosphonate for a long period, minor traumas can cause fractures close to the femur diaphysis with enlargement seen in the broken region and thickening of the lateral cortex (10,20). Schilcher and Aspenberg reported that of 91956 females over 55 years old, 3087 used bisphosphonates continuously. In this population, the incidence of fracture in the femur diaphysis was 1/1000 in the group that used bisphosphonates and 0.02/1000 in the group that did not (21). In our study, 17 cases had fractures of the femur diaphysis and 4 cases had subtrochanteric fractures, defined as atypical fractures based on radiological findings.

In a multicenter study investigating the pharmacological treatment preferences in osteoporosis, 33.4% of physicians prescribed alendronate to patients with primary osteoporosis and 36.8% prescribed alendronate to patients with secondary osteoporosis (22). In our study the most commonly used bisphosphonate was alendronate, consistent with the literature, and 7.2 years of bisphosphonate use was associated with an increased incidence of atypical femur fracture.

Thigh pain in long term bisphosphonate users is an alarming symptom before the occurrence of an atypical femur fracture. The atypical femur fracture is frequently preceded by a history of persistent thigh pain prior to low-energy trauma (23). This is one of the factors shown to be associated with atypical femoral fractures and the prevalence is reported to be 63.6% to 70% (7). Similarly, in our study, all of the patients stated that they had complained of thigh pain for a long time before the femur fracture.

Simultaneous bilateral diaphyseal femoral fractures are rare; it is reported in the trauma literature that only 2% to 7%



Figure 2— Operated bilateral femur fracture.

of femoral fractures are bilateral. They usually result from pathologic fractures (24). Bilateral femur fracture is one of the minor criteria for atypical femur fractures and in our study, 4 cases had femur fracture surgery on the other side, 42 months, on average, after the initial surgery (Figure 2). Although this number was comparable to similar studies in the literature, relatively few patients were enrolled in this study.

In conclusion, the underlying cause and subsequent mechanisms in the development of atypical fractures remain undefined. Further long-term, prospective observational research is needed to address the role of prolonged bisphosphonate therapy in the development of these fractures. The possibility of atypical fractures should be considered in patients who report unexplained thigh or groin pain, and radiographic evaluation is recommended to identify prodromal symptoms in patients with a history of long-term bisphosphonate therapy.

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