SHORT COMMUNICATION

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Low-Energy Femoral Fractures Associated with the Long-Term Use of Bisphosphonates

A Case Series from a Swiss University Hospital

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Abstract

Background: Bisphosphonates are effective and well tolerated anti-resorptive drugs used for the treatment of osteoporosis. However, some concerns about their potential long-term negative effects are emerging.

Objective: We report a series of patients with a history of bisphosphonate treatment admitted to our institution with a low-energy subtrochanteric fracture.

Patients and methods: Eight patients fulfilling these two criteria within the last 2 years were included in our retrospective analysis. All cases were reported to the Swiss National Pharmacovigilance Centre.

Results: All patients presented with a typical radiological pattern consisting of a cortical thickening at the lateral femoral subtrochanteric cortex with a horizontal fracture line originating precisely at this level. Four patients eventually developed a stress fracture or complete fracture of the contralateral femur. Two patients demonstrated delayed healing of their fracture. Five patients had been on alendronate therapy for a period ranging from 16 months to 8 years, two had been on ibandronate for 4 months and 1 year, respectively, after changing from alendronate, and one patient had been on pamidronate until 1 year before the fracture occurred. Seven patients were also receiving long-term proton pump inhibitor (PPI) treatment which could have contributed to the increased risk of fracture. Four patients were receiving both PPI and long-term corticosteroid treatment. The hypothesis of a negative pharmacodynamic interaction between bisphosphonates, PPIs and corticosteroids which could lead to a decrease in bone strength after long-term use needs further investigation.

Conclusion: Prescribers should be aware of the possibility of these rare adverse reactions and the prolonged use of bisphosphonates should be reconsidered until long-term robust safety data are available.

Background

Osteoporosis is a skeletal disorder characterized by compromised bone strength predisposing to an increased risk of fracture. It is in part a natural consequence of aging in postmenopausal women, but can also be drug induced (e.g. by corticosteroids). The most common consequences of osteoporosis are fractures of the hip, wrist and vertebrae.[1] Most currently available osteoporosis drugs are anti-resorptive agents that act to decrease bone turnover, such as the bisphosphonates (e.g. etidronate, alendronate, risedronate).[1-3] Bisphosphonates are synthetic, nonhydrolyzable analogues of naturally occurring pyrophosphates. They inhibit bone resorption through their effects on osteoclast function. These agents demonstrated a clinically important benefit in the secondary prevention of the majority of osteoporotic fractures. However, some concerns about their potential long-term negative effects are emerging.[4,5] Recently there have been several reports in the literature of atypical low-energy fractures occurring in patients who had been treated with alendronate for 1–10 years.[6-14]

An increase in the frequency of subtrochanteric fractures, all sharing the same typical radiological aspect, involving a cortical thickening at the lateral subtrochanteric cortex with a horizontal fracture line originating at this precise level and eventually extending medially, was noticed in our institution. As this fracture pattern is quite uncommon in osteoporotic patients, we retrospectively reviewed these cases to assess the use of bisphosphonates. This is a report of the first eight patients fulfilling these criteria. This report follows the guidelines for submitting adverse event reports for publication recently proposed by a task force composed of members of the International Society for Pharmacoepidemiology (ISPE) and of the International Society of Pharmacovigilance (ISoP).[15]

Patients and Methods

Cases of low-energy or spontaneous femoral fractures presenting with the same typical radiological appearance in patients admitted to our division of orthopaedics and trauma surgery within the last 2 years were analysed. Nine cases were identified. Only patients with a history of bisphosphonate treatment were retained for our case series. Eight patients fulfilled these two criteria (low-energy femur fracture and bisphosphonate treatment). The ninth patient had never received bisphosphonate treatment.

Clinical data and drug history were obtained from the patients' medical records and via telephone interviews with the GP or patient by a staff member of the regional pharmacovigilance centre.

All cases were then reported to the Swiss Health Authorities and consequently to the WHO Collaborating Centre for International Drug Monitoring, the Uppsala Monitoring Centre (UMC), in Uppsala, Sweden.

Results

Case Presentation

The history and clinical findings of these eight patients are described in table I. Relevant co-morbidities and concomitant therapies are described in table II. Their average age at the time of the first fracture was 67.5 years and seven patients (88%) were female. All patients were admitted with a fracture that developed following a fall from standing height or less; the fractures were even spontaneous in some cases.

In addition to biphosphonates, all patients were receiving oral calcium supplementation. Five patients (1, 2, 3, 7 and 8) were being treated with alendronate at the time of fracture. The duration of alendronate therapy in those receiving alendronate at the time of fracture ranged from 16 months to 8 years. Patient 7 had been

Table I. Summary of patient details

Case	Sex	Age (y)[a]	Mechanism	Fracture	Contralateral stress reaction/fracture	Bisphosphonate (duration of treatment before first fracture)	Indication	Pain before	BMD[b]/T-score[c] (date)
1	F	86	Slipped and fell	Right femoral shaft in 2007	No	Alendronate (16 mo)	Osteoporosis	No	0.615/–2.80 (2006)
2	M	61	Spontaneous pain while on the stairs	Right subtrochanteric in 2004	Thickened cortex in 2004, stress fracture in January 2008	Alendronate (2 y)	Osteoporosis	Yes, on the left	NA
3	F	79	Details not available	Left subtrochanteric in 2005	Thickened cortex in 2006, femoral shaft fracture in 2007 after falling from a standing height	Risedronate (duration unknown), then switched to alendronate (2 y)	Osteoporosis	No	0.628/–2.09 (2001)
4	F	57	Fell from a standing height	Right subtrochanteric in February 2006	Thickened cortex in April 2006, femoral shaft fracture in September 2006 after accidentally falling	Alendronate (10 y in total), then switched to ibandronate (4 mo before first facture)	Corticosteroid-induced osteoporosis	No	NA
5	F	67	Fell from a standing height	Right subtrochanteric in 2006	No	Alendronate (3 y in total), then switched to ibandronate (1 y)	Osteoporosis	No	NA
6	F	61	Tripped and fell	Left subtrochanteric in 2007	No	Pamidronate (5 y; stopped 1 y before fracture)	Osteoporosis	No	NA
7	F	66	Fell after pain	Left subtrochanteric in 2003	Thickened cortex, femoral shaft insufficiency fracture diagnosed in January 2008	Alendronate (5 y in total, 2 y before first fracture), then switched to ibandronate (1 y before second fracture)	Osteoporosis	Yes, both sides	0.614/–2.12 (2001)
8	F	63	Slipped and fell	Right subtrochanteric in 2008	No	Alendronate (8 y)	Osteopenia	No	0.657/–1.7 (2004)

a Age at the time of the first fracture.

b Bone mineral density (BMD) of the femoral neck (g/cm^2); most recent value available.

c The T-score is the bone density value expressed in relation to a young healthy population in standard deviation (SD) units. According to the WHO criteria, osteoporosis is defined as a BMD that lies 2.5 SD or more below the average value for young healthy women.[16]

F = female; **M** = male; **NA** = not available.

Table II. Patients' relevant co-morbidities and therapies

Case	Sex	Age (y)	Significant co-morbidities	Corticosteroid treatment	Proton pump inhibitor treatment	Calcium supplementation	Calcium levels[a] (date)
1	F	86	Hypertension, atrial fibrillation, hiatal hernia and gastro-oesophageal reflux	N	Y (pantoprazole)	Y	NA
2	M	61	Rheumatoid arthritis (treated by prednisone and methotrexate), hypertension	Y (oral prednisone)	Y (esomeprazole)	Y	2.15 (2004)
3	F	79	Hypertension, gastro-oesophageal reflux	N	Y (esomeprazole)	Y	NA
4	F	57	Chronic obstructive pulmonary disease (since 1968), dyslipidaemia, hiatal hernia	Y (oral and inhaled corticosteroids)	Y (esomeprazole)	Y	2.03 (2006)
5	F	67	No significant co-morbidities	N	N	Y	NA
6	F	61	Renal transplantation in 1994 (treated by prednisone, azathioprine and ciclosporin), hypertension, reflux, postmenopausal treatment (transdermal estradiol)	Y (oral prednisone)	Y (esomeprazole)	Y	NA
7	F	66	Postmenopausal treatment (tibolone), chronic low back pain, gastro-oesophageal reflux, hypertension, asthma	Y (inhaled corticosteroids)	Y (rabeprazol)	Y	2.34 (2007)
8	F	63	Hypertension, hypercholesterolaemia, hypothyroidism	N	Y (esomeprazole)	Y	2.42 (2008)

a Units: mmol/L; normal values: 2.20–2.52; most recent value available.

F = female; **M** = male; **N** = no; **NA** = not available; **Y** = yes.

receiving alendronate for 2 years at the time of the first fracture. She continued this treatment for 3 additional years and then changed to ibandronate for 1 year before an insufficiency fracture occurred on the contralateral femur. Two patients (4 and 5) were being treated with ibandronate at the time of their first fracture, but had previously been treated with alendronate for 10 and 3 years, respectively. Finally, patient 6 had only been treated with pamidronate for 5 years, but had ceased treatment 1 year before the fracture occurred. Two patients (6 and 7) were also receiving hormone replacement therapy. Three patients (2, 4 and 6) were being treated with long-term oral corticosteroids and patient 7 was being treated with inhaled corticosteroids. Finally, all patients except one (5) were receiving a proton pump inhibitor (PPI), in most cases as a long-term treatment of gastro-oesophageal reflux.

Bone mineral density (BMD) measurements of the femoral neck and calcium values were available for four of our patients (tables I and II).

Figure 1 shows a representative radiograph of the femoral fractures observed in our patients, generally consisting of cortical thickening and a transverse fracture. Four patients (2, 3, 4 and 7) also developed a stress fracture or complete fracture of the contralateral femur in a period of months to years after the first fracture. Two patients (2 and 3) demonstrated delayed healing of one of the fractures.

A bone biopsy was obtained in two patients (2 and 7). Figure 2 shows a photomicrograph of the biopsy of the cortex obtained in patient 7. This patient had only been treated surgically for a subtrochanteric fracture of the left femur in 2003. In January 2008, she presented to us with complaints of pain in her right thigh and had radiographic findings of cortical thickening in the proximal shaft. She underwent prophylactic intramedullary nailing and biopsy. The biopsy shows that the fracture crosses the whole thickness of the lateral cortex. While partial bone bridging can be seen in the periosteum, suggesting a chronic process, there is a total absence of fracture healing or even remodelling within the cortex.

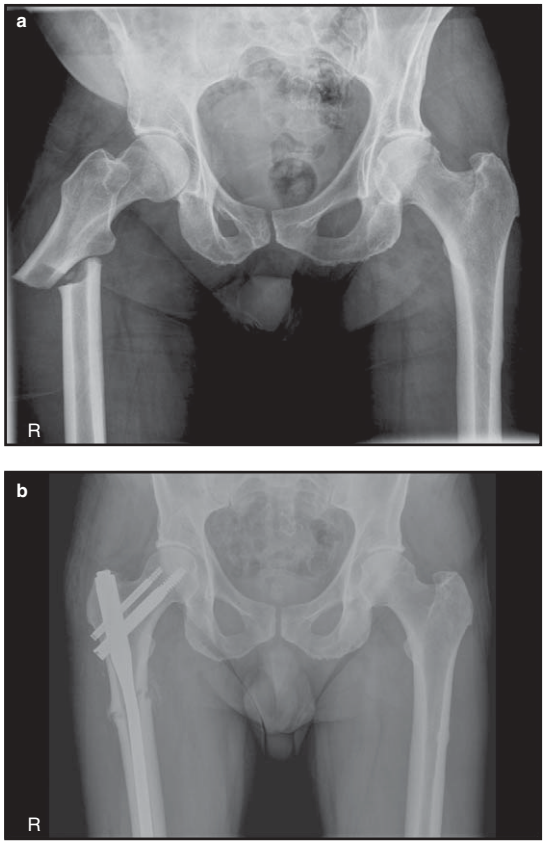

Fig. 1. (**a**) Radiograph of a spontaneous subtrochanteric fracture of the right femur presented by patient 2 in 2004 when he was 61 years of age. At that time, he had been receiving alendronate treatment for more than 2 years. A thickening of the lateral cortex of the femur with a transverse fracture originating at this level, a very typical radiological finding, was observed. A similar cortical thickening was evident on the contralateral femur, although the patient was asymptomatic at that time. (**b**) Radiograph after intramedullary fixation. A delayed union of the fracture was observed 6 months later, but the fracture finally healed after 12 months. This patient was seen again 3 years later with severe left thigh pain. Radiographs were consistent with a stress fracture of the left femur at the level of the cortical thickening. Prophylactic fixation is being considered at this time. **R** = right-hand side.

Outcome and Follow-Up

All eight patients required intramedullary nailing of their fracture. Two patients developed delayed healing of the fracture, and a second surgery due to non-union was required in one of these two patients to obtain union. Four of our eight patients exhibited cortical thickening in the contralateral femur. This cortical thickening was observed either at the time of the initial fracture or several months to years later. Two of these four patients developed a stress fracture, one of which required a prophylactic intramedullary nailing. The two other patients developed a complete fracture and required intramedullary nailing.

Discussion

We describe here eight cases of femoral shaft or subtrochanteric fractures occurring after at least 1 year of bisphosphonate treatment. Insufficiency fractures of the femoral shaft are rare, contrary to the traditional triad of wrist, spine and hip fractures seen as the defining feature of osteoporosis.[6] The proximal femoral shaft and subtrochanteric region is subject to high stress and not expected to fracture from minimal trauma unless there is severe underlying metabolic bone pathology. Neviaser et al.[14] did not observe such a fracture pattern in their untreated patients with osteoporosis, which suggests that this condition alone is not sufficient to cause this specific failure of the femoral shaft.

The clinical benefit of bisphosphonates in the secondary prevention of osteoporotic fractures has been demonstrated by several studies.[1-3] More recently, the efficacy of zoledronic acid once yearly has also been demonstrated.[17] No increased incidence of serious adverse effects were detected with alendronate, etidronate, risedronate or zoledronic acid, but the potential risk of upper gastrointestinal events and, less commonly, osteonecrosis of the jaw and atrial fibrillation could not be ruled out. Participants from FIT (the Fracture Intervention Trial)[18-21] who received alendronate during at least three years were eligible for the FLEX (the FIT Long-term Extension), which lasted 5 years.[22] The authors concluded that the long-term safety of alendronate was confirmed by this study. No increased fracture risk was observed with the long-term use of alendronate. The conclusion of the FLEX study confirmed previously published results from Bone et al.[23]

Nevertheless, several recent publications have reported low-energy fractures associated

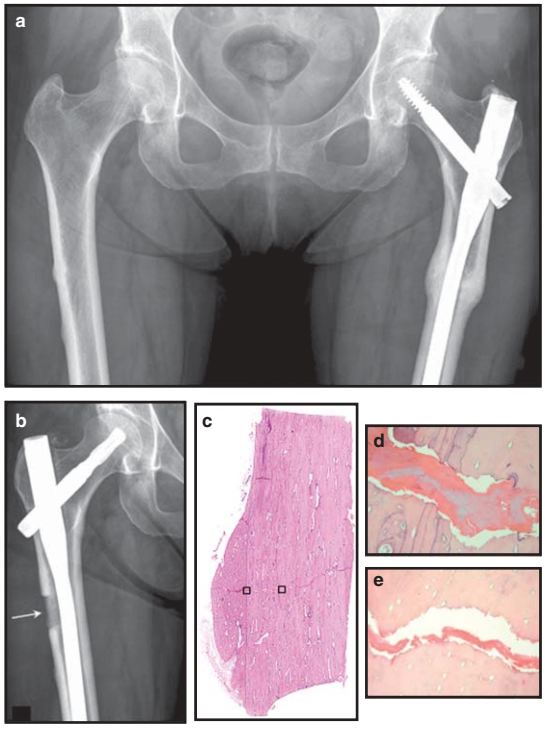

Fig. 2. (**a**) Radiograph of a spontaneous subtrochanteric fracture of the left femur presented by patient 7 in 2003 when she was 66 years of age, after intramedullary fixation. At that time, she had been receiving alendronate treatment for more than 2 years. (**b**) In January 2008, she presented with severe pain in her right thigh. Radiograph showed a subtrochanteric insufficiency fracture line. She underwent prophylactic intramedullary nailing and a biopsy of the lateral subtrochanteric cortex (arrow) at the same time. (**c**) Photomicrograph of the biopsy (haematoxylin and eosin stain). Two representative regions of the biopsy (squares) are shown in (**d**) and (**e**). (**d**, **e**) High magnification (×400) of the left and right squares, respectively. The fracture line is filled with blood, and no cellular reaction or osteoclasts are visible.

with the long-term use of alendronate. Four case reports concerning single patients have been published in 2006 and 2007.[6-9] In 2005, Odvina et al.[10] reported the first case series of nine patients. They described the development of spontaneous non-spinal fractures in patients treated with alendronate for 1–8 years. Evidence of impaired fracture healing was observed in six of their patients. The bone biopsies obtained in all patients showed a severe depression of bone formation with an absence of double-tetracycline labelling. Goh et al.[11] were the first to document fractures occurring in the subtrochanteric region of the femur in nine patients who had been taking alendronate. These reports were followed by three additional case series of patients presenting with a low-energy subtrochanteric or proximal femoral shaft fracture from Kwek et al.[12] (16 patients taking alendronate therapy and one taking risedronate after switching from alendronate), Lenart et al.[13] (15 patients taking alendronate) and Neviaser et al.[14] (25 patients taking alendronate). Our patients exhibited fracture patterns (below the lesser trochanter and above the distal one-third of the diaphysis) that were very similar to those reported by Neviaser et al.[14] This fracture pattern is probably a rare complication of bisphosphonates, which could explain why this adverse reaction had not been observed in the long-term studies of Black et al.[22] and Bone et al.[23] Coadministration of estrogens or corticosteroids seems to be a predisposing factor as suggested by Odvina et al.[10] Four of our patients were on corticosteroid therapy and two on postmenopausal hormonal treatment. Further investigation is needed to identify factors that increase the risk of such complications in order to define the proper balance between benefits and potential risks of bisphosphonate treatment.[8]

Bisphosphonates are the most widely used antiresorptive agents for the treatment of diseases involving an increased activity of osteoclasts.[24] Bisphosphonates can be classified into two major groups with different mechanisms of action. The first group comprises the non-nitrogen-containing bisphosphonates (e.g. clodronate, etidronate) which closely resemble pyrophosphate.[4,24] These compounds can be metabolically incorporated into nonhydrolyzable analogues of adenosine triphosphate. The accumulation of these metabolites in the cytosol of osteoclasts results in the inhibition of osteoclast function and may cause cell death. Induction of osteoclast apoptosis seems to be the primary mechanism by which non-nitrogen-containing bisphosphonates inhibit bone resorption. Nitrogen-containing bisphosphonates (e.g. alendronate, pamidronate, ibandronate) act by inhibiting farnesyl diphosphate (FPP) synthase, a key enzyme of the mevalonate pathway.[4,24,25] FPP is required for post-translational modification

(prenylation) of proteins, including small GTPases. GTPases are important signalling proteins that positively regulate several structural properties and cell processes important for osteoclast function. Inhibition of these processes by bisphosphonates leads to an inhibition of bone resorption.

The effect of bisphosphonates on osteoclasts has recently been assessed by Weinstein et al.[26] These authors observed an increase in the number of osteoclasts in bone biopsies from patients receiving alendronate, in contrast to animal studies that showed a decreased number of osteoclasts. Giant osteoclasts with pyknotic nuclei were found in some of the biopsies. Histological data were unfortunately available for only two patients in our study, and no osteoclasts were visible. However, Weinstein et al.[26] reported giant osteoclasts in only 25–56% of the patients treated with alendronate, which could explain our findings. Their observations suggest that the mechanism by which bisphosphonates inhibit bone resorption is still not fully understood and underscore the need for more investigation on the effect of these drugs on human osteoclasts.[27]

Bisphosphonates reduce fracture rates in part by reducing bone turnover.[28] As 'bone hardeners',[29] they produce increases in BMD, sometimes used as a surrogate marker of fracture risk.[30] However, measurements of surrogate markers alone may not be reliable to assess a decrease in fracture incidence.[31] In our study, BMD of the femoral neck could be obtained for four patients, but for two of them the BMD evaluation was performed several years before the first fracture occurred.

By slowing bone turnover, bisphosphonates allow secondary mineralization to progress, thereby increasing the tissue mineral content. The potential harmful effect on bone strength resulting from an inhibition of bone turnover is an important issue.[32] Increased mineralization and accumulation of microdamage are two separate but related consequences of bone turnover inhibition. The higher the tissue mineral content, the stiffer bone becomes, tolerating more peak stress. However, highly mineralized and homogeneous bone can become brittle and less tough, which may lead to the development of microdamages.[28] Microscopic cracks occur in normal bone after stresses encountered in day-to-day life.[32] They are physiologically detected by osteocytes leading to the initiation of a bone-remodelling repair of the damage. If bone resorption is inhibited, this physiological process is impaired and the natural repair of lesions cannot take place, eventually leading to their local extension. Mashiba et al.[33] reported a negative association between turnover and microdamage, although a direct causal relationship of low bone turnover to increased microdamage levels could not be demonstrated by their data. The effects of bisphosphonates on bone mechanical properties were investigated by Yang et al.[34] in a rat osteoporosis model. These authors showed that high concentrations of pamidronate in the bone were associated with a decrease in the mechanical strength of the intact femur.

Most of our patients were receiving alendronate therapy, but three of them developed a fracture after they had been switched to ibandronate therapy. As they previously received long-term alendronate (for 3–10 years), we cannot exclude that the fracture might have been related to a sustained effect of alendronate even after its discontinuation. Kwek et al.[12] also reported the case of a patient who was switched from alendronate to risedronate. From a pharmacokinetic point of view, alendronate has been reported to have a skeletal half-life of 10.9 years.[35] No other bisphosphonate pharmacokinetic studies report such long follow-up.[25] Unlike most other drugs, bisphosphonates remain in the body for decades.[32] They are not metabolized, but either excreted by the kidney or deposited within the bones, and the amount of drug within the bone will accumulate over time. This long-term skeletal half-life has to be considered when assessing the patients' follow-up after discontinuation of bisphosphonate therapy. One of our patients presented with a femur fracture 1 year after discontinuation of pamidronate therapy. A similar observation with alendronate has also been made by Armamento-Villareal et al.[8] Our patient is the only case of low-energy fracture that has been observed with

pamidronate. Although the data are still limited, our cases and those of Kwek et al.[12] suggest that the risk of a low-energy femoral fracture might be a class effect of bisphosphonate. This effect has thus far only been described with alendronate. The fact that this molecule has been available for the longest time and is the most widely prescribed may explain why this complication has to date not been linked to the use of other bisphosphonates.[14]

In the WHO database, 295 cases of fracture have been reported with alendronate thus far (data extracted on 24 July 2008) of 33 244 adverse drug reactions reported with this compound. These cases do not include ours. A majority of these 295 cases were unspecified fractures (n = 243), and there were 23 cases of impaired fracture healing, 27 cases of pathological fractures, one case of spontaneous fracture and one case of osteoporotic fracture. Few cases of such adverse drug reactions have been reported with other bisphosphonates in the WHO database, except for pamidronate, as shown in table III. This database of the WHO Programme for International Drug Monitoring contains spontaneous reports of adverse reactions from member countries, describing suspicions that have arisen from observation of an unexpected or unwanted event. In most instances it cannot be proven that a pharmaceutical product or ingredient is the cause of an event. The volume of reports for a particular product may be influenced by the extent of use of the product, publicity and other factors. No information is provided on the number of patients exposed to the product.[36] The extracted data for a given drug must be taken in the context of a spontaneous reporting system. In any case, these data cannot be used to calculate an incidence rate.

It is interesting to point out that all of our patients except one were receiving long-term treatment with a PPI (mostly esomeprazole). Limited animal and human studies have shown that PPI therapy may decrease insoluble calcium absorption or bone density. A recent case-control study found an association between the long-term use of PPI therapy and an increased risk of hip fracture.[37] The adjusted odds ratio (OR) for hip fracture associated with more than 1 year of PPI treatment was 1.44 (95% CI, 1.30, 1.59). The results of two recently published studies were consistent with these findings.[38,39] The first study[38] analysed data from prospective cohorts of men and women over the age of 65 who were enrolled in the MrOS (Osteoporotic Fractures in Men Study)[40,41] and the SOF (Study of Osteoporotic Fractures)[42] to examine the association between acid-suppressive medication use and bone density, rates of hip bone loss and fracture risk. Analysis of fracture outcomes showed that the use of PPIs conferred a 34% increased risk of nonspine fracture in the cohort of women. Among men who were not taking calcium supplements, there was a 49% greater risk of nonspine fracture compared with those not taking PPIs. The second study,[39] which included more than 15 000 cases of fracture (vertebra, wrist or hip), found a significant association between more than 7 years use of PPI and any assessed fracture (adjusted OR 1.92; 95% CI 1.16, 3.18). The fact that three large, well designed studies consistently report an association between the use of PPI and fractures is a strong basis for encouraging further investigation.[43]

Table III. Bisphosphonate adverse drug reactions (ADRs) reported in the WHO database (until 24 July 2008)

Compound	Total number of ADRs	Total number of fractures	Unspecified fractures	Fracture healing impaired	Fracture pathological	Fracture osteoporotic	Fracture spontaneous
Alendronate (since 1995)	33 244	295	243	23	27	1	1
Risedronate (since 1991)	5 788	31	26	0	4	0	1
Ibandronic acid (since 1996)	633	6	4	0	2	0	0
Ibandronate sodium (since 2006)	5 490	14	14	0	0	0	0
Pamidronate (since 1986)	7 901	50	26	2	22	0	0

A possible mechanism to explain this increase in fracture risk may be via the decreased absorption of calcium among those taking acid suppressive medication. An acidic environment in the gastrointestinal tract facilitates the release of ionized calcium from insoluble calcium salts. Calcium solubility may be important for its absorption. An acid suppressive therapy could therefore hinder calcium absorption. Consequently, potential bone loss may occur if acid production is suppressed. Nevertheless, it is unclear whether calcium malabsorption is sufficiently severe to influence bone modelling, and long-term studies on calcium malabsorption and the negative effects on skeletal metabolism are lacking.[43] All of our patients were receiving calcium supplementation. Calcium values could be obtained for four of our patients. Although we cannot make conclusion from such limited data, it is interesting to note that in two cases, the calcium value within the year of the fracture was below the normal values.

The simultaneous administration of bisphosphonate and PPIs could lead to a potentialization of their respective negative effect on bone strength and thus to an increased risk of fracture. This negative pharmacodynamic interaction is a novel hypothesis that should be investigated by mechanistic and epidemiologic studies.

In addition to bisphosphonates and PPIs, four of our patients were also receiving oral or inhaled corticosteroids. The administration of oral glucocorticoids is associated with a significant increase in fracture risk at the hip and spine.[44] The concomitant use of three drugs having potential negative long-term effects on bone could increase the risk of fracture, which could explain why such a rare adverse effect had not been detected in previous studies.

The retrospective design and the lack of a control group constitute the main limitations of our study. After drug marketing, case reports and case series raise hypotheses about drug effects, but more rigorous study designs are mandatory to test these hypotheses.[45] Although there have been several reports indicating that the long-term use of bisphosphonates may be associated with insufficiency fracture of the femur, we cannot make robust conclusions from case series. Prospective large-scale studies with long-term follow-up are warranted to address the specific question of this rare adverse drug reaction.

Conclusion

We report on a number of patients who developed low-energy or spontaneous fractures of the femur (subtrochanteric or femoral shaft) while on long-term bisphosphonate therapy. This observation might be a class effect of bisphosphonates. Moreover, we are the first to report the concomitant long-term use of PPIs in most of our patients, which could have contributed to the increased risk of fracture. Given the seriousness and the rarity of these cases, we have reported them to the National Health Authorities and consequently to the WHO Collaborating Centre for International Drug Monitoring as well as to the manufacturers of the drugs. Although we cannot draw a conclusion from our case series and other published reports, we believe that prescribers and users of these drugs should be alert to the possibility of such rare adverse reactions. We invite every prescriber of bisphosphonates and PPIs who has patients presenting with similar fracture patterns to report the case to the pharmacovigilance authorities.

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