Subtrochanteric fractures after long-term treatment with bisphosphonates: a European Society on Clinical and Economic Aspects of Osteoporosis and Osteoarthritis, and International Osteoporosis Foundation Working Group Report

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Abstract

Summary This paper reviews the evidence for an association between atypical subtrochanteric fractures and long-term bisphosphonate use. Clinical case reports/reviews and case–control studies report this association, but retrospective phase III trial analyses show no increased risk. Bisphosphonate use may be associated with atypical subtrochanteric fractures, but the case is yet unproven.

Introduction A Working Group of the European Society on Clinical and Economic Aspects of Osteoporosis and Osteoarthritis and the International Osteoporosis Foundation has reviewed the evidence for a causal association between subtrochanteric fractures and long-term treatment with bisphosphonates, with the aim of identifying areas for further research and providing recommendations for physicians.

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Methods A PubMed search of literature from 1994 to May 2010 was performed using key search terms, and articles pertinent to subtrochanteric fractures following bisphosphonate use were analysed.

Results Several clinical case reports and case reviews report a possible association between atypical fractures at the subtrochanteric region of the femur in bisphosphonate-treated patients. Common features of these 'atypical' fractures include prodromal pain, occurrence with minimal/no trauma, a thickened diaphyseal cortex and transverse fracture pattern. Some small case–control studies report the same association, but a large register-based study and retrospective analyses of phase III trials of bisphosphonates do not show an increased risk of subtrochanteric fractures with bisphosphonate use. The number of atypical subtrochanteric fractures in association with bisphosphonates is an estimated one per 1,000 per year. It is recommended that physicians remain vigilant in assessing their patients treated with bisphosphonates for the treatment or prevention of osteoporosis and advise patients of the potential risks.

Conclusions Bisphosphonate use may be associated with atypical subtrochanteric fractures, but the case is unproven and requires further research. Were the case to be proven, the risk–benefit ratio still remains favourable for use of bisphosphonates to prevent fractures.

Keywords Atypical · Bisphosphonate · Femur · Low trauma · Osteoporosis · Subtrochanteric

Introduction

Treatment with bisphosphonates significantly reduces the risk of fractures in men and women with osteoporosis. The evidence is based on high-quality phase III randomized controlled trials (RCTs) with fracture as an endpoint [1–10]. The benefits of bisphosphonates also extend to other disorders of bone metabolism such as glucocorticoid-induced osteoporosis [11], Paget's disease [12] and bone metastases [13, 14].

Treatment with bisphosphonates is not without adverse effects, but they are generally minor and occur in a minority of patients. The most common adverse effect is gastrointestinal upset with the oral formulations, the frequency of which decreases with intermittent treatment such as once-weekly or monthly regimens. Intravenous (IV) administration of nitrogen-containing bisphosphonates may induce an acute phase reaction which manifests as fever, myalgia and arthralgia, although these side effects usually resolve within a few days of onset [3, 7, 15]. High doses of bisphosphonates given intravenously may impair renal function, and the kidney is a major route of elimination of the bisphosphonates. For this reason, bisphosphonates are not recommended for use in patients with severe renal impairment [16–18]. The use of bisphosphonates has been associated with osteonecrosis of the jaw, but most cases have occurred in patients receiving high-dose IV bisphosphonates for neoplastic bone disease, and osteonecrosis of the jaw has rarely been reported in patients with benign bone diseases [19, 20]. An increased risk of atrial fibrillation has been reported for zoledronic acid [3], but the association may be coincidental [7]. Other uncommon or rare side effects of bisphosphonates include anaemia [21], urticaria [22, 23] and symptomatic hypocalcaemia [22].

In recent years, several clinical case reports and case reviews have reported an association between atypical fractures in patients receiving treatment with bisphosphonates. The majority of these cases have described fractures at the subtrochanteric region of the femur [24–31].

Against this background, the aim of this report was to critically review the evidence for an increased incidence of subtrochanteric fractures after long-term treatment with bisphosphonates, to identify gaps in our knowledge that warrant further research and to provide guidance for healthcare professionals. A PubMed search of literature from 1994 to May 2010 was performed using the search terms 'bisphosphonate(s)' AND/OR 'alendronate' AND/OR 'risedronate' AND/OR 'ibandronate/ibandronic acid' AND/OR 'zoledronate/zoledronic acid' AND/OR 'subtrochanter(ic)' AND 'fracture' AND/OR 'femur/femoral' AND/OR 'atypical' AND/OR 'low-trauma' AND/OR 'low-energy'. Scientific papers pertinent to subtrochanteric fractures following bisphosphonate use were analysed and included in the evidence base.

Characteristics of subtrochanteric fractures

Subtrochanteric fractures have been defined as occurring in a zone extending from the lesser trochanter to 5 cm distal to the lesser trochanter [32]. However, this anatomical classification of subtrochanteric fracture has several variations [33, 34], resulting in variable definitions in published studies [26, 30, 35].

Regardless of the definition used, many case reports and case reviews have suggested that there are several common features of subtrochanteric fractures associated with bisphosphonate use. Major features were that the fractures arose with minimal or no trauma and, on radiography, the fracture line was transverse. Minor features were that fractures were commonly preceded by prodromal pain and, on radiographs, there appeared beaking of the cortex on one side and bilateral thickened diaphyseal cortices [26, 28, 36–39]. This fracture pattern has often been referred to as an 'atypical subtrochanteric fracture' [40–42] although,

as reviewed below, the distinction between typical and atypical subtrochanteric fractures has not yet been firmly established.

It is worth noting that, on radiography, the appearance of atypical subtrochanteric fractures is similar to that of stress fractures, including a periosteal reaction, linear areas of bone sclerosis and a transverse fracture line. Prodromal pain prior to diagnosis is also common [43]. However, stress fractures are more commonly associated with repeated episodes of increased activity (e.g. participation in sports). Nevertheless, stress fractures due to non-traumatic loading in patients with low bone density do occur (insufficiency fractures) [43]; thus, the terms 'atypical' and 'stress' are often used interchangeably or in conjunction to describe subtrochanteric fractures in this context. However, this terminology also requires clarification, as not all stress fractures are atypical.

Epidemiology of subtrochanteric fractures

Subtrochanteric fractures are a relatively rare type of hip fracture [44–46], usually resulting from high-energy trauma, pathologic fracture or, in the elderly, low-energy injury involving osteoporotic bone. Several series report the incidence of this fracture [25–28, 30, 36, 37, 47], although the definition of the subtrochanteric site has varied. Nieves et al. reported a large, 11-year epidemiological study of fractures of the hip, subtrochanter, femoral shaft and distal femur in the US population aged ≥50 years using National Hospital Discharge Survey data from the National Center for Health Statistics and MarketScan® (medical claims experience) data [46]. Of all femoral fractures, 3% were at the subtrochanteric region, 5% at the femoral shaft, 5% at the distal femur and 87% were at the proximal femur (i.e. hip). Importantly, this study classified fractures solely according to their location in the femur and did not evaluate the fracture patterns radiographically. Thus, they were not

able to determine the incidence of 'typical' vs 'atypical' subtrochanteric fractures. In men and in women, the incidence rate of each type of fracture remained stable over 5 years but increased exponentially with age (Fig. 1). Each fracture type was more prevalent in women than in men. Seventy-five percent of all femur fracture cases were in women. The mean age at fracture was 80 years old, and those with a subtrochanteric fracture were of a similar age to those with a hip fracture.

Leung et al. published a retrospective analysis that aimed to document the incidence of low-trauma subtrochanteric or femoral diaphyseal fractures in a Hong Kong hospital over a 5-year period [42]. In all, 88 cases of subtrochanteric fractures and 66 of diaphyseal fractures were identified, accounting for 3.9% and 2.9% of all recorded osteoporotic fractures, respectively.
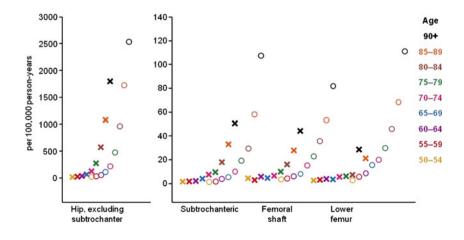
Thus, although the incidence of subtrochanteric fractures is much lower than other femoral fractures, they are not rare and account for about 3% of all femoral fractures in the elderly. If these estimates were applied to the UK, then more than 2,000 subtrochanteric fractures are expected to occur each year [48], and approximately 48,000 are expected annually worldwide [49].

Subtrochanteric fractures and bisphosphonate exposure

Case reports and case reviews

Twenty-six published case reports and case reviews were identified that were considered relevant, a similar number to that identified in a recent review by Giusti et al. [50].

Concern about bisphosphonate use in relation to atypical subtrochanteric fractures arose from case reports that described patients with subtrochanteric fractures who had been exposed to bisphosphonates, particularly long-term treatment with alendronate (Fosamax®/Fosavance®, alendronate sodium, Merck Sharp & Dohme Limited). The

Fig. 1 Age-specific incidence of femoral fractures according to fracture site in men (X) and women (O) aged ≥50 years (adapted from Nieves et al. [46])

association between long-term bisphosphonate use and unusual diaphyseal fractures was first described by Odvina et al. in 2005 [31] who reported nine patients with osteoporosis or osteopenia who had been treated with alendronate for 3–8 years and sustained atraumatic fractures in the course of their normal daily activities. Three patients had fractures of the femoral shaft and two had fractures of the proximal femur. Of these five patients, fracture healing was radiographically assessed in four. All four patients had delayed or absent fracture healing ranging from 4 months to 2 years while on alendronate treatment.

This and subsequent case reports are summarized in Table 1. The mean and median age of patients was 65 years (range 35–85). All cases involved treatment with alendronate, except for five patients who took risedronate (Actonel®, risedronate sodium, Procter and Gamble Pharmaceuticals) and three who took pamidronate (Aredia®, pamidronate disodium, Novartis Pharmaceuticals Limited). One patient had been taking ibandronate (Bonviva®/Boniva®, ibandronic acid, Roche) for 1 year following long-term alendronate use, and one had been taking risedronate for 5 years following 7 years of pamidronate use. There were no published case reports of subtrochanteric fractures following the use of once-yearly zoledronic acid 5 mg (Aclasta®/Reclast®, zoledronic acid anhydrous, Novartis Pharmaceuticals Limited), although cases following treatment with the monthly 4-mg dose have been reported [36, 38]. The mean and median duration of bisphosphonate 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%).

In addition to case reports, several case reviews have been published, which are summarized in Table 2. For example, the characteristics of low-trauma subtrochanteric and diaphyseal fractures were studied retrospectively by Neviaser et al. in all patients admitted to a US trauma centre over a 5-year interval (Table 2) [30]. Radiographs were examined by independent experts to identify fractures with a simple, transverse or short oblique pattern in areas of cortical hypertrophy with a cortical beak. The observers were blinded to patient characteristics, including alendronate use. Seventy patients were identified, of whom 25 were treated with alendronate. Nineteen out of 25 (76%) alendronate-treated patients had the radiographic pattern compared with one out of 45 (2%) non-alendronate-treated patients. Thus, the risk of having an 'atypical' subtrochanteric fracture pattern was significantly associated with alendronate use (odds ratio=139; 95% confidence interval (CI) 19–939; $p<0.0001$). The mean duration of treatment with alendronate was 6.2 years (6.9 years in those who had the fracture pattern vs 2.5 years in those who did not) [30]. The authors concluded that there are unique features to bisphosphonate-associated fractures.

Controlled studies

Six studies that utilized control groups were identified that have investigated the association of subtrochanteric fractures with the use of bisphosphonates. In the study of Nieves et al. described above, the rate of subtrochanteric and femoral shaft fractures appeared to be higher than that of other fractures in women taking oral bisphosphonates (Fig. 2) [46], although there is no statistical information provided. It is not known whether excess fractures were due to trauma or not. The study concluded, however, that there was no evidence of an increase in the incidence of subtrochanteric or femoral shaft fracture between 1996 (around the time that bisphosphonates were first introduced) and 2006. Limitations of these data include the lack of radiological and clinical verification and no information on the type of bisphosphonate used or the duration of treatment.

In a study by Leung et al., ten patients with subtrochanteric fractures who had received alendronate were identified over a 5-year period. This included one patient who had taken alendronate for 1 year followed by ibandronate for 2 years [42]. The crude incidence of subtrochanteric/ femoral diaphyseal fractures associated with prior bisphosphonate use increased over 5 years from 0% in 2003/2004 to 6% in 2004/2005, 8.6% in 2006/2007 and 25% in 2007/2008. This trend was despite a steady annual incidence of subtrochanteric/femoral diaphyseal fractures. It is difficult to draw meaningful conclusions from these data because of the very small sample size (ten subtrochanteric fractures in patients exposed to a bisphosphonate) and the lack of information on bisphosphonate use at other fracture sites. At best, the study documents the increasing use of bisphosphonates over the time of study.

In a small retrospective case–control study, Lenart et al. aimed to identify an association between low-energy subtrochanteric/femoral shaft fractures (according to the Müller AO classification) and long-term bisphosphonate use [29]. Forty-one low-energy subtrochanteric or femoral shaft fracture cases were identified and matched by age, body mass index and race to one low-energy intertrochanteric and femoral neck fracture each.

Fifteen out of the 41 (37%) cases of subtrochanteric or femoral shaft fracture cases were taking bisphosphonates, compared with nine out of 82 (11%) controls (OR=4.4; 95% CI 1.8–11.4; $p=0.002$). Alendronate was the bisphosphonate taken in all cases. Eight out of nine cases in the control group were taking alendronate (one had previously taken etidronate). A radiographic pattern of a simple transverse or oblique fracture, beaking of the cortex on one side and cortical thickening at the fracture site, was observed in ten of the 15 (67%) subtrochanteric/femoral shaft fracture cases taking bisphosphonate and three of the

Table 1 Case reports of incidents of subtrochanteric fracture following bisphosphonate use (all cases in women unless otherwise indicated)

Reference	Total patients (patients ST/FS/PF fracture)	Age (years)	Location	Radiographic features	Bilateral?	Prodromal symptoms (duration)	Osteoporosis diagnosis?	Prior bisphosphonate	Duration of use (years)	Concomitant therapy	Healing (months of follow-up)
Odvina et al. [31]	9 (5)	52	Femoral shaft		No		No (osteopenia)	ALN	8	Ca, D	No (9)
		68[a]	Femoral shaft		Yes		Yes	ALN	8	Ca, D	No (8)
		67	Femoral shaft		Yes		No (osteopenia)	ALN	5	Oestrogen, Ca, D	Yes (5)
		49	Proximal femur		No		Yes (GIO)	ALN	3	Pred, Ca, D	No (8)
		64	Proximal femur		No		Yes (GIO)	ALN	4	Pred, Ca, D	Yes (3)
Husada et al. [51]	1	72	Femoral shaft	Cortical thickening in lateral mid-shaft of contralateral femur	Yes	Severe pain in back and hip (1 month)	Yes	ALN	Not specified	Ca, amlodipine, metaprolol, aspirin	
Schneider [52]	1	59	Upper femur	Cortical thickening	No	Moderate pain in thigh (3 months)	No (family history of osteoporosis)	ALN	7	Ca, hormone replacement therapy	Yes (>9)
Armamento-Villareal et al. [53]	1	35[a]	Subtrochanteric femur		No			ALN	6	Ca	No (36)[c]
Cheung et al. [54]	1	82	Femoral shaft		No		Yes	ALN	10	Ca, glucosamine, chondroitin	
Demiralp et al. [55]	1	65	Femoral shaft	Fracture line, callus, cortical thickening, bowing deformity	Yes	Incapacitating bilateral femoral shaft pain (1.5 months)	Yes	ALN	7	Ca, D, steroid, thyroxine replacement therapy	
Lee et al. [56]	1	73	Femoral diaphysis		No	Bilateral groin pain, difficulty walking (10 months)	Yes	ALN	1.5		Yes
Sayed-Noor and Sjoden [57]	1	72	Subtrochanteric femur	Cortical thickening of lateral femoral cortex, medial beaking at fracture site	No	Diffuse pain in hips and thighs (18 months)	Yes	ALN	7	Ca	No (3)/yes (6)
Visekruna et al. [39]	3	51	Femoral metadiaphysis		Yes	Bilateral, lateral hip pain	Yes	ALN	5	Pred	No (3 while on ALN; 12 after stopping ALN)
		62	Femoral metadiaphysis		Yes	Bilateral thigh pain		ALN	10	Raloxifene, pred	Yes (12)[d]
		75	Femoral metadiaphysis		No			ALN	10	Pred	No (22)
Odvina et al. [58]	13 (11)	57	Subtrochanteric, contralateral femur shaft (3 years later)	Cortical thickening	Yes	Pain at fracture site (1–6 months)	No (osteopenia)	ALN	6	Ca, D	Yes (36)
		74	Femoral shaft	Cortical thickening	No		Yes	ALN	10	Ca, D	No

Table 1 (continued)

Reference	Total patients (patients ST/FS/PF fracture)	Age (years)	Location	Radiographic features	Bilateral?	Prodromal symptoms (duration)	Osteoporosis diagnosis?	Prior bisphosphonate	Duration of use (years)	Concomitant therapy	Healing (months of follow-up)
		67	Femoral shaft	Cortical thickening	No	Pain at fracture site (1–6 months)	Yes	RIS	>5	Ca, D	Yes (6)
		58	Femoral shaft (fractured twice in 3 years)	Cortical thickening	No	Pain at fracture site (1–6 months)	No	ALN	7	Ca, D, tamoxifen	Yes (6)
		62	Femoral shaft	Cortical thickening	No		No (osteopenia)	RIS	2	Ca, D, tamoxifen	
		63	Femoral shaft	Cortical thickening	No		Yes	ALN	10	Ca, D, oestrogen	Yes (6)
		72	Femoral shaft	Cortical thickening	No	Pain at fracture site (1–6 months)	Yes	ALN	9	Ca, D, oestrogen	Yes
		76	Femoral shaft	Cortical thickening	No		Yes (GIO)	ALN	11	Ca, D, pred	Yes (12)
		72	Left and right femoral shaft	Cortical thickening	Yes	Pain at fracture site (1–6 months)	Yes (GIO)	ALN	10	Ca, D, pred	Yes
		77	Femoral shaft	Cortical thickening	No		Yes (GIO)	ALN	9	Ca, D, pred	Yes
		38	Left and right femoral shaft	Cortical thickening	Yes		Yes (GIO)	ALN	3	Ca, D, pred	Yes
Ali and Jay [59]	1	82	Femoral shaft	Cortical thickening	No			ALN	8		Yes (3)
Goddard et al. [60]	1	67	Femoral diaphysis	Cortical thickening, unicortical beaking	No			ALN	16		Yes (12)
								Ibandronate	1		
Sayed-Noor and Sjoden [61]	2	78	Tip of femoral stem	Cortical thickening	No		Yes	ALN	9		No (6)
		55	Subtrochanteric femur	Cortical thickening, medial beaking, cortical thickening on contralateral femur	No	Diffuse pain in thighs, walking difficulties (several months)	Yes	ALN	9	D	Yes (9)
Cermak et al. [62]	4	64	Subtrochanteric femur	Cortical thickening	No	Pain in left thigh (3 months)	No	ALN	5.5		Yes (6)
		70	Femur	Medial cortical beaking	Yes	Pain in thighs	Yes	ALN	6		Yes (4)
			Other femur (3 months later)								Yes (7)
		77	Femoral shaft	Cortical thickening	No	Pain in right thigh	Yes	ALN	12		Yes (12)
		59	Subtrochanteric femur	Cortical thickening, medial cortical beaking	No	None	Yes	ALN	10		Yes (5)
Bush and Chew [63]	1	85	Subtrochanteric femur	Focal beak of cortical thickening of lateral cortex	No	Limp, persistent pain in anterior thigh (2–3 months)	Yes (GIO)	RIS	>6	Ca, D, pred	Yes (2)
Lee [64]	1	82	Left femoral diaphysis Right femoral diaphysis (4 years later)	Horizontal fracture lines at thickest part of femoral cortex extending lateral–medial,	Yes		Yes	ALN	8	Ca, D	Yes (5)

Reference	n	Age	Fracture site	Radiographic feature		Pain		Bisphosphonate	Duration (years)	Concomitant medications	
Edwards et al. [65]	1	60	Right femoral diaphysis; Left femoral diaphysis (2 years later)	followed by short oblique fracture (identical at both sites); (Taken after initial, right fracture) Minor lateral cortical thickening on left femur	Yes	Mild pain in right thigh before right fracture, none before left fracture	Yes (GIO)	ALN	8	Pred	No (6)
Giusti et al. [50]	8	60	Right subtrochanteric femur; Left subtrochanteric femur (9 months later)		Yes	Pain in right hip	No	ALN	4	Ca, D, inhaled GCs, esomeprazole, repaglinide, metformine, azathioprine, rosuvastatin	
		36	Femoral shaft		No		Yes	ALN	8	D, pred, simvastatine, cyclosporine, amlodipine, atenolol, lisinopril	Yes
		64	Left and right subtrochanteric femur (1 complete, 1 insufficiency fracture)		Yes	Pain in right thigh	No	ALN	2.5	Ca, D, pred, omeprazole, azathioprine, losartan, triamteren, HCT	No (18)
		62	Right and left femoral shaft[b]		Yes	Pain in right thigh and hip	Yes	Oral pamidronate	4	Ca, D,	Yes
		58	Femoral shaft		No	Pain in left thigh	Yes	Intravenous pamidronate	3	Ca, D	No (12)
		58	Subtrochanteric femur		No	Pain in left hip	No	RIS	5.5	Ca, D, pred, inhaled GCs, omeprazole, pravastatine, ibuprofen	No (12)
		72	Left subtrochanteric femur; Right subtrochanteric femur (insufficiency fracture 1 year later)		Yes	Pain in left thigh and hip	Yes (GIO)	Oral pamidronate followed by ALN	7+5	Ca, D, inhaled GCs, esomeprazole, simvastatine, captopril, irbesartan, clopidogrel	Yes (12)
		75	Femoral shaft (insufficiency fracture); Femoral shaft (insufficiency fracture 1 year later)		Yes	Severe pain in left thigh and hip; Pain in hip	Yes	RIS	6	Ca, D, esomeprazole, etoricoxib	

ALN alendronate, BP bisphosphonate, Ca calcium, D vitamin D, FS femoral shaft, GCs glucocorticoids, GIO glucocorticoid-induced osteoporosis, HCT hydrochlorothiazide, PF proximal femur, RIS risedronate, ST subtrochanteric, Pred prednisone

[a] Male patient

[b] First fracture prior to BP treatment; contralateral fracture following 4 years' BP treatment; refracture of contralateral femoral shaft 4 years after second fracture

[c] Patient was prescribed alendronate in 1996 and took it for 6 years. Fracture occurred 1 year after discontinuation and had not completely healed when reported in 2006

[d] Patient began teriparatide immediately after fracture

26 (11%) subtrochanteric/femoral shaft fracture cases not taking bisphosphonate (OR=15.3; 95% CI=3.1–76.9; p<0.001). The duration of bisphosphonate exposure was significantly longer in patients with this X-ray pattern [29].

Koh et al. carried out a retrospective clinical and radiological review of geriatric hip fracture patients at a Singapore tertiary centre over 4 years to assess features that predispose to complete stress fractures [38]. Thirty-two patients with spontaneous or low-energy fractures with metaphyseal–diaphyseal involvement and on bisphosphonate therapy were identified. All were on alendronate therapy except for one who was on monthly zoledronic acid 4 mg and one who had been on risedronate for 6 years following 4 years of alendronate. Of these, 16 patients (median duration of therapy 4.5 years) had radiographic evidence of lateral cortical thickening. Four had cortical stress lesions on the prefracture radiograph (group F) and 12 had cortical stress lesions on the contralateral femur (group C). The type of bisphosphonate taken by patients according to group was not detailed. All patients in group F experienced prodromal thigh discomfort, compared with 25% of patients in group C (p=0.019), and radiographic evidence of a stress line across the cortical thickening occurred in 100% and 8% of patients, respectively (p=0.003). At a median follow-up of 23 months, none of the patients in group C had developed a complete fracture. All of these patients except for one had discontinued bisphosphonate therapy; five had not taken any alternative therapy since discontinuation. Nevertheless, eight out of the 11 were asymptomatic, and no new cortical thickening was detected in any of the patients. The authors concluded that, in people taking long-term bisphosphonate therapy, symptomatic cortical stress reactions accompanied by evidence of a stress line across the cortical thickening suggest an increased risk of a complete stress fracture [38].

In the only population-based study that included radiological review of all cases, Schilcher and Aspenberg studied the incidence of stress fractures at the femoral shaft in bisphosphonate-treated patients in four hospitals in Sweden. Women aged over 55 years with fractures of the femoral diaphysis or subtrochanteric region were identified from the operation registry. Preoperative radiographs were examined to identify stress fractures, defined as a transverse fracture of the femoral shaft with cortical thickening. Of 91,956 women identified, 3,087 bisphosphonate users were identified, of whom five had femoral stress fractures. All of these five patients were aged >75 years, and their mean duration of treatment was 5.8 years [66]. Three patients that were not treated with bisphosphonates had stress fractures. All were aged <75 years. The annual incidence of femoral shaft stress fractures in bisphosphonate users was 1/1,000 per year (95% CI 0.3–2) vs 0.02/1,000 (0.004–0.1) per year in control patients. Thus, the risk of such fractures was

estimated to be 46 times greater with bisphosphonate use (95% CI 11–200) [65]. An obvious weakness of the study is that, although the confidence intervals were corrected for sample size, the findings were based on just eight femoral shaft stress fractures. The results thus raise a hypothesis to be tested on larger samples.

A larger study is provided by Abrahamsen et al. who studied the epidemiology of subtrochanteric and diaphyseal femur fractures in patients in Denmark treated with alendronate [67]. However, in contrast to the Schilcher and Aspenberg report, in this study, radiographic fracture patterns were not reviewed, and thus, fractures were identified purely based on their location. In patients aged ≥60 years that had subtrochanteric, diaphyseal femur and hip fractures in 2005, the incidence of subtrochanteric (n=898) and diaphyseal fractures (n=720) were similar, and the ratio of high-to-low-energy trauma fractures was the same for each of these fracture types (approximately 2.5:1 for each). Exposure to alendronate was also similar between fracture types (approximately 7% each). Patients with subtrochanteric fractures and diaphyseal fractures were more likely to have taken glucocorticoids in the year before fracture than patients with hip fracture (10.9%, 8.4% and 6.5% of patients, respectively).

In a register-based matched cohort analysis, Abrahamsen et al. investigated whether the increase in risk of 'atypical' femur fracture in alendronate-treated patients was greater than the increase in risk of 'typical' osteoporotic femur fractures ('typical' and 'atypical' were not defined). In total, 15,187 patients who took alendronate for ≥6 months after the fracture event (the treatment cohort) were compared with two randomly assigned sex-, age- and fracture-matched controls (n=10,374). The use of alendronate was associated with an increase in the hazard ratio (HR; adjusted for baseline comorbidities) for both subtrochanteric/diaphyseal fractures (HR=1.46; 95% CI 0.91–2.35; p=0.12) and hip fracture (HR=1.45; 95% CI 1.21–1.74; p<0.001). Subtrochanteric/diaphyseal fractures were equally common in the alendronate-treated (14% of hip fractures) and control patients (13%; p=0.70). Both hip fractures and subtrochanteric/diaphyseal fractures were significantly lower in patients with higher adherence (HR=0.47 [0.34–0.65; p<0.001] and 0.28 [0.12–0.63; p<0.01], respectively). In a sub-analysis of 178 compliant (medication possession ratio >80%) patients who took alendronate for >6 years, long-term alendronate use was associated with no change in both hip (HR=1.24 [0.66–2.34]; p=0.52) and subtrochanteric/diaphyseal fractures (HR=1.37 [0.22–8.62]; p=0.74). The incidence of subtrochanteric/diaphyseal fractures was similar in the long-term alendronate (10%) and control (12.5%) groups (10% vs 12.5%, respectively) [67].
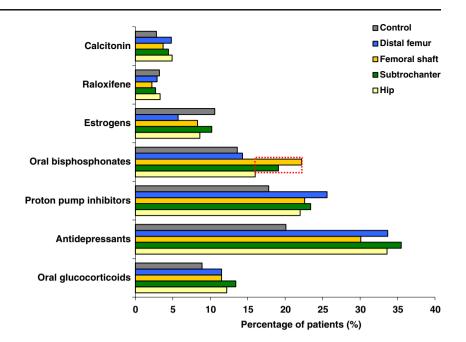
This study, in a large number of patients, does not support the hypothesis that exposure to alendronate is

Table 2 Case reviews of incidents of subtrochanteric fracture following bisphosphonate use (all cases in women unless otherwise indicated)

Reference	Review location/ period	Inclusion criteria	Patients eligible (n)	Mean age (years [range])	Fracture location	Radiographic features (n)	Bilateral? (n)	Prodromal symptoms (duration)	OP diagnosis? (n)	Prior BP (duration of use, years)	Concomitant therapy (n)
Goh et al. [26]	2 Singapore hospitals/May 2005–February 2006	ST fracture[a] due to low-energy trauma	13 ALN (9) No ALN (4)	66.9 (55–82) 80.3 (64–92)	NA NA	Cortical thickening (6=lateral, 3=contralateral)	NR NR	5 pts (2–6 months) None	Yes (3) No (4) Unknown (2) Yes (all)	ALN (4.2 [2.5–5]) NA	Ca (all); long-term oral steroids (1) Ca (2)
Kwek et al. [28]	Singapore hospital/May 2005–January 2007	ST fracture[b] due to low-energy trauma in patients taking ALN	17	66 (53–82)	NA	Lateral cortical thickening, medial cortical beaking (all)	ST stress fracture (2) Femoral shaft stress fracture (1) Femoral shaft fracture (1)	Yes, 13 pts (1 week–24 years)	Yes (10) No (6) Unknown (1)	ALN (4.4 [2–8]) [1 patient taking RIS after 4 years on ALN]	Ca (all); long-term prednisolone (1)
Neviaser et al. [30]	US trauma centre/January 2002–March 2007	Low-energy ST and mid-shaft femur fractures[c]	70 (11 male)	74.7	ST femur (50) Femoral shaft (20)	Lateral cortical thickening, unicortical beaking (20)[d]	NR	NR	Yes (31)[e]	ALN (6.2 [1–10]) [25 pts][f]	NR
Glennon [47]	Australian tertiary hospital, 12 months	ST stress fracture with characteristic radiological/clinical features	6	60–87	NA	Transverse fracture, unicortical beaking, cortical thickening (all)	1 patient	Pain in 5 pts (1 week to 6 months)	NR	ALN (1.5–16) [5 pts] RIS (>3) [1 pt]	NR
Ing-Lorenzini et al. [27]	Swiss university hospital/2 years	Low-energy ST fracture, history of BP use	8 (7 females)	67.5	ST femur (7) Femoral shaft (1)	Cortical thickening, also in contralateral femur in 4 patients	Yes, in 4 patients 0.5–5 years after first fracture	Pain in 2 pts, 1 lateral side, 1 both sides	Yes (all; 1 pt GIO)	ALN alone (1.5–8) [3 pts] ALN (3–10) switched to ibandronate (1 NK)[g] [3 pts] RIS (NK) switched to ALN (2) [1 pt] Pamidronate (5)[h] [1 pt]	Ca (all), glucocorticoids (4), proton-pump inhibitors (7)
Armamento-Villareal et al. [25]	US medical school/November 2004–March 2007	Low-energy fracture, mainly at cortical sites, 2 years' BP therapy, bone biopsy	15 (12 females, 3 males)	43–75	Femoral shaft (7) [1 male] Other (9)		Yes (2)	NR	NR	ALN (4–10) [6 pts]	Ca (6); vitamin D (6); infliximab (1); triamcinolone (1); tamoxifen (1); levothyroxine (1); fluticasone (1); HCT (1); mometazone (1)
Capeci and Tejwani [37]	US university hospital/4 years	Bilateral low-energy femoral diaphyseal or ST fracture, long-term ALN	7	61 (53–75)	Simultaneous femoral diaphysis (1) Sequential ST femur (2) ST and impending contralateral ST femur (3) Femoral diaphysis and impending	Cortical thickening, medial beaking (all)	Yes (all)	Thigh pain (4 pts with impending ST stress fractures)	NR	RIS (2) [1 pt] ALN (8.6 [5–13])	None affecting bone metabolism

Table 2 (continued)

Reference	Review location/period	Inclusion criteria	Patients eligible (n)	Mean age (years [range])	Fracture location	Radiographic features (n)	Bilateral? (n)	Prodromal symptoms (duration)	OP diagnosis? (n)	Prior BP (duration of use, years)	Concomitant therapy (n)
Bunning et al. [36]	US rehabilitation hospital/7 years	Atypical low- or no-impact femoral fracture	4 (1 male)	49–59	Diaphyseal femoral (3); left ST/right diaphyseal femoral (1) contralateral ST femur (1)	Medial cortical thickening (1)	1 pt	Pain in hip (1–3 months) [all], pain in knee [1 pt]	Yes (all)	None [1 patient] Pamidronate (0.5)/ zoledronic acid 4 mg (>4.5) [1 pt] ALN (5) [1 pt] ALN (6) [1 pt]	NR

ALN alendronate, *BP* bisphosphonate, *Ca* calcium, *GIO* glucocorticoid-induced osteoporosis, *HCT* hydrochlorothiazide, *NA* not applicable (described in inclusion criteria), *NK* not known, *NR* not reported, *OP* osteoporosis, *Pt* patient, *RIS* risedronate, *ST* subtrochanteric

[a] 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

[b] Within the region of the femur 5 cm distal to the lesser trochanter

[c] Muller AO classification type 32 and type 31 A3 fractures involving or extending distally to the lesser trochanter

[d] Nineteen had been treated with alendronate

[e] Twenty-one had been treated with alendronate

[f] All females. Eighteen cases confirmed through physician/patient contact. Duration of use established in 16 cases

[g] One patient had been on ibandronate for 1 year. One switched to ibandronate 4 months before first fracture in February 2006; one switched 1 year before second fracture in Jan 2008

[h] Stopped 1 year before fracture

Fig. 2 Medical and prescription drug history in US female fracture patients (2002–2006) during the 1 year before index date (adapted from Nieves et al. [46])

associated with an increased frequency of subtrochanteric fractures compared with controls. However, the same study reported that treatment with alendronate was associated with an increased risk of hip fracture. This should not be interpreted as 'alendronate causes hip fracture', but only that high-risk patients are exposed to alendronate. The finding also illustrates the difficulties in the interpretation of retrospective observational studies, particularly accounting for selection bias that likely confounds the other much smaller observational studies.

Randomized controlled trials

Black et al. recently reported an analysis of subtrochanteric and diaphyseal fractures in the Fracture Intervention Trial (FIT) of alendronate and its extension [1, 2, 5, 68] and the HORIZON Pivotal Fracture Trial (PFT) of zoledronic acid 5 mg [3]. Twelve fractures in ten patients were documented in the subtrochanteric or diaphyseal region (Table 3) a combined rate of 2.3 per 10,000 patient-years [69]. However, radiographs were not available to confirm typical vs atypical radiographic features. There was no significant increase over placebo in the risk of subtrochanteric/ diaphyseal fractures during the FIT, FIT Long-Term Extension (FLEX) or HORIZON-PFT trials. Compared with placebo, the relative hazard was 1.03 (95% CI 0.1–16.5) for alendronate use in the FIT trial, 1.5 (95% CI 0.3–9.0) for zoledronic acid in the HORIZON-PFT and 1.3 (95% CI 0.1–14.7) for continued alendronate use in the FLEX trial. The interpretation of this analysis is limited by the small number of events and the large confidence intervals.

Bilezikian et al. reported the incidence of subtrochanteric fractures in the randomized, placebo-controlled phase III studies of risedronate in post-menopausal osteoporosis, which enrolled more than 15,000 patients. In trials of up to 3 years duration, the mean incidence of subtrochanteric fractures was 0.14% in risedronate 2.5-mg treated patients ($n=4,998$), 0.13% in risedronate 5-mg treated patients ($n=5,395$) and 0.17% in placebo-treated patients ($n=5,363$) [70]. In active control studies of risedronate involving various doses (35 mg once weekly, 75 mg on two consecutive days per month, 150 mg once monthly), no subtrochanteric fractures were reported, and the incidence of hip/femoral fractures was similar to that in the placebo-controlled studies [70].

The manufacturers of ibandronate have assessed their clinical trials database to determine the incidence of subtrochanteric and diaphyseal femoral fractures in women taking ibandronate for post-menopausal osteoporosis. Atypical fractures were defined as 'mostly non-spine fractures including hip or femur fractures in the subtrochanteric region or shaft and occurring without trauma or in association with low-energy trauma'. For femur fractures, subtrochanteric fracture location was considered as atypical for osteoporosis-related fractures, defined as a region below the lesser trochanter and a junction between the proximal and middle third of the femoral shaft. In the pivotal trials (MF 4380, BONE, MOBILE and DIVA) [4, 71–73], there were nine fracture cases corresponding to these defined locations and characteristics (subtrochanteric, femoral shaft, stress or multiple fractures): six occurred in placebo-treated patients ($n=1,924$) and three in ibandronate-treated patients ($n=6,830$). In addition, there was one identified case of a

femoral shaft fracture in an ibandronate-treated patient in the extension and major phase IIIb trials (MOBILE LTE, DIVA LTE, MOTION and PREVENTION; n=2,451) [74–77]. Some fractures were reported without identifying the precise location. However, all of these fractures were associated with trauma and thus did not meet the definition for atypical fractures. An additional 5-year analysis of the marketed regimens of ibandronate (150 mg once monthly and 3 mg IV quarterly) was also carried out from the active comparator-controlled trials and their extensions (MOBILE, DIVA, MOTION, MOBILE LTE and DIVA LTE) [71, 72, 74, 75, 77]. No atypical subtrochanteric/diaphyseal femoral fractures were found for either of the marketed regimens (150 mg, n=1,279; 3 mg, n=469).

Pharmacovigilance data

Since fractures are the clinical outcome of osteoporosis and no treatments are fully effective, fractures are expected in treated patients. It is likely, however, that the number of reports through pharmacovigilance will be small. The number of postmarketing reports of atypical stress fractures in association with alendronate to circa July 2008 was 115 (of which 84 were femur fractures) and included a large number of the cases reported in the literature [78].

Bilezikian et al. have reported that in more than 10 years of risedronate post-approval surveillance to September 2008 (18 million patient-years of exposure), the reporting rate for subtrochanteric fractures was <0.1 per 100,000 patient treatment years of exposure [70].

Postmarketing data from the manufacturers of zoledronic acid have revealed a similarly low rate of subtrochanteric fractures with zoledronic acid 5 mg. Using the last cutoff date for worldwide Health Authority Reporting prior to January 2010 (Periodic Safety Update Report v6) and assessing all adverse event reports for zoledronic acid 5 mg (579,501 patient-years of exposure), the rate of femoral subtrochanteric fracture reporting was three per 1,000,000 patient treatment years of exposure.

Postmarketing data from the manufacturers of ibandronate have also revealed a low rate of possible atypical fractures occurring in patients receiving ibandronate for the management of postmenopausal osteoporosis. According to their global safety database as of June 2009, cumulative postmarketing exposure of ibandronate yielded a crude reporting rate of possible atypical fractures of approximately one per 1,000,000 patients. Three of the cases involved alendronate treatment followed by ibandronate treatment and were reported in the case series of Ing-Lorenzini et al. [27].

Regulatory perspective

In July 2008, the Pharmacovigilance Working Party (PhVWP) of the Committee for Medicinal Products for

Table 3 Characteristics of ten patients with 12 low-trauma subtrochanteric or femoral diaphyseal fractures in the FIT, FLEX and HORIZON-PFT trials (adapted from Black et al. [69])

Study	Age (years)	Study medication	Time from randomization to fracture (days [years])	Bilateral?	Prodromal symptoms	Compliance	Concomitant therapy
FIT	75	Placebo	962 (2.6)			>75%	None
FIT	69	Alendronate	1,682 (4.6)			>75%	None
FLEX	79	Alendronate (first fracture)	1,250 (3.4)			Stopped 3 years before first fracture	Alendronate, 6 years (in FIT before FLEX)
		Alendronate (second fracture)	1,369 (3.8)				
FLEX	80	Alendronate/ placebo	1,257 (3.4)			Stopped 3 years before fracture	Alendronate, 6 years (in FIT before FLEX)
FLEX	83	Alendronate/ alendronate	1,006 (2.8)			>75%	Alendronate, 5 years (in FIT before FLEX)
HORIZON	65	Zoledronic acid	454 (1.2)		Hip pain	100%	Raloxifene
HORIZON	78	Placebo	1,051 (2.9)		Hip pain	100%	None
HORIZON	65	Zoledronic acid	732 (2.0)			100%	None
HORIZON	72	Placebo	321 (0.9)			100%	Calcitonin
HORIZON	71	Zoledronic acid (2 fractures)	934 (2.6)	Yes	Bone pain	100%	Bisphosphonate and hormone replacement therapy, both before study

Human Use (CHMP) initiated a class review on bisphosphonates and atypical stress fractures. Marketing Authorization Holders supplied information about all preclinical, clinical and future studies, published case reports, post-marketing data, possible mechanisms and proposed risk-minimization activities. Following a PhVWP review of these data in December 2008, the CHMP concluded that there was an association between atypical stress fractures and long-term use of alendronate, due to the distinct fracture pattern, prodromal pain and poor fracture healing. However, the benefit–risk balance of alendronate use was considered favourable. The CHMP highlighted that there was uncertainty concerning a class effect for other bisphosphonates and that switching of bisphosphonates should be avoided at this time. Ultimately, the CHMP recommended that information about atypical stress fractures should be added to the product information for medicinal products containing alendronate [78]. Consequently, the labelling for alendronate (Fosamax®/Fosavance®, Merck Sharp & Dohme Limited) now includes a special warning/precaution for alendronate use, advising discontinuation of bisphosphonate therapy in patients with stress fracture pending evaluation, based on an individual benefit–risk assessment [22, 79]. Alendronate is the only bisphosphonate for osteoporosis treatment that currently carries this warning.

In addition to the 2008 class review, the EMEA released a statement in August 2009 highlighting their 2010 priorities for drug safety research with regards to the long-term adverse skeletal effects of bisphosphonates: (1) generate methodologies to study the link between bisphosphonate use and long-term adverse skeletal events in human populations and (2) measure the incidence of stress/insufficiency fractures in association with high-dose/long-term use of bisphosphonates by class, compound, mode of administration, dose etc. Methods could include meta-analysis or nested case–control studies [80].

In June 2008, the US Food and Drug Administration (FDA) initiated a review of bisphosphonates for a possible association with increased risk of atypical subtrochanteric femur fractures. All available case reports and clinical trial data were requested from all bisphosphonate drug manufacturers and were reviewed alongside the registry data from the large observational study of Abrahamsen et al. [67]. In March 2010, the FDA announced that the data reviewed had not shown a clear connection between bisphosphonate use and the risk of atypical subtrochanteric fractures. Physicians were urged to continue to follow the labelling when prescribing bisphosphonates and patients were instructed not to discontinue their medication unless instructed to do so by their physician [81].

Pathophysiology of subtrochanteric fractures associated with bisphosphonate use

The pathophysiology of atypical low-trauma subtrochanteric fractures following bisphosphonate use is not known. However, preclinical and clinical studies of the effects of bisphosphonates on bone suggest that there are several possible mechanisms that work either alone or in tandem. The organic matrix of the bone determines its toughness, and this matrix is partly made up of bone collagen, which impacts on the bone's mechanical properties. Bisphosphonate use may negatively affect collagen by preventing or reducing its maturation [82], although this finding has not been consistently replicated [83]. Bisphosphonates may also affect bone mineralization density distribution (BMDD). The more heterogeneous the BMDD, the slower that cracks in the bone will develop and the lower the risk of new cracks and fractures forming [84]. As bisphosphonate treatment reduces bone turnover, the increase in overall mineralization leads to more homogeneous bone—as evidenced by a narrow BMDD [85, 86]—and thus an increased risk of cracks and fractures. Reduced bone turnover also increases the accumulation of microdamage, as cracks are not repaired [87], and reduces bone toughness, which contributes to the increased susceptibility of bone to new cracks [88–90]. Finally, bisphosphonates have differing impacts on different types of fracture. Acute fractures of long bone are not affected by bisphosphonates in the initial healing stages [91–93], as they heal via endochondral ossification. However, stress fractures heal by normal bone remodelling, and thus, bisphosphonates may prevent or delay healing, increasing the likelihood of a complete fracture with little or no trauma. Several reports have reported on bone quality in people with low-trauma fractures taking bisphosphonate therapy.

For example, Odvina et al. reported that cancellous bone histomorphometry in alendronate-treated patients (3–8 years) who sustained spontaneous non-vertebral fractures showed markedly suppressed bone formation, with reduced or absent osteoblastic surface in most patients. Osteoclastic surface was also low in most patients, and eroded surface decreased in half [31]. Odvina et al. reported similar findings in a later report in a comparable patient population [58]. In a case report by Armamento-Villareal et al. of a man who had a low-trauma subtrochanteric fracture after discontinuing 6 years of alendronate treatment, a bone biopsy showed severely decreased trabecular connectivity, a lack of osteoid on trabecular surfaces and an absence of tetracycline labelling [53]. Armamento-Villareal et al. later reported that of 15 bisphosphonate-treated patients (2–10 years; Table 2) who underwent bone biopsies following a low-energy cortical (femoral shaft, pelvis, rib, metatarsal, ankle) fracture, ten had an absence of double-tetracycline

label, reduced osteoid surface and thickness suggestive of suppressed trabecular bone remodelling. However, there was no difference in cortical thickness between patients with suppressed ($n=10$) and normal ($n=5$) turnover [25]. Recent findings by Somford et al., however, suggest an alternative pathophysiology for subtrochanteric fractures associated with bisphosphonate treatment. In a patient who was treated with alendronate for 8 years and subsequently developed spontaneous bilateral subtrochanteric/diaphyseal fractures, biopsies showed a marked decrease in bone formation as expected; however, this was not coupled with the expected decrease in bone resorption. In fact, bone resorption parameters such as osteoclast number were markedly increased in the femur sample. In addition, there was no evidence of hypermineralized bone. This suggests that an imbalance between bone resorption and bone formation at the affected femur—the cause of which is currently unknown—rather than excessive suppression of bone turnover may be the underlying mechanism for subtrochanteric/diaphyseal femoral fractures in bisphosphonate-treated patients [94].

Summary of evidence

The view that bisphosphonates increase the risk of subtrochanteric femoral fractures arises from the case reports and retrospective case reviews that have reported 'atypical' subtrochanteric and diaphyseal fractures in patients exposed to bisphosphonates. In all, these data highlight the scope of the problem, i.e. a trend that warrants further investigation. However, the data in their entirety are insufficient proof that long-term bisphosphonate use is the only cause of atypical low-trauma subtrochanteric fractures.

There are several limitations to the existing evidence base: lack of a consensus definition of an atypical subtrochanteric fracture, small numbers of patients involved, lack of radiographs which precludes characterization of the radiographic features of the fractures and incomplete reporting of subject characteristics. In addition, subtrochanteric fractures in general are not atypical fractures; rather, they are part of the natural history of fragility fractures in osteoporosis. They increase in frequency with age in much the same way as does the incidence of other osteoporotic fractures [95]. Although their incidence is much lower than other femoral fractures, they are not rare and account for approximately 3% of all femoral fractures [46]. Thus, the term 'atypical' is not synonymous with 'unexpected' which is the common interpretation. Rather, the term should be reserved for subtrochanteric fractures that have atypical features, of which some are similar to with those associated with stress.

Therein lies an additional problem in that it has been difficult to provide characteristics of the fracture that are associated with the use of bisphosphonates. Candidate features, which include the prodromal manifestation of incomplete (fissure) fractures, a thickened cortex and a transverse fracture pattern with cortical beaking may be associated with the use of bisphosphonates but, in the absence of blinded evaluation in all cases, may be subject to large observer biases. In addition, in many instances, cases have been complicated, for example, by concomitant exposure to glucocorticoids [25–28, 31, 39, 50, 55, 58, 63, 65], which appears to be a risk factor for subtrochanteric fractures [46].

In terms of evidence-based medicine, the ultimate arbiter for a causal relationship between subtrochanteric fractures and exposure to bisphosphonates might be expected to derive from information from RCTs. All the information available fail to show an association of this fracture with exposure to bisphosphonates, although all RCTs were completed before attention was drawn to the problem, so the documentation of the sites of fracture and any associated features is inevitably incomplete. Furthermore, the frequency of the event is sufficiently low that even large RCTs are insufficiently powered to identify meaningful associations with drug exposure. Finally, the duration of exposure to bisphosphonates may be too short in the setting of RCTs if, as has been suggested, the complication were to increase in frequency with exposure time. Against this background, data from observational studies might be expected to contribute to our understanding, but such studies are fraught with biases and limitations for which it may be difficult to adjust.

Research agenda

The ultimate question for physicians is what type of patient is at the highest risk of an atypical low-trauma subtrochanteric fracture. Thus far, apart from long-term alendronate therapy, suggested risk factors include glucocorticoid, proton-pump inhibitor or calcitonin use and female gender [26, 46, 67]. Thus, a number of urgent issues and areas for research have been identified as follows:

1. Standardized definition of 'subtrochanteric fracture', including a definition of 'atypical' and 'typical' fractures
2. Provision of descriptive epidemiology based on large-scale studies with characterization of radiographic features
3. Definition of fracture incidence by femoral location, mechanism of injury and underlying pathology
4. Identification of risk factors, with greater clarity as to the precise risk factors in patients taking bisphosphonates

5. Pathophysiological studies in relation to risk factors
6. Pathophysiological studies at the tissue level, i.e. is the mechanism of atraumatic (insufficiency) fractures different to that of low-trauma fractures?
7. Long-term, large, prospective, observational studies to assess incidence of subtrochanteric fractures in bisphosphonate-treated vs bisphosphonate-naïve patients. Methods should include (1) futility analysis and (2) radiographic measurements. Outcomes should include (1) adherence, (2) number needed to harm and (3) assessment of temporal relationship between bisphosphonate treatment and fracture type
8. Long-term, large, prospective, observational studies allowing for systematic follow-up of patients with subtrochanteric fractures treated long-term with bisphosphonates, in order to assess fracture healing characteristics (e.g. time to healing, choice of fracture treatment device, adjuvant bone anabolic intervention etc.)
9. Large, prospective, randomized, controlled clinical trials of the efficacy and safety of pharmacological treatment (e.g. strontium ranelate, teriparatide) for patients with subtrochanteric fractures

Conclusions and recommendations

A sense of proportion may be helpful in alleviating the concerns of the medical community. A plausible scenario is that long-term exposure to bisphosphonates (more than 5 years) increases the risk of subtrochanteric femoral fractures twofold. In the UK, using the guidance of the National Osteoporosis Guideline Group, the relative risk of hip fracture is expected to be approximately threefold increased in postmenopausal women identified for treatment [96]. Assuming that the average population risk of hip fracture is 1% per year in postmenopausal women, then 300 hip fractures are expected for every 10,000 patients identified to be at high risk. If these patients were treated and assuming an effectiveness of bisphosphonates of 36% (RR=0.64) [97], then 108 hip fractures are averted by treatment (and approximately 750 fractures at other sites). On the debit side, three subtrochanteric fractures (both typical and atypical) are to be expected, which might increase to six if bisphosphonates doubled the risk of all subtrochanteric fractures. Under the assumptions of this scenario, the risk–benefit ratio remains very favourable.

Evidence, including that from an EMEA class review, suggests that alendronate use may potentially increase the risk for atypical, low-trauma subtrochanteric fractures, although it is unclear whether this applies to other bisphosphonates. Irrespective of exposure to bisphosphonates, the occurrence of subtrochanteric fractures is an expected finding in patients with osteoporosis. If atypical fractures do occur, then their characteristics are poorly defined, their causality with bisphosphonate exposure insecure and their frequency rare. Bisphosphonates as the cause of atypical fractures at the subtrochanteric site is therefore still merely a hypothesis, though no less important for that. Clearly more research is required from well-designed prospective observational studies, meta-analyses and nested case–control studies.

Thus, the available evidence does not suggest that the well-known benefits of bisphosphonate treatment are outweighed by the risk of these rare, atypical, low-trauma subtrochanteric fractures. Nevertheless, it is recommended that physicians remain vigilant in assessing their patients treated with bisphosphonates for osteoporosis or associated conditions. They should continue to follow the recommendations on the drug label when prescribing bisphosphonates and advise patients of the potential risks. Patients with pain in the hips, thighs or femur should be radiologically assessed and, where a stress fracture is evident, the physician should decide whether bisphosphonate therapy should be discontinued pending a full evaluation, based on an individual benefit–risk assessment. The radiographic changes should be evaluated for orthopaedic intervention—since surgery prior to fracture completion might be advantageous—or be closely monitored.

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