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Thigh pain among bisphosphonate users in Oslo – a pilot study

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Abstract

Background

Recently, a possible correlation between atypical femur fractures and long-term use of bisphosphonates has been found. Thigh pain and radiographic skeletal changes are possible prodromal symptoms and findings.

Objective

The aim of the current study was to elucidate if prodromal thigh pain could be could be used as a screening tool to find patients at high risk of atypical femoral fractures in patients with low BMD measured by the Osteoporosis centre at the Orthopaedic department of Oslo University Hospital Ullevål.

Methods

All available DEXA-data at Oslo University Hospital Ullevål were collected. We included patients who had T-score equal to or lower than -2.5 and searched their journals for available information on fracture history, drug history, bisphosphonate use, and DEXA-data. Patients were interviewed by telephone in order to complete the data. We used multivariable binary logistic regression and Pearson's Chi-Square test to test correlation between thigh pain and other factors.

Results

DEXA-data provided us with 338 patients, of which 120 were included. 9 patients reported thigh pain, of which one already had experienced an atypical femur fracture. The other patients had pain related to other illnesses. Specificity of bone pain is 11%. We found a correlation between thigh pain and age ($p = 0.003$, 95% CI 1.06-1.13) but no correlation to length of bisphosphonate use ($p = 0.112$, 95% CI 0.99-1.07), nor other drugs affecting bone metabolism ($p = 0.196$, 95% CI 0.48-35.49).

Conclusion

Thigh pain asked by telephone is an unspecific symptom. Previous studies imply that caution should be maintained when the duration of bisphosphonate therapy exceeds 4-5 years. Examination of bone mineral density should be performed, the continuation of bisphosphonate therapy should be re-evaluated and the physician should consult the patient regarding thigh pain. Patients should also be informed about atypical femur fractures so that they can contact a physician for clinical and radiographic examination if thigh pain occurs.

Background

Norwegians suffer 9,000 hip fractures and 15,000 distal radius fractures each year. Norway and other Scandinavian countries have the highest incidence of hip fractures in the world. Osteoporosis is a major contributing risk factor (1).

Osteoporosis – diagnosis and therapy

According to WHO guidelines osteoporosis is defined as Bone Mineral Density (BMD) equal to or lower than 2.5 standard deviations from the expected value of a young adult, of the same sex and ethnicity (2). BMD is usually measured by *Dual-Energy X-ray Absorptiometry* (DEXA).

DEXA is a technique in which X-rays are generated in two energy levels in one plane. DEXA measures the Bone Mineral Content (BMC) and the Bone Area (BA), and thus calculates the BMD. The BMD value itself is not usually used as a measure in the clinic. Physicians use the T-score to evaluate the bone mass (3). The T-score describes the number of standard deviations between the patient's BMD and the expected BMD of a young adult-population. The WHO classification is given in table 1 (2):

	Normal	Osteopenia (low bone mass)	Osteoporosis	Established osteoporosis
T-score	≥1	< -1 og >-2.5	≤ -2.5	≤-2.5
Additional condition				Fragility fracture

Table 1: The WHO osteoporosis classification

Patients with established osteoporosis, which is T-score ≤ -2.5 with the presence of a fragility fracture, are usually treated medically. According to guidelines (4;5), the first choice of medical treatment is bisphosphonates, primarily alendronate 70 mg weekly, combined with calcium (800-1,000 mg) and vitamin D (400-800 units) (4). Alternative bisphosphonates are risedronate 5 mg daily, ibandronate 50 mg daily and zoledronic acid 5mg yearly. The guidelines do not specify duration of the bisphosphonate treatment (5;6). Long term-treatment is not well defined in literature, but > 5-6 years is usually used.

Bisphosphonates – pharmacology, clinical use and side effects

Bisphosphonates are analogues of pyrophosphate. They bind to hydroxyapatite, one of the building blocks of bone, which gives bisphosphonates an effect that's mainly bone-specific. Bone undergo a constant maintenance process called *bone remodelling* or *bone turnover*, where osteoclasts resorb the bone and the osteoblasts reform it. When osteoclasts begin to resorb bone that is impregnated with bisphosphonate, the bisphosphonate is released to the osteoclasts. They impair bone resorption by reducing the osteoclasts' ability to form the ruffled border, to adhere to the bony surface, and to produce acid. In addition they also reduce differentiation of the osteoclasts' progenitor cells and induce apoptosis. Because resorption and reformation are coupled processes, it is believed that use of bisphosphonates reduces the total bone turnover through its inhibitory effect on osteoclasts (7).

Bisphosphonates have several areas of use, e.g. osteoporosis, hypocalcaemia, early breast cancer, prostate cancer metastasis, multiple myeloma, skeletal metastasis, Paget's disease and osteogenesis imperfecta (7). Bisphosphonates has been characterised as a drug with few side effects, the most common being stomach pain (8).

The most common side effects include Flu-like symptoms, which are common after

intravenous infusion and usually lasts 24-74 hours; musculoskeletal pain, kidney failure and hypocalcaemia (6;9). These are rare in patients with normal kidney function, but bisphosphonates are not recommended if the patient's creatinine clearance is below 30-35; Ocular toxicities including conjunctivitis, uveitis, scleritis, and orbital inflammation are very rare.

Osteonecrosis of the jaw (ONJ) has been discussed as a possible side effect of bisphosphonates, but has almost exclusively appeared in patients with terminal cancer and use of bisphosphonates for treating hypercalcaemia or skeletal metastases, and seems to be a very rare side effect when treating primary osteoporosis (6;9). Another feared side effect is oesophageal ulcers, but it is usually prevented by following the instructions for the tablets (6).

Subtrochanteric low energy fractures – a side effect?

In 2005 Odvina et al. (10) presented the first case series of patients on bisphosphonates suffering from low and ultra-low energy femoral shaft fractures. In 2007 Goh et al. presented the first retrospective study on subtrochanteric low energy femoral shaft fractures where they suggested an association between the fractures and the long term use of bisphosphonates (11).

In the recent years several case series (12-21) and retrospective studies (11;22-25) have continued to investigate and point out the statistical association between long term use of bisphosphonates and low energy fractures in the subtrochanteric and diaphyseal region of the femur. Neviaser et al. calculated that the usage of bisphosphonates was a significant risk factor for the fracture (OR 139.3, 95% CI 19.0-939.4). Giusti et al.(23) got a similar result (OR 17.00, 95% CI 2.55-113.26). Isaacs et al. and Lenart et al., using the same case material, have shown that patients suffering from the fractures had a significantly longer use of bisphosphonates compared to patients with other fractures. (Isaacs et al: 7.1 years vs. 3.2 years, Lenart et al: 7.3 years vs. 2.8 years). The fracture case with the shortest use of bisphosphonates, 1.5 years, was reported by Lee et al.(13).

Animal studies (26;27) have pointed out that bisphosphonates reduce bone turnover and may induce the accumulation of microdamage. Biopsy studies of human patients on bisphosphonates show a tendency of reduced bone turnover, but demonstrate variable results considering microdamage, and usually normal bone is found. A biopsy study by Armamento-Villareal et al. (15) with 15 patients on bisphosphonates with cortical fractures in different bones demonstrated that low bone turnover was more frequent with patients using bisphosphonates, but it did not show a difference in bone mineral density. They suggested that there might be a congenital risk factor which contributes to the fractures.

In the Norwegian drug description (8), subtrochanteric low energy fractures are included under the title ”very rare side effects” (<1/10.000), named ”stress fracture in the upper part of the femoral shaft”, but it is not included in the description of other bisphosphonates: etidronate (28), risedronate (29), pamidronate (30) and zoledronate (31).

Radiographic fracture pattern and nomenclature

The fracture pattern (figure 1) of the supposedly bisphosphonate-induced subtrochanteric low energy fractures is characterised by a lateral horizontal fracture line, increased lateral cortical thickness and a medial cortical spike (19). Some studies have not included radiographic descriptions at all (10) and others studies, while having radiographic descriptions, did not mention this pattern (15;26;27).

The name of the fracture varies in the literature.

- Atypical femoral fracture (20;23)
- Subtrochanteric stress fracture (12)
- Subtrochanteric insufficiency fractures (11)
- Low-energy femoral shaft (14;16;22;24;32)
- Subtrochanteric femoral stress fractures (18)
- Femoral insufficiency fracture (25)

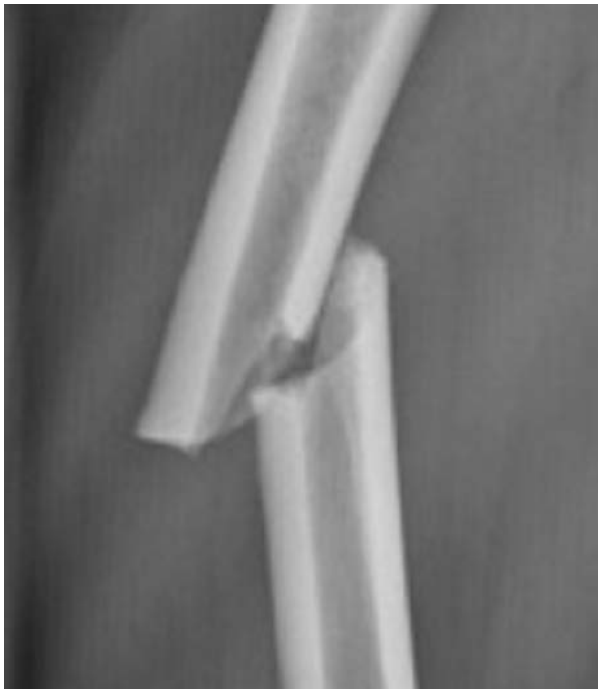

Figure 1. X-ray pattern of the fracture: A horizontal fracture line and a medial cortical spike. Notice the thickened lateral cortex.

Associated symptoms and clinical findings

Koh et al. (33) investigated the connection between the long term use of bisphosphonates, subtrochanteric fractures and radiographs. They found 4 patients with radiographs before the fracture, and all of them had a cortical stress lesion which they named *dreaded black line* (figure 2), a thin black line in a thickened lateral cortex. These 4 patients also experienced thigh pain in the affected leg. The term *dreaded black line* is originally a radiographic finding on cortical stress fractures of the anterior tibia, which often advances into a complete fracture (34).

Prodromal thigh pain has been reported by many papers. This has raised a question on whether it may be a symptom of a non-dislocated fracture. In the task force report for ASMBR Shane et al. (35) found thigh pain in 70% (158 of 227). Dell et al. (36) have in their study found thigh pain among 67% of their patients.

There has also been reported several cases of bilateral fractures, including cases where both femurs fractured simultaneously or a second femur fracture soon after the first. Shane et al. (35) found pain to be bilateral in 28% (60 of 215) in their task

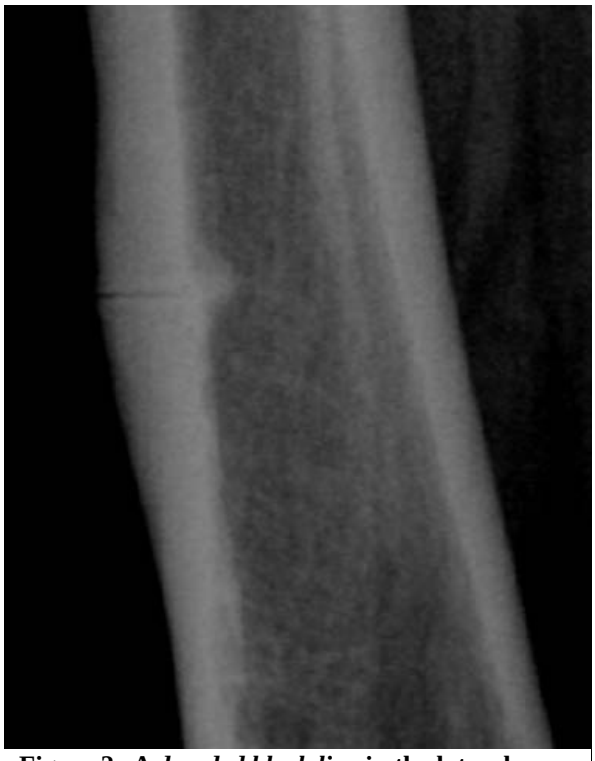

Figure 2. A *dreaded black line* in the lateral cortex with a localised periostal reaction. This could be a partial fracture which could advance into a complete fracture. The patients usually experience strong pain when straining the affected leg.

report, whilst Dell et al. (36) found bilateral pain in 25.9% among 135 patients.

Later studies

IOF (International Osteporosis Foundation) and ESCEO (European Society on Clinical and Economic Aspects of Osteoporosis and Osteoarthritis) published in November 2010 a summary of all existing literature concerning the question (37). They conclude with that direct causality between bisphosphonates and subtrochanteric low energy fractures has yet to be established and that there is a need to do extensive pathological, epidemiological and clinical research on the issue. Use of bisphosphonates does not need to be limited, but physicians need to be attentive to long term-users of bisphosphonates. They conclude that the benefit of bisphosphonate therapy greatly outweighs the side effects.

Shane et al. (35) released a task force report on behalf of The American Society for Bone and Mineral Research. They also conclude with the need for more research on different aspects of the problem, but still recommend using bisphosphonates as a treatment for osteoporosis. They also proposed a definition of major and minor features of the fractures (table 2):

Atypical Femoral Fracture: Major and Minor Features[a]
Major features[b] • Located anywhere along the femur from just distal to the lesser trochanter to just proximal to the supracondylar flare • Associated with no trauma or minimal trauma, as in a fall from a standing height or less • Transverse or short oblique configuration • Noncomminuted • Complete fractures extend through both cortices and may be associated with a medial spike; incomplete fractures involve only the lateral cortex. *Minor features* • Localized periosteal reaction of the lateral cortex[c] • Generalized increase in cortical thickness of the diaphysis • Prodromal symptoms such as dull or aching pain in the groin or thigh • Bilateral fractures and symptoms • Delayed healing • Comorbid conditions (eg, vitamin D deficiency, RA, hypophosphatasia) • Use of pharmaceutical agents (eg, BPs, GCs, PPIs)
a) Specifically excluded are fractures of the femoral neck, intertrochanteric fractures with spiral subtrochanteric extension, pathologic fractures associated with primary or metastatic bone tumors, and periprosthetic fractures. b) All major features are required to satisfy the case definition of atypical femoral fracture. None of the minor features are required but sometimes have been associated with these fractures. c) Often referred to in the literature as *beaking* or *flaring*.

Table 2: Diagnostic criteria for atypical femur fractures by the ASMBR task force (35).

Schilcher et al. (38) published in 2011 a study based on the entire Swedish female population. They established an age-adjusted absolute risk of 0.0005 and relative risk of 47.3 with any bisphosphonate use for sustaining an atypical femoral fracture in bisphosphonate users. In their case-control study they established that the risk of an atypical fracture was higher with an increasing duration of bisphosphonate use, with an odds ratio of 1.3 (95% CI, 1.1 to 1.6) per 100 daily doses prescribed. They also establish an incidence of 59 atypical femur fractures among 1.5 million Swedish women aged 55 or more. Among them, 46 used bisphosphonates. In total, there were 83 311 female bisphosphonate users aged 55 or more.

Objective

The aim of the current study was to elucidate if prodromal thigh pain, could be used as a screening tool to find patients at high risk of atypical femoral fractures in patients with low BMD measured by the Osteoporosis centre at the Orthopaedic department of Oslo University Hospital. We wanted to investigate if any of our osteoporosis patients had thigh pain and if that thigh pain could correspond to radiographic skeletal changes induced by bisphosphonate use.

Methods

1. We collected all available DEXA-data from Oslo University Hospital (OUS), Ullevål. The database had measurements from Feb 2004 until Jan 2011. All measurements past Dec 31st 2008 were excluded because of short follow-up. Only measurements of *Total femur* and *Total spine* (L1-L4) were included. Measurements with T-scores over -1.5 were not included. The measurements were then grouped into 2 groups: *Osteoporosis* included patients with at least one T-score measurement below or equal to -2.5 and *osteopenia* included patients with T-score between –2.5 and –1.5. If a patient had two or more measurements of the same area in one day, we included only the latter of the two measurements. Information from the database are patient ID, birth date, name, date of measurement and T-score for spine and femur.
2. We searched through the patient journals and collected information regarding fractures, recommendations of bisphosphonate use and side effects where available.
3. All patients were interviewed by telephone and the following information were collected:
    - Bisphopshonates:
        - Which bisphosphonate does the patient use?
        - Does the patient use it correctly?
        - When did the patient initiate bisphosphonate treatment?
        - How long has the patient used bisphosphonates?
    - Has the patient experienced any side effects from bisphosphonate therapy?
    - Has the patient experienced thigh pain after initiating bisphosphonates?
        - Is the pain bilateral?
        - How severe is the pain? VAS-score was utilized.
    - Does the patient use other medications, emphasizing:
        - Hormone therapy

- Glucocorticoids
- Antiepileptics
- Aromasine inibitors
- Calcium and vitamin D

- Has the patient experienced any fractures after initiating bisphosphonate therapy?

Patients with thigh pain were offered a consultation at the Department of Orthopaedics, OUS Ullevål.

We used binary logistic regression to investigate the correlation between pain and length of bisphosphonate use, Pearson's Chi-square test to investigate correlations between pain and other factors. All calculations were done by PASW Statistics ver. 18.

Results

The DEXA data set gave us 338 patients, among them 294 women and 45 men. 218 were excluded (figure 3).

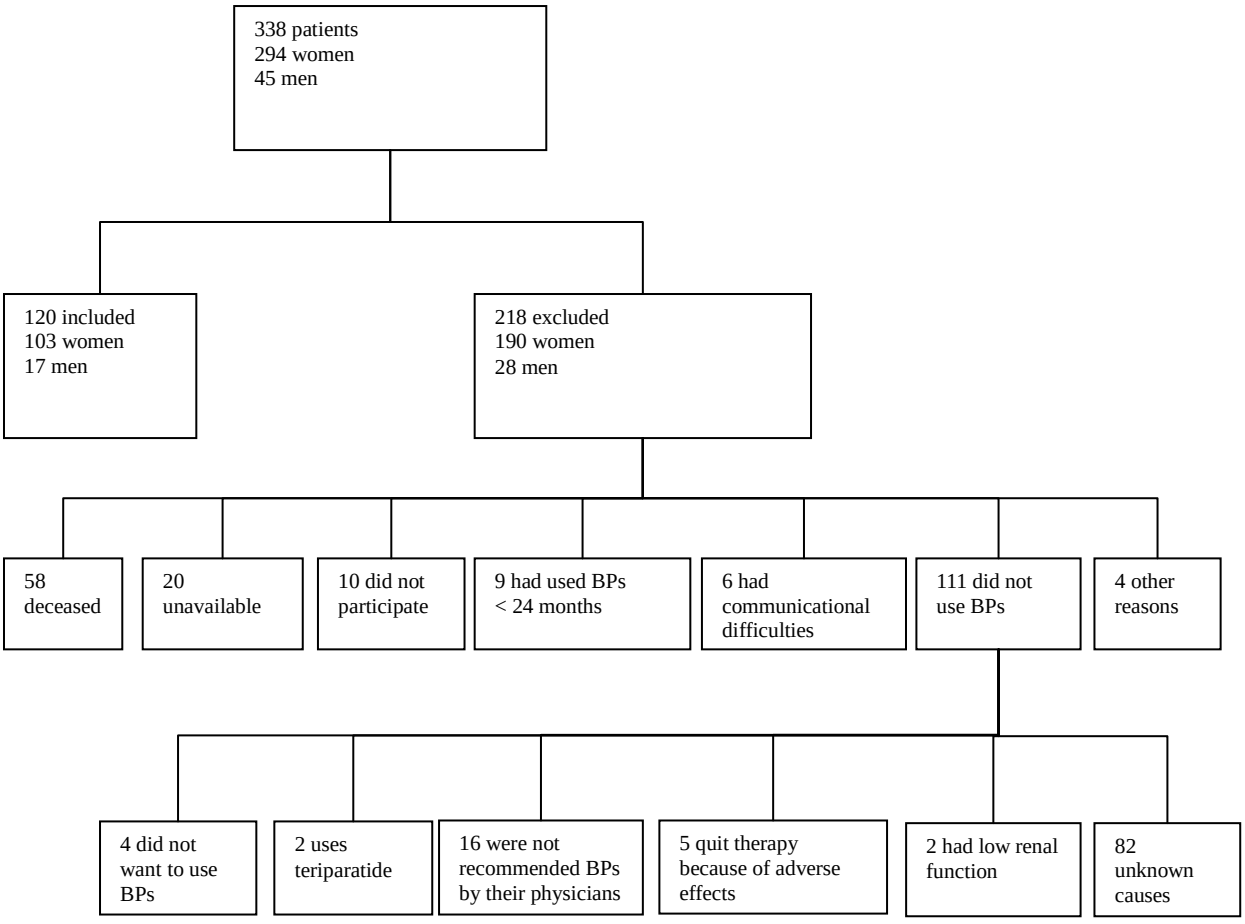

Figure 3: Excluded patients

Among the 120 included there were 103 females and 17 males. The mean age was 67, range 35 to 90. 73% of the patient had experienced fractures earlier, 21% confimed no previous fractures and 7% were unknown. 17% of the patients had breast cancer. 24% uses drugs that affect bone metabolism (corticosteroids, hormone replacement therapy, aromasine inhibitors), whilst 73% of the patients were on other medications in addition to alendronate; not counting calcium and vitamin D supplements. Mean duration of bisphosphonate use was 56 months. Most patients used alendronate (88%) (table 3).

	Frequency	Percent
Alendronate	106	88.3
Zoledronate	11	9.2
Risedronate	1	0.8
Ibandronate	2	1.7

Table 3: Distribution of bisphophonates.

9 patients reported of leg pain (table 4). Clinical examination and radiographs of the femurs did not reveal bisphosphonate-induced skeletal changes like dreaded black lines or atypical femur fractures with patient 2-9. Thigh pain specificity in our case is 1/9 = 11 %.

Patient	Age	Sex	BP	BP time (months)	Pain (VAS)	Location	Cancer mammae	Bone affecting medications	Other drugs
1[a]	82	F	Risedronate	56	50	Unilateral	No	No	Yes
2	90	F	Alendronate	83	15	Unilateral	No	No	Yes
3	82	F	Alendronate	138	45	Bilateral	No	No	Yes
4	83	F	Zoledronate	45	20	Unilateral	No	No	Yes
5	65	F	Zoledronate	42	35	Bilateral	Yes	Yes[b]	Yes
6	81	F	Alendronate	76	50	Bilateral	No	No	Yes
7	87	F	Alendronate	44	45	Unilateral	No	No	Yes
8	81	F	Alendronate	59	40	Unilateral	No	No	Yes
9	60	F	Zoledronate	75	15	Bilateral	Yes	Yes[b]	Yes

Table 4: Description of the patients who has experienced thigh pain

a) Patient 1 has experienced a radiographically confirmed atypical femur fracture. She used alendronate for 1-2 weeks before changing to risedronate due to oesophageal ulcers. She used bisphosphonates for more than 4.5 years. She had prodromal thigh pain for 1-2 weeks before the fracture.
b) Patient 5 and 9 used aromasine inhibitors.

Binary logistic regression (table 5) was used to investigate if thigh pain could be correlated to age, length of bisphosphonate use and usage of drugs affecting bone metabolism. Each variable was investigated in a univariate model and in a multivariable model incorporating all three (table 4). Sex was not included because no male patients experienced thigh pain.

Variable	Univariable model			Multivariable model		
	P-value	Odds ratio, 95% CI		P-value	Odds ratio, 95% CI	
		Lower	Upper		Lower	Upper
Age	0.002	1.057	1.271	0.003	1.058	1.312
Length of bisphosphonate use	0.073	0.998	1.055	0.112	0.993	1.067
Usage of other drugs affecting bone metabolism	0.776	0.153	4.052	0.196	0.481	35.488

Table 5: Results of the binary logistic regression.

Discussion

We found no new atypical femoral fractures or bisphosphonate induced skeletal changes with our strategy. We think there are at least three reasons for this. Firstly, it could be due to the combination of a rare phenomenon and a small study population. Secondly, it could have been that the observation period was short and our patients had yet to develop long term complications. The timing of a telephone interview may also be a problem. Patients experience thigh pain a limited time before the atypical fracture and telephone interview will most likely not coincide with that period. Thirdly, it could have been due to the method of detection; the interview did not differentiate patients with regards to the pattern of their pain history; e.g. one patient had a previous periprosthetic femoral fracture which caused chronic thigh pain.

Our study shows no significant correlation between thigh pain and length of bisphosphonate use, but there is a trend in our data. Age is as expected correlated to thigh pain, but there was no correlation between age and length of bisphosphonate use. We think that it is natural for pain to accumulate among the elderly considering number of diseases and length of exposure to different risk factors that may contribute to a disease causing pain in the thigh region.

Schilcher et al. (38) reported a number needed to harm of 2,000. It was thus not expected to find new diagnoses of bisphosphonate-induced skeletal changes. We did however find one patient that had already experienced an atypical femoral fracture. Even though the patient did experience thigh pain prior to the fracture it is uncertain whether it could have been detected by a telephone interview.

Shane et al. (35) reported of a 70% prevalence of prodromal thigh pain among all the fractures in their task force report, but there were no numbers on the specificity of the symptom. In our case we found it to be 11%, but considering the small number of patients we had in our study and the NNH (needed to harm) of 2000 per year of use calculated in the study by Schilcher et al. (38), the specificity is probably lower.

Black et al, the authors of FIT (39-41), FLEX (42), and HORIZON-PFT (43), randomised controlled studies on the effect of bisphosphonates, have investigated the incidence of fractures in their patients. In 14.195 female patients, 284 patients developed fractures of the hip and the femur. There were 10 patients with a total of 12 subtrochanteric low energy fractures. Comparison proved no difference between the patients who received bisphosphonates and those who received placebo (44). There are two major weaknesses of this study. First is the lack of radiographs, which makes it difficult to evaluate the result. Second, there were only about 1000 patients in this study who had taken bisphosphonate over 4.5 years.

In a cohort by Kim et al, a comparison was performed between the incidence of all subtrochanteric and diaphyseal fractures in patients using bisphosphonates and in patients using raloxifene or calcitonin. They could not prove a difference (HR 1.03, 95% CI 0.70-1.52) (45). This study also lacks radiographs.

A potential confounding factor when studying the fracture-inducing property of bisphosphonates may be the inclusion of patients on glucocorticoids (10;11;15;16;23). Glucocorticoids increases fracture risk (46).

Some studies have questioned some of the proposed mechanism behind the atypical femur fractures; in one case Jamal et al. (47) reported a patient with bilateral atypical femur fractures with normal bone turnover. Somford et al. (48) could in another case not find increased mineralization in a patient with bilateral atypical femur fractures. Yates et al. (49) reported a

possible contributing factor , with a case study of a 35-year-old patient with pycnodysostosis, who suffered an atypical femur fracture without a history of osteoporosis therapy.

Our study has several limitations. The number of patients was too low to expect statistically significant results given a low specificity of thigh pain as a symptom of bisphosphonate induced skeletal changes in a telephone interview. We attempted to do a set of Pearson's Chi-square tests, but the results are not reliable due to several individual expected frequencies with low values.

Conclusion

We found 9/120 patients who had experienced thigh pain. We did not find a relationship between length of bisphosphonate therapy and thigh pain, but this suggests that thigh pain in a telephone setting is an unspecific symptom.

In our opinion, physicians should not stop prescribing bisphosphonates to patients diagnosed with osteoporosis; the benefits by far outweigh the disadvantages. The case finding strategy we chose has a limited value until a better definition of high risk patients and perhaps better ways of elucidating symptoms by phone have been found. Caution should be maintained when the length of bisphosphonate therapy exceeds 4-5 years. Examination of bone mineral density should be performed, the continuation of bisphosphonate therapy should be re-evaluated and the patient should be asked of thigh pain. Patients should also be informed about atypical femur fractures so that they can contact a physician for clinical and radiographic examination if thigh pain occurs.

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