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ORIGINAL ARTICLE

The clinical characteristics of patients with hip fractures in typical locations and atypical femoral fractures

Soledad Velasco · Sandra Kim · Robert Bleakney · Sophie A. Jamal

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Abstract
Summary The pathophysiology of atypical fractures is unknown. We compared characteristics of patients with atypical femoral fractures and hip fractures in typical locations of the femur. Patients with atypical fracture reported a longer duration of use of bisphosphonates, had higher body mass index, and higher total hip bone mineral density. Further studies are needed.
Introduction This study aims to describe the characteristics of patients with typical and atypical fractures of the femur assessed in a tertiary care osteoporosis center.
Methods We abstracted clinical, laboratory, and radiographic data on subjects with a history of a low-impact fracture at the femur and/or hip (confirmed by review of radiograph and/or radiology report) from January 2008 to October 2011. Available radiographs were reviewed and fracture categorized as typical or atypical by a radiologist blinded to the original diagnosis.
Results Radiology reports were available for 72 subjects: 40 hip fractures in typical locations (typical fracture), 16 atypical femoral fracture (atypical fracture), and 16 were excluded. While both those with typical and atypical fractures reported taking bisphosphonates at the time of fracture, duration of use was longer with atypical fractures (104.2±42.0 months) compared with typical (71.1±62.8 months) (p=0.04). Body mass index (BMI) was higher in patients with atypical fractures (26.2±3.2 kg/m^2) than in those with typical (23.1±4.3 kg/m^2) (p=0.006). Total bone mineral density (BMD) was higher in patients with atypical fracture (0.795±0.102) versus typical (0.686±0.130) (p=0.003) Previous history of cancer was reported by 7 of 16 patients with atypical and 7 of 40 patients with typical fracture (p=0.04).
Conclusions Compared to those with typical fractures, patients with atypical fracture report a longer duration of use of bisphosphonates, higher BMI, and higher total hip BMD. Future studies should examine if these differences contribute to the pathophysiology of atypical fractures.

Keywords Atypical fracture · Atypical femoral fracture · Bisphosphonate

S. Velasco
Unidad de Endocrinología, Clínica Alemana de Santiago, Facultad de Medicina Clínica Alemana, Universidad del Desarrollo, Santiago, Chile

S. Kim · S. A. Jamal (✉)
Division of Endocrinology and Metabolism, Women's College Hospital, University of Toronto, Toronto, ON, Canada
e-mail: sophie.jamal@utoronto.ca

R. Bleakney
Department of Medical Imaging, Mount Sinai Hospital, University of Toronto, Toronto, ON, Canada

S. A. Jamal
Women's College Research Institute, University of Toronto, Toronto, ON, Canada

Introduction

Bisphosphonates are the most commonly prescribed medications for the treatment of osteoporosis worldwide. Bisphosphonates are highly effective: epidemiologic studies report that the incidence of typical femoral fractures (femoral neck and intertrochanteric fractures) have decreased since the introduction of these agents. That said, epidemiologic studies also report that the incidence of fractures at the subtrochanteric or femoral shaft may be increasing since the introduction of bisphosphonates [1–3]. Case–control studies have also reported an association between fractures occurring in the outer part of the femur without prior injury, called atypical fractures, and long-term bisphosphonate use [4–7]. While that association between bisphosphonate use and atypical fractures is well

accepted, the cause and incidence of these fractures is not known. Indeed, a recently published report from the American Society for Bone and Mineral Research (ASBMR) concluded that more epidemiologic and clinical data is needed to assess the true incidence and the risk factors related to this type of fractures [8].

Our chart review, which reports on the clinical, laboratory, and radiographic characteristics of patients with atypical fracture compared to those with typical femoral fractures (typical fracture) aims to address the identified knowledge gaps.

Methods

Subject recruitment and data collection

We conducted a chart review of all subjects attending the Multidisciplinary Osteoporosis Clinic at Women's College Hospital, a tertiary referral center located in Toronto, ON, Canada, from January 2008 to October 2011. Charts of subjects with low-impact hip or femur fractures were identified for data abstraction. Low-trauma fractures were defined as a fracture that occurred as a result of no or minimal trauma, equivalent to a fall from standing height or less [9]. We excluded hip fractures that were periprosthetic or associated with local primary or metastatic bone tumor.

We abstracted the following data: age at fracture, gender, race, body mass index (BMI), calcium and vitamin D supplementation, prescription medications, vitamin D levels, markers of mineral metabolism (serum alkaline phosphatase, calcium, phosphorus, creatinine, and parathyroid hormone), bone mineral density (BMD), comorbidities, localization of the fracture, radiologic characteristics of atypical fractures from radiology reports, and treatment of the fracture. For all cases, the data we abstracted were values recorded closest in time to the occurrence of the fracture.

We also collected data on use of the following prescription medications at the time of fracture : bisphosphonates (alendronate (ALN), risedronate (RIS), etidronate (ETI), pamidronate (PAM), and zolendronate (ZOL)), estrogen therapy, selective estrogen receptor modulators (SERMs), calcitonin, denosumab, teriparatide, oral steroids (other than those used for adrenal insufficiency), thiazolidinediones, anticonvulsants, statins, selective serotonin recapture inhibitors (SSRIs), and proton pump inhibitors (PPIs). We recorded length of use (in months) of each bisphosphonate, and the specific indication for the prescription: osteoporosis or osteopenia (based on BMD testing), prior low-trauma fracture, prevention of postmenopausal bone loss, prevention of cancer-induced bone loss, and Paget's disease. We also noted the previous use of estrogen therapy and SERMs.

We abstracted data on the following comorbidities: vitamin D insufficiency (25 (OH) D levels of 20–29 ng/ml) or deficiency (25 (OH) D levels of less than 20 ng/ml), cancer, renal calculi, hypercalciuria, rheumatoid arthritis, diabetes mellitus (types 1 or 2), chronic kidney disease, malabsorption syndrome, chronic obstructive pulmonary disease, asthma, hypophosphatasia, previous joint replacement, hypothyroidism, and early menopause (last menstrual period younger than 45 years). Previous low-trauma fracture was also collected.

Bone mineral density

We recorded BMD results in grams per square meter at the femoral neck, total hip, lumbar spine (LS), and radius obtained either shortly before or after fracture occurrence. Results based on *T* score were also recorded.

Radiology reports

We included data on subjects who had radiologic reports and/or images available. When images were available, they were reviewed and classified as typical or atypical fractures by a radiologist blinded to original diagnosis and clinical history.

Typical fractures were fractures located at the femoral neck or intertrochanteric fractures, complete or incomplete. Atypical fractures were fractures located anywhere along the femoral diaphysis distal to the lesser trochanter and proximal to the supracondylar flare of the distal femoral metaphysis [8]. Atypical fractures were categorized as complete or incomplete (involving only the lateral cortices of the femur). We reported major and minor features for atypical fractures. Major features included: fracture associated with minimal or no trauma; the fracture line originates at the lateral cortex and is substantially transverse in its orientation, although it may become oblique as it progresses medially across the femur; noncomminuted or minimally comminuted; complete fractures extend through both cortices and may be associated with a medial spike and incomplete fractures involve only the lateral cortex; and localized periosteal or endosteal thickening of the lateral cortex is present at the fracture site. Minor features included generalized increase in cortical thickness of the femoral diaphysis, unilateral or bilateral prodromal symptoms such as dull or aching pain in the groin or thigh, bilateral incomplete or complete femoral diaphysis fractures, and delayed healing. Fractures at sites other than the hip or femur were excluded from our analyses. To consider a fracture as an atypical femoral fracture (atypical fracture), at least four of the five major features must be present.

Statistical analysis

We reported means and standard deviation (SD) for continuous variables and number of subjects for categorical variables. We compared differences in clinical characteristics among subjects with typical and atypical fractures using the Student's

t test for continuous variables and Fisher's or chi-square test for categorical variables if applicable. A p value of <0.05 was considered statistically significant and we did not adjust for multiple comparisons. All analysis were performed using MiniTab v16 for Windows (Minitab Inc). This study was approved by the Research Ethic Board at Women's College Hospital.

Results

General characteristics

We reviewed the charts of 3,846 subjects who attended the osteoporosis clinic from January 2008 to October 2011. Of these 3,846 subjects, 85 had a chart note indicating that they may have had a femoral or hip fracture and 72 had a radiology report available for review. From the 72, we excluded a further 16 (five had femoral fracture related to previous hip prosthesis, five had fractures at another site (femoral condyle, acetabulum, tibia, and sacrum), two had femoral fracture at the medial cortex related to osteomalacia, one had avascular necrosis of the hip, and three did not have a fracture by the radiology report), leaving 56 subjects; 40 had typical hip fracture and 16 atypical femoral fractures. Figure 1 images were available for review by our radiologist for 40 of the 56 subjects included (26 with typical fracture and 14 with atypical fracture). Classification of fractures as typical and atypical by our radiologist was identical to the radiology report. The mean age of subjects at the time of fracture was 65.9±9.8 for atypical and 69.8±15.6 years for typical fractures (p=0.27). Most of the subjects were female (94 % with atypical and 95 % with typical fractures) and Caucasian (75 % with atypical and 100 % with typical fractures). In the group with atypical fractures, three patients had an Asian ethnic background. Subjects with atypical fractures had higher BMI (mean 26.2±3.2 kg/m^2), compared to those with typical fractures (23.1±4.3 kg/m^2; p=0.006) (Table 1). Most of the subjects were taking calcium (81 % with atypical and 85 % with typical fractures) and vitamin D (94 % with atypical and 88 % with typical fractures), and there was no significant difference in use by type of fracture.

Use of prescription medications

Almost all of the subjects with atypical fractures (94 %) and 32 of 40 (80 %) subjects with typical fractures, reported that they were taking bisphosphonates at the time of the event. The mean duration of use was greater in those with atypical fractures (104.2±42 months) compared to those with typical fractures (71.1±62.8 months, p=0.04). Indeed, more than half of the subjects with typical fractures used bisphosphonates for less than 6 years whereas among those with atypical fractures most subjects used bisphosphonates for more than 6 years (Fig. 2). Many subjects reported the use of more than one bisphosphonate prior to the fracture (40 % reported more than one bisphosphonate with atypical fractures and 53 % reported more than one bisphosphonate with typical fractures). Specifically among those with atypical fractures, nine reported use of ALN monotherapy, three reported sequential ETI–ALN or ALN–RIS and three reported sequential ETI–ALN–RIS. No subject had reported prior use of PAM or ZOL.

The main indication for the use of bisphosphonates was osteoporosis by BMD testing and/or previous low trauma fracture. None of the subjects in our study reported use of bisphosphonates for prevention of postmenopausal or cancer-induced bone loss or Paget's disease.

There were no differences in the current use of estrogen therapy, SERMs, calcitonin, teriparatide, oral steroids, anticonvulsants, statins, SSRIs, and PPIs by type of fracture. Prior use of estrogen was more common in subjects who subsequently had atypical fractures (38 %) than typical fractures (15 %), although this difference was not statistically significant (p=0.06). Use of SERMs previous to the fracture was similar on both groups (6 % in atypical and 5 % in typical fractures, p=1.0). No subjects reported the use of denosumab or thiazolidinediones.

Markers of bone mineral metabolism

Blood work was done within 0.6±12.3 months of the atypical fracture and within 2.4±10.3 months of the typical fracture (p=0.62). Mean serum vitamin D levels did not differ by fracture type (40.7±12.6 ng/ml in atypical fractures and 37.8 ±15.0 in typical fractures (p=0.49). Alkaline phosphatase was 65.4±17.6 IU/L (normal range, 40–120 UI/L) in those with atypical and 85.4±33.8 IU/L in those with typical fractures (p=0.014). Three subjects with typical fractures and known kidney disease had an increased serum creatinine and increased PTH. Otherwise, serum calcium, phosphorus, creatinine, and parathyroid hormone were in the normal range and not significantly different by fracture type.

BMD

BMD was measured by dual-energy X-ray absorptiometry (DXA) within 1.0±5.3 months before or after the atypical fracture and 1.6±6.5 months before or after the typical fracture (p=0.73). There were no statistically significant differences in BMD measures at the lumbar spine by type of fracture (0.861± 0.111 g/cm^2 (T score, −2.37±1.25) in atypical fractures and 0.864±0.159 g/cm^2 (T score, −2.65±1.29) in typical fractures, p=0.7). BMD at the total hip was lower among those with typical fractures (0.686±0.130 g/cm^2; T score, −2.63±1.07) compared to atypical (0.795±0.102 g/cm^2; T score, −1.72± 0.85; p=0.003). Similarly, femoral neck BMD was lower in

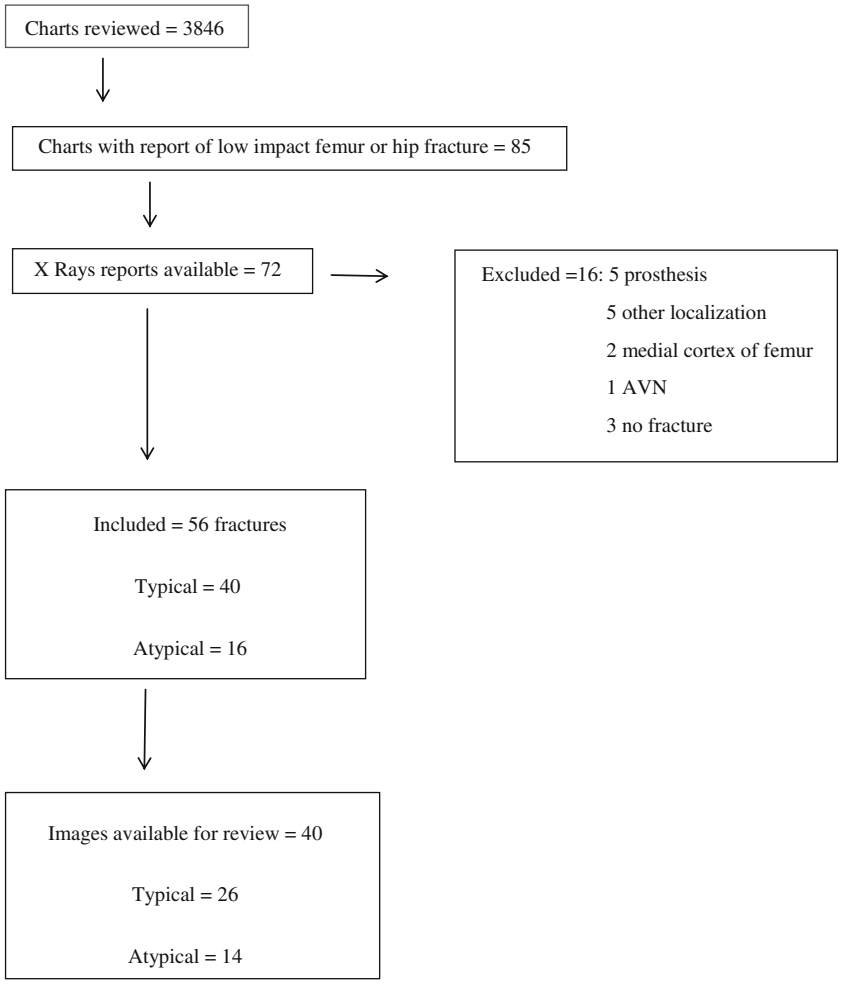

Fig. 1 Disposition of charts/ radiographs

Table 1 Characteristics of subjects by fracture type

	Atypical (N=16)	Typical (N=40)	p value
Age at fracture, years	65.9 (9.85)	69.8 (15.6)	0.27
Female gender, n (%)	15 (94 %)	38 (95 %)	1.0
BMI, kg/m^2	26.16 (3.17)	23.14 (4.32)	0.006
Use of bisphosphonates at time of fracture, n (%)	15 (94 %)	32 (80 %)	0.42
Duration of bisphosphonate use (months)	104.2 (42.0)	71.1 (62.8)	0.04
Time of BMD related to fracture (months)	−0.98 (5.3)	−1.56 (6.52)	0.73
Lumbar spine BMD, g/cm^2	0.861 (0.111)	0.846 (0.159)	0.71
Lumbar spine T score	−2.37 (1.25)	−2.65 (1.29)	0.46
Femoral neck, g/cm^2	0.736 (0.096)	0.670 (0.131)	0.05
Femoral neck T score	−2.05 (0.84)	−2.64 (1.07)	0.04
Total hip, g/cm^2	0.795 (0.102)	0.686 (0.130)	0.003
Total hip T score	−1.72 (0.85)	−2.63 (1.07)	0.003
Prior fragility fracture, n	12	26	0.469
Serum 25 $(OH)_2$ D, ng/ml	40.7 (12.6)	37.8 (15)	0.49

Presented as means ± Standard Deviation (SD) unless otherwise specified

those with typical fracture (0.670±0.131 g/cm^2; T score, −2.64 ±1.07) compared to atypical fracture (0.736±0.102 g/cm^2; T score −2.05±0.84; p=0.05). BMD at the radius was available in six subjects with atypical fractures and seven subjects with typical fracture and did not differ by fracture type (0.646± 0.110 g/cm^2 in atypical and 0.535±0.134 g/cm^2 in typical; p=0.13)

Comorbidities

Two subjects in each group had vitamin D deficiency. The combined endpoint of vitamin D insufficiency and deficiency was present in 3 patients with atypical (19 %) and 11 patients with typical fracture (28 %; p=1.0). A previous history of cancer was reported by 7 of 16 subjects with atypical fracture and 7 of 40 subjects with typical fracture (p=0.04). The most common type of cancer was breast cancer reported by four subjects with atypical and three subjects with typical fractures. A history of renal calculi was reported by three subjects with atypical (19 %) and one subject with typical (2.5 %) fractures (p=0.066). Previous history of renal calculi or hypercalciuria

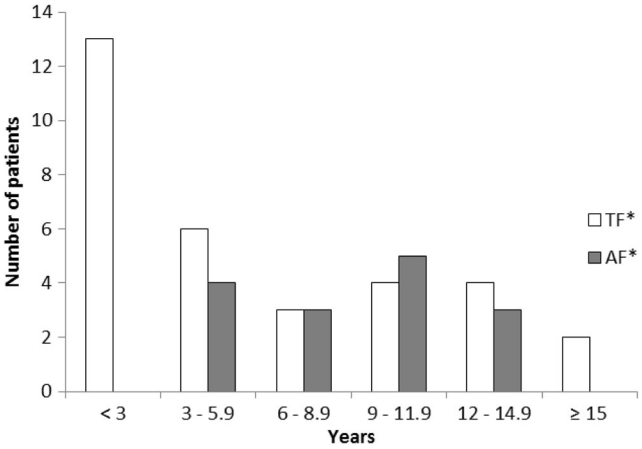

Fig. 2 Years of bisphosphonate use and type of fracture. *TF* typical hip fractures, *AF* atypical femoral fractures

was reported by four subjects with atypical (25 %) and two subjects with typical (5 %) fractures (p=0.049) There were no differences in the prevalence of rheumatoid arthritis, diabetes mellitus, chronic kidney disease, malabsorption syndrome, chronic obstructive pulmonary disease, asthma, previous joint replacement, hypothyroidism, and premature menopause by fracture type.

Previous low-trauma fracture was noted in 12 (75 %) subjects with atypical and 26 (65 %) subjects with typical fracture (p=0.47). About 50 % of these were morphometric spine fracture.

Characteristics of the fracture

Typical hip fracture was present in 40 subjects, 15 localized at the femoral neck and 25 at the intertrochanteric region. Of this group, 34 were treated surgically and 6 were undisplaced or stress fractures not requiring surgical intervention. Atypical fracture was present in 16 subjects, 5 localized at the subtrochanteric region and 11 at the femoral shaft (Table 2). Surgery (placement of intramedullary nail, screws, or rod) was performed on 10 subjects with atypical fracture, eight with complete fractures and two with incomplete fracture.

Table 2 Radiologic characteristics of the 16 atypical fractures

Major features	
Transverse/oblique	14/2
Complete/incomplete	8/8
Noncomminuted	16
Localized periosteal reaction or endosteal thickening	9
Minor features	
Bilateral incomplete or complete fracture	3
Generalized increase in cortical thickness	7
Delayed healing	3
Prodromal symptoms	7

Number of patients presenting with major or minor features

Discussion

Compared to subjects presenting with typical fractures (n=40), those with atypical fractures (n=16) are heavier, have a greater duration of bisphosphonate use, are more likely to have had cancer, and have higher BMD at the total hip and femoral neck. Few studies compare the clinical characteristics of patients with typical fracture and atypical fracture, and generally speaking only report on age and other comorbidities. As such, our findings add to the existing literature and may help to increase our understanding of the etiology of atypical fractures.

Not surprisingly, the majority of patients with both typical and atypical fractures reported use of bisphosphonates. This reflects the fact that our chart review was conducted among patients referred to a tertiary care osteoporosis clinic—as such, these patients are typically at high-fracture risk. Indeed, more than half of the patients had a previous osteoporotic fracture. Compared to patients with typical fracture, patients with atypical fracture had a longer duration of bisphosphonate use (71.1 ±62.8 and 104.2±42.0 months, respectively). The duration of use among those with atypical fractures in our cohort was similar [10, 11] or longer than previous publications [2, 12–14].

This longer duration of use of bisphosphonates together with the lower alkaline phosphatase in the group with atypical fractures (65.4±17.6 compared to 85.4±33.8 IU/L in those with typical) may be consistent with the concept that oversupression of bone turnover may be a risk factor for this rare type of fracture. However, it is important to note that we did not have tetracycline-labeled bone biopsies—the gold standard for assessing turnover and thus could not directly test this hypothesis. Further, a previous case report by our group demonstrated normal bone turnover by biopsy in a patient with an atypical fracture [15].

We found that BMD at the total hip was lower in those with typical fractures, compared to atypical fracture. Our findings are consistent with what has been reported using data from the Study of Osteoporotic [16], leading the authors to conclude that low hip BMD is a risk factor for atypical fracture, but the association is weaker than for typical fracture.

In our study, patients with atypical fracture had higher BMI and body weight than those with typical fractures. Two other studies report on weight and fracture type—one reported no difference in weight by fracture type while the other reported lower weight among those with typical fractures [10, 16]. Low weight, especially involuntary weight loss during the last 6 years, is a known independent risk factor for typical hip fracture [17, 18]. The difference in weight by fracture type

suggests that there may be differences in the mechanism by which these fractures occur.

Surprisingly, nearly half of patients with atypical fracture, compared to 17 % with typical fractures, reported a previous history of cancer. Our findings may reflect the fact that the data was collected from a tertiary referral center. It may also be a chance finding related to the small sample size or it may be due to the use of adjuvant cancer therapies, such as radiotherapy which may increase fracture risk. Alternatively, it may be due to differences in the underlying pathophysiology of typical compared to atypical fractures. A similar set of explanations can be applied to our observations that the prevalence of hypercalciuria and kidney stones was more common in those with atypical (25 %) compared with typical fractures (5 %).

Contrary to what has been published previously [4, 6], we did not find differences in the prevalence of vitamin D deficiency or history of steroid use by fracture type. The differences in findings between our study and others might be due to the fact that ours was a tertiary care clinic where vitamin D levels are measured and vitamin D deficiency is corrected, so levels were higher than what has been described previously.

In our study, among those with atypical fracture, only half of those had a complete fracture. This is different from one prior study [11] that reported a majority of complete fractures in patients with atypical femur fracture, but is similar to data published in a systematic review [14]. The fact that we had such a high incidence of incomplete atypical fracture might reflect the fact that patients in our osteoporosis clinic are specifically asked about thigh/hip or groin pain which may prompt radiographic screening and enable an earlier diagnosis.

This chart review is one of the first that has collected and compared the clinical, laboratory, and radiographic data among those with and without atypical fractures [16, 19, 20]. In addition, we had a radiologist review the films. This work adds to the small body of knowledge concerning the physiopathology and risk factors for atypical fracture.

Our work has some limitations. Data was collected retrospectively and from a tertiary care osteoporosis clinic. This limits both the data collected the generalizability of our findings. Further, we had a small number of patients with both typical and atypical fractures as such we may have lacked power to demonstrate associations and could not perform subgroup analyses (for example, we could not examine the associations between type of fracture and specific bisphosphonates).

There are few studies describing clinical characteristics and potential risk factors for atypical fractures and even fewer comparing characteristics between typical and atypical fractures. Our study, which adds to the paucity of literature in this area, found some differences in clinical characteristics by fracture type. These differences may be due to differences in the etiology of typical and atypical fractures. More studies are needed to obtain additional clinical data which may enhance our understanding of the etiology of this uncommon event.

Conflicts of interest None.

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