Atypical Osteoporotic Fractures

Andreas F. Mavrogenis, MD
Associate Professor of Orthopaedics

ΜΕΤΑΒΟΛΙΚΑ ΝΟΣΗΜΑΤΑ ΤΩΝ ΟΣΤΩΝ
Βιβλιογραφική Ενημέρωση

Osteoporotic Fractures

- Occur spontaneously or as the result of mild or no trauma
  - Fall from a standing height or less
- Such trauma would not ordinarily cause fractures in a healthy, 30-yr-old woman
- Hip, spine, proximal humerus, distal radius

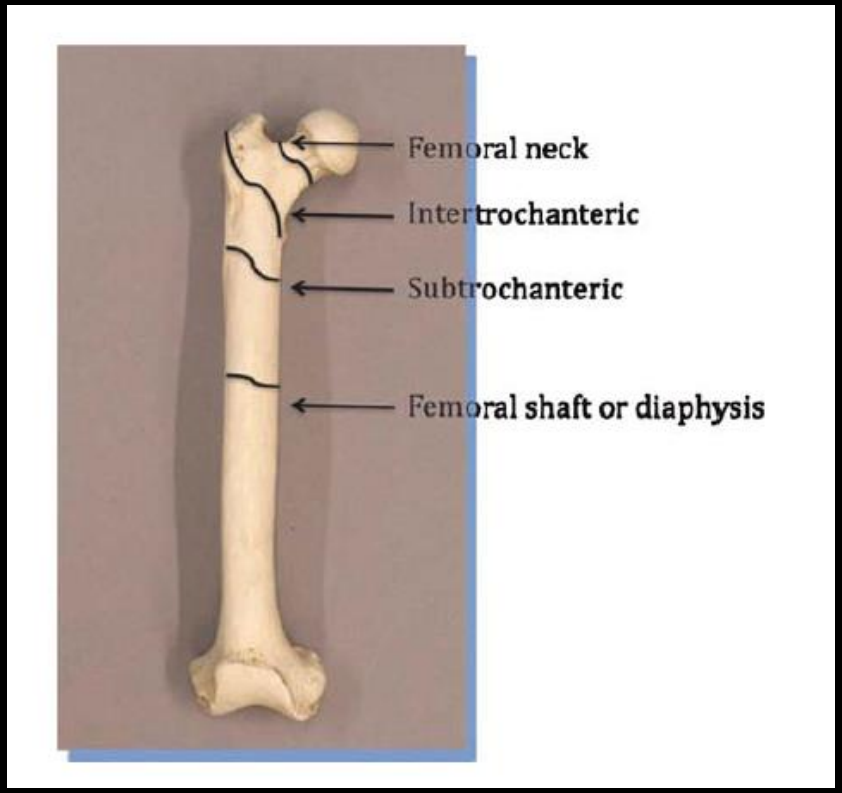
Typical vs. Atypical

Typical

- Pertrochanteric + Fem neck

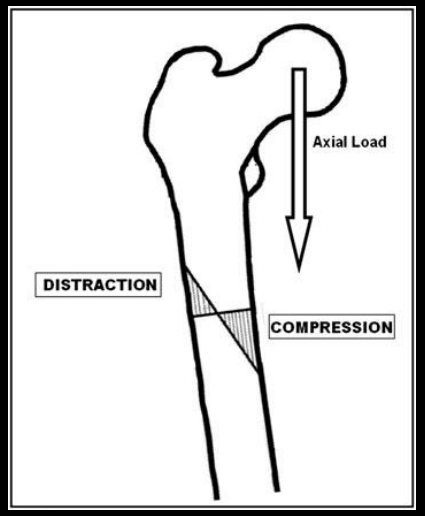
Atypical

- Most commonly in the proximal one-third of the femoral shaft
- Anywhere along the femoral diaphysis from just distal to the lesser trochanter to proximal to the supracondylar flare of the distal femoral metaphysis



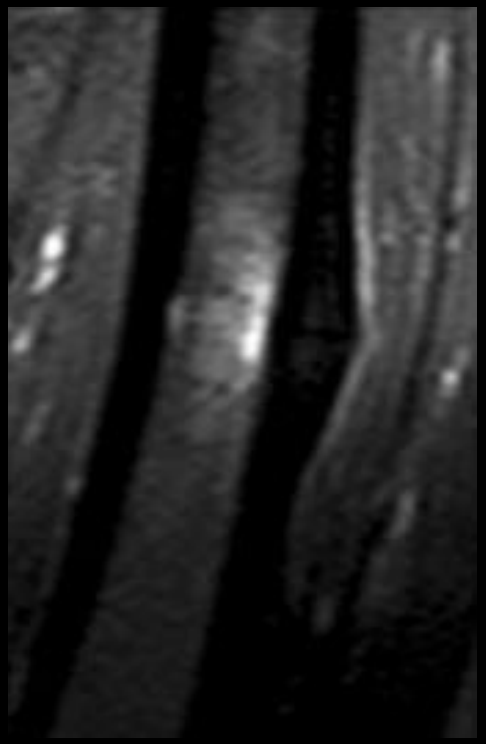
Shane et al. J Bone Miner Res 2010

Typical vs. Atypical



Typical & Atypical

- Stress fx
- Periosteal stress reaction and thickening of the lateral cortex at the fracture site

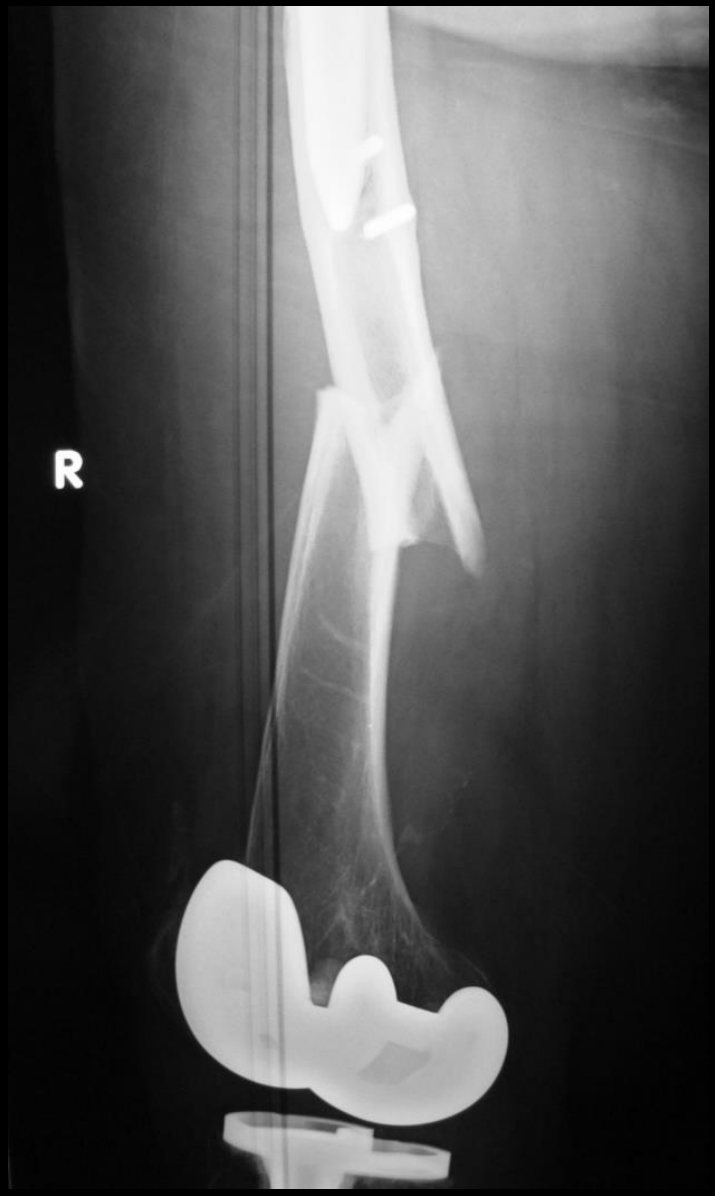


Chermak et al. CORR 2010
Shane et al. J Bone Miner Res 2010
Mavrogenis et al. EJOST 2013

Atypical

Epidemiology

- Subtroch and diaphyseal femoral fx account for only about 5% to 10% of all hip/femoral fractures
  - Of these, atypical is 17% to 29%
  - Range depends on fractures after high-impact trauma or periprosthetic fractures



Lenart et al. Osteoporos Int. 2009
Neviaser et al. JOT 2008
Schilcher et al. Acta Orthop 2009
Bunning et al. PMR 2010
Gagnon et al. J Clin Endocrinol Metab 2010
Shane et al. J Bone Miner Res 2013

Atypical

Epidemiology

- Common in patients exposed to long-term BPs
  - usually for >3 years (median, 7 years)
- May occur in patients not exposed to BPs
  - 5% to 45%

Lenart et al. Osteoporos Int. 2009
Neviaser et al. JOT 2008
Schilcher et al. Acta Orthop 2009
Bunning et al. PMR 2010
Gagnon et al. J Clin Endocrinol Metab 2010
Shane et al. J Bone Miner Res 2013

Atypical – ASBMR Criteria 2010

Table 1. Atypical Femoral Fracture: Major and Minor Features[a]

Major features[b]

- Located anywhere along the femur from just distal to the lesser trochanter to just proximal to the supracondylar flare
- Associated with no trauma or minimal trauma, as in a fall from a standing height or less
- Transverse or short oblique configuration
- Noncomminuted
- Complete fractures extend through both cortices and may be associated with a medial spike; incomplete fractures involve only the lateral cortex.

Minor features

- Localized periosteal reaction of the lateral cortex[c]
- Generalized increase in cortical thickness of the diaphysis
- Prodromal symptoms such as dull or aching pain in the groin or thigh
- Bilateral fractures and symptoms
- Delayed healing
- Comorbid conditions (eg, vitamin D deficiency, RA, hypophosphatasia)
- Use of pharmaceutical agents (eg, BPs, GCs, PPIs)

[a]Specifically excluded are fractures of the femoral neck, intertrochanteric fractures with spiral subtrochanteric extension, pathologic fractures associated with primary or metastatic bone tumors, and periprosthetic fractures.

[b]All major features are required to satisfy the case definition of atypical femoral fracture. None of the minor features are required but sometimes have been associated with these fractures.

[c]Often referred to in the literature as *beaking* or *flaring*.

Shane et al. J Bone Miner Res 2010

Atypical – ASBMR Criteria 2014

Table 3. ASBMR Task Force 2013 Revised Case Definition of AFFs

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[a]

- 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

Changes are in bold.

ASBMR = American Society for Bone and Mineral Research; AFF = atypical femur fracture.

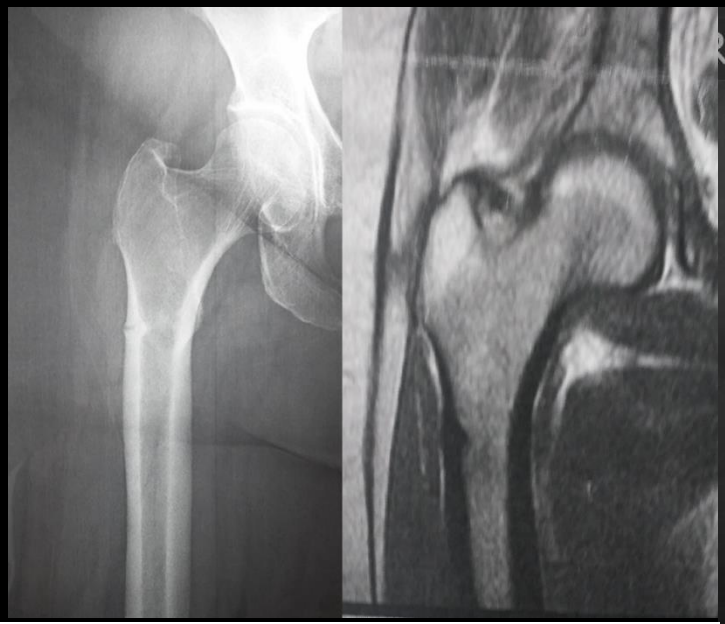
[a]**Excludes** fractures of the femoral neck, intertrochanteric fractures with spiral subtrochanteric extension, periprosthetic fractures, and pathological fractures associated with primary or metastatic bone tumors and miscellaneous bone diseases (eg, Paget's disease, fibrous dysplasia).

Shane et al. J Bone Miner Res 2014

Atypical

Incomplete

- Looser line (pseudo-fracture)
- Thickening of lateral cortex



ΟΣΤΟΥΝ (2019) 26 (4): 92 Κοιν.

Ποια η διάγνωση και θεραπεία;
Γυναίκα 55 ετών με πόνο στο δεξί μηρό. Ιατρικό ιστορικό ελεύθερο

Α.Φ. ΜΑΥΡΟΓΕΝΗΣ
Α' Ορθοπαιδική Πανεπιστημιακή Κλινική, Εθνικό και Καποδιστριακό Πανεπιστήμιο Αθηνών, Ιατρική Σχολή, Π.Γ.Ν. ΑΤΤΙΚΟΝ

What is the diagnosis and treatment?
A 55-year-old woman with right thigh pain. Past medical history unremarkable

A.F. MAVROGENIS
First Department of Orthopaedics, National and Kapodistrian University of Athens, School of Medicine, Athens, Greece, ATTIKON General Hospital

(συνέχεια στη σελίδα 122)

Ποια η διάγνωση και θεραπεία; Γυναίκα 55 ετών με πόνο στο δεξί μηρό. Ιατρικό ιστορικό ελεύθερο

Γυναίκα 55 ετών προσήλθε με πόνο στο δεξί μηρό από έτους επιδεινούμενο στη φόρτιση, υφιάμενο στην ηρεμία. Δεν ανέφερε ιστορικό πτώσης, προαγούμενων καταγμάτων ή άλλο σημικό και οικογενειακό ιστορικό. Δεν λάμβανε φάρμακα. Η απλή ακτινογραφία και η μαγνητική τομογραφία έδειξαν απλές κάταγμα (ψευδοκάταγμα) στο άνω άκρο του δεξιού μηριαίου οστού, στο επίπεδο του ελάσσονα τροχαντήρα. Η μέτρηση οστικής πυκνότητας στο αριστερό ισχίο πίσω εντός των φυσιολογικών ορίων και η μέτρηση της 25(OH) βιταμίνης D έδειξε ανεπάρκεια. Από την κλινική και απεικονιστική εικόνα τέθηκε η διάγνωση του ψευδοκατάγματος (βλ. Looser).

Συζήτηση

Ζώνες του Looser (**Emil Looser**, Ελβετός χειρουργός, 1877-1936) ή εμφράκτα του φλοιού ή γραμμές του Milkman (**Louis Arthur Milkman**, Αμερικανός ακτινολόγος, 1896-1961), ή ψευδοκατάγματα (Εικόνα 1). Είναι ακτινοδιαυγαστικές γραμμές οι οποίες εντοπίζονται στο φλοιό των οστών, φέρονται συνήθως εγκάρσια και συνοτέρα σκεπτζονται με οστεομαλακία ή ραχίτιδα και λιγότερο συχνά με νεφρική οστεοδυστροφία, ινώδη δυσπλασία, υπερθυρεοειδισμό, νόσο Paget, κ-φιλοκυτταρικό υποφωσφαταιμία, απλή οστεογένεση και υποφωσφαταιμία. Ο όρος ψευδοκάταγμα υποδηλώνει κατάγματα ανεπάρκειας. Στις απεικονιστικές εξετάσεις, οι βλάβες έχουν σκληρυντικά ακανόνιστα όρια και συνήθως είναι συμμετρικές με εύρος από 1 χιλ. έως 1 εκ. Η συχνότερη εντόπιση αφορά στους ηβικούς κλάδους, το άνω άκρο του μηριαίου οστού, τα έξω κείλος της ωμοπλάτης, το οπίσθιο κείλος του άνω άκρου της ωλένης, και τις θωρακικές πλευρές.

Λόγω έντονου πόνου και εντόπισης της βλάβης, η εν λόγω ασθενής αντιμετωπίσθηκε με προφυλακτική ενδομυελική ήλωση, σε συνδυασμό με θεραπευτική χορήγηση υψηλών δόσεων βιταμίνης D καθημερινά για 2 εβδομάδες και στη συνέχεια ανά μήνα, με πλήρη υποκατάσταση του πόνου και πώρωση του ψευδοκατάγματος 1 έτος μετεγχειρητικά (Εικόνα 2).

Εικ. 2. Απλή ακτινογραφία του δεξιού μηριαίου οστού δείνει προφυλακτική ενδομυελική ήλωση και πώρωση του ψευδοκατάγματος.

Correspondence
Andreas F. Mavrogenis
E-mail: afm@otenet.gr

Αλληλογραφία
Ανδρέας Φ. Μαυρογένης
E-mail: afm@otenet.gr

Atypical

Complete

- Transverse
- Not comminuted
- Medial spike
- Thickening of the lateral cortex

Atypical

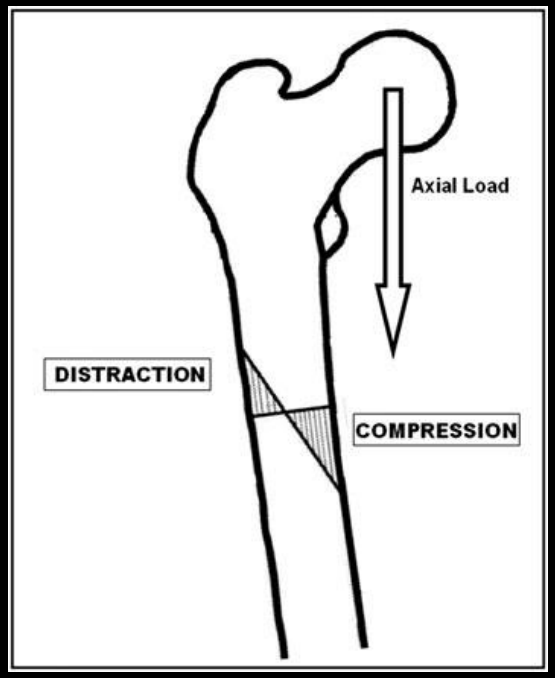
Complete & Incomplete

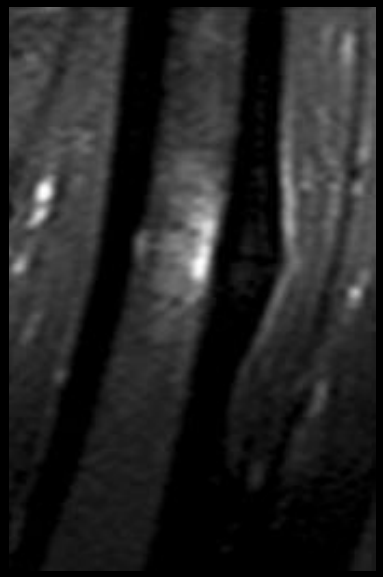
- Often prodromal symptoms (groin or thigh pain)
- May be bilateral
- May delay healing (incomplete)
- May be associated with a variety of comorbid conditions
  - vitamin D deficiency, RA, DM, hypophosphatasia
- May be associated with the use of pharmaceutical agents
  - BPs, GCs, PPIs

Chermak et al. CORR 2010
Shane et al. J Bone Miner Res 2010
Mavrogenis et al. EJOST 2013

Atypical – Pathogenesis

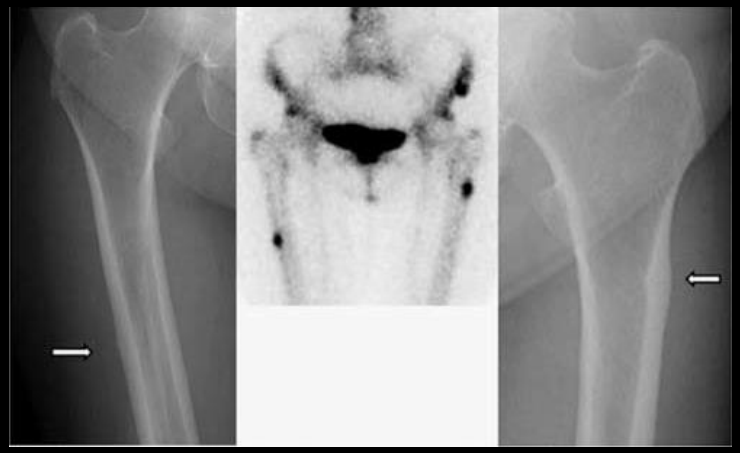
- Stress fractures
  - Thickening of cortices
  - May be a normal genetically determined variant of femoral shape
  - Asian population





Atypical – Pathogenesis

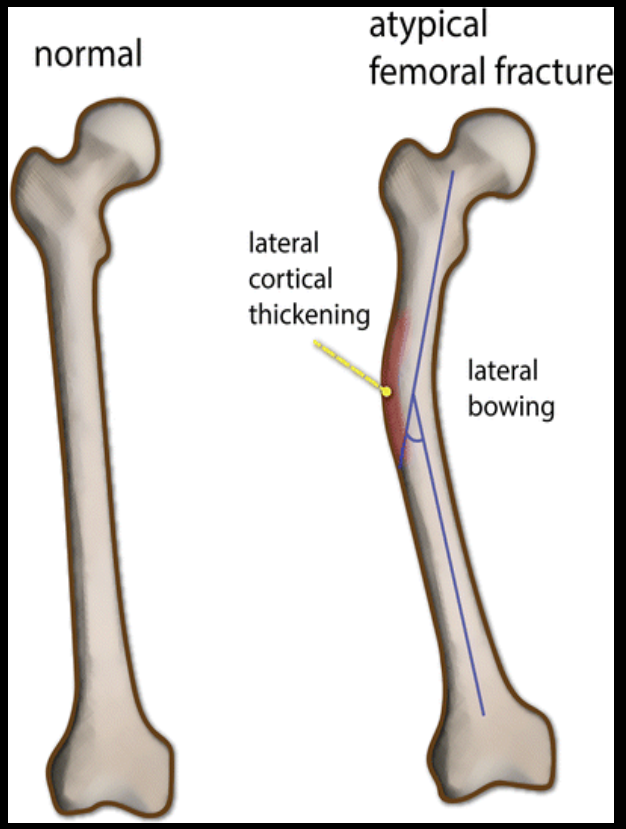
- Stress fractures
  - Thickening of cortices
  - Periosteal new bone formation

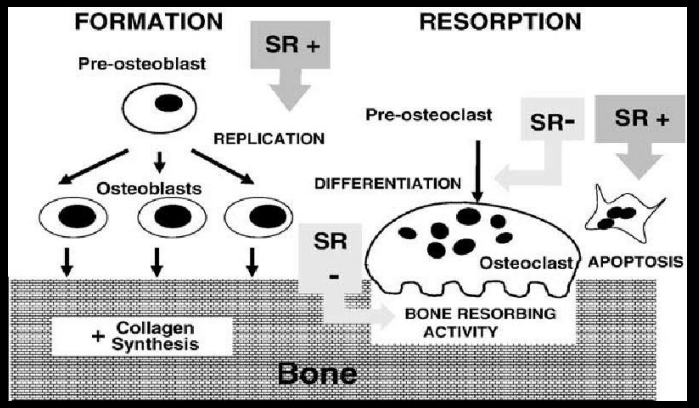


Shane et al. JBMR 2020

Atypical – Pathogenesis

- BPs
  - Alter collagen maturity and cross-linking
  - Reduce bone turnover, increase overall mineralization, but leave mineral particle shape, thickness, and orientation unaffected
  - Increase bone strength and decrease fracture risk by suppressing excessive bone remodeling
    - Reduction of remodeling, however, is associated with increased microdamage accumulation because cracks are not removed efficiently
  - Delay fracture healing
    - Delaying the remodeling of the calcified callus to mature bone
    - Antiangiogenic effect: inhibit periosteal vascularity
- A potentially significant effect of a median treatment period of 5-7 years





Guisti et al. Bone 2010

Shane et al. J Bone Miner Res 2010

Atypical – Pathogenesis

Type of BPs

- Various
  - Ibandronate, risedronate, or zoledronic acid
- Most cases have been reported after long-term administration of alendronate
  - Etiology for this observation is unclear

Goh et al. JBJS Br 2007
Neviaser et al. JOT 2008
Kwek et al. Injury 2008
Abrahamsen et al. JBMRes 2009
Glennon Bone 2009

Chermak et al. CORR 2010
Odvina et al. Clin Endocrinol 2010
Shane et al. J Bone Miner Res 2010
Ward et al. CORR 2012
Mavrogenis et al. EJOST 2013

Atypical – Pathogenesis

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Eur J Orthop Surg Traumatol
DOI 10.1007/s00590-014-1443-y

ORIGINAL ARTICLE

Low-energy femoral shaft fractures after long-term alendronate therapy: report of seven cases

Atypical – Pathogenesis

Comorbidities in patients on BPs

- GCs: reduce osteoblast activity, increase osteoblast apoptosis, and are also associated with osteonecrosis of the femoral head
- DM: high glucose levels cause the accumulation of advanced glycation end products (AGEs)
  - associated with an increased risk of fracture and brittleness of bone

Atypical – Pathogenesis

Comorbidities

- PPIs: High dose or long-term use carries a possible increased risk of bone fractures (not found with short-term, low dose use)
  - Omeprazole (Losec)

Proton pump inhibitors and risk of fractures: a meta-analysis of 11 international studies

Elaine W. Yu, MD,[1] Scott R. Bauer, BS,[2] Paul A. Bain, PhD,[3] and Douglas C. Bauer, MD[4]

Atypical – Pathogenesis

Comorbidities

- FDA warned regarding this on PPI drug labels in 2010
  - "FDA Drug Safety Communication: Possible increased risk of fractures of the hip, wrist, and spine with the use of proton pump inhibitors". U.S. Food and Drug Administration (FDA). 23 March 2011. Retrieved 23 August 2015.

PPIs modestly increased the risk of hip, spine, and any-site fractures, whereas H2RAs were not associated with fracture risk.

Further skeletal evaluation should be considered for patients who are taking PPIs and are also at risk for osteoporotic fracture.

Atypical – Pathogenesis

Denosumab

- RANK ligand inhibitor human monoclonal antibody
- Similarly to BPs, denosumab appears to be implicated in increasing risk of jaw osteonecrosis and recently in low-energy femoral diaphysis fractures

Shane et al. J Bone Miner Res 2013

http://www.proliahcp.com/safety-profile

Atypical – Treatment

- Imaging of both femurs
- Conservative treatment
  - If minimal pain and incomplete fx
  - NWB, analgesics
  - Cessation of the BP
  - Calcium and vitamin D supplementation
  - TPTD for those who appear not to heal on conservative therapy
- Surgical treatment

Cosman et al. J Bone Miner Res 2010
Lo et al. Bone 2012
Shane et al. J Bone Miner Res 2013
Mavrogenis et al. EJOST 2013

Atypical – Treatment

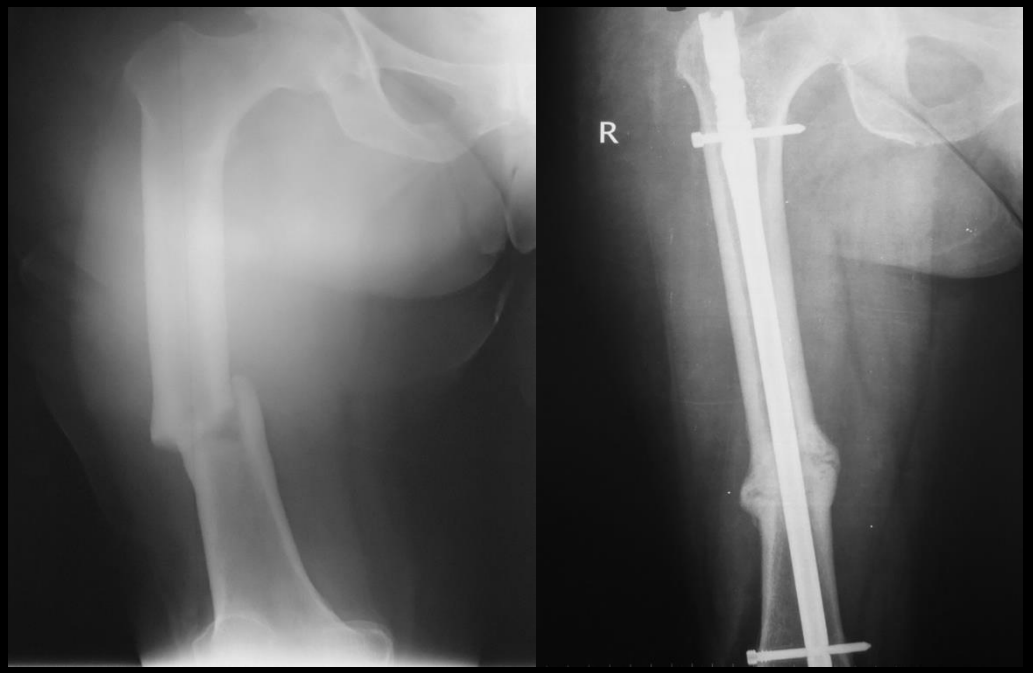
- Incomplete fx + pain: prophylactic reconstruction IM nail fixation
- Incomplete fx + minimal pain: a trial of conservative therapy
  - Limited weight-bearing with crutches or a walker
  - If no symptomatic and radiographic improvement after 2-3 months of conservative therapy: prophylactic IM nail fixation
- Incomplete fx + no pain
- Periosteal thickening but no cortical lucency

Limited weight-bearing and vigorous activity restriction until there is no bone edema detected on MRI or no increased activity detected on bone scan

Atypical – Treatment

IM vs plate and screws

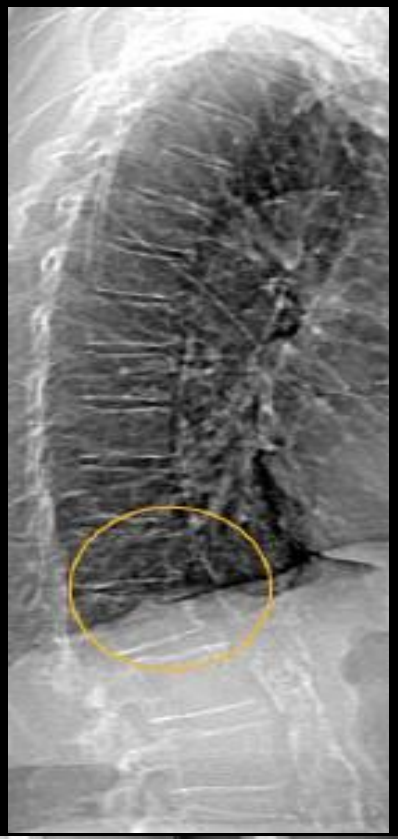
- No data exist comparing plate versus nail fixation for atypical femoral fractures
- IM nailing should be supported
  - endochondral repair

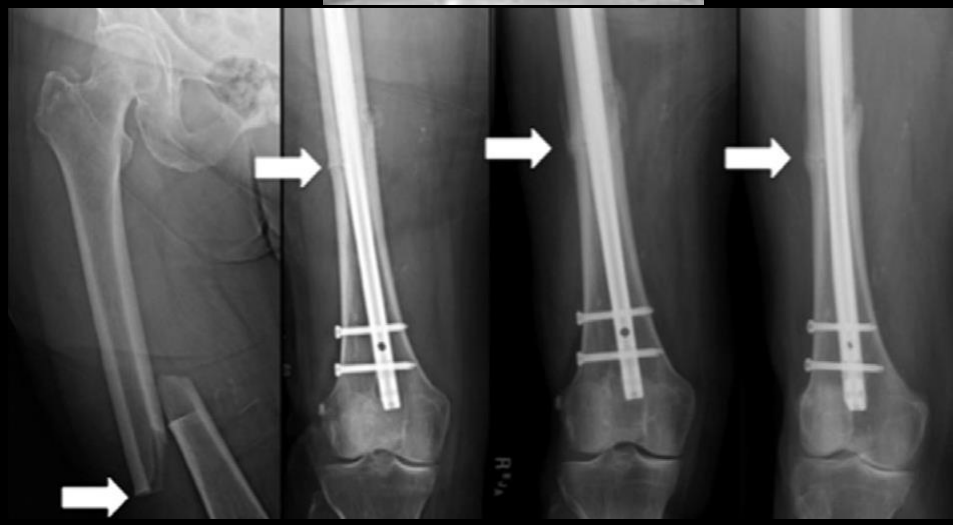


Atypical – Treatment

Medical Treatment

- Discontinue BP
  - No evidence when to restart
- Alternative drugs
  - Raloxifene
  - Other BP
  - Teriparatide
    - Preferred
    - Especially for pts w/o evidence of healing by 4-6 wks





Journal of Clinical Densitometry: Assessment & Management of Musculoskeletal Health, vol. 25, no. 1, 3–19, 2022

1094-6950/25:3–19/$36.00
https://doi.org/10.1016/j.jocd.2021.10.001

Proceedings of the 2021 Santa Fe Bone Symposium: Advances in the Management of Osteoporosis and Metabolic Bone Diseases

E. Michael Lewiecki,[1,] Paul A. Anderson,[2] John P. Bilezikian,[3] Neil Binkley,[2] Angela M. Cheung,[4] Erik A. Imel,[5] Diane Krueger,[2] Michael R. McClung,[6] Paul D. Miller,[7] and Micol S. Rothman[8]*

[1] New Mexico Clinical Research & Osteoporosis Center, Albuquerque, NM, USA; [2] University of Wisconsin School of Medicine and Public Health, Madison, WI, USA; [3] Columbia University Vagelos College of Physicians and Surgeons, New York, NY, USA; [4] University of Toronto, Toronto, Ontario, Canada; [5] Indiana University School of Medicine, Indianapolis, IN, USA; [6] Oregon Osteoporosis Center, Portland, OR, USA, and Mary MacKillop Center for Health Research, Australian Catholic University, Melbourne, Australia; [7] Colorado Center for Bone Health, Denver, CO, USA; and [8] University of Colorado Health School of Medicine, Aurora, CO, USA

Update on Atypical Femur Fractures

Angela M. Cheung, MD, PhD

- AFF appears to be a type of stress fracture due to repetitive loading, with impaired capacity for repair of microdamage, often due to antiresorptive therapy (i.e., bisphosphonates, denosumab) for osteoporosis
- AFF has also been reported in patients treated with romosozumab, an osteoanabolic agent that has a dual effect on bone remodeling, increasing bone formation, and reducing bone resorption
- When iAFF or AFF is suspected or confirmed, the opposite femur should be imaged, since bilaterality is common
- For patients treated with bilateral IM nails, bisphosphonate/denosumab could be considered after completion of teriparatide/abaloparatide, although these potent antiresorptive therapies may increase the risk of atypical humeral, and other stress fractures

UPDATE ARTICLE
DOI: http://dx.doi.org/10.1590/1413-785220223002238821
HIP AND OSTEOMETABOLIC DISEASES

ATYPICAL FEMORAL FRACTURES DUE TO THE USE OF BISPHOSPHONATES: EPIDEMIOLOGIC STUDY IN A TERTIARY HOSPITAL

FRATURAS ATÍPICAS DE FÊMUR POR USO DE BIFOSFONATOS: ESTUDO EPIDEMIOLÓGICO EM UM HOSPITAL TERCIÁRIO

FERNANDA DA COSTA GOLFIERI[1], *MAURÍCIO ZANON*[2], *PEDRO PAULO VERONA PERCIO*[1]

1. Fundação Hospitalar São Lucas, Centro Especializado em Ortopedia e Traumatologia, Cascavel, PR, Brazil.
2. Centro Universitário Assis Gurgacz, Cascavel, PR, Brazil.

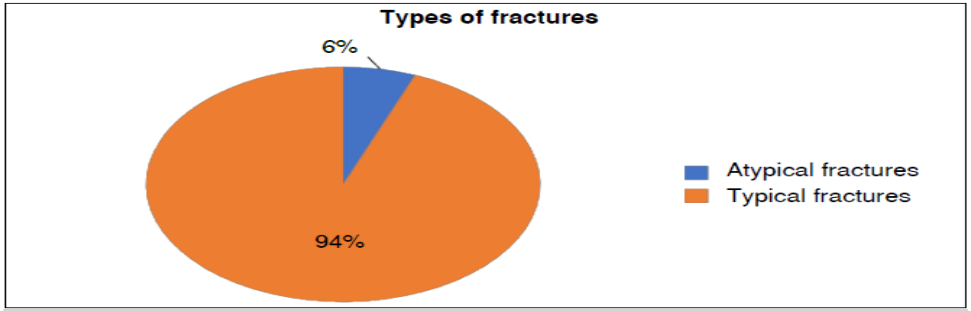


Figure 5. Typical fractures × Atypical fractures.

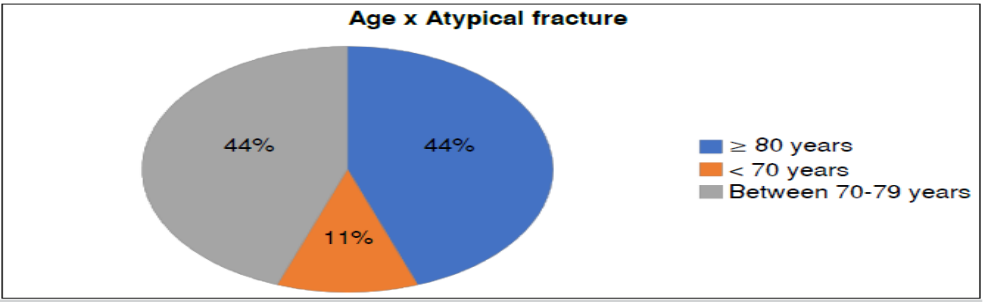


Figure 6. Age × Atypical fracture

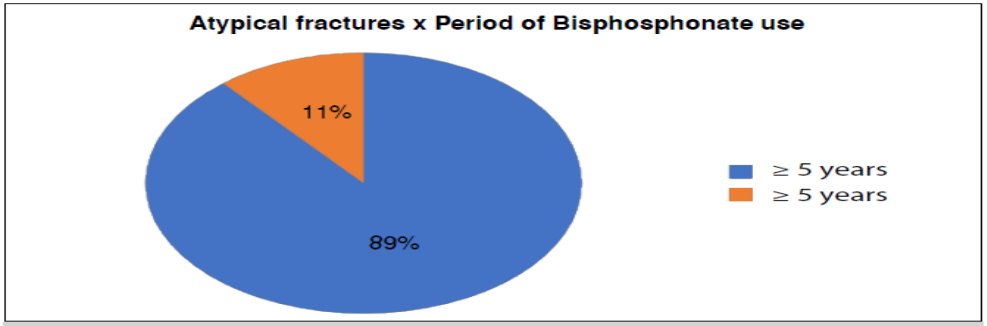


Figure 7. Atypical fractures × period Bisphosphonate of use.

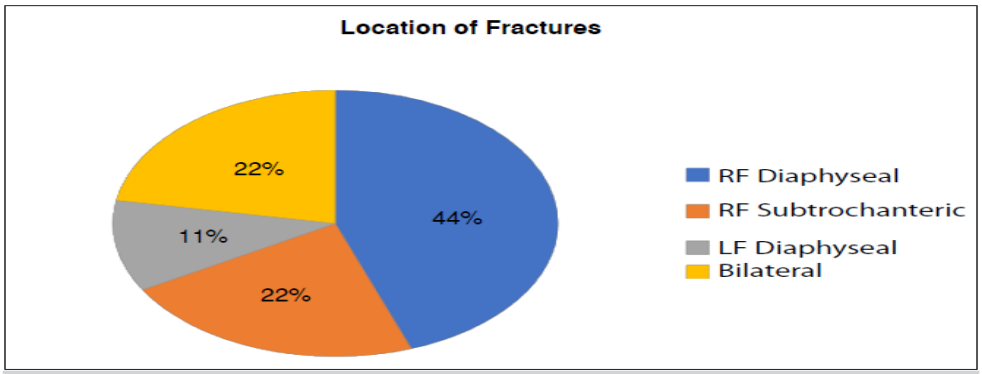


Figure 8. Location of atypical fractures.

Figure1. Female patient, 73 years old, three years of bisphosphonate use. Radiography of femur evidencing atypical fracture of the right femur, simple traits, medial spur, and cortical thickening.

Joint Diseases and Related Surgery

Jt Dis Relat Surg
2022;33(1):24-32

ORIGINAL ARTICLE

Bisphosphonate therapy associated with bilateral atypical femoral fracture and delayed union

István Gárgyán[1], Dávid Dózsai[3], István Csonka[1], Ferenc Rárosi[2], Tamás Bodzay[3], Ákos Csonka[1]

[1]Department of Traumatology, University of Szeged, Szeged, Hungary
[2]Department of Medical Physics And Informatics, University of Szeged, Szeged, Hungary
[3]Department of Traumatology, National Institute of Traumatology, Budapest, Hungary

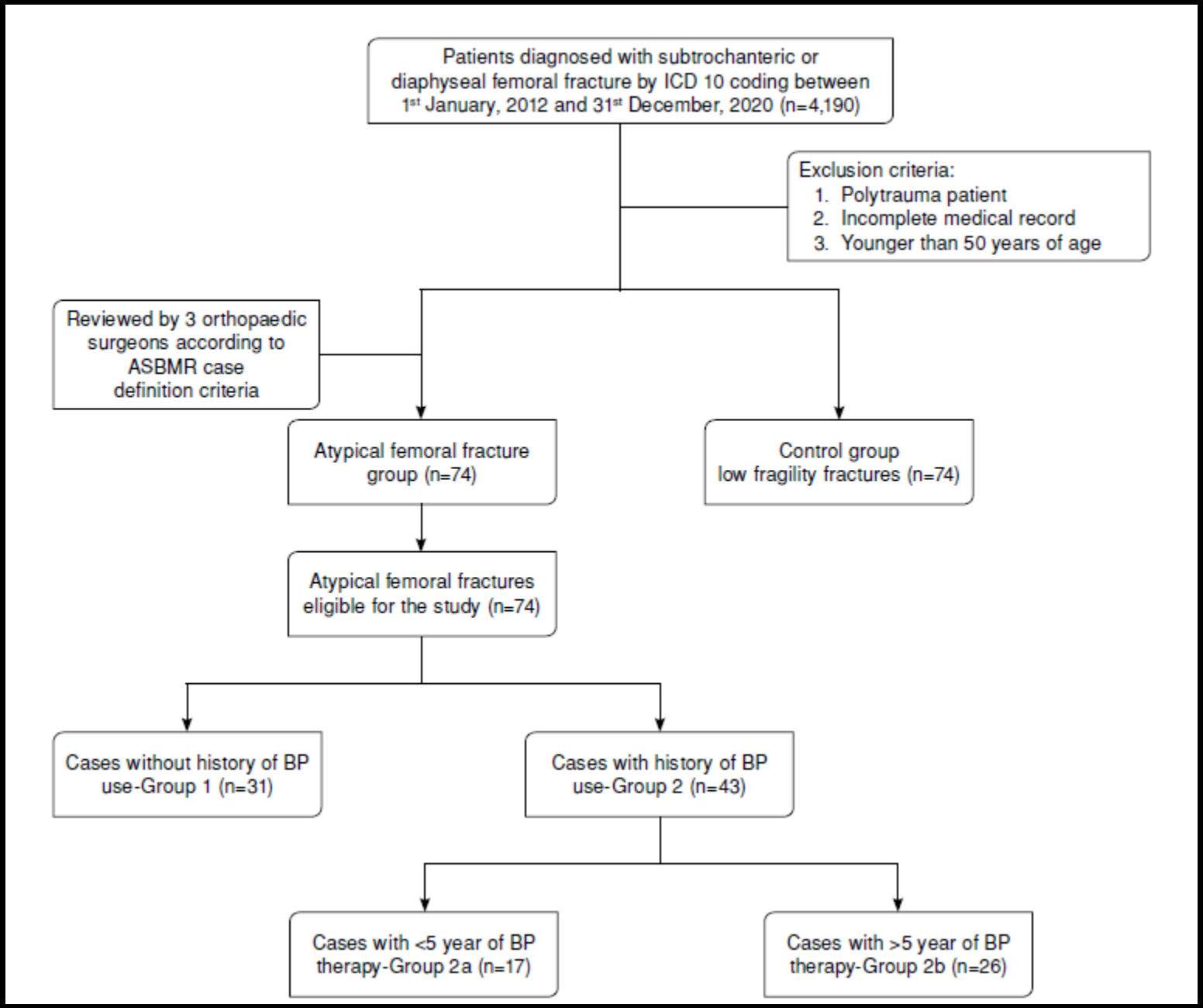

Patients diagnosed with subtrochanteric or diaphyseal femoral fracture by ICD 10 coding between 1st January, 2012 and 31st December, 2020 (n=4,190)
Exclusion criteria:
1. Polytrauma patient
2. Incomplete medical record
3. Younger than 50 years of age
Reviewed by 3 orthopaedic surgeons according to ASBMR case definition criteria
Atypical femoral fracture group (n=74)
Control group low fragility fractures (n=74)
Atypical femoral fractures eligible for the study (n=74)
Cases without history of BP use-Group 1 (n=31)
Cases with history of BP use-Group 2 (n=43)
Cases with <5 year of BP therapy-Group 2a (n=17)
Cases with >5 year of BP therapy-Group 2b (n=26)

TABLE II

Demographic and chronic diseases data on AFF and control group patients

	AFF group (n=74)			Control group (n=143)			
Demographic data of patients	n	%	Mean±SD	n	%	Mean±SD	*p*
Age (year)			75.4±7.2			74.3±11.8	0.403*
Sex							0.017†
Male	8			35			
Female	66			108			
Diabetes	9	12		33	23		0.054†
Rheumatoid arthritis	4	5		2	1		0.184‡
Thyroid disease	11	15		10	7		0.063†
Malignancy	5	6		5	3		0.315‡
Neurologic disease	7	9		9	6		0.398†
Hypertension	49	66		115	80		0.021†
Osteoporosis	50	67		25	17		<0.0001†
Bisphosphonate use	43	58		8	6		<0.0001†
Corticosteroid use	5	6		4	3		0.279‡

AFF: Atypical femoral fractures; SD: Standard deviation; * Welch two sample t-test; † Chi-squared test; ‡ Fisher exact test.

ORIGINAL ARTICLE

JBMR PLUS Open Access ASBMR

Incidence of Atypical Femoral Fracture and Its Mortality in a Single Center in Singapore

Linsey Gani,[1] Natasha Anthony,[1] Lily Dacay,[1] Pei Tan,[2] Le Roy Chong,[3] and Thomas FJ King[1]

[1]Department of Endocrinology, Department of Medicine Changi General Hospital, 2 Simei Street 3, 529889, Singapore, Singapore
[2]Centre of Trial Research Unit, Changi General Hospital, Singapore, Singapore
[3]Department of Radiology, Changi General Hospital, Singapore, Singapore

Table 1. Demographics and Clinical Variables of Patients With Atypical Femoral Fracture (AFF) and Typical Subtrochanteric Femoral Fracture

	Atypical femoral fracture ($n = 69$)	Typical subtrochanteric femoral fracture ($n = 393$)	p Value
	n (%)	*n* (%)	
Age (years), mean (SD)	71.2 (8.7)	73.8 (12.3)	0.087
BMI (kg/m^2), mean (SD)	23.5 (3.8)	23.9 (5.9)	0.754
Female	60 (87.0)	295 (75.1)	0.031
Race			
Chinese	51 (83.6)	266 (74.3)	0.144
Malay	5 (8.2)	66 (18.4)	
Indian/others	5 (8.2)	26 (7.3)	
eGFR mean (SD)	76.5 (21.5)	75.8 (35.1)	0.870
Creatinine median (IQR)	73 (62, 88)	77 (60, 100)	0.262
25OHD (µg/L), mean (SD) ($n = 353$)	28.6 (8.3)	22.3 (11.5)	0.061
Charlson comorbidity score, mean (SD)	3.2 (1.4)	3.9 (2.0)	0.002
Smokers	1 (1.5)	14 (3.7)	0.354
Fragility fracture history	15 (22.7)	105 (27.3)	0.433
Rheumatoid arthritis	5 (7.3)	4 (1.0)	0.001
Type 2 diabetes mellitus (DM2)	9 (13.0)	153 (38.9)	<0.001
HbA1c (%) in DM2, mean (SD) ($n = 131$)	6.52 (0.51)	7.25 (2.5)	0.257
TSH (mIU/L), median (IQR) ($n = 277$)	1.19 (0.56, 3.95)	1.50 (0.92, 2.50)	0.439
Prodromal symptoms	7 (10.1)	18 (4.6)	0.060
Bilateral fracture	3 (4.4)	10 (2.5)	0.403
Delayed healing	2 (2.9)	2 (2.3)	0.760
Surgical management	65 (94.2)	289 (73.9)	<0.001
Repeat surgical procedure	2 (2.9)	8 (2.1)	0.643
Time to healing (months), median (IQR)	2 (1, 3)	3 (1, 3)	0.480
Antiresorptive drug use (either oral BP/zoledronic acid/denosumab)	35 (50.7)	44 (11.2)	<0.001
• Oral BP (either alendronate or risedronate)	28	35	
• Oral BP sequential (alendronate and risedronate)	5	6	
• Oral BP to denosumab	2	2	
• Zoledronic acid	0	1	
Duration of BP use (months), median (IQR)	56.5 (28, 66)	15.5 (4, 36)	<0.001
Glucocorticoid use	5 (7.3)	5 (1.3)	0.002

SD = standard deviation; BMI = body mass index; eGFR = estimated glomerular filtration rate; IQR = interquartile range; 25-OHD = 25-hydroxyvitamin D; HbA1C = hemoglobin A1c; TSH = thyroid-stimulating hormone; BP = bisphosphonate.

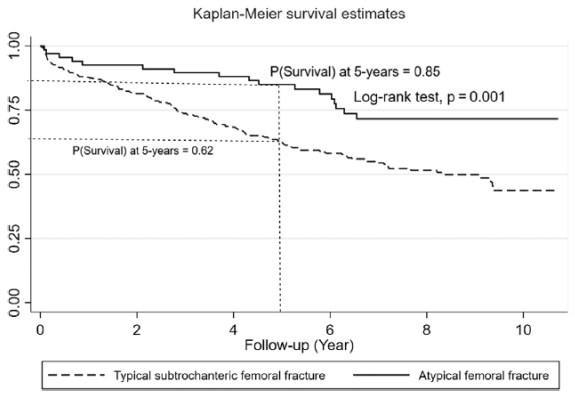


Fig 3. Kaplan–Meier curve for 5-year survival in atypical femoral fracture versus typical subtrochanteric femoral fracture.

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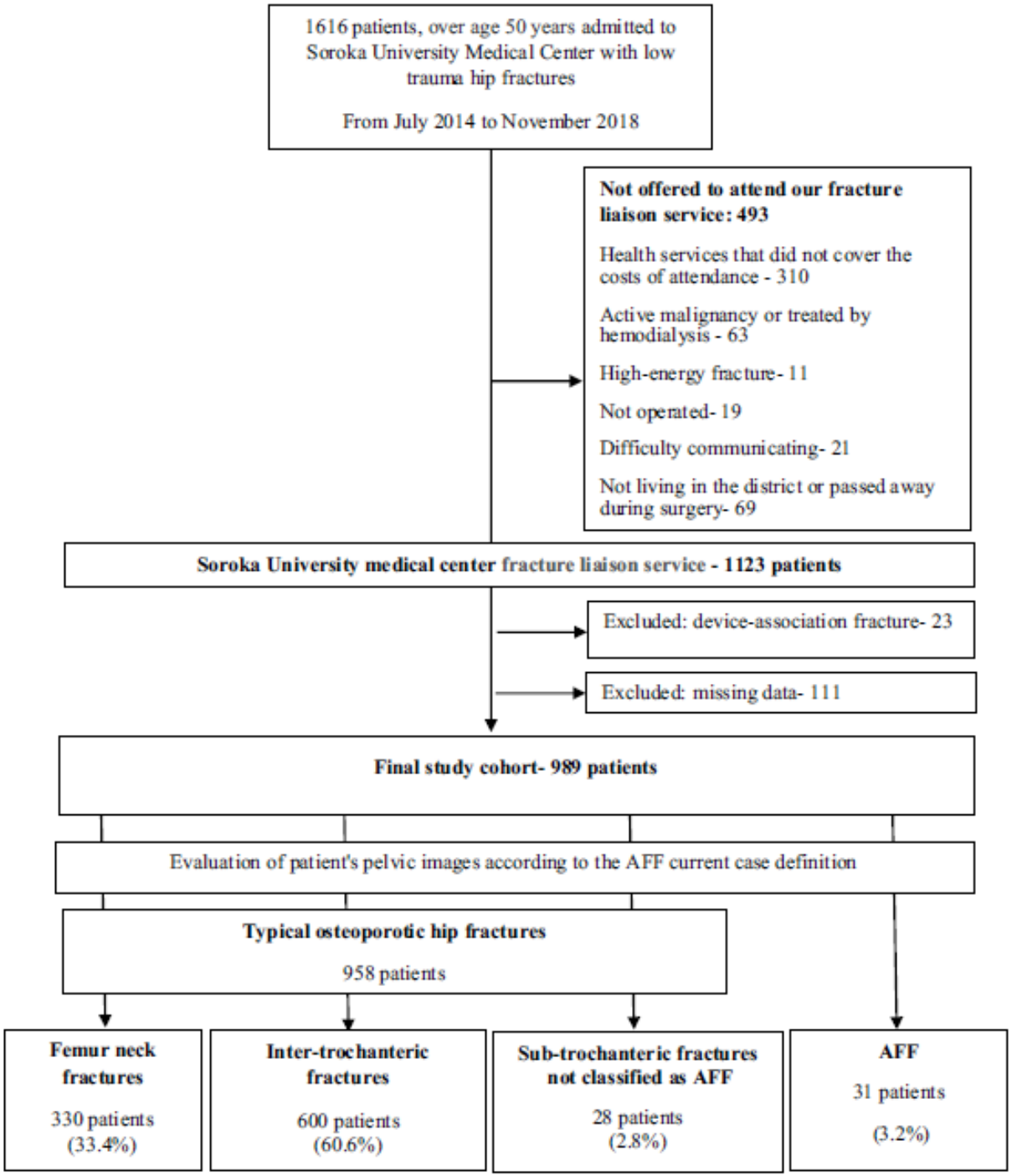
ORIGINAL ARTICLE

Bisphosphonate treatment and the risk of atypical femoral fracture among patients participating in a Fracture Liaison Service of a tertiary medical center

Noa Bareli[1] · Roni Gat[1,2] · Victoria Makarov[1,3] · Ethel Siris[4] · Merav Fraenkel[1,5] · Uri Yoel[1,5]


1616 patients, over age 50 years admitted to Soroka University Medical Center with low trauma hip fractures
From July 2014 to November 2018
Not offered to attend our fracture liaison service: 493
Health services that did not cover the costs of attendance - 310
Active malignancy or treated by hemodialysis - 63
High-energy fracture- 11
Not operated- 19
Difficulty communicating- 21
Not living in the district or passed away during surgery- 69
Soroka University medical center fracture liaison service - 1123 patients
Excluded: device-association fracture- 23
Excluded: missing data- 111
Final study cohort- 989 patients
Evaluation of patient's pelvic images according to the AFF current case definition
Typical osteoporotic hip fractures
958 patients
Femur neck fractures
330 patients
(33.4%)
Inter-trochanteric fractures
600 patients
(60.6%)
Sub-trochanteric fractures not classified as AFF
28 patients
(2.8%)
AFF
31 patients
(3.2%)

	Typical osteoporotic hip fracture $n=93$	AFF $n=31$	p value
Age (years) mean ± SD	72.4 ± 9.4	72.3 ± 10.3	0.991
Sex, female n, %	78 (83.9)	26 (83.9)	1.000
Creatinine (mg\dL)	1.04 ± 1.05	0.8 ± 0.2	0.409
eGFR (mL\min), mean ± SD	90.5 ± 44.3	87.6 ± 31.3	0.848
Hb (gr\dL) mean ± SD	12.3 ± 2.1	13.4 ± 1.2	0.118
PTH (pg\dL) mean ± SD	120.8 ± 112.69	97.4 ± 50.4	0.579
Vit D (nmol\L) mean ± SD	45.2 ± 21.09	45.1 ± 15.2	0.994
Diabetes mellitus n (%)	33 (35.5)	7 (22.6)	0.183
Charlson's Comorbidity Index mean ± SD	4.7 ± 4.2	2.9 ± 3.7	0.030
Any treatment with BP[a] n (%)	20 (21.5)	20 (64.5)	<0.001
PPIs n (%)	48 (51.6)	6 (18.8)	0.002
Steroids n (%)	27 (29.0)	10 (32.2)	0.734
Anti-depressants n (%)	20 (21.5)	3 (9.7)	0.142
Statins n (%)	61 (65.6)	15 (48.4)	0.089

AFF atypical femoral fracture, *PTH* parathyroid hormone, Vit D-25(OH)-Vitamin D, *BP*- bisphosphonate, *PPI* proton pump inhibitors

[a]One or more purchases of BP prior to hip fracture

Table 3 Bisphosphonate treatment years among patients included in the final study cohort, according to the type of fracture[a]

Years of treatment with BPs[b]	Typical osteoporotic hip fracture $n=958$	AFF $n=31$	p value
1 year *n* (%)	10 (1.0)	0 (0.0)	0.567
2 years *n* (%)	21 (2.2)	1 (3.2)	0.701
3 years *n* (%)	14 (1.5)	0 (0.0)	0.498
4 years *n* (%)	15 (1.6)	1 (3.2)	0.471
5 years or more *n* (%)	153 (16.0)	18 (58.1)	<0.001
Any treatment with BP[c] *n* (%)	213 (22.2)	20 (64.5)	<0.001

AFF atypical femoral fracture, *BP* bisphosphonate

[a]Computerized BP purchase data were available for 5 years prior to the fracture date

[b]A year of BP treatment was defined as a period of 6 months and more of oral BP purchase per year or one purchase of zoledronic acid per year

[c]One or more purchases of BP

ORIGINAL ARTICLE

JBMR®

Fracture Risk Following an Atypical Femoral Fracture

Marie-Josée Bégin,[1] Marie-Claude Audet,[1] Thierry Chevalley,[1] Marina Portela,[1] Ivan Padlina,[1] Didier Hannouche,[2] Kuntheavy Ing Lorenzini,[3] Raphaël Meier,[4] Robin Peter,[2] Brigitte Uebelhart,[1] René Rizzoli,[1] Serge Ferrari,[1] and Emmanuel Biver[1]

[1]Division of Bone Diseases, Geneva University Hospitals and Faculty of Medicine, University of Geneva, Geneva, Switzerland
[2]Division of Orthopedic Surgery, Department of Surgery, Geneva University Hospitals and Faculty of Medicine, University of Geneva, Geneva, Switzerland
[3]Division of Clinical Pharmacology and Toxicology, Geneva University Hospitals and Faculty of Medicine, University of Geneva, Geneva, Switzerland
[4]Department of Surgery, Geneva University Hospitals and Faculty of Medicine, University of Geneva, Geneva, Switzerland

Table 1. Baseline Characteristics and Follow-Up of Patients With AFF and With pMOFs

Characteristic	AFF ($n = 55$)	pMOF ($n = 165$)	p
Gender (women), (%)	95	95	1.000
Age (years), mean ± SD	75 ± 10	75 ± 10	0.896
Weight (kg), mean ± SD	66 ± 13	65 ± 15	0.951
Height (cm), mean ± SD	158 ± 8	161 ± 9	**0.005**
Body mass index (kg/m^2), mean ± SD	26.3 ± 5.1	25.0 ± 5.4	0.063
Charlson Comorbidity Index, mean ± SD	3.9 ± 1.6	4.6 ± 2.1	**0.013**
Prior clinical fracture (excluding index AFF or pMOF) (%)	67	33	**<0.001**
Lumbar spine *T*-score, mean ± SD[a]	−1.4 ± 1.7	−1.3 ± 1.6	0.799
Total hip *T*-score, mean ± SD[a]	−1.3 ± 1.3	−1.7 ± 1.0	0.216
Femoral neck *T*-score, mean ± SD[a]	−1.9 ± 0.9	−2.0 ± 1.0	0.626
Osteoporotic status on DXA[a]			0.980
Normal BMD, (%)	14	13	
Osteopenia, (%)	40	40	
Osteoporosis, (%)	46	47	
Prior AR therapy, (%)[b]	89	12	**<0.001**
AR therapy during follow-up, (%)[c]	38	16	**<0.001**
Follow-up duration (years), mean ± SD	6.2 ± 3.7	4.3 ± 2.6	**<0.001**

Bold values are significant at $p < 0.05$.

AFF = atypical femoral fracture; AR = anti-resorptive; BMD = bone mineral density; DXA = dual energy X-ray absorptiometry; pMOF = peripheral major osteoporotic fracture; SD = standard deviation.

[a]Osteoporosis defined as at least one *T*-score ≤ −2.5 SD and osteopenia as at least one T-score between −1 and −2.5 SD with none ≤ − 2.5 SD at the lumbar spine, total hip, or femoral neck. Data available for a subgroup of patients (spine $n = 148$, total hip $n = 131$, femoral neck $n = 136$).

[b]Before index fracture.

[c]Continued or started after index fracture or during the follow-up.

Table 2. Incidence of Fracture and Mortality During the Follow-Up

	All incident low-trauma fractures					Incident MOF					Mortality				
Parameter	Patients *n* (%)	PY	Incidence per 1000 PY (95% CI)	IRR (95% CI)	*p*	Patients *n* (%)	PY	Incidence per 1000 PY (95% CI)	IRR (95% CI)	*p*	Patients *n* (%)	PY	Incidence per 1000 PY (95% CI)	IRR (95% CI)	*p*
Total follow-up															
AFF ($n = 55$)	31 (56)	218	142 (100–202)	1.30 (0.82–2.04)	0.117	23 (42)	220	104 (69–157)	1.28 (0.74–2.15)	0.171	5 (9)	340	15 (6–35)	0.29 (0.09, 0.75)	**0.002**
pMOF ($n = 165$)	61 (37)	560	109 (85–140)			46 (28)	562	82 (61–109)			36 (22)	713	50 (36–70)		
Imminent risk*															
AFF ($n = 55$)	13 (24)	91	143 (83–246)	1.11 (0.54–2.15)	0.364	9 (16)	105	86 (45–165)	0.86 (0.36–1.86)	0.359	0 (0)	105	0	NA	**0.038**
pMOF ($n = 165$)	36 (22)	280	128 (93–178)			30 (18)	301	100 (70–143)			9 (5)	318	28 (15–54)		

Bold values are significant at $p < 0.05$.. AFF = atypical femoral fracture; CI = confidence interval; IRR = incidence rate ratio; MOF = major osteoporotic fracture; pMOF = peripheral major osteoporotic fracture; PY = patient-years. * follow-up censored at maximum 2 years.

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Bisphosphonates and the risk of atypical femur fractures

Dennis M Black [1], Katherine Condra [2], Annette L Adams [3], Richard Eastell [4]

Affiliations – collapse

Affiliations

1 University of California, San Francisco, Department of Epidemiology & Biostatistics, United States of America; Department of Research & Evaluation, Kaiser Permanente Southern California, Pasadena, CA, United States of America. Electronic address: Dennis.Black@ucsf.edu.
2 San Francisco VA Health Care System, Department of Endocrinology & Metabolism, San Francisco, United States of America.
3 Department of Research & Evaluation, Kaiser Permanente Southern California, Pasadena, CA, United States of America.
4 University of Sheffield, Department of Oncology & Metabolism, United Kingdom.

Abstract

Bisphosphonates are effective in reducing hip and other fractures. However, concerns about atypical femur fractures (AFFs) have contributed to substantially decreased bisphosphonate use, and hip fracture rates may be increasing. Despite this impact, important uncertainties remain regarding AFF risks including the association between bisphosphonate use and other risk factors such as BMD, age, weight, and race. To address this evidence gap, a cohort study of 196,129 women ≥50 years of age in the Southern California Kaiser Permanente HMO women (with ≥1 bisphosphonate prescription) were studied; the primary outcome was radiographically-adjudicated AFF between 2007 and 2017. Risk factors including bisphosphonate use and race were obtained from electronic health records. Multivariable Cox models were used for analysis. Benefit-risk was modeled for 1-10 years of bisphosphonates to compare fractures prevented vs. AFFs associated. Among 196,129 women, 277 (0.1%) sustained AFFs. After multivariable adjustment, AFF risk increased with longer bisphosphonate duration: hazard ratio (HR) increased from HR = 8.9 (95%CI: 2.8,28) for 3-5 years to HR = 43.5 (13.7138.1) for >8 years. Hip BMD, surprisingly, was not associated with AFF risk. Other risk factors included Asian ancestry (HR = 4.8 (3.6, 6.6)), short stature, overweight, and glucocorticoid use. Bisphosphonate discontinuation was associated with rapid decrease in AFF risk. Decreases in osteoporotic and hip fractures risk during 1-10 years of bisphosphonates far outweighed the increase AFF risk in Caucasians, but less so in Asians. In Caucasians, after 3 years 149 hip fractures were prevented with 2 AFFs associated compared to 91 and 8 in Asians. The evidence for several potential mechanisms is summarized with femoral geometry being the most likely to explain AFF risk differences between Asians and Caucasians. The results from this new study add to the evidence base for AFF risk factors and will help inform clinical decision-making for individual patients about initiation and duration of bisphosphonate therapy and drug holidays.

Keywords: Atypical femur fracture; Bisphosphonates; Fracture; Osteoporosis.

Journal Pre-proof

Evaluation of factors affecting the occurrence of second atypical fracture after bone union of the first atypical fracture

Hiroyuki Tsuchie, Naohisa Miyakoshi, Yuji Kasukawa, Koji Nozaka, Kimio Saito, Hayato Kinoshita, Moto Kobatyashi, Norio Suzuki, Toshiaki Aizawa, Hidekazu Abe, Shigeto Maekawa, Takanori Tomite, Yuichi Ono, Kentaro Ouchi, Nobusuke Shibata, Itsuki Nagahata, Masaaki Takeshima, Manabu Akagawa, Yusuke Yuasa, Chie Sato, Yoichi Shimada

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Reference: BON 115671

- Factors affecting the recurrence of AFF
- Appropriate treatment for osteoporosis after bone union
  - administration of TPTD for the maximum period after occurrence first AFF and the use of active vitamin D3 after the completion of teriparatide treatment may be the most effective strategy to prevent the recurrence of AFF

Table 3. Results of univariate and multivariate analyses of factors affecting the second fracture of AFF

Variables	Univariate analysis			Multivariate analysis		
	OR	95% CI	*p*-value	OR	95% CI	*p*-value
Age	1.034	0.942-1.135	0.4827			
Fracture pattern - complete	1.843	0.388-8.740	0.4416			
Past duration of bisphosphonate or denosumab usage	1.012	0.988-1.038	0.3326			
History of fragility fractures	0.375	0.047-3.011	0.[illegible]56			
Surgical treatment	0.760	0.095-6.104	0.7906			
Surgical method - plate fixation	0.775	0.096-6.267	0.8122			
Laboratory examination - Ca level	1.251	0.[illegible]7..32	0.8038			
Femoral curvature - lateral	1.083	0..+7-1.237	0.2445			
- anterior	1.100	0.998-1.212	0.0538			
BMD - lumbar spine	1.[illegible]67	0.009-156.508	0.9535			
- proximal femur	0.02[illegible]	0.000-48.606	0.3430			
Healing time of the fracture	0.984	0.908-1.066	0.6857			
Administration period after AFF onset						
Teriparatide	0.923	0.854-0.997	0.0429	0.920	0.849-0.997	0.0408
Daily teriparatide	0.935	0.864-1.013	0.0988			
Weekly teriparatide	0.976	0.863-1.103	0.6925			
Bisphosphonate or denosumab	0.996	0.965-1.028	0.8170			
Active vitamin D_3	0.938	0.881-0.999	0.0477	0.943	0.892-0.996	0.0366

OR: odds ratio, 95% CI: 95% confidence interval, AFF: atypical femoral fracture ,Ca: calcium, BMD: bone mineral density,

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Review Article

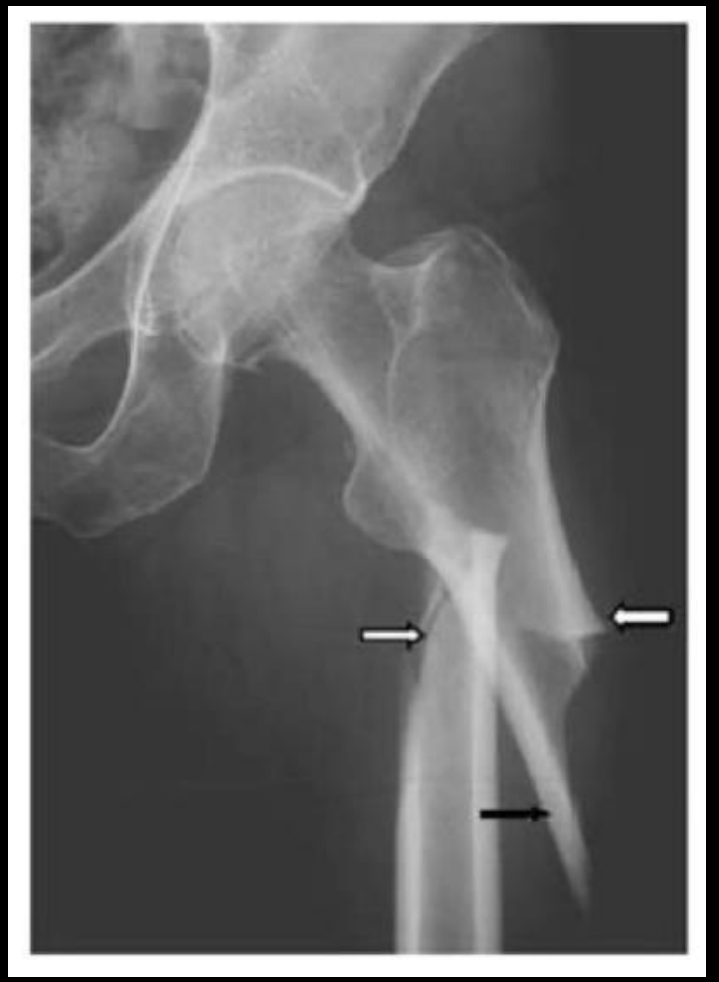
Biomechanical mechanisms of atypical femoral fracture

Ani Ural

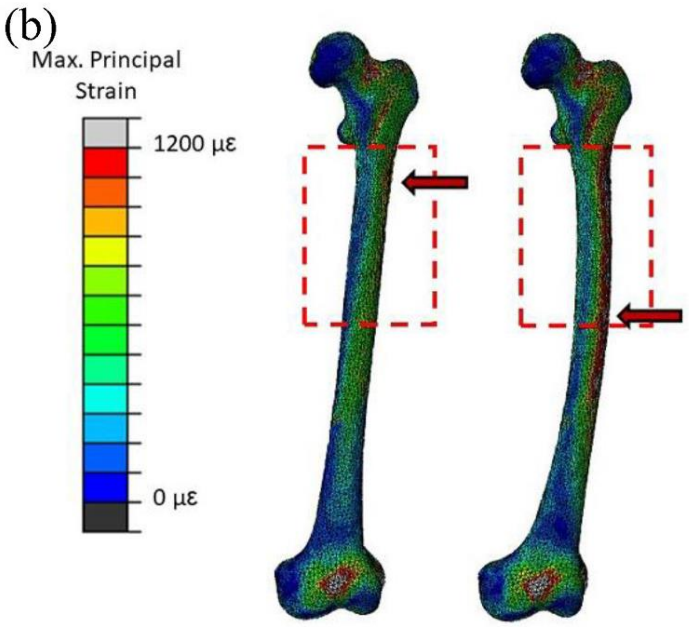
Department of Mechanical Engineering, Villanova University, 800 Lancaster Avenue, Villanova, PA, 19085, USA

Three major potential mechanical mechanisms of AFF

- (1) macroscale femoral geometry which influences the stress/strain distribution in the femur under loading;
- (2) bone matrix composition, potentially altered by long-term remodeling suppression by BPs, which directly influences the material properties of bone and its mechanical behavior; and
- (3) microstructure, potentially altered by long-term remodeling suppression by BPs, which impacts fracture resistance through interaction with crack propagation.

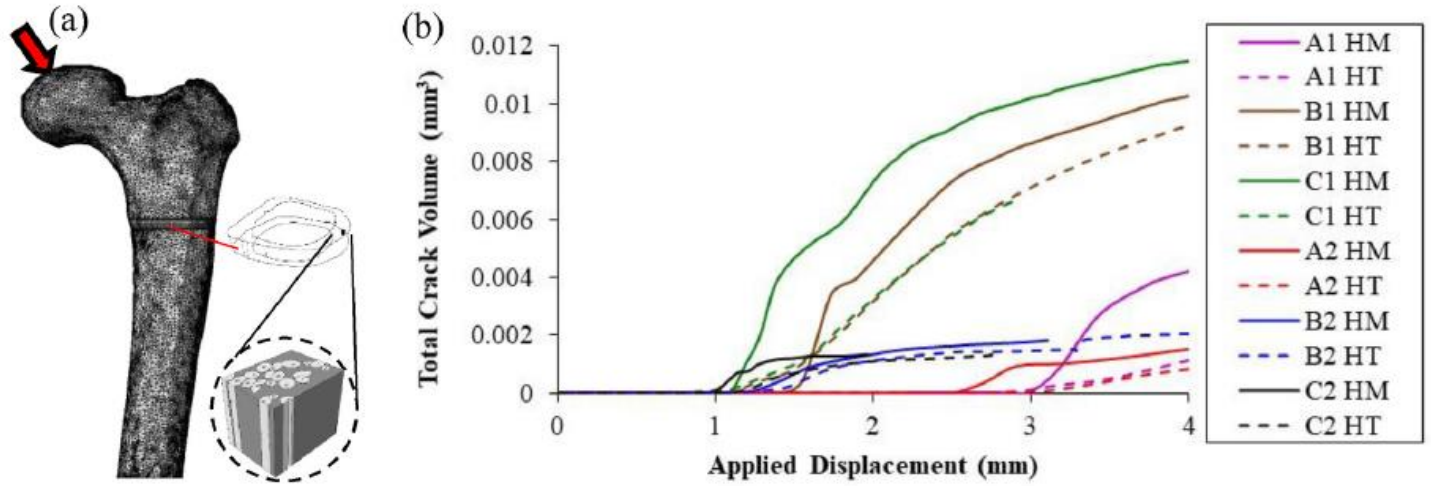


- Macroscale femoral geometry



Majority of the studies that focus on the impact of macroscale geometry on AFF are based on retrospective case-control studies. Although these studies do not provide a mechanistic understanding of the impact of femoral geometry on AFF risk, they identify candidate geometrical features which may increase the risk of AFF occurrence. AFF patients were found to have larger lateral bowing angle than patients with no fracture history (mean: −3.2° vs. −0.8°) (Morin et al., 2016). In addition, AFF patients had larger anterior (mean: 12.39° vs. 3.97°) and lateral (mean: 15.71° vs. 10.72°) bowing angle (Jang et al., 2017) as well as larger coronal (mean: 4.93° vs. 3.10°) and sagittal (mean: 8.46° vs. 5.94°) femoral curvature than typical fracture patients (Lim et al., 2018). Lateral bowing angle also had an impact on the location of the AFF. Patients with higher lateral bowing angle experienced diaphyseal AFF whereas patients with lower lateral bowing angles experienced subtrochanteric AFF (diaphyseal vs. subtrochanteric mean: $> 7°$ vs. $\leq 7°$; 7.8° vs. 1.6°; -4.3° vs. -0.9°, respectively) (Chen et al., 2014; Kim et al., 2017; Morin et al., 2016). Several studies also found that AFF patients have smaller femoral neck-shaft angle compared to both non-fracture (mean: 129.5° vs. 133.8°; 126.4° vs. 130.3°, respectively) (Hagen et al., 2014; Taormina et al., 2014) and typical fracture patients (mean: 128.9° vs. 134°; 126.4° vs. 131.1°, respectively) (Mahjoub et al., 2016; Taormina et al., 2014) although a couple of studies reported no difference in neck-shaft angle in AFF patients (Chou et al., 2015; Lim et al., 2018). Besides these geometrical features, larger femoral offset (mean: 43.1 mm vs. 38.3 mm) (Mahjoub et al., 2016), greater proximal cortical thickness (medial, 50 mm below lesser trochanter mean: 8.1 mm vs. 7.2 mm; lateral, 50 mm below lesser trochanter mean: 7.7 mm vs. 6.8 mm; medial, at the level of the lesser trochanter mean: 5.1 mm vs. 2.8 mm; lateral, at the level of the lesser trochanter mean: 4.3 mm vs. 3.8 mm) (Mahjoub et al., 2016), and narrower center-edge angle (mean: 42.6 mm vs. 45.8 mm) (Taormina et al., 2014) were observed in AFF patients compared to typical femoral fracture controls. AFF patients also demonstrated shorter hip-axis length than both non-fracture and typical fracture controls (mean: 120.3 mm vs. 127.3 mm and 128.2 mm) (Taormina et al., 2014).

- Microscale compositional and structural changes due to prolonged BP treatment
  - Bone matrix composition, potentially altered by long-term remodeling suppression by BPs



Open Access Technical Report

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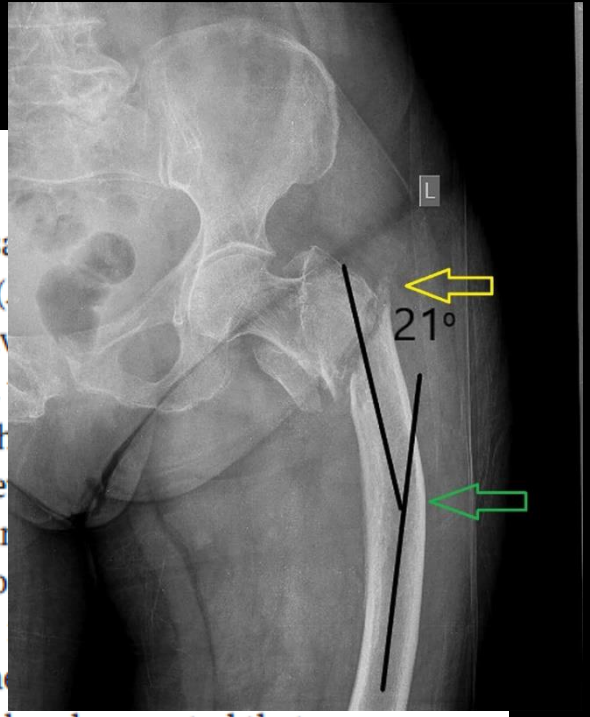
Femoral Bowing and Femoral Neck-Shaft Angle Evaluation Can Reduce Atypical Femoral Fractures in Osteoporotic Patients: A Scientific Report

Ioannis Papaioannou [1], Georgia Pantazidou [2], Andreas Baikousis [1], Panagiotis Korovessis [1]

1. Orthopedics and Traumatology and Spine Surgery, General Hospital of Patras, Patras, GRC 2. Public Health Postgraduate MSc Program, University of Patras, Patras, GRC



Abstract

Bisphosphonates (BPs) are the mainstay of osteoporosis treatment due to their sa
evidence that BPs medication may be complicated by atypical femoral fractures (
administration of BPs is even more strongly associated with AFFs. AFF is a relativ
BPs when taking into account the huge population worldwide that benefits from
is, however, a serious complication of BPs treatment, which includes prolonged h
revision rate when operative treatment is required. Less frequently, AFFs occur e
administration, while these fractures have all the characteristics of "stress" or "i
critical point of view in AFFs pathogenesis seems to be not only the biology of co
mechanical issue. It has been proven that BPs, glucocorticoids and proton pump
bone turnover suppression and affect the biological parameter of AFFs pathogen
femoral bone properties predispose to AFFs pathogenesis. Several studies have already reported that increased femoral bowing > 5.25^0 degrees or decreased femoral neck-shaft angle <125 degrees, are associated with increased risk for diaphyseal and subtrochanteric AFFs respectively, regardless of BPs uptake. If these two parameters are simultaneously present, the probability for AFFs occurrence increases dramatically. Our scientific report, which is based on the current evidence about AFFs, is that if both femoral bowing angle and femoral neck-shaft angle are evaluated before BPs administration, this intervention may reduce the incidence of AFFs. Thus, in cases with excessive lateral femoral shaft bowing or very small femoral neck-shaft angle, the prescription of another anti-osteoporotic treatment than BPs should be recommended. If, however, BPs can't be avoided, clinicians should be aware of the fact that long-term administration may be implicated with AFFs occurrence. In these cases, short term BPs administration with timely drug holiday between three and five years may be reasonable. Finally, roentgenographic evaluation of both femurs every six months and medical reference in case of any emerging thigh pain are also logical interventions to prevent and reduce AFFs.

Case Report

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A Rare Case of an Intertrochanteric Hip Fracture Combined with an Ipsilateral Incomplete Atypical Femoral Fracture Treated with a Long Gamma Intramedullary Nail

Georgios F Georgiadis[1], Stamatios Theodoros D Chatzopoulos[1], Konstantinos A Maniatis[1], Dimitrios G Begkas[1]

- Denosumab (one dose)
- Femoral bowing and vit. D deficiency

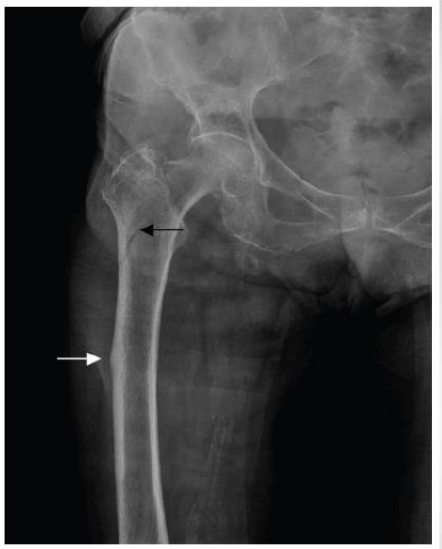

Figure 1: Plain radiograph of the right femur (upon arrival of the patient), revealing an AO A3.1 peritrochanteric fracture (black arrow) and a focal thickening of the lateral cortex of the proximal femoral diaphysis (white arrow).

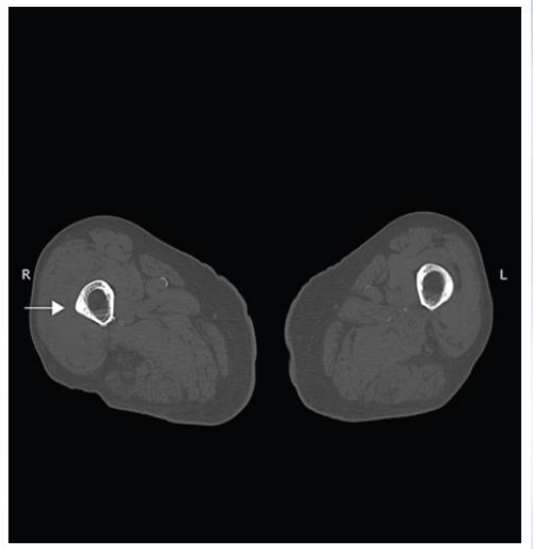

Figure 2: Axial multidetector computed tomography image of the right proximal femoral diaphysis (on arrival of the patient), demonstrating a focal lateral cortex thickening (white arrow).

Figure 3: Plain radiograph of the right femur, 1 day after surgery, showing intramedullary nail fixation of the perirtrochanteric fracture and simultaneous stabilization of the lateral cortex thickening of the proximal diaphysis. Initially, the nail could not be advanced distal enough, as it was diverging toward the anterior cortex, thus a shorter than the desired nail was inserted.

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CASE REPORT

Progression of atypical femur stress fracture after discontinuation of bisphosphonate therapy

K.D. Gu [1] · B. Ettinger [2] · C.D. Grimsrud [3,4] · J.C. Lo [1,2,4]

- Importance of follow-up even with early healing with anabolic therapy
- Challenge in managing older patients with incomplete AFF at risk for progression to complete AFF
- Ethnicity is a risk factor

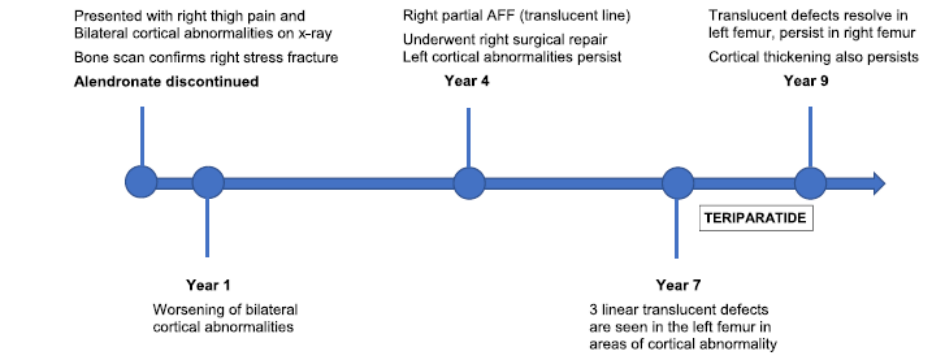
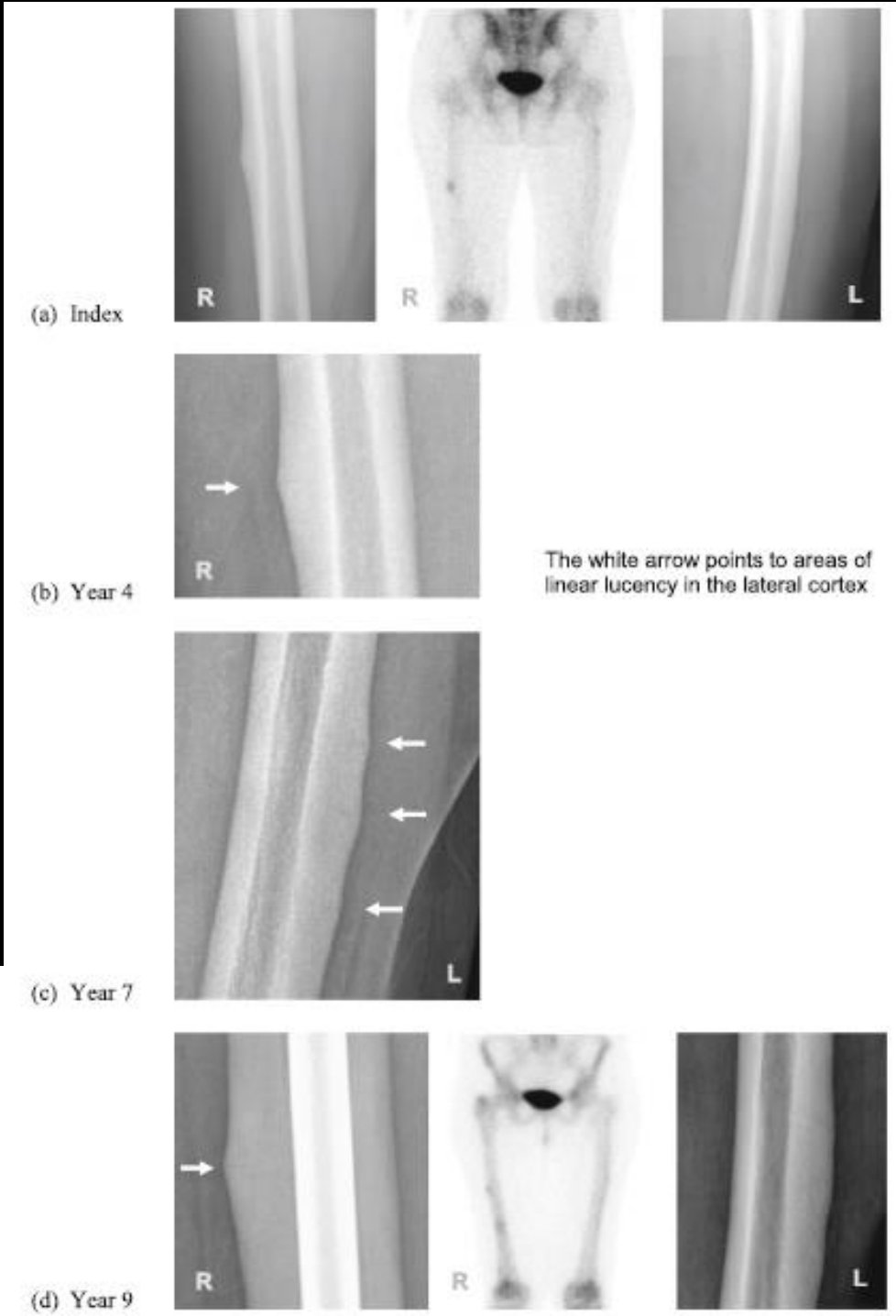


Fig. 2 Timeline of presentation and evolution of partial atypical femur fractures (AFF) in both the right and left femurs



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Case Report

Bilateral atypical fractures of the femur: Ten years AFTER ten years of bisphosphonate therapy

Matthew D. Smith [a,*], Olen J. Haseman [a], Jorge A. Velez Garza [b], Jan M. Bruder [c]

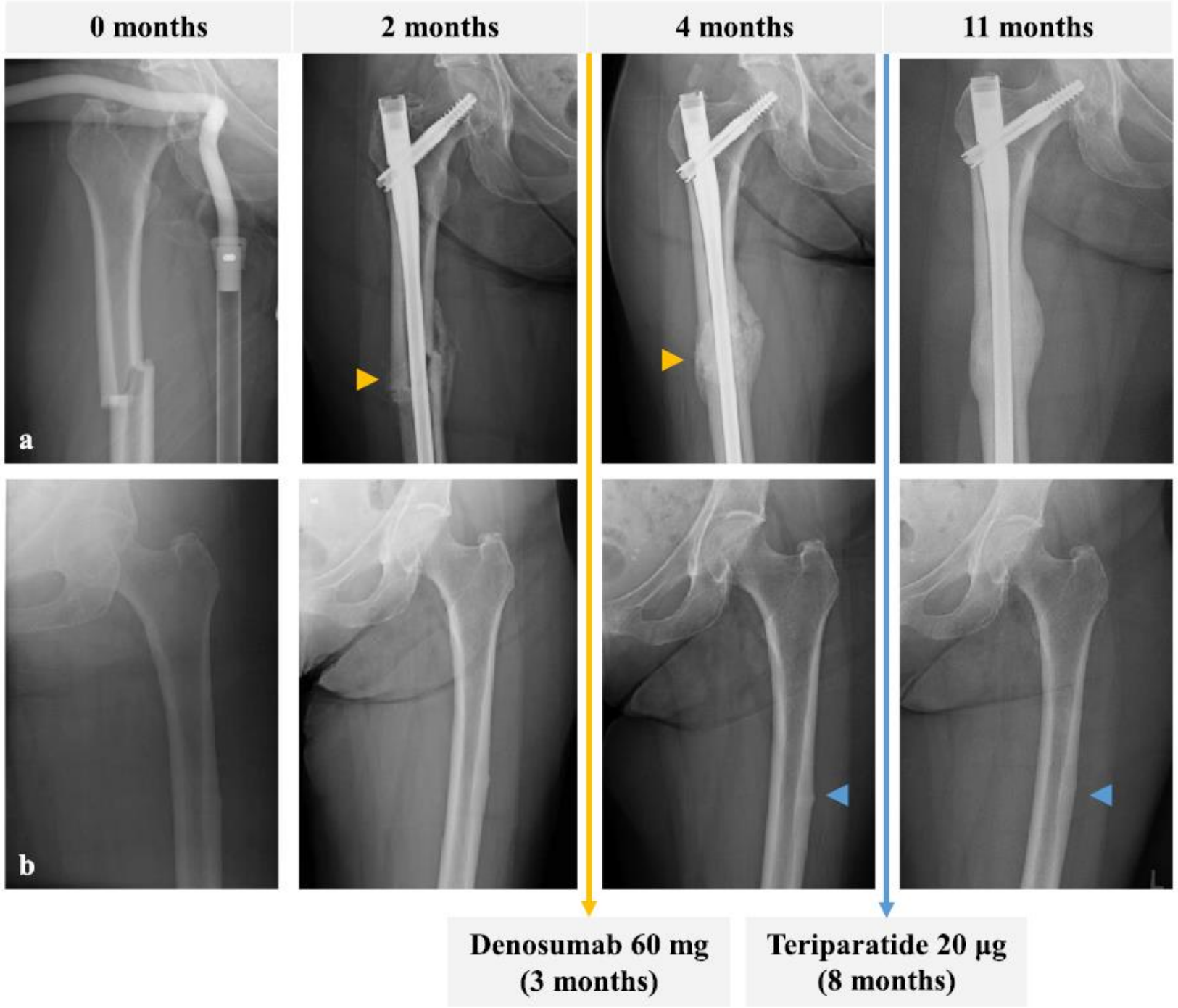
[a] Long School of Medicine, University of Texas Health Science Center at San Antonio, 7703 Floyd Curl Drive, San Antonio, TX 78229, USA
[b] Texas Diabetes Institute, University Health System, 701 S. Zarzamora Street, San Antonio, TX 78207, USA
[c] UT Health Medical Arts & Research Center, Department of Endocrinology, 8300 Floyd Curl Drive, 3rd Floor - 3A, San Antonio, TX 78229, USA

ABSTRACT

Background: Atypical femur fracture (AFF) is a clinically important complication of bisphosphonate (BP) use in the treatment of osteoporosis. The benefits of long-term BP therapy in preventing osteoporotic fractures have been shown to outweigh the risks of treatment. Discontinuation of BPs or "drug holidays" have been implemented as a strategy to reduce the risk of rare complications such as AFF.

Case report: We present the case of a 70-year-old postmenopausal woman who suffered bilateral AFF ten years after discontinuation of BP treatment. Management of this patient included fixation of the complete AFF with an intramedullary rod. A single dose of denosumab was administered prior to referral to endocrinology and seemed to contribute to callus formation. Denosumab was discontinued to prevent progression of the contralateral incomplete AFF. Teriparatide was indicated for the treatment of this patient's osteoporosis and also led to the resolution of the incomplete AFF.

Conclusion: Patients receiving long-term BP therapy should be periodically reevaluated in order to maximize the benefit and minimize the risk of treatment. Current research supports the implementation of drug holidays to decrease the risk of AFF; however, this case report confirms the need for continued monitoring after discontinuation of BP therapy. Additionally, our review of current literature highlights the need for more specific research regarding duration of BP treatment and drug holidays.


0 months
2 months
4 months
11 months
a
b
Denosumab 60 mg
(3 months)
Teriparatide 20 μg
(8 months)

Conclusion

- The true incidence of atypical femoral fractures is unknown
- Should be screened:
  - general population of patients without osteoporosis who are unexposed to BPs
  - patients with osteoporosis both exposed and unexposed to BPs and other agents used to treat osteoporosis
  - specific populations distinguished by concomitant drug exposures and comorbid diseases

Table 7. Information That Should Be Included in Future Reports of Atypical Femoral Fractures

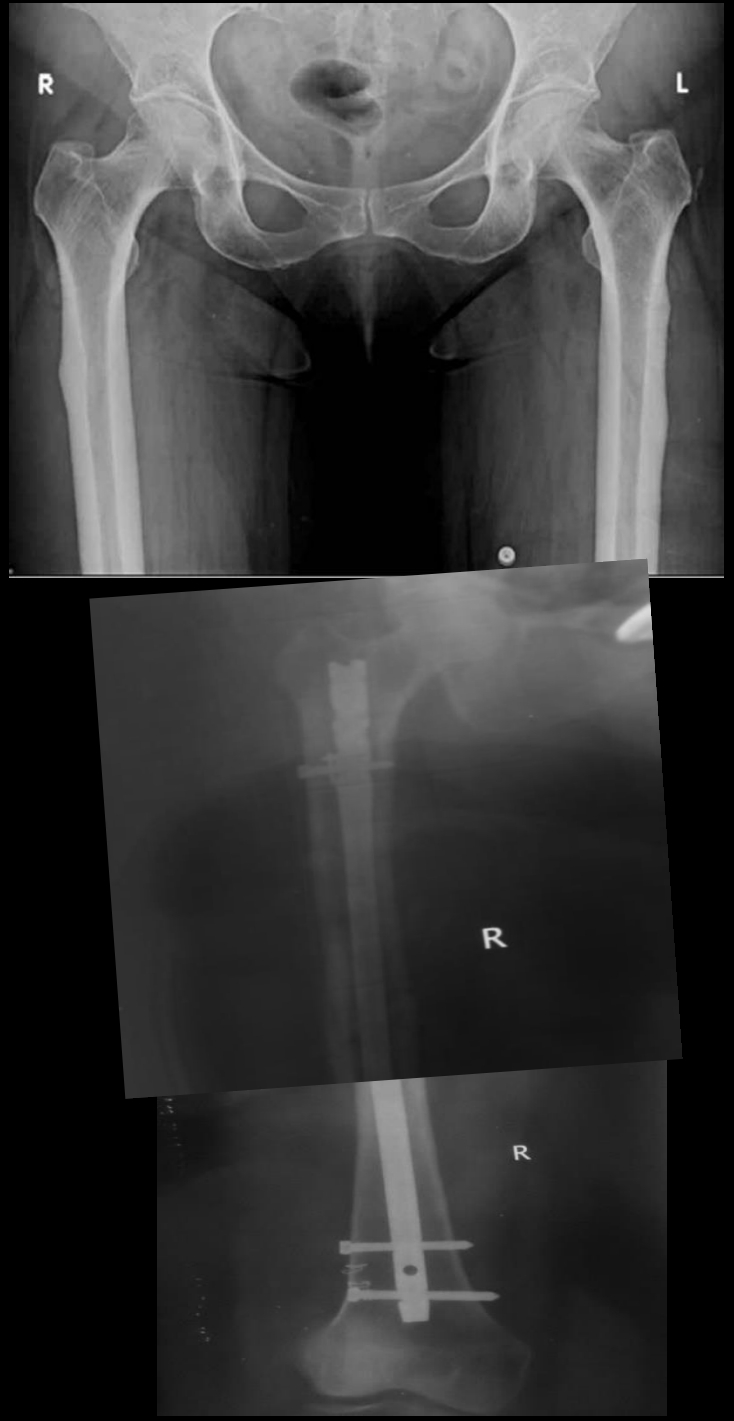
- Standard demographic data (age, gender, height, weight, race, ethnicity)
- Anatomic location of the fracture (subtrochanteric or diaphyseal)
- Key radiographic features of atypia (see Table 1)
- Information on osteoporosis therapies
  - Doses, routes, duration of, and adherence to osteoporosis therapy
  - Indication for therapy (eg, osteoporosis, osteopenia, bone loss prevention, cancer, Paget disease)
- Prior fracture history
- Concomitant medications: GCs, thiazolidenediones, PPIs, anticonvulsants, statins, HRT, SERMs
- Comorbid medical conditions: Diabetes, RA, chronic kidney disease, malabsorption, errors of phosphate metabolism, joint replacement
- Family history (for genetic studies)
- Bone mineral density: before treatment and at time of fracture
- Biochemistries
  - Serum calcium, creatinine, 25(OH)D, PTH
  - Biochemical markers of bone turnover (P1NP, osteocalcin, total or bone alkaline phosphatase, C-telopeptide)
- Surgical management of the fracture (intramedullary rod, locking plates): documentation of delayed healing

Conclusion

- The association between atypical femoral fractures and concomitant GC therapy is a concern
  - BP administration and GC-induced osteoporosis may increase the risk of atypical femoral fractures

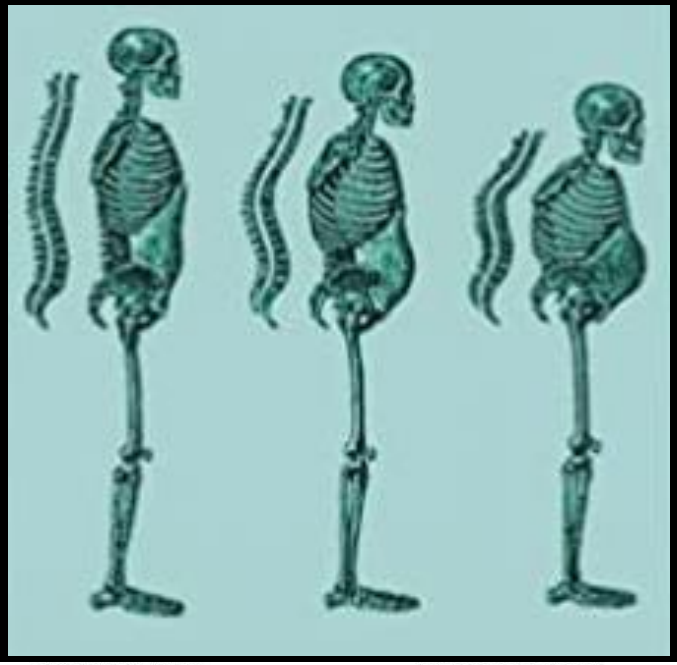
Conclusion

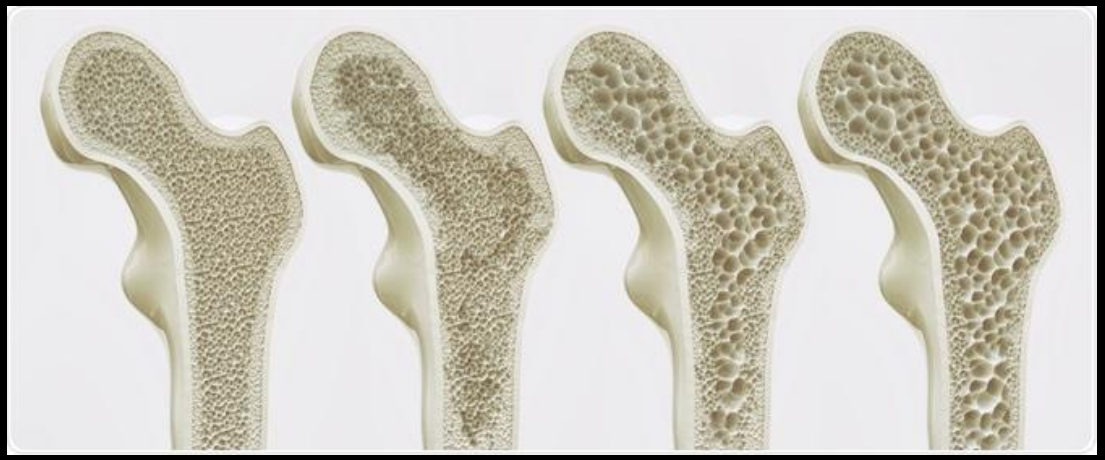
- Surgical treatment strategy
  - Thigh or groin pain in a patient on BPs
  - Bilaterality
- Conservative Tx
  - Incomplete fx, minimal pain
- Surgical Tx
  - IM nailing preferred
  - Minimally invasive
  - Endochondral healing

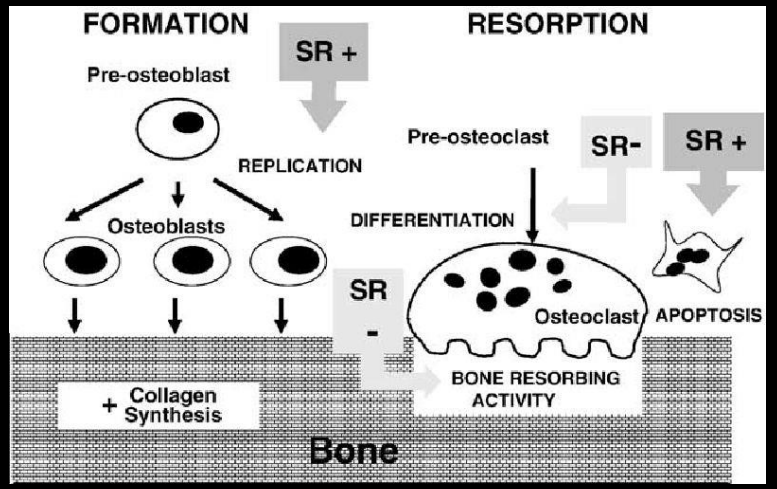


Conclusion

- Medical treatment strategy
  - No consensus
  - Individualize
  - TPTD, other BP, Denosumab, other







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