REVIEW

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Atypical Subtrochanteric and Diaphyseal Femoral Fractures: Second Report of a Task Force of the American Society for Bone and Mineral Research

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Author affiliations appear on pp. 16–20

ABSTRACT

Bisphosphonates (BPs) and denosumab reduce the risk of spine and nonspine fractures. Atypical femur fractures (AFFs) located in the subtrochanteric region and diaphysis of the femur have been reported in patients taking BPs and in patients on denosumab, but they also occur in patients with no exposure to these drugs. In this report, we review studies on the epidemiology, pathogenesis, and medical management of AFFs, published since 2010. This newer evidence suggests that AFFs are stress or insufficiency fractures. The original case definition was revised to highlight radiographic features that distinguish AFFs from ordinary osteoporotic femoral diaphyseal fractures and to provide guidance on the importance of their transverse orientation. The requirement that fractures be noncomminuted was relaxed to include minimal comminution. The periosteal stress reaction at the fracture site was changed from a minor to a major feature. The association with specific diseases and drug exposures was removed from the minor features, because it was considered that these associations should be sought rather than be included in the case definition. Studies with radiographic review consistently report significant associations between AFFs and BP use, although the strength of associations and magnitude of effect vary. Although the relative risk of patients with AFFs taking BPs is high, the absolute risk of AFFs in patients on BPs is low, ranging from 3.2 to 50 cases per 100,000 person-years. However, long-term use may be associated with higher risk (~100 per 100,000 person-years). BPs localize in areas that are developing stress fractures; suppression of targeted intracortical remodeling at the site of an AFF could impair the processes by which stress fractures normally heal. When BPs are stopped, risk of an AFF may decline. Lower limb geometry and Asian ethnicity may contribute to the risk of AFFs. There is inconsistent evidence that teriparatide may advance healing of AFFs.

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In contrast to ONJ, which came to attention in patients receiving high dose BP therapy for malignancy, most though not all patients with AFFs were receiving the lower doses of BPs typically used to treat osteoporosis or osteopenia.

The initial publications were followed by many case reports and case series. Recently, however, two case series were reported in patients with cancer

Shane E et al, 2014

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To satisfy the case definition of AFF, the fracture must be located along the femoral diaphysis from just distal to the lesser trochanter to just proximal to the supracondylar flare.

In addition, at least four of five Major Features must be present. None of the Minor Features is required but have sometimes been associated with these fractures.

Major features

- The fracture is associated with minimal or no trauma, as in a fall from a standing height or less

- 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

- Complete fractures extend through both cortices and may be associated with a medial spike; incomplete fractures involve only the lateral cortex

- The fracture is noncomminuted or minimally comminuted

- Localized periosteal or endosteal thickening of the lateral cortex is present at the fracture site ("beaking" or "flaring")

Minor features

Generalized increase in cortical thickness of the femoral diaphyses

Unilateral or bilateral prodromal symptoms such as dull or aching pain in the groin or thigh

Bilateral incomplete or complete femoral diaphysis fractures

Delayed fracture healing

Shane E et al, 2014

Fig. 1. An AFF of the femoral diaphysis (courtesy of Fergus McKiernan). (*A*) Note the transverse fracture line in the lateral cortex that becomes oblique as it progresses medially across the femur (white arrow). (*B*) On radiograph obtained immediately after intramedullary rod placement, a small area of periosteal thickening of the lateral cortex is visible (white arrow). (*C*) On radiograph obtained at 6 weeks, note callus formation at the fracture site (white arrow). (*D*) On radiograph obtained at 3 months, there is mature callus that has failed to bridge the cortical gap (white arrow). Note the localized periosteal and/or endosteal thickening of the lateral cortex at the fracture site (white arrow).

Fig. 2. A 76-year-old woman with osteoporosis who presented with an AFF. (*A*) Anteroposterior radiograph of the right femur shows a displaced AFF characterized by both periosteal and endosteal beaking with an endosteal lesion (black arrow) superior to it. (*B*) Anteroposterior radiograph of the left femur shows multifocal endosteal thickening (white arrowheads). Reprinted with permission from Mohan and

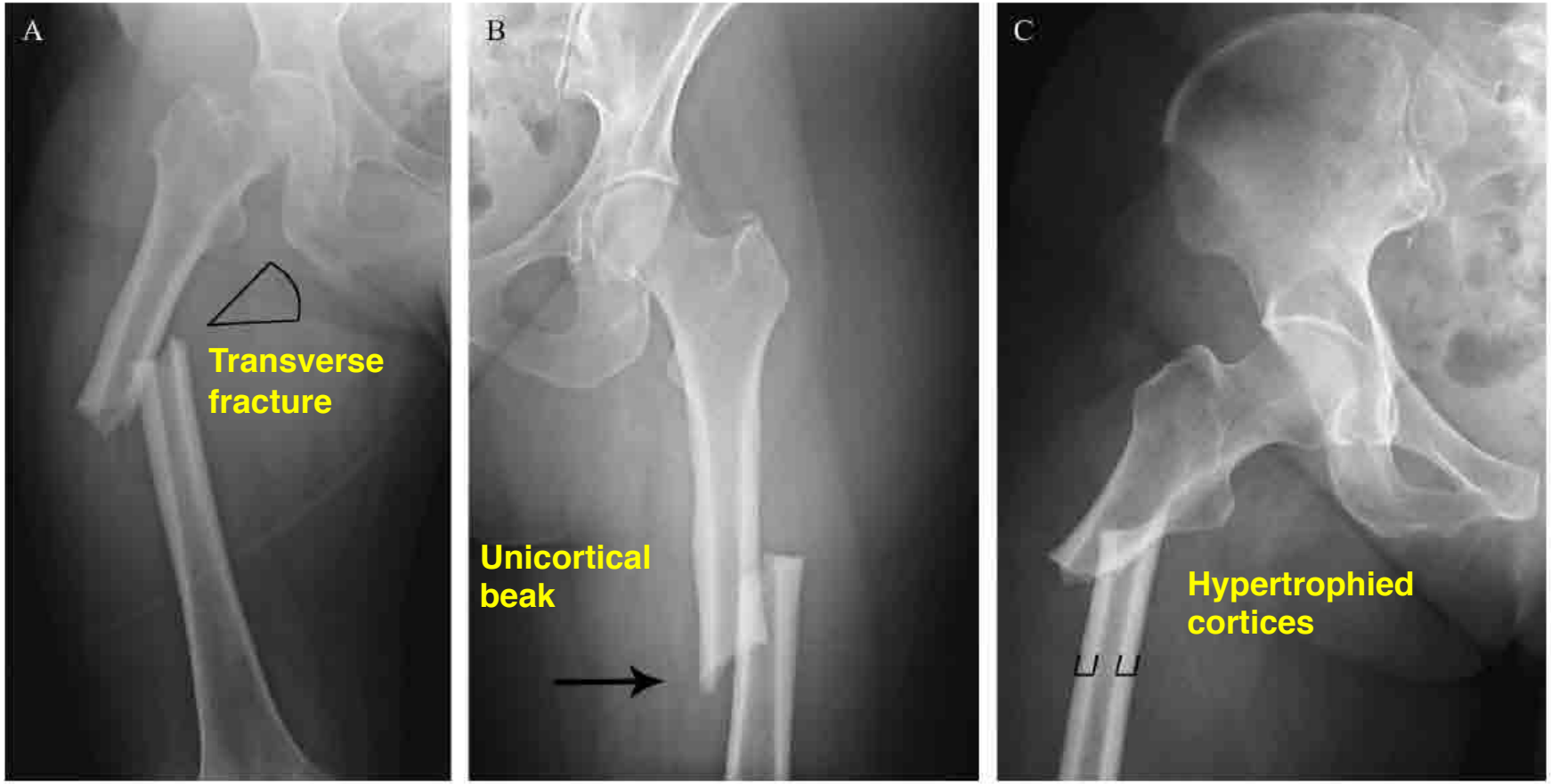

FIGURE 1. Representative radiographs of femoral shaft fractures sustained from minimal trauma in patients taking alendronate. Although each radiograph demonstrates the pattern in its entirety, we have highlighted the following features. A, Fracture pattern pictured with an arch measuring 30 degrees to highlight transverse nature. B, The arrow pointing out the unicortical beak C, Hypertrophied cortices outlined.

Neviaser et al J. Ortho trauma 2008

Epidemiology and Risk Factors

Subtrochanteric and femoral shaft (ST/FS) fractures are identified using large registry or **database approaches** with International Classification of Diseases, 9th edition (ICD-9) codes but there is no radiographic adjudication to ascertain whether the fractures have atypical features.

Most, though not all, of these studies have found that rates of ST/FS fractures have not risen since BPs were approved for osteoporosis or among patients exposed to BPs.

Such studies provide useful information on the prevalence and incidence of ST/FS fractures and the upper boundary of any potential harm associated with BPs.

As a note of caution, however, diagnostic codes may misclassify fracture location.

Because this type of study includes substantial numbers of ordinary subtrochanteric and femoral shaft fractures that are ***not atypical***, they yield incidence rates for AFFs that are too high and associated odds ratios (ORs) with potential exposures that may be too low.

Shane E et al, JBMR 2014

Epidemiology and Risk Factors

In the other category of studies, subtrochanteric and femoral shaft (ST/FS) fractures are identified utilizing **radiographs** that are reviewed and the fractures categorized according to whether or not they meet consensus criteria for AFFs.

Most of these studies suggest that AFFs are strongly associated with BPs, although the absolute incidence of AFFs is very low.

However, such studies may be limited by smaller size, incomplete ascertainment of past drug exposure, and other biases

Shane E et al, JBMR 2014

ORIGINAL ARTICLE

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Trends in Incidence of Subtrochanteric Fragility Fractures and Bisphosphonate Use Among the US Elderly, 1996–2007

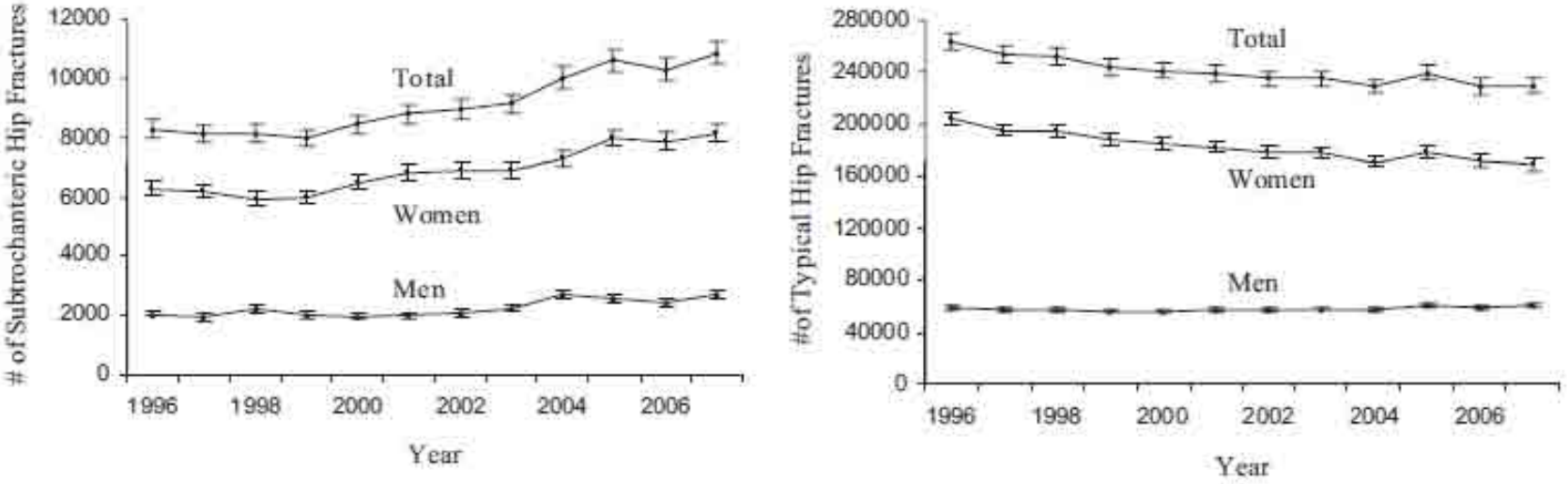
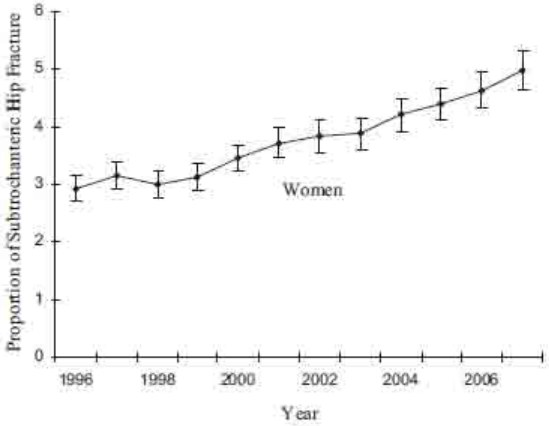


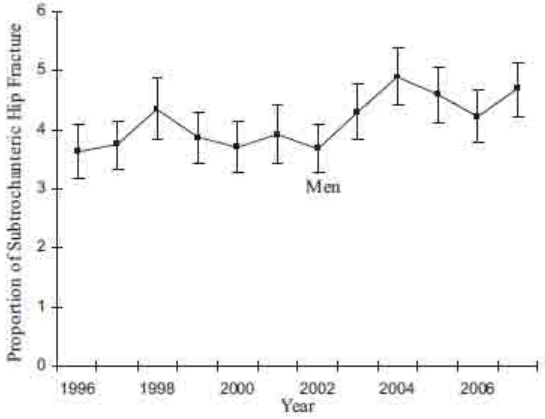
Fig. 1. National estimate of subtrochanteric and typical hip fractures in patients aged 65 and older. Data are based on Nationwide Inpatient Samples. Error bars indicate standard deviation.

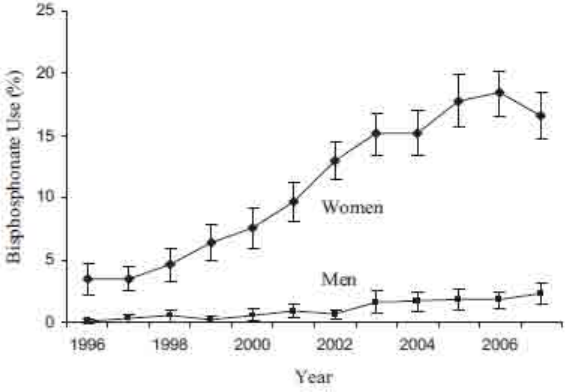
Wang Z et al, 2011

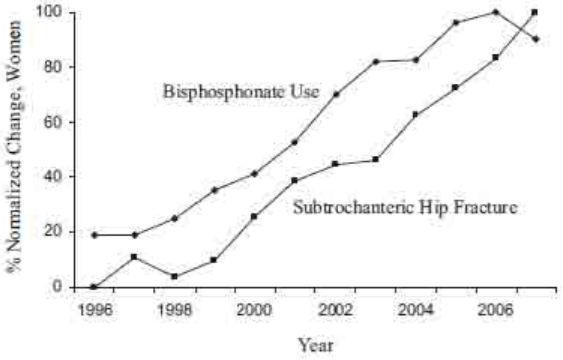
JBMR

Trends in Incidence of Subtrochanteric Fragility Fractures and Bisphosphonate Use Among the US Elderly, 1996–2007









Wang Z et al, 2011

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Bisphosphonate Use and Atypical Fractures of the Femoral Shaft

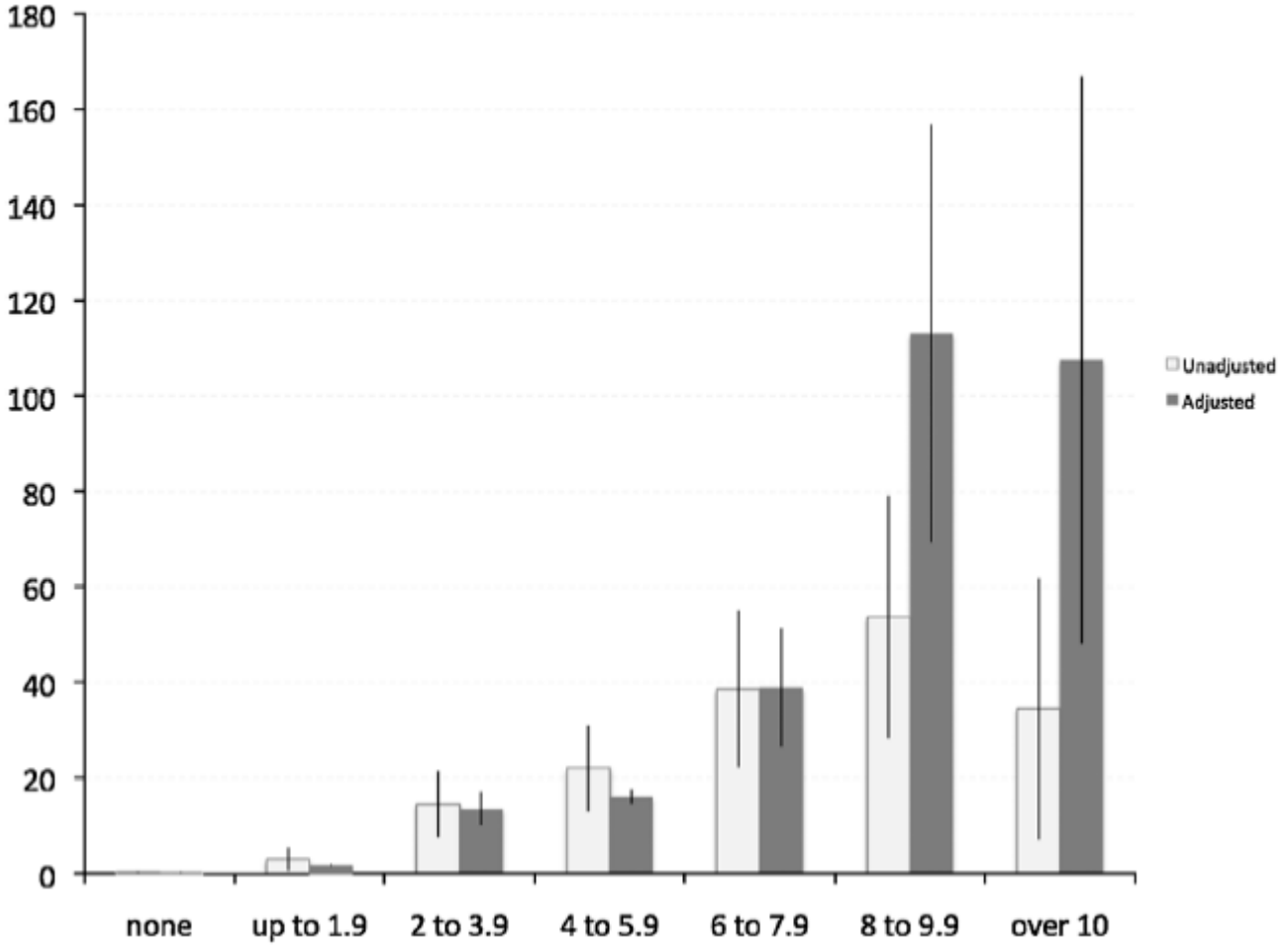
Table 1. Risk of Atypical Femoral Fracture Associated with Bisphosphonate Use during the 3 Years (2005–2008) Preceding the Fracture.*

Variable	No. of Women	Cases of Atypical Fracture		Age-Adjusted Relative Risk (95% CI)	Age-Adjusted Absolute Risk (95% CI)
		No. of Atypical Fracture Cases	Crude Incidence *no./10,000 patient-yr*		
Bisphosphonate use					
Never	1,437,820	13	0.09	1.0 (reference)	
Ever	83,311	46	5.5	47.3 (25.6–87.3)	0.0005 (0.0004–0.0007)
Duration of use					
<1.0 yr	15,672	3	1.9	18.4 (5.3–64.3)	0.0002 (0.0000–0.0004)
1.0–1.9 yr	21,406	4	1.9	17.0 (5.7–50.7)	0.0002 (0.0000–0.0004)
≥2.0 yr	46,233	39	8.4	67.0 (35.8–125.8)	0.0008 (0.0006–0.0011)
Time since last use					
<1.0 yr	83,311	42	5.0	42.9 (22.9–80.4)	0.0005 (0.0004–0.0007)
1.0–1.9 yr	70,036	1	0.1	3.5 (1.0–11.9)	<0.0001 (0.0000–0.0000)
≥2.0 yr	75,583	3	0.4	3.2 (1.0–10.1)	<0.0001 (0.0000–0.0001)

Schilcher J et al 2011

Incidence of atypical femur fractures according to duration of bisphosphonate exposure

(unadjusted and age-adjusted, showing incidence and 95% confidence intervals)



Dell RM et al, JBMR 2012

ORIGINAL ARTICLE

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Incidence of Atypical Nontraumatic Diaphyseal Fractures of the Femur

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ABSTRACT

Bisphosphonates reduce the rate of osteoporotic fractures in clinical trials and community practice. "Atypical" nontraumatic fractures of the diaphyseal (subtrochanteric or shaft) part of the femur have been observed in patients taking bisphosphonates. We calculated the incidence of these fractures within a defined population and examined the incidence rates according to duration of bisphosphonate use. We identified all femur fractures from January 1, 2007 until December 31, 2011 in 1,835,116 patients older than 45 years who were enrolled in the Healthy Bones Program at Kaiser Southern California, an integrated health care provider. Potential atypical fractures were identified by diagnostic or procedure codes and adjudicated by examination of radiographs. Bisphosphonate exposure was derived from internal pharmacy records. The results showed that 142 patients had atypical fractures; of these, 128 had bisphosphonate exposure. There was no significant correlation between duration of use (5.5 ± 3.4 years) and age (69.3 ± 8.6 years) or bone density (T-score -2.1 ± 1.0). There were 188,814 patients who had used bisphosphonates. The age-adjusted incidence rates for an atypical fracture were 1.78/100,000/year (95% confidence interval [CI], 1.5–2.0) with exposure from 0.1 to 1.9 years, and increased to 113.1/100,000/year (95% CI, 69.3–156.8) with exposure from 8 to 9.9 years. We conclude that the incidence of atypical fractures of the femur increases with longer duration of bisphosphonate use. The rate is much lower than the expected rate of devastating hip fractures in elderly osteoporotic patients. Patients at risk for osteoporotic fractures should not be discouraged from initiating bisphosphonates, because clinical trials have documented that these medicines can substantially reduce the incidence of typical hip fractures. The increased risk of atypical fractures should be taken into consideration when continuing bisphosphonates beyond 5 years.

Osteoporos Int (2013) 24:373–376
DOI 10.1007/s00198-012-1938-5

SHORT COMMUNICATION

Ten-year hip fracture incidence rate trends in a large California population, 1997–2006

Conclusion

Hip fracture incidence has been declining in all age groups over the past 10 years. While many factors may contribute to this decline, the results are consistent with a potential benefit of the active bone health intervention.

SUMMARY 1

- Atypical Femoral Fractures are more frequent in patients on BP therapy
- Longer BP treatment is associated with higher risk
- Most studies with radiographic review have reported significant association between GC use and AFFs
- Although a causal relationship between BPs and AFFs has not been established, evidence for an association has been accumulated and is quite robust

Osteoporos Int (2011) 22:373–390
DOI 10.1007/s00198-010-1453-5

POSITION PAPER

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

R. Rizzoli · K. Åkesson · M. Bouxsein · J. A. Kanis · N. Napoli · S. Papapoulos · J.-Y. Reginster · C. Cooper

- 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.

Pathogenesis

- AFFs are stress or insufficiency fractures that develop over time
- AFFs initiate on the lateral cortex, are located between the lesser trochanter and the femoral condyles, and result in a smooth transverse surface, more characteristic of a brittle material
- BPs suppress remodeling and also likely affect adversely intracortical repair of a developing stress fracture in AFFs, allowing the crack to grow to critical size
- It is possible that lower limb geometry contributes to the risk for developing an AFF (difference in risk between ethnic groups)

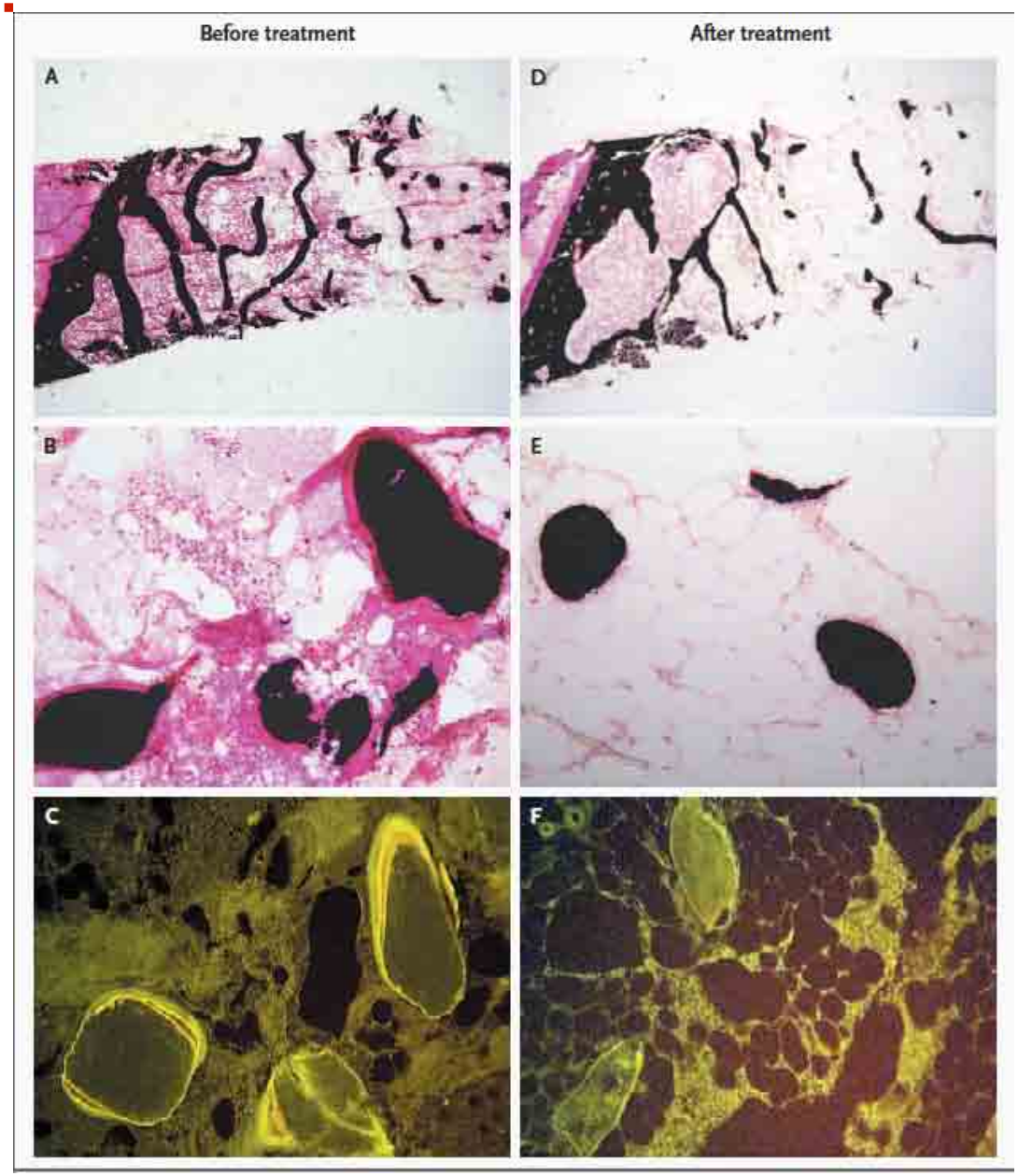
Shane E et al, 2014

Bone-Biopsy Specimens Obtained before and after Alendronate Treatment

reduced trabecular bone volume and trabecular connectivity

Increased amount of osteoid over the trabecular surface

increased osteogenesis (as seen after fluorescent tetracycline double labeling) at the entire interface between osteoid and mineralized bone



severely decreased trabecular connectivity, with many small islands of bone

decreased marrow cellularity, a lack of osteoid on trabecular surfaces

absence of tetracycline labeling

Armamento-Villareal R et al, NEJM 2006

Natural History and Management 1

AFFs suggests that they **evolve over time**, with initial development of a cortical "bump" that represents early periosteal thickening, and the eventual appearance of a transverse cortical lucency (fracture) in the region of periosteal thickening, which may or may not progress to a complete fracture

Such lesions, whether they are detected on DXA scans or plain radiographs, should be further evaluated with higher-order imaging to determine whether a cortical lucency is associated with the periosteal thickening
- **MRI** could detect a cortical fracture line and associated bone and marrow edema or hyperemia, indicative of a stress fracture
-If MRI cannot be performed, **CT** could detect the cortical fracture or lucency and associated new-bone formation

If higher order imaging detects a cortical lucency, such a lesion could be considered an **incomplete AFF**.
If no cortical lucency is present but marrow edema is present, then such lesions could be considered a **stress reaction**.

Shane E et al, 2014

Natural History and Management 2

For patients with a stress reaction, stress fracture, or incomplete or complete subtrochanteric or femoral shaft fracture, **potent antiresorptive agents should be discontinued**.

Dietary calcium and vitamin D status should be assessed, and adequate supplementation prescribed.

Prophylactic reconstruction nail fixation is recommended for incomplete fractures (with cortical lucency) accompanied by pain.

If the patient has minimal pain, a **trial of conservative therapy**, in which weight-bearing is limited through the use of crutches or a walker, may be considered. However, if there is no symptomatic and radiographic improvement after 2 to 3 months of conservative therapy, prophylactic nail fixation should be strongly considered, because these patients may progress to a complete fracture

For patients with incomplete fractures and no pain, or those with periosteal thickening but no cortical lucency, limited weight-bearing may be continued and vigorous activity avoided

Shane E et al, 2014

Incomplete Atypical Femoral Fractures: Assessing the Diagnostic Utility of DXA by Extending Femur Length

Images from a 78-yr-old woman on alendronate for 10 yr.

A.DXA image suggesting periosteal flare on outer aspect of right femur (arrow).

B.Plain X-ray confirming periosteal flare due to AFF (arrow).

McKenna MJ et al, J Clin Densit 2013

Incomplete Atypical Femoral Fractures: Assessing the Diagnostic Utility of DXA by Extending Femur Length

Images of 46-yr-old woman with prior renal transplant; treated with alendronate for about 10 yr.

A.DXA image suggesting periosteal reaction (arrow).

B. X-ray image showing incomplete AFF (arrow).

C. Showing incomplete fracture (arrow) after elective femur fixation with intramedullary nail.

McKenna MJ et al, J Clin Densit 2013

Medical treatment of patients with AFF

- Discontinuation of BPs

- Adequate calcium and vitamin D

-Consideration of TPTD for those who appear not to heal on conservative therapy

Shane E et al, 2014

Grazie per l’attenzione