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Atypical Femur Fractures after Long-Term Treatment with Alendronate: A Review

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Abstract

The effect of long-term use of alendronate for the treatment of patients with osteoporosis is widely known. However, side effects of this drug, such as its effect on atypical femoral fractures, may have received less attention. Alendronate is one of the bisphosphonates used to treat fractures caused by osteoporosis. Oral or injectable bisphosphonates are used to treat osteoporosis. Atypical femur fracture, a rare type of fracture that has been associated with the long-term use of alendronate, is a potentially devastating consequence of osteoporosis treatment. Several literatures have been reported the effects of long-term alendronate use (over a period of 5 years) and the occurrence of low-energy subtrochanteric/femoral fractures. However, its exact mechanism remains unknown and has not yet been proven. Recently, a relationship between low-energy femoral fracture, profound osteoclast inhibition, the suppression of bone turnover, bone remodeling, and femoral shaft fractures has been elucidated.

Here, we provide an overview based on the latest findings from the pathophysiological mechanism, therapeutic management strategies, and the relationship between femoral fracture and short- and long-term use of alendronate. Despite the treatment recommendations of the literature, treating unusual femoral fractures with alendronate is still difficult, and more attention should be paid to the clinical trials of the therapeutic procedures.

Keywords: Osteoporosis; Atypical Femur Fractures; Bisphosphonates; Long-Term Alendronate Use

Introduction

Alendronate is in a group of drugs called bisphosphonates. Alendronate block the absorption of minerals from the bones, making them stronger. Alendronate reduces the risk of fractures in osteoporosis by increasing bone density [1]. Less than one percent of alendronate is absorbed by the body after oral administration, and consumption with food or any beverage other than water reduces this absorption. Alendronate acts on osteoclasts in the body and inhibits their activity. Osteoclasts are present in the bone and continuously extract minerals from the bone throughout life. In addition to osteoclast, there are other cells called osteoblasts that are responsible for depositing minerals inside the bone. Alendronite also inhibits the activity of osteoclasts by retaining calcium salts in the bone and reducing the process of osteoporosis [2,3]. Long-term alendronate use, however, is not without consequences.

In a study, Odvina, et al. [2] stated the first case report of atypical fractures possibly related to alendronate use. The results of their study showed that severe suppression of bone rotation may occur during long-term treatment with alendronate, which increases susceptibility to non-spinal fractures and delays healing. Despite the reduction in the overall risk of fractures at the beginning of alendronate treatment, there is more evidence of an association between atypical fractures associated with the long term use of alendronate [3,4]. Alendronate use may be associated with abnormal subtrochanteric fractures, but these reports have not been substantiated and require further investigation [5-8].

In a study conducted by Prinsloo, et al. [9] nine patients developed low-energy invertebrate fractures with long-term use of alendronate. However, three of these nine patients had unusual subtrocentric fractures. About 30 to 70% of patients with atypical subtrochanteric fractures had persistent non-traumatic pain in the pelvis and groin.

In this regard, they stated that if patients have an unusual form of femoral fracture with severe pain while receiving alendronate, this should be a signal to take the lower extremity radiograph. Basic evidence is currently divided between a number of studies showing an association between the occurrence of subtrocentric/femoral shaft fractures and alendronate consumption, and several population-based studies that do not confirm such an association [5-13]. Thus, a degree of uncertainty surrounds this key issue in patients with osteoporosis.

In addition, alendronate is drug that inhibit bone turnover by decreasing the resorption. Since it suppresses bone remodelling, alendronate may limit the repair of micro damage, create the risk of low-energy fractures, and decrease bone metabolism and strength [14,15]. However, the mechanical features of femur are directly related to the determination of fracture risk, alendronate effects on the related factors have scarcely been investigated.

The aim of this review is to present the latest findings to find out the increased incidence of femoral fractures after long-term treatment with alendronate. This review can lead to a better understanding of our knowledge gaps in this field.

Characteristics of Femur Fractures

The femur is one of the strongest bones in the body, and a break or fracture in the femur bone is often caused by severe injury such as trauma with obvious swelling, deformity, pain, and tenderness in the affected thigh (Figure 1). Atypical femoral fractures are defined as subtrochanteric femoral fractures characterized by: (1) location in the femoral shaft, (2) a substantially transverse and minimally comminuted configuration, (3) flaring of the lateral cortex at the fracture site, and (4) minimal or no trauma energy [16,17].

A femoral shaft fracture is defined as a fracture of the diaphysis occurring between 5 cm distal to the lesser trochanter and 5 cm proximal to the adductor tubercle occurs by chronic. Femoral fractures can be located at three different places including proximal femur fractures, femoral shaft fractures, and supracondylar femur fractures [18]. Imaging tests allow the physician to identify the exact location of the fracture. Another type of non-traumatic fracture segmentation is seen in patients with low bone density. Therefore, terms such as 'atypical' and 'stresses are often used interchangeably or in the same direction for a type of subtrochanteric fracture [19,20].

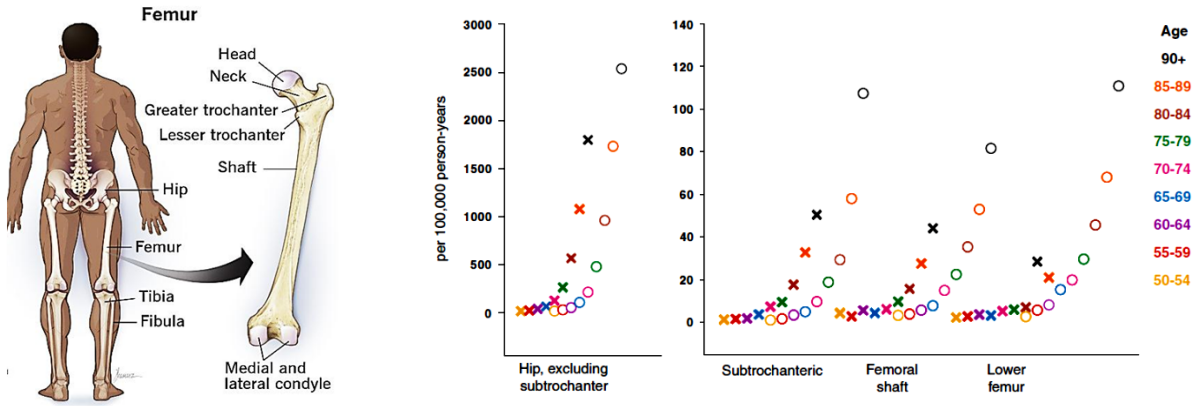

Figure 1: a) Femur anatomy, and b) view the distribution of femoral bone fractures in adults older than 50 years. Men (X) and women (O). The image taken from reference of [21] with permission from (https://my.clevelandclinic.org/) and Springer.

Femur Fractures and Alendronate Exposure

Odvina, et al. [2] published the first set of reports about of the association between long-term use of alendronate and unusual diaphysis fractures. Alendronate is an oral bisphosphonate with long-lasting effects. This chemical compound is the most common bisphosphonate used in the pharmacological treatment of femur fractures [22]. In animal and human experiments, alendronate administration can increase the volume of bone tissue and maintain its natural histological shape. Several possible mechanisms are involved in the functional cycles of the medicine, such as direct cytotoxicity, blockade of osteoclast-mediated bone resorption, direct intracellular effects, and blocking of maturation of osteoclasts [23].

In a study, Lo, et al. (2020) [24] investigated the level of unusual femoral fractures risk using alendronate on a large population of women in health systems. They reported that alendronate therapy for 3 or more years was associated with greater the risk of finding an atypical femur fracture than treatment for less than 3 years [24]. Atypical femur fractures were uncommon among alendronate-treated women. This increased risk should be considered when counselling women about long-term alendronate use.

In this line, Bone, et al. (2004) [25] concluded that clinical indexes significantly improved with long-term use of alendronate in elderly postmenopausal women with osteoporosis [25]. However, the results obtained from a number of recent studies have shown that long-term use of alendronate will be suppressed the resorption of bone tissue excessively, which can lead to unusual femoral fractures. One of the most important negative effects of decreased osteoclast function is impaired natural bone repair capacity. Therefore, alendronate use causes a small accumulation of bone microdamage, bone-remodeling cycle, and long-term bone fragility [26-28]. Decreased bone resorption in alendronate users is thought to reduce bone turnover with the accumulation of small fractures and homogeneous mineral bones. This can make the bone more fragile and also causes spontaneous femoral fractures [29,30]. However, it is not entirely clear whether long-term use of alendronate is associated with atypical femoral fractures. In a few cases, atypical femoral fractures also occurred in people who did not take alendronate [27,28].

Prolonged suppression of bone turnover might increase the average age of the tissue. This leads to higher concentrations of advanced glycation endproducts in the extracellular collagen matrix. This can also lead to increased bone fragility during long periods of alendronate therapy [31,32]. A review of some literatures showed the association between atypical fractures in the subtrocentric region of the femur in treated patients with alendronate [33-35]. The main factors in atypical fractures are prodromal symptoms, fractures with minimal or no trauma, thickened diaphragmatic cortex, and transverse fracture patterns.

Some results showed a similar relationship in this regard. However, based on the results of clinical trials in the third phase of treatment with alendronate, individuals did not show an increased risk of subcutaneous fractures. The number of atypical subtrochanteric fractures in accordance with alendronate consumption is an estimated one per 1,000 per year [36,37]. The reviews showed that the risk of unusual femoral fractures was reduced by about 70% each year with the last dose of antiresorptive therapies [37-39]. However, it is not possible to say with certainty that this reduction has also been seen in patients with a history of atypical femoral fractures.

Safety in Long-Term Alendronate Use

Alendronate is generally used as a safe and effective medicine in the treatment of osteoporosis. However, there is a potential risk of over-suppression of bone rotation, which can lead to poor biomechanical function in bone over long-term use of alendronate. The use of this compound causes the accumulation of fine structural damage and excessive suppression of bone rotation, which ultimately leads to secondary mineralization in the bone structure and increases the risk of bone fragility [40,41].

Atypical femur fracture, a rare side effect of long-term use of alendronate, has recently received more attention from researchers. A review of articles has shown that alendronate treatment for 3 to 4 years reduced the risk of unusual femoral fractures in women with osteoporosis [2,42]. According to available sources, the incidence of atypical femur fracture in upper femoral fractures is less than 4%, and most of the literature on atypical femur fracture has been case studies (Table 1).

Atypical Femur Fractures Number	Treatment Time (Average)	Average Age	References
7	5.6	60	[2]
9	4.2	66.9	[42]
26	4.4	66.1	[43]

12	7.3	70.4	[44]
19	6.9	6205	[18]
2	7	72	[45]
2	9	57	[46]
14	8.6	61	[20]
3	9	66.5	[47]
3	7.3	63.3	[48]
2	6	60	[49]
16	4.5	68	[31]
59	7.1	73.7	[50]

Table 1: Some references of atypical femur fractures associated with long-term alendronate use.

The obtained results showed that alendronate therapy in postmenopausal women for more than 5 years had a higher risk of clinical atypical femur fractures [51]. These results may not apply to younger women depending on factors such as race and even gender. The mechanism of action in these fractures is still unknown.

Allen, et al. [52] found that alendronate use can induce partial bone damage and increase more than sevenfold compared with control samples. This was associated with a 40% reduction in bone mineral density, which increased the fracture rate. Considering the potential for the increased risk of atypical femur fractures, Liu, et al. [1] stated that the use of alendronate should not exceed 5 years, and it will be appropriate for patients to discontinue the use of alendronate after 5 years. Moreover, most of the experts also recommend that the application of alendronate should not exceed 5 years.

Pharmacokinetic studies show that alendronate remain in the bone matrix for many years (up to 10 years) and the existing alendronate remain inactive until they are gradually released during bone resorption. In a clinical study, after 5 years of alendronate use, biochemical markers of bone circulation were suppressed for at least 3 years after cessation [53].

Using the range of pharmacokinetic parameters determined from a study with a dose of 10 mg per day, Rodan, et al. [54] concluded that the remaining dose of alendronate in bone matrix was approximately 75 mg per 2 kg of mineral after 10 years of treatment.

In one study using an experimental model in mice, Yang, et al. [55] concluded that the use of bisphosphonates decreased bone mineral density over time and could lead to reduced mechanical strength and bone fractures. They also concluded that healing and callus formation after fracture in femurs reduced with high concentrations of bisphosphonates use over a long period of time. However, this result was not confirmed for the aldronates used.

Pathogenesis

The two concepts of fracture associated with stress or fracture are used to create unusual femoral fractures. Factors such as the joint shape and geometry of the femur, the lack of local crushing and thickening of the cortex at the fracture site help to prove this. Also, similar types of fractures in other bone-related diseases are associated with decreased bone resorption such as hypophosphatase and osteopetrosis [56].

Case Reports in this Field

Concerns about long-term use of alendronate for atypical femoral fractures have been reported using case reports. The first study was performed by Odvina, et al. [2] that referred to 9 patients with alendronate-treated osteoporosis over 3 to 8 years. These patients suffered traumatic fractures during their normal daily activities. Three of the 9 people had fractures of the femoral shaft and two had fractures of the proximal femur. Radiographs were taken in four of these individuals. All four patients had delayed or absent fracture healing ranging from 4 months to 2 years while on alendronate treatment [2]. Four patients in the age range (35-85) were treated with alendronate. In this study, the mean and median duration of alendronate use was 7.3 and 7.5 years, respectively (range 1–16), and the majority of patients had unilateral fractures (29 out of 43; 67.4%) [2]. Other similar cases are summarized in (Table 2), (Figure 2).

In this line, the characteristics patients with low-trauma subtrochanteric or proximal diaphyseal femur fracture were studied retrospectively by Neviaser, et al. [18] at US trauma center over a 5-year interval. Radiographic patterns were examined to identify simple, transverse, or short oblique fractures in areas of cortical hypertrophy with the cortical beak.

Twenty-five patients out of 70 were treated with aldronate. Nineteen out of 25 (76%) alendronate-treated patients had the radiographic pattern compared with one out of 45 (2%) non-alendronate-treated patients. Finally, it was concluded that the risk of having an "unusual" fracture pattern was significantly associated with alendronate use for a long time (odds ratio=139; 95% confidence interval (CI) 19–939; p<0.0001). For people who had a fracture pattern, the average duration of treatment with alendronate was about 6 years compared to persons who did not have such a problem (about 2 years) [56].

In another study, in six groups of patients, the association between aldronate consumption and femoral fracture was compared with the control group. In this study, the rate of femoral shaft fractures appeared to be higher than that of other fractures in women taking oral bisphosphonates [21]. It is not yet known whether the many fractures were due to trauma. Limitations of these results include non-confirmation of radiological data, clinical results, and lack of information on the type of bisphosphonates used during the period.

Female Patients	Age (in years)	Failure Position	Radiographic Characteristics/ Study Design	Prodromal Symptoms (Duration)	Duration of use (years)	References
9(5)	52	Femoral shaft	Cortical thickening in lateral mid-shaft of contralateral femur	Severe pain in back and hip (1 month)	8	[2]
	68	Femoral shaft			8	
	67	Femoral shaft			5	
	49	Proximal femur			3	
	64	Proximal femur			4	
155	(61-69)	bone mineral density at spine and femur	The effects of alendronate on trabecular and cortical femoral bone using a DXA-based 3D modeling approach****.	Overall increase in BMD *- increase in trabecular and cortical vBMD** with no change in Cth***. a decrease of the cortical porosity	2	[57]
5	69-77	Trochanter, femoral shaft	Cohort study	The results revealed that the use of ALN will not increase the risk of AFF in short term (PO0.05), but there will be a risk of AFF (P!0.05) with long-term (O5 years) use of ALN.	5-10	[1]
96	70	in the distal part of the femur and proximal part of the tibia	Therapeutic study	bone mineral density improvement	1	[58]
1	72	Femoral shaft	Cortical thickening in lateral mid-shaft of contralateral femur	Severe pain in back and hip (1 month)	Not specified	[59]
131	62-63	femoral cortices at the subtrochanteric region	A DXA scan that was uploaded to a PACS	Long-term alendronate treatment does not cause thickened femoral cortices at the subtrochanteric region****	5 years or more	[28]

1	59	Upper femur	Cortical thickening	Moderate pain in thigh (3 months)	7	[59]
22	50-81	Subtrochanteric femoral fractures	The imaging studies included radiography (n = 34), bone scintigraphy (n = 4), CT (n = 4), and MRI (n = 5).	In complete fractures, these include minor or no trauma, initial involvement of the lateral proximal femoral cortex, transverse orientation, medial beak, skirt-like focal thickening at the opposing lateral cortical surfaces, superior displacement of the distal fragment, and varus angulation at the fracture site.	a minimum of 4 years and up to 14 years (mean, 6 years)	[60]
13	55-82	ST fracture***** due to low-energy trauma	Cortical thickening (6=lateral, 3= contralateral)	-	2.5-5	[42]
17	53-82	ST fracture****** due to low-energy trauma in patients taking ALN	Lateral cortical thickening, medial cortical beaking (all)	Subtrochanteric stress fracture, Femoral shaft stress fracture, and Femoral shaft fracture	4	[43]
1	76	Left femoral Diaphysis, Right femoral diaphysis (4 years later)	Horizontal fracture lines at thickest part of femoral cortex extending lateral–medial, followed by short oblique fracture)identical at both sites)	-	8	[61]
8	60	Right subtrochanteric Femur, Left subtrochanteric femur (9 months later)	Long-term alendronate use was associated with no change in both hip and subtrochanteric/ diaphyseal fractures.	Pain in right hip	4	[62]

Table 2: Presented results of femoral fractures in women treated with alendronate.
* Bone mineral density
** Cortical volumetric bone mineral density in milligrams per cubic centimeter
*** Cortical thickness in millimeters
**** In the region of the femur which extended from the lesser trochanter to the junction of the proximal and middle third of the femoral shaft.

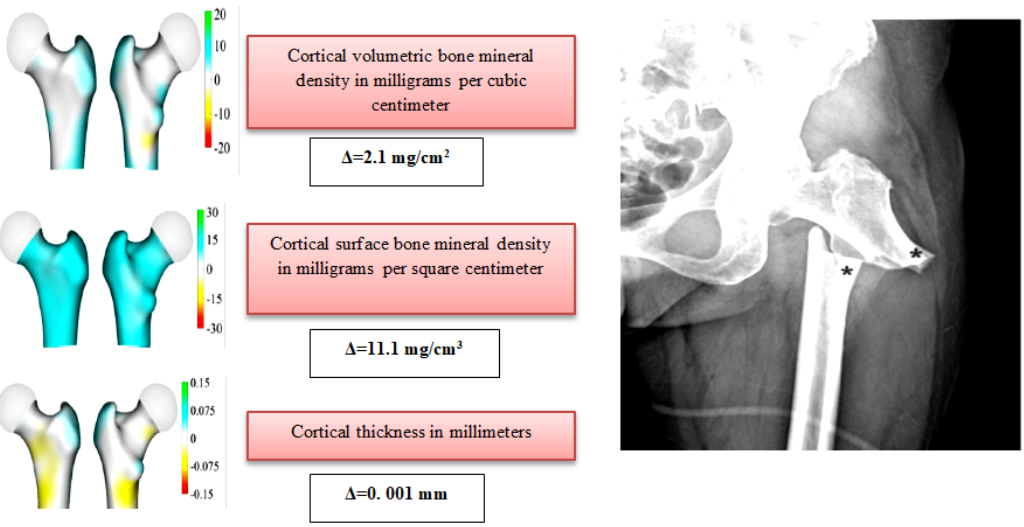

Figure 2: a) Distribution of the average changes (difference between follow-up and baseline) observed after two years among patients treated with alendronate. The amount of increase was shown in blue-green and the amount of decrease was shown in red-yellow. Cortical thicknesses are consistent with the results obtained on use of alendronate studies where no change in cortical thickness modification was observed. Empty triangle indicates change averaged over the total femur region of interest. (The image adapted from references of [63,64] with permission from Springer. b) **** Radiographs example for an adult patient with an atypical subtrochanteric femoral insufficiency fracture. The asterisks indicate cortical hypertrophy of the femoral cortices at the proximal and distal fragments [43].

Discussion

A wide range of studies were conducted by Abrahamsen B, et al. [65] on epidemiology of subtrocentric and diaphyseal hip fractures in treated patients with alendronate. The incidence of subtrocentric and diaphyseal fractures was similar in patients older than 60 years who underwent subtrocentric, diaphyseal femoral, and femoral fractures approximately four years ago. Similarly, an equilibrium state was observed for each type of fracture with high and low strokes. Alendronate treatment protocols were similar among fracture types. The pathophysiology of atypical low-trauma subtrochanteric fractures following alendronate use is not known. However, clinical and pre-clinical studies have shown that possible mechanisms occur alone or simultaneously on bone. Prolonged use of alendronate may reduce or prevent the maturation of collagen as a determinant of bone function. However, these results have not been consistently repeated in clinical trials. As alendronate treatment reduces bone turnover, the increase in overall mineralization may lead to more homogeneous bone-as evidenced by a narrow bone mineralization density distribution and thus an increased femoral fractures risk [66,67]. Alendronate has various impacts on different types of fracture. Severe fractures in the elderly often occur with relatively low-energy trauma.
However, in younger patients who previously had healthy bones, these fractures are usually caused by higher-energy shocks. This type of fracture is not affected by alendronate in the early stages of healing (91-93), as they heal via endochondral ossification [68,69]. However, stress fractures heal by normal bone remodelling, and thus, alendronate may control or reduce healing, increasing the likelihood of a complete fracture with little or no trauma.

Medications have many benefits for treating osteoporosis. However, concerns have also been reported about the detrimental effect of long-term use of these drugs, such as aldronate, on femoral fractures. This point has been raised in some studies that prolonged use of alendronate may be a risk for fractures caused by a relatively low-energy mechanism. Alendronate inhibits the natural regeneration of bone. Therefore, it restricts the local repair and leads to the accumulation of small fractures and the patient is at greater risk for long-bone fractures. Fractures of the proximal femur that may extend proximally into the piriformis fossa or distally into the isthmus of the femur associated with alendronate therapy have typical clinical and radiographic patterns. In the case of complete fractures, things like minor or no trauma, the lateral cortex of the proximal femoral diaphysis with or without a transverse lucent line, transverse fracture orientation, medial metaphyseal beak angle, skirt-like focal thickening at the opposing lateral cortical surfaces,

superior displacement of the distal fragment, and varus deformity at the fracture site can happen to anyone at any time and at any age. Incomplete fractures show focal lateral cortical thickening with or without an incomplete transverse fracture line, which are known as "beaking" or "flaring." This radiographic fracture pattern is strongly associated with long term alendronate use.

Further studies are needed to determine the most appropriate treatment strategies used for patients with osteoporosis, so that patients can use effective treatments for minimizing the risk of fractures. In this line, the researchers suggested that physicians should assess each patient's condition individually. Since the mechanism and optimal duration of alendronate treatment remain somewhat unknown, this treatment should be considered according to the specific conditions of each patient. As described in this review, abnormal femoral fractures are the only side effect of alendronate. Therefore, alendronate is still a viable treatment option for patients with osteoporosis. According to this approach, specialists should not completely stop taking alendronate. Long-term use of alendronate may be associated with atypical subtrochanteric fractures. However, this has not yet been properly proven and needs further study. If this is proven, the risk ratio of alendronate to its therapeutic benefits remains low.

Conclusion

Overall, in review suggests that patients may be at an increased risk of atypical femur fractures associated with long-term alendronate use. The results of some studies in this field have shown that long-term use of alendronate suppresses excessive bone circulation, which ultimately leads to excessive accumulation of micro-damage in the bone and the occurrence of atypical femur fractures. However, current guidelines for the optimal and long-term use of alendronate to reduce the incidence of osteoporosis after abnormal fractures are not yet clear, and new strategies may be needed to prevent persistent injury in patients with certain conditions (evaluation of patients' clinical evidence in terms of age, sex, underlying diseases, drug interactions and special conditions such as lactation and menopause in women and other cases.). There is a need for experiments in the animal model system and further clinical studies to elucidate the mechanism of atypical femur fractures.

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