ΑΤΥΠΑ ΚΑΤΑΓΜΑΤΑ ΜΗΡΙΑΙΟΥ

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Ερευνητική Ομάδα C.O.RE / ΚΕ.Δ.Ε.Κ / Α.Π.Θ

ΑΡΙΣΤΟΤΕΛΕΙΟ ΠΑΝΕΠΙΣΤΗΜΙΟ ΘΕΣΣΑΛΟΝΙΚΗΣ

Atypical Femoral Fractures (AFF)

- *AFFs are Unusual Femoral Shaft Fractures*

  located between Lesser trochanter & Supracondylar area of femur,

  with minimal or no trauma.

- *The characteristic Absence of Warning Signs & Symptoms*

  in some patients, pose a Challenge, in Identifying patients at High risk.

- *In General population, there is no excess Mortality risk, related to AFFs.*

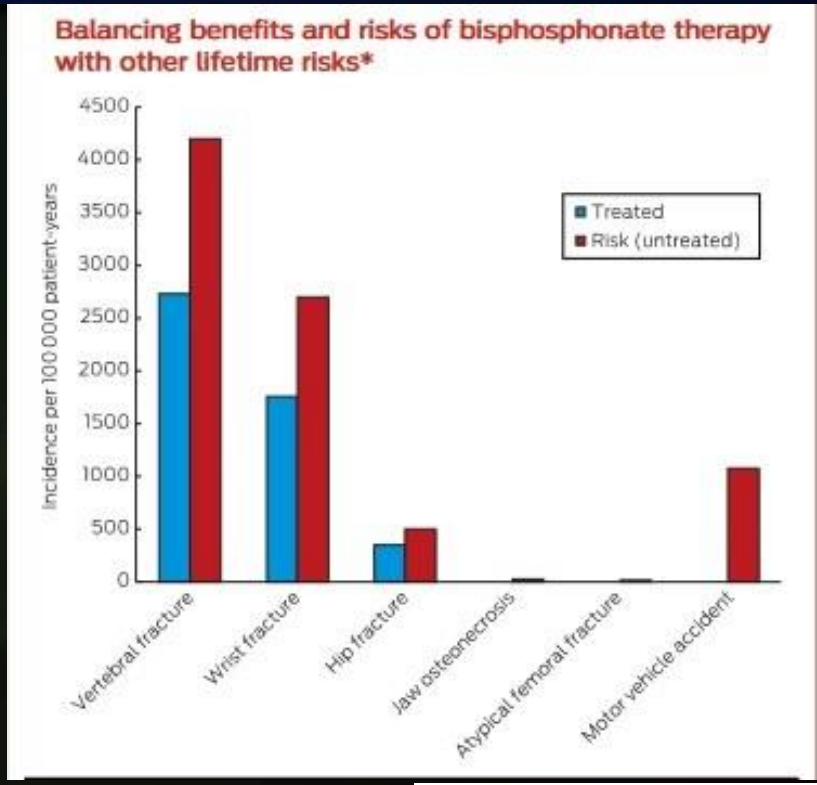
- *The Pathogenesis of AFF, remains Obscure.*

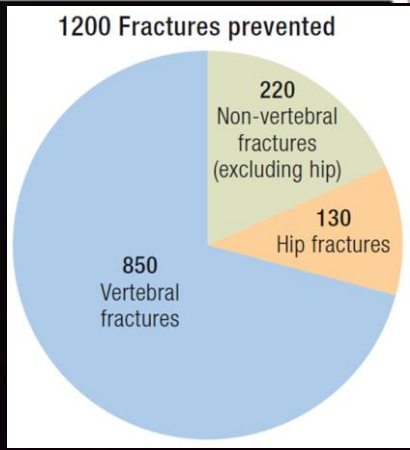
Risk for AFF with BP therapy

Divan V, Sudhaker D. Dhaliwal R & R. Curr Opin Endocrinol Diabetes Obes. 2019; 26(6):283-290
Qiu S, Divine GW, Palnitkar S, et al. Calcif Tissue Int 2017; 100:235–243
Kharazmi M, Hallberg P, Schilcher J, et al. J Bone Miner Res 2016; 31:491–497

Atypical Femoral Fractures (AFF)

- *AFFs are Extremely Rare & although Associated with BP's use (particularly long-term use), they are Much Rarer than the common HF & VF, that can be effectively prevented by BP's.*
- *The Absolute risk of AFFs in patients taking BP's, which ranged ~3.2 - 50 cases per 100,000 person-years for Short-term use (< 5y). However, Long-term use (> 5y) appeared to be associated with Higher risk ~ 113 cases per 100,000 person-years.*
- *The Benefit/AFF Risk ratio, for 3y to 5y of BP's use in Osteoporotic women, is Overwhelmingly positive: For each AFF caused by BP's, ~1200 FF: 130 HF, 850 VF, 220 N-VF, would be prevented.*





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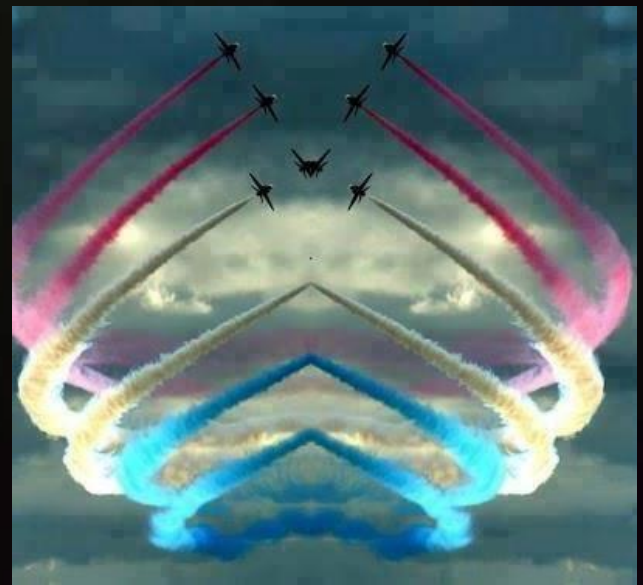
Factors associated with AFF

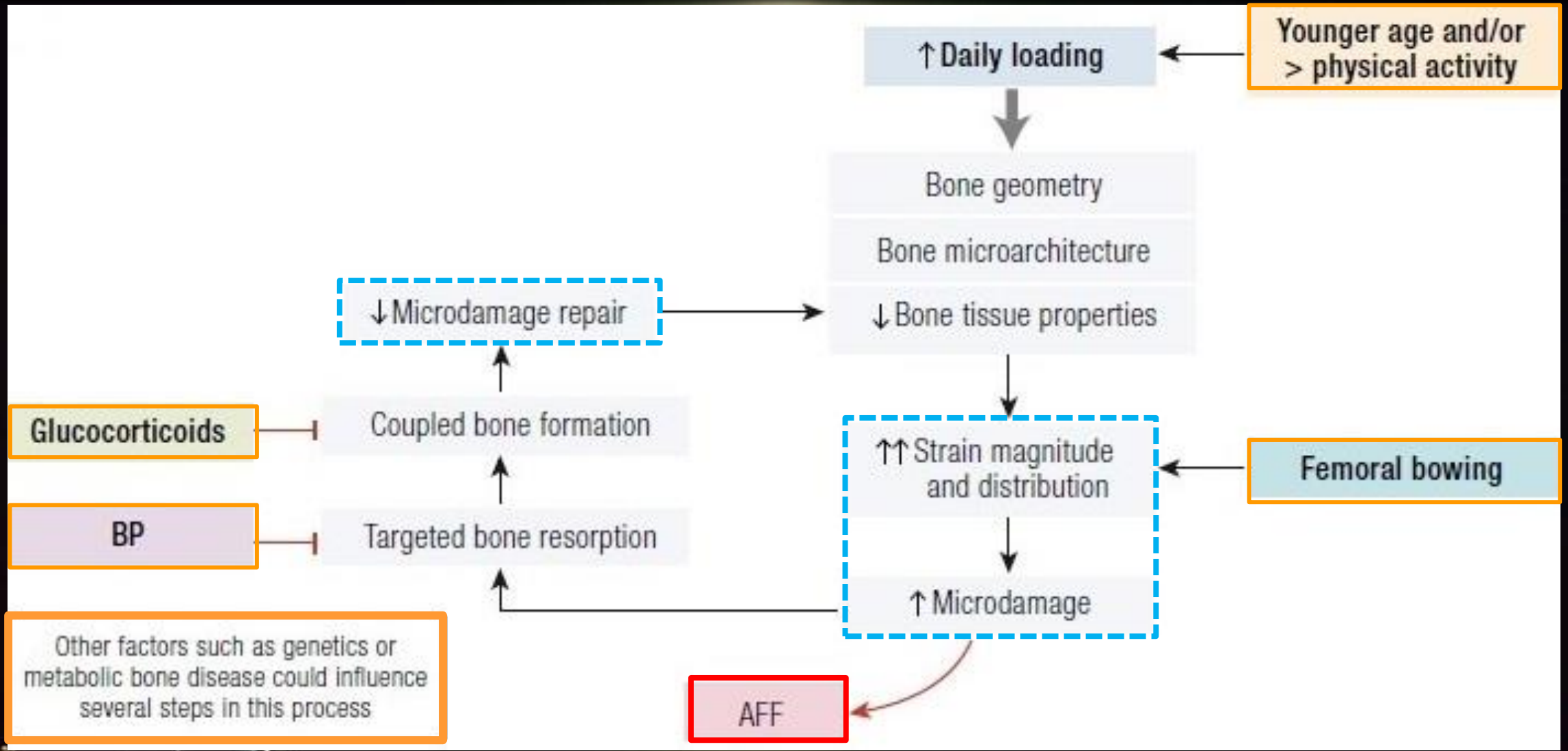
1. Long term BP's
2. Contralateral recent AFF
3. Femur geometry
4. Varus neck-shaft angle
5. Genu Varus
6. Genetic predisposition
7. Demographics
8. Sex: women
9. Race: Asian
10. Age: younger (<65y)
11. Medications other than BP's: Proton pump inhibitors, Glucocorticoids, High-dose vitamin D therapy (>50.000 IU daily), Medical conditions
12. Collagen diseases
13. Rheumatoid arthritis
14. Type-2 diabetes



Nguyen HH, van de Laarschot DM, Verkerk A, et al. JBMR Plus 2018;2:1–11
Roca-Ayats N, Balcells S, Garcia-Giralt N, et al. N Engl J Med 2017;376:1794–1795
LeBlanc ES, Rosales AG, Black DM, et al. J Bone Miner Res 2017;32:2304–2314

Possible Pathogenesis of AFF

Factors influencing the Accumulation & Repair of microdamage - may be related to the pathogenesis of AFF

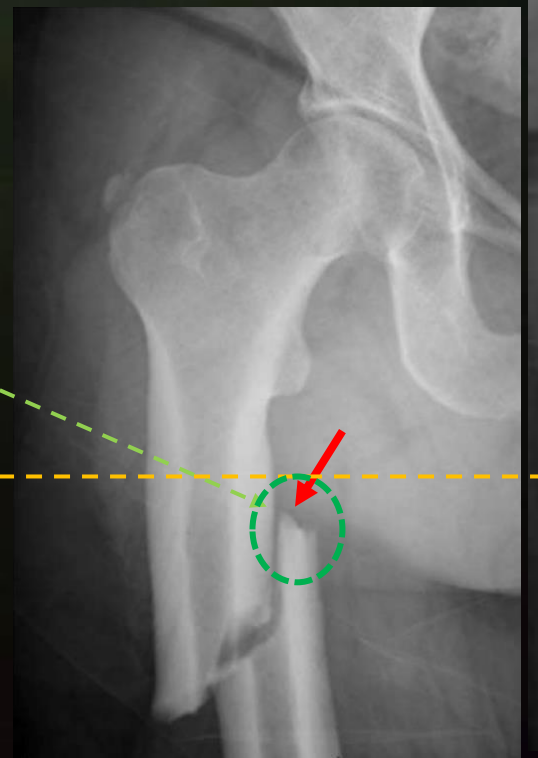


Black DM, Abrahamsen B, Bouxsein ML, Einhorn T, Nicola Napoli N. Endocr Rev. 2019 Apr 1;40(2):333-368
Bauer DC, Black DM, Bouxsein ML, Lui LY, Cauley JA, et al. J Bone Miner Res. 2018;33(4):634–642
Roca-Ayats N, Balcells S, Garcia-Giralt N, et al. N Engl J Med. 2017;376(18):1794–1795

ASBMR - Criteria for Case detection of AFF

Major Criteria

- 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 & is Substantially Transverse in its Orientation, although it may become Oblique as it progresses Medially across the femur.
- Complete fractures extend through both Cortices & 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").



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Shane E, Burr D, Abrahamsen B, Adler RA, et al. J Bone Miner Res. 2014;29:1–23

ASBMR - Criteria for case detection of AFF

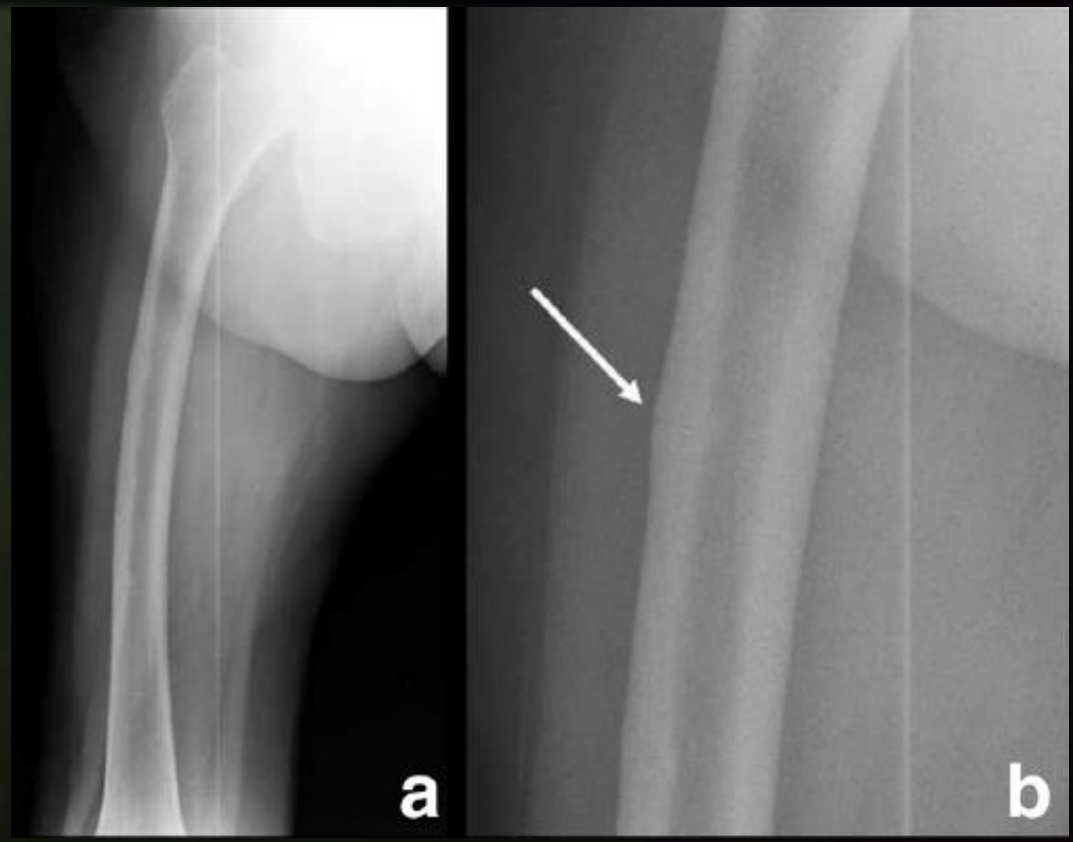
Minor Criteria

- 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.
- Delayed fracture healing.

ASBMR Criteria:

>> 4 of 5 Major criteria should be observed.

>> Additional, Minor criteria are not necessary for diagnosis, but could be Observed in association to the Major criteria.



a. Femoral bowing
b. The location of the fracture line on the lateral cortex
The focal cortical thickening at the fracture site

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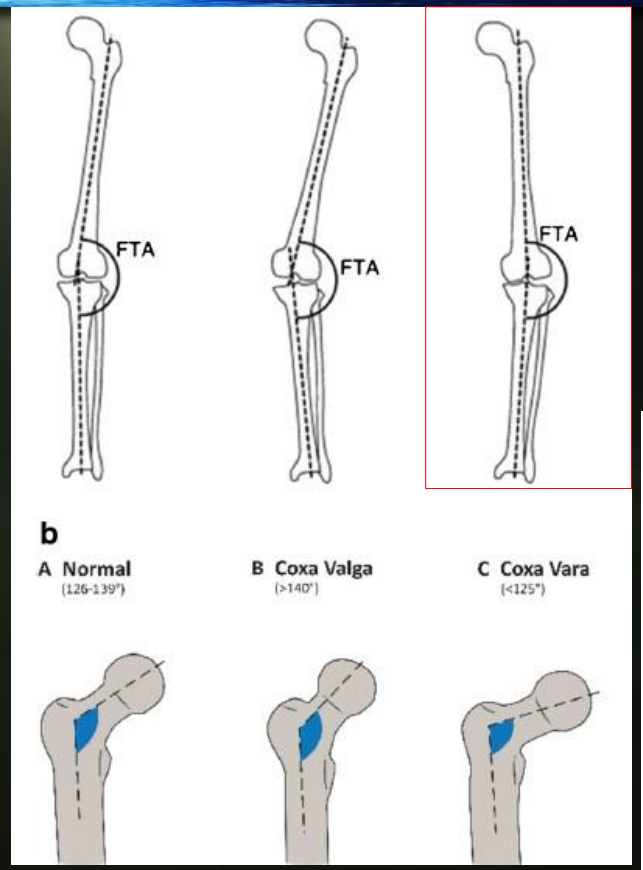
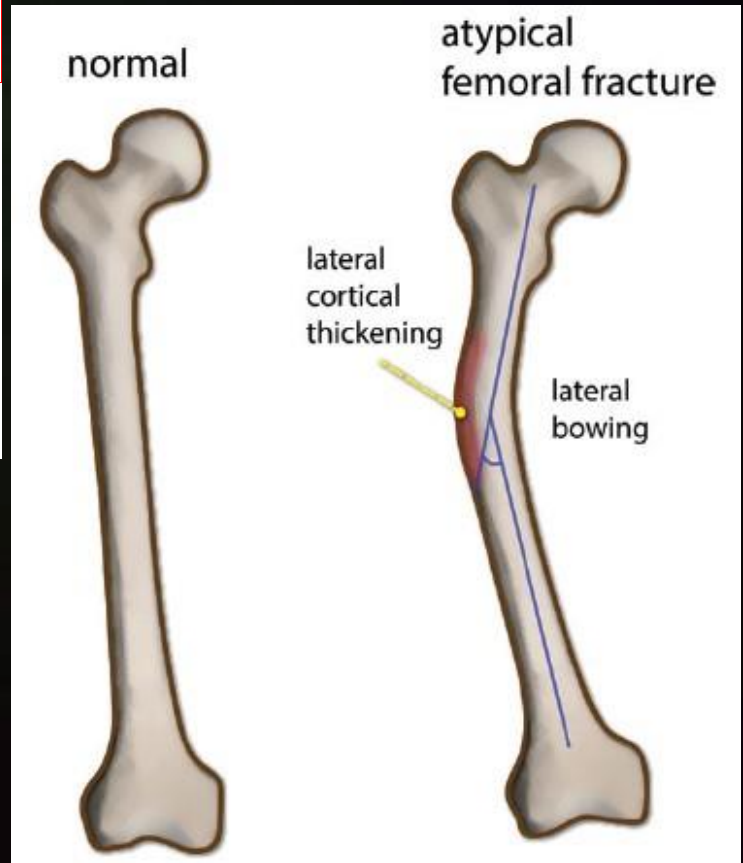
Shane E, Burr D, Abrahamsen B, Adler RA, et al. J Bone Miner Res. 2014;29:1–23

Relationship Between Hip Geometry & AFFs

- *There is increasing evidence that……*
  the Presence of a more Varus FemoroTibial angle (FTA) & Lateral Femoral Bowing, influences Mechanical forces on the Lower limb & the region of Maximal tensile loading on the Lateral femoral cortex.
- *Such Biomechanical factors may account, for the more Proximal Location of such fractures, in individuals with more Varus FemoroTibial angles.*
- *They may also predispose toward a higher rate of AFF, by increasing the Maximal tensile stresses imposed on the Lateral femoral cortex.*



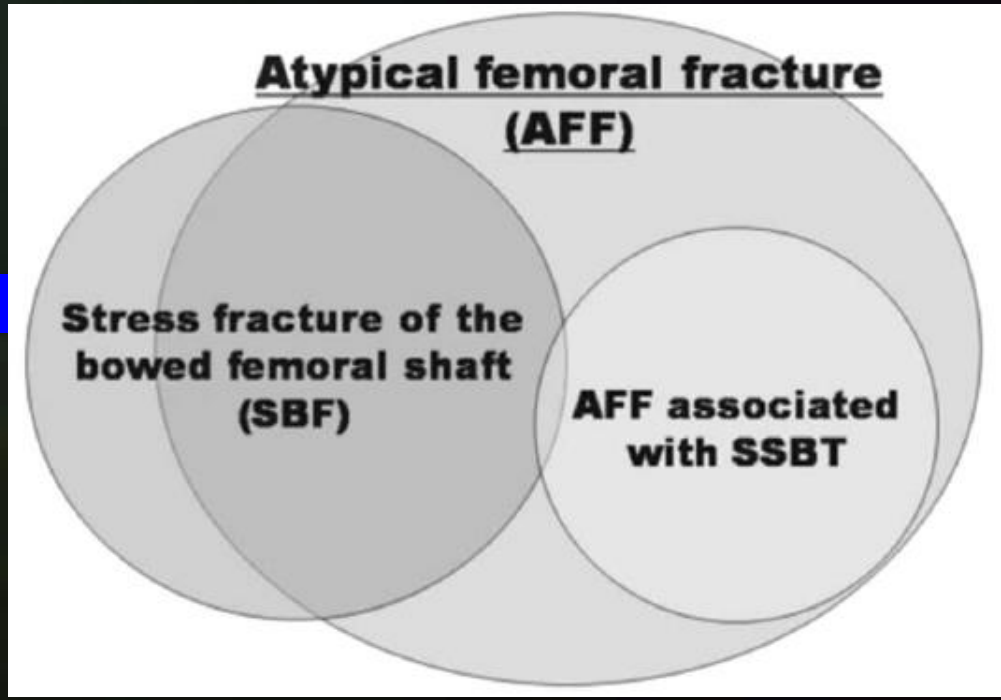


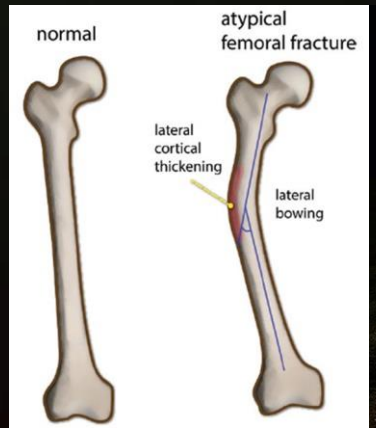
Haider IT, Schneider P, Michalski A, Edwards WB. Bone. 2018;110:295–303
Mahjoub Z, Jean S, Leclerc J-T, Brown JP, et al. J Bone Miner Res. 2016;31(4):767–776
Hagen JE, Miller AN, Ott SM, Gardner M, et al. JBJS. 2014;96(22):1905–1909

Stress fracture of the Bowed femoral shaft, is another cause of AFF…

- Cases with AFF are reported in the literature, Involved an AFF associated with a Bowed Femoral Shaft, but without BP's use.
- Also reported cases of Normal Bone Remodeling, in Low-energy Cortical fractures, during BP's administration.
- These findings indicate that, AFFs Occur by other Mechanisms in addition to Severe Suppressed Bone Turnover (SSBT).
- There is thought that, Bowing deformity should also be regarded as a Major cause of AFFs (SBFs) &

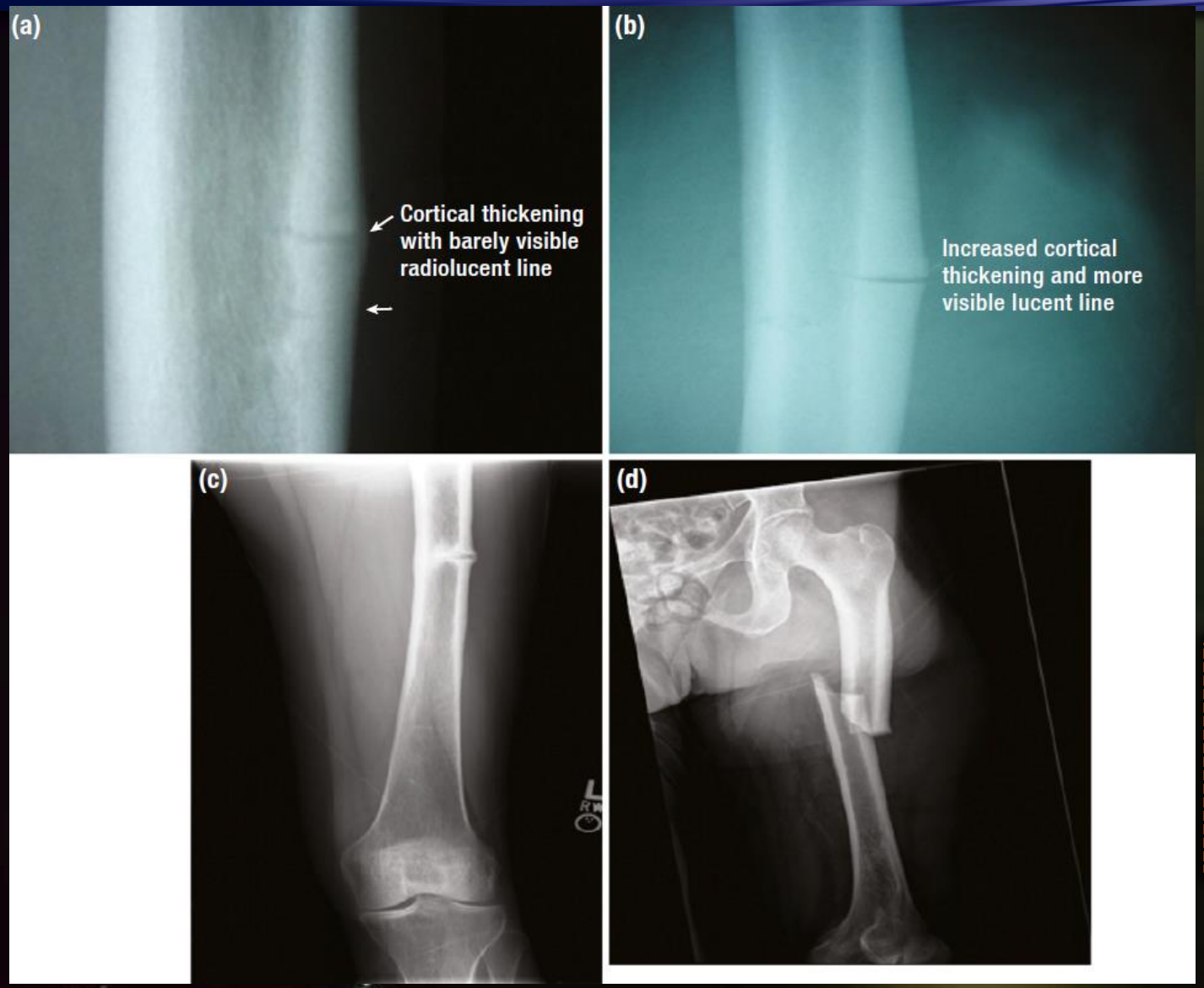
  Advocate that, Stress fractures of the Bowed Femoral Shaft (SBFs), should be distinguished from AFFs caused by SSBT.

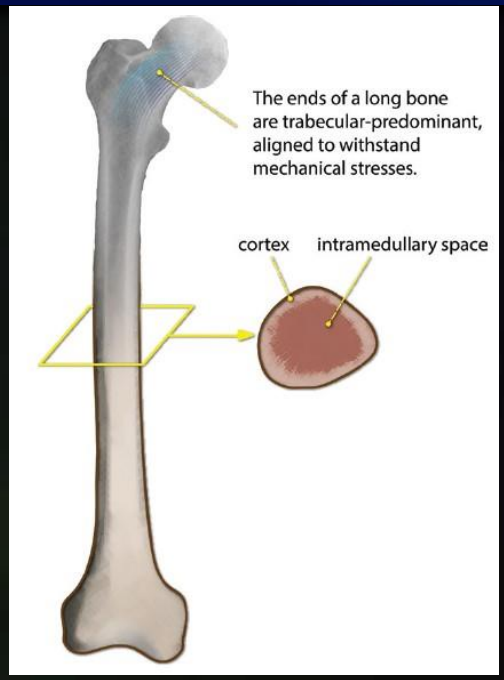




Toro G, Ojeda-Thies Cr, Calabrò G, et al. BMC Musculoskeletal Disorders 2016;17:227-239
Oh Y, Wakabayashi Y, Kurosa Y, et al. J Orthop Sci. 2014 Jul;19(4):579-586
Armamento-Villareal R, Napoli N, Diemer K, et al. Calcif Tissue Int. 2009;85:37–44

Progression Stages of an AFF





- *Cortical Thickening with barely visible Radiolucent line*
- *Increased Cortical thickening & more visible Radiolucent line*
- *Visible fracture in the lateral cortex with visible Radiolucent line*
- *Full AFF*

Black DM, Abrahamsen B, Bouxsein ML, Einhorn T, Nicola Napoli N. Endocr Rev. 2019 Apr 1;40(2):333-368
Hughes JM, Popp KL, Yanovich R, Bouxsein ML, Matheny RW Jr. Exp Biol Med (Maywood). 2017;242(9):897–906

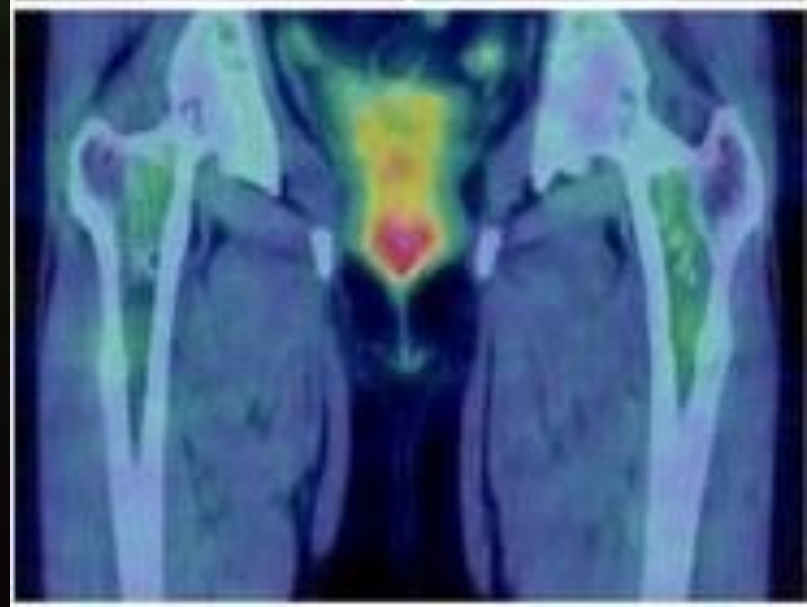
AFFs in Patients with Osteoporosis Managed with Denosumab

- *AFFs have been reported in Osteoporosis patients, receiving Dmab.*
- *AFFs have been reported in patients on Dmab, with brief prior BP's exposure.*
- *In the FREEDOM Trial open-label extension:*

  2 Participants developed AFFs (0.8 per 10,000 participant-years)

  1 after 7y of Dmab exposure

  1 after +3y of Dmab exposure

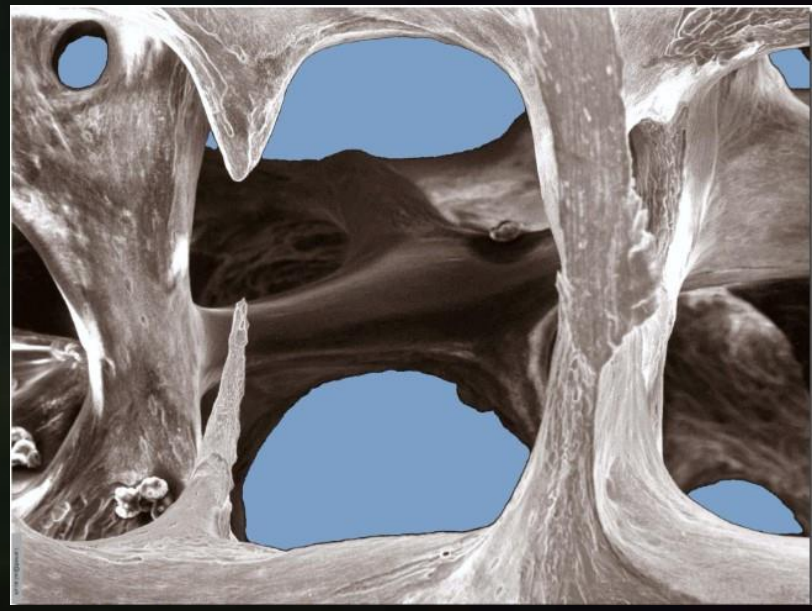


Starr J, Donovan Tay YK, Shane E. Curr Osteoporos Rep. 2018;16(4):519-529
Bone HG, Wagman RB, Brandi ML, Brown JP, et al. Lancet Diabetes Endocrinol. 2017;5(7):513–523
Selga J, Nunez JH, Minguell J, et al. Osteoporos Int. 2016;27(2):827–832

AFFs in Patients with Osteoporosis Managed with Romosozumab

- *In the Fracture Study of Postmenopausal Women with Osteoporosis (FRAME), 1 of 3521 participants in the Rmab group had an AFF after 3.5 months of exposure; that Individual had a history of prodromal pain at the fracture site prior to enrollment.*

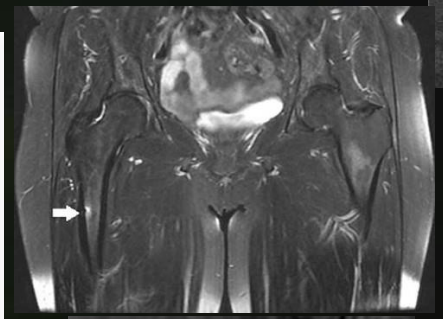
- *In the Active-Controlled Fracture Study in PM Women with Osteoporosis at High Risk (ARCH) study, 4093 PM Women with Osteoporosis & a FF, were randomly assigned to monthly Romosozumab or weekly oral Alendronate for 12 months, followed by open label Alendronate for another 12 months. There were no AFFs during in the initial 12 months in either group; In the second 12 months, 2 AFFs occurred in the Rmab to Alendronate group (< 0.1%) & 4 AFFs in the Alendronate to Alendronate group (0.2%).*

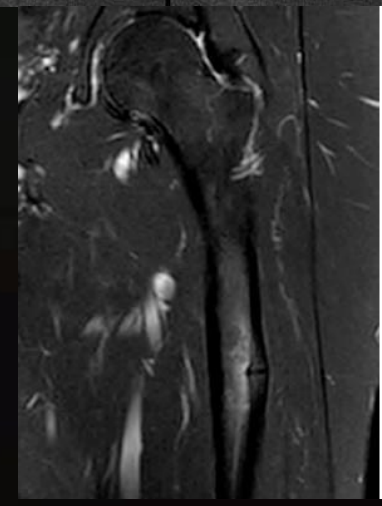


Saag KG, Petersen J, Brandi ML, et al. N Engl J Med. 2017;377(15):1417–1427
Cosman F, Crittenden DB, Adachi JD, et al. N Engl J Med. 2016;375(16):1532–1543

Imaging of AFF

- *Standard x-rays of the Femur in Anteroposterior & Lateral views, are usually able to Identify the Fracture & Describe its pattern.*
- *CT, MRI & other Imaging Modalities are of use, particularly in case of Incomplete AFF.*
- *CT is usually able to demonstrate Abnormal bone texture & Incomplete fractures.*
- *MRI is the most Sensitive & Specific imaging modality to identify Stress fractures (which present as an Increased Fluid Signal. Cortical thickening can also be observed in AFF).*
- *Bone Scintigraphy demonstrated a high Ability to early Individuate AFF (Mild Radiotracer Uptake with Endosteal Thickening, along the Lateral proximal diaphysis, is considered a relatively specific finding in these fractures)*

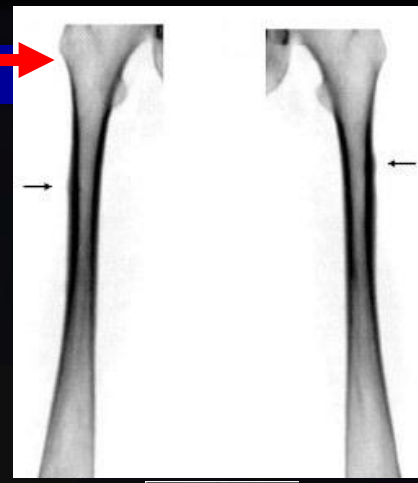


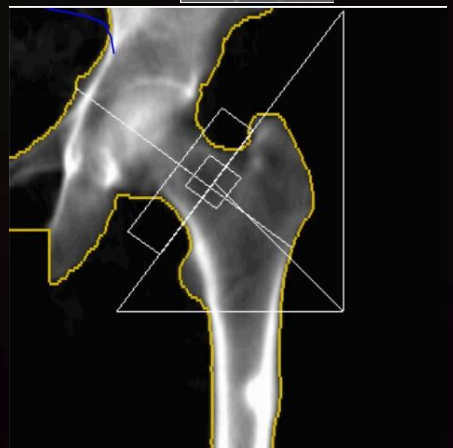


Cheung AM, McKenna MJ, van de Laarschot DM, et al. J Clin Densitom. 2019;22(4):506-516
van de Laarschot DM, Smits AA, Buitendijk SK, et al. J Bone Miner Res 2017;32:1632–1639
Tins BJ, Garton M, Cassar-Pullicino VN, et al. Insights Imaging. 2015;6:97–110

Imaging of AFF

- *DEXA scans could be useful for the early detection of AFF.*
- *Extended Femur DEXA is the Contemporaneous screening tool to detect AFF, in patients on prolonged Antiresorptive treatment. This method is easily incorporated in standard DEXA instruments, to extend the routine clinical scan, lower to Include Entire femur. The most common findings associated with AFF are: Focal Cortical changes both Periosteal & Endosteal.*
- *Newer Densitometers offer the ability to scan the entire femoral shaft.*
- *Although most AFFs occur in the proximal one-third of the femur >> Full-length Femur Imaging (FFI), from the lesser trochanter to the supracondylar flare, is the preferred DEXA mode to detect AFFs.*
- *A long femur scan at the time of routine DEXA in patients on prolonged BP's therapy is a simple means for the early detection of incomplete AFF.*
  This approach needs further Evaluation, before it could be considered as a routine procedure in at-risk patients on prolonged BP's therapy, at the time that they attend for DEXA.





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Focal Cortical Thickening

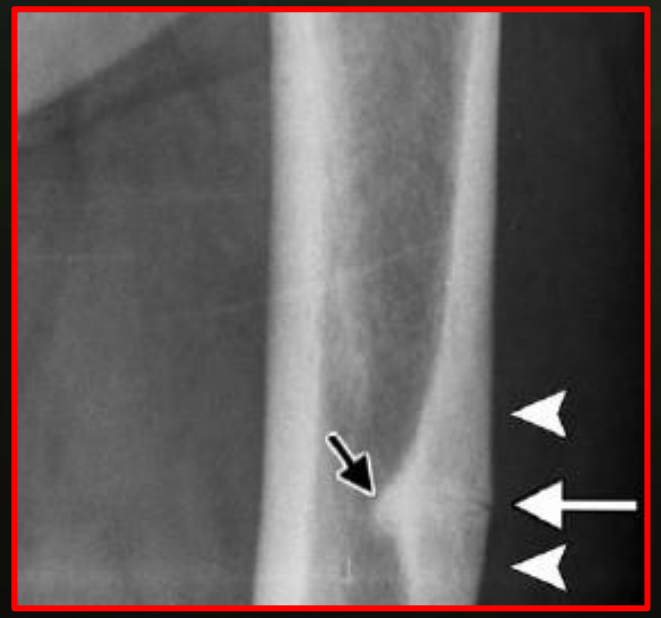
- *Seen on DEXA extended femur scan*
- *Confirmed by a radiograph*

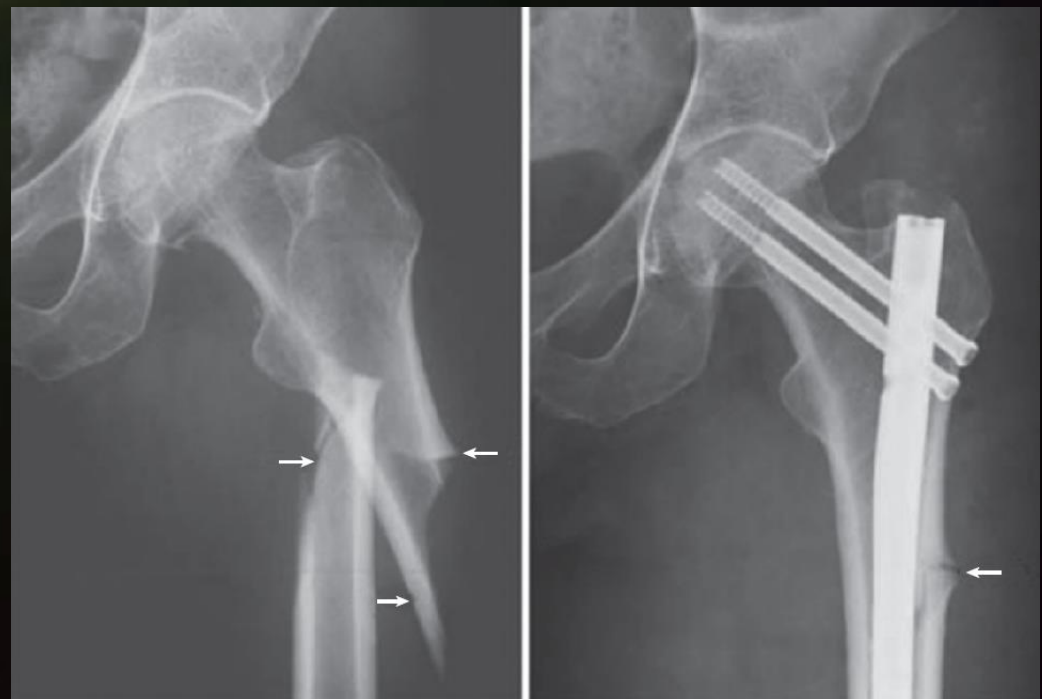
van de Laarschot DM, Smits AAA, Buitendijk SKC, et al. J Bone Miner Res 2017;32(8):1632–1639

Radiographic features of Incomplete AFF

Radiological Imaging:

- *"Beaking" in the Lateral cortex,*
- *Transverse fracture line,*
- *Cortical thickening in Lateral cortex.*





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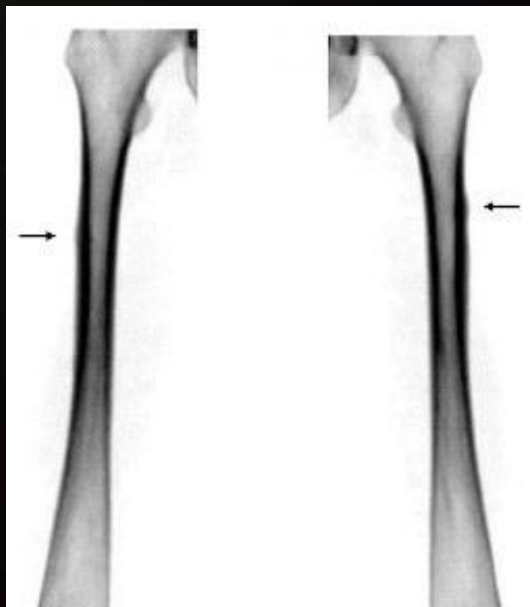
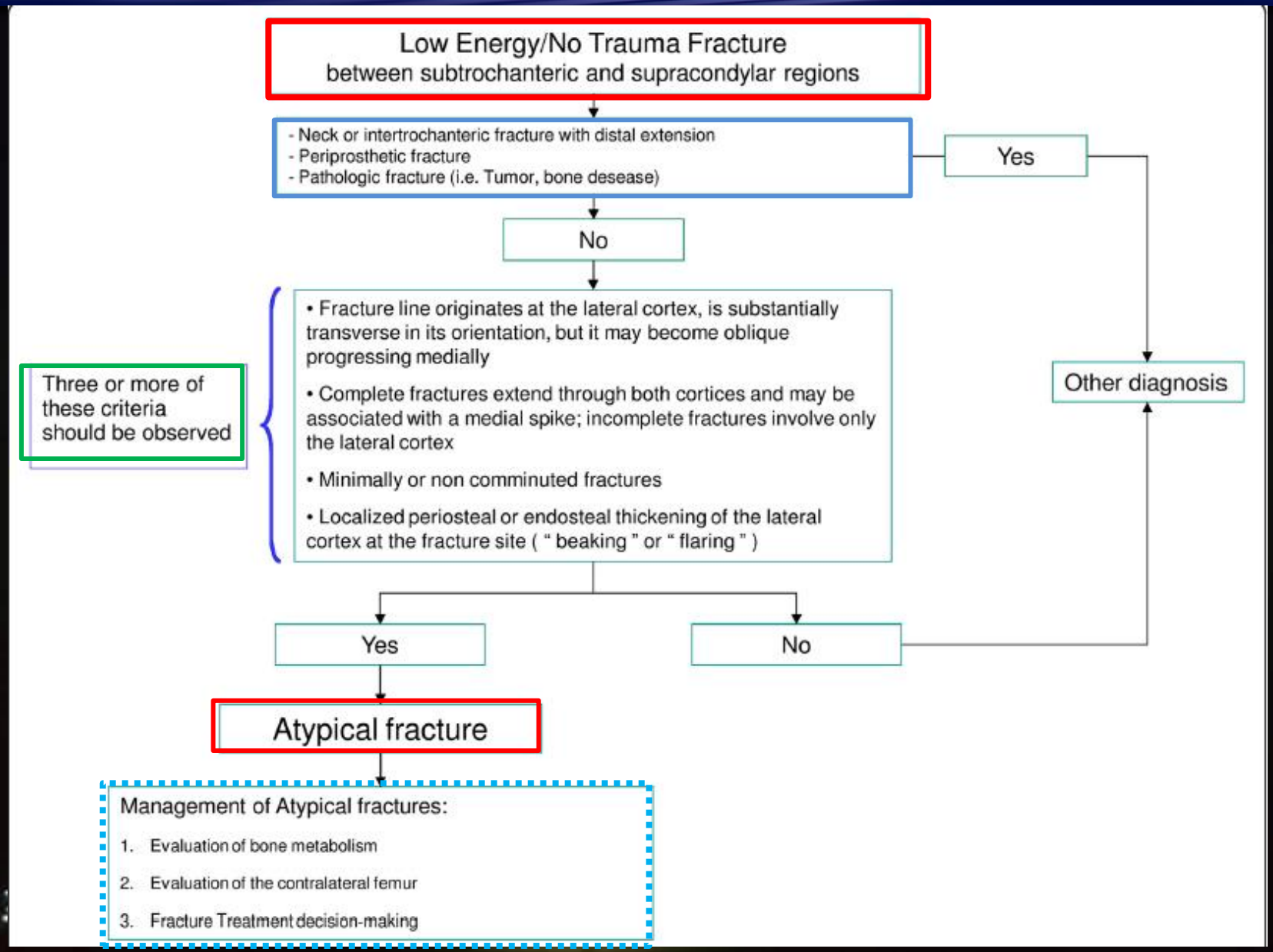
AFF - Making the Diagnosis

- ✓ *An Accurate Clinical history is Essential.*
- ✓ *The Circumstances surrounding the injury should also be Obtained.*
- ✓ *It is not uncommon for patients to report, that they Felt their fracture to Occur, before Falling.*
- ✓ *34% - 70% of patients Experience Pain in the groin or thigh, before injury.*
- ✓ *Patients should be Questioned about Pain in the Contralateral extremity because they may be experiencing similar prodromal symptoms on the uninjured side.*
- ✓ *The Radiographic characteristics of an AFF, are Unique & well Described.*



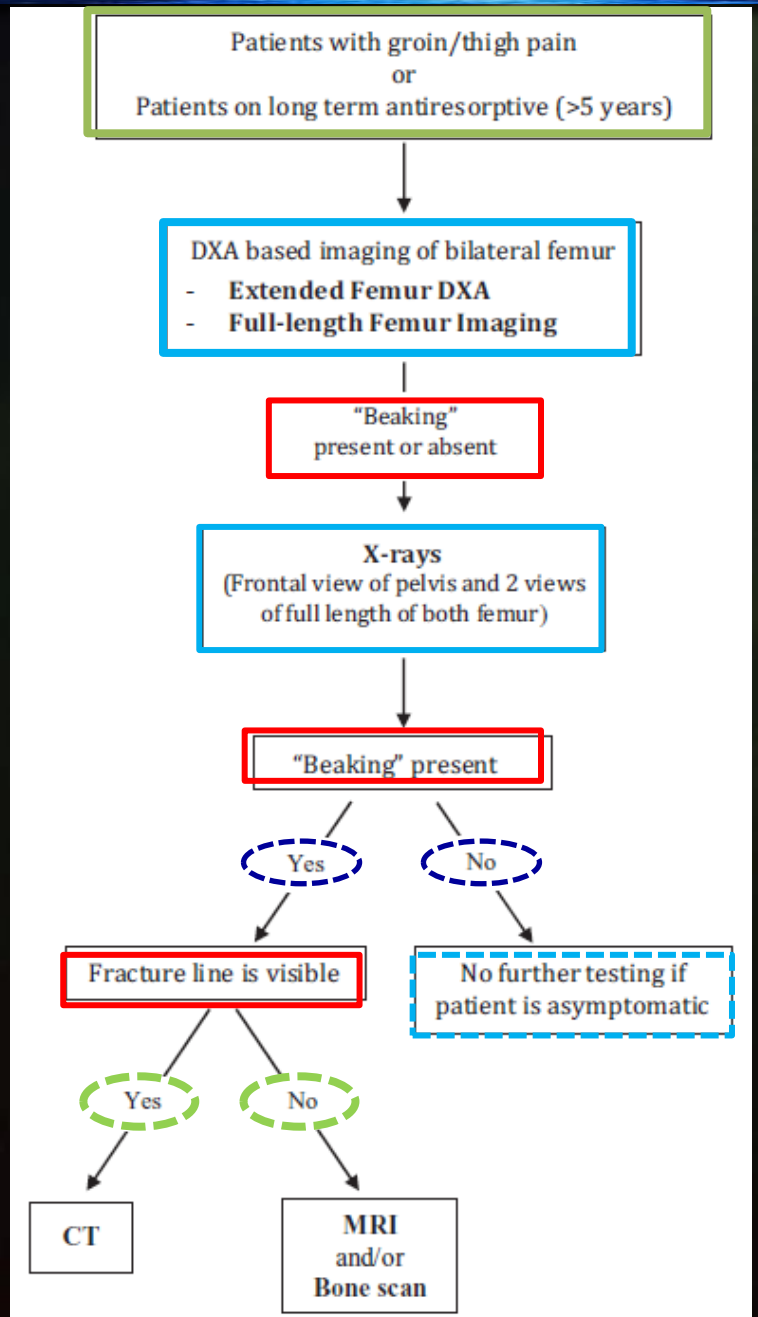
Githens M, Garner MR, Firoozabadi R. J Am Acad Orthop Surg. 2018 Dec 15;26(24):864-871
Black JD, Kancherla VK, De Long WG. J Orthop Trauma 2016;30:182-188
Bogdan Y, Tornetta P, Einhorn TA, et al. J Orthop Trauma 2016;30:177-181

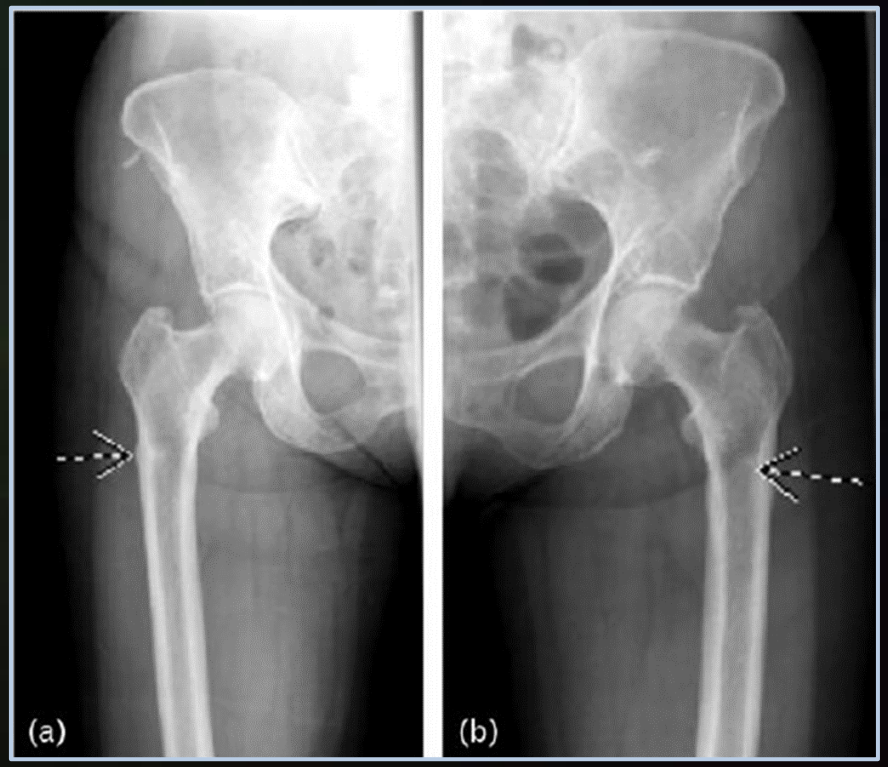
Diagnostic Algorithm for AFF



Toro G, Ojeda-Thies Cr, Calabrò G, et al. BMC Musculoskeletal Disorders 2016;17:227-239

Algorithm for Assessment of AFF





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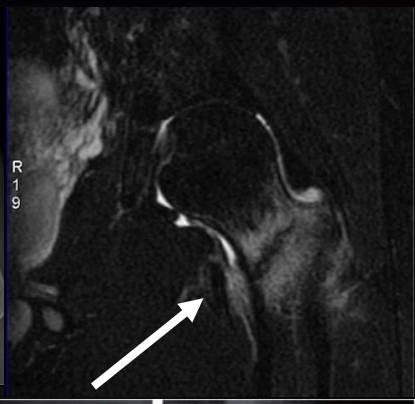
van de Laarschot DM, Smits AA, Buitendijk SK, et al. J Bone Miner Res 2017;32:1632–1639
Adams AL, Xue F, Chantra JQ, et al. Osteoporos Int 2017;28:413–417

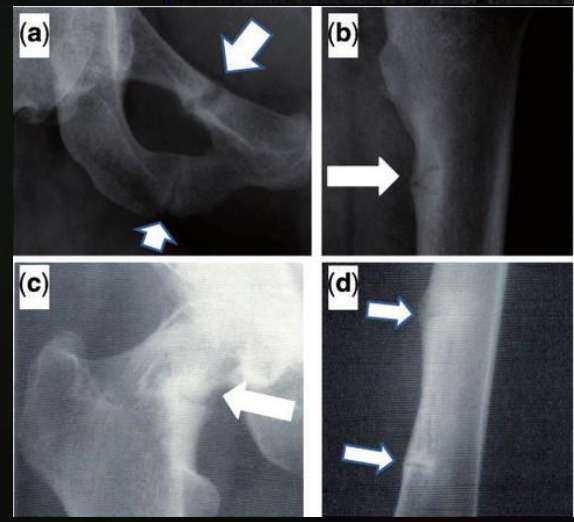
Differential diagnosis of AFF

- Differential diagnosis of AFF includes: Stress fracture of Proximal femur, Osteomalacia (Vit-D deficiency), Hypophosphatasia, Pathological fracture.
- Stress fracture of the Proximal Femur: Can also occur below the Lesser trochanter & typically begin at the Medial cortex, unlike AFFs which almost always Involve Lateral cortex.
- Looser Zones of Osteomalacia (because of Vit-D deficiency): Also observed in the Medial cortex.
- Stress fractures in Hypophosphatasia may mimic AFF, but can Involve either Medical or Lateral cortex.
- As AFF on one Side increases the risk of AFF on Contralateral side, plain radiographs of contralateral side, should be obtained to detect Incomplete or Impending AFF. Additional Imaging should be considered in Symptomatic patients with a History of BP's use, in whom plain radiographs are nondiagnostic. Further imaging studies should also be considered, to confirm the findings from plain radiographs or DXA, as not all focal thickenings on X-ray or DXA, Represent AFF.

SFF



LZO

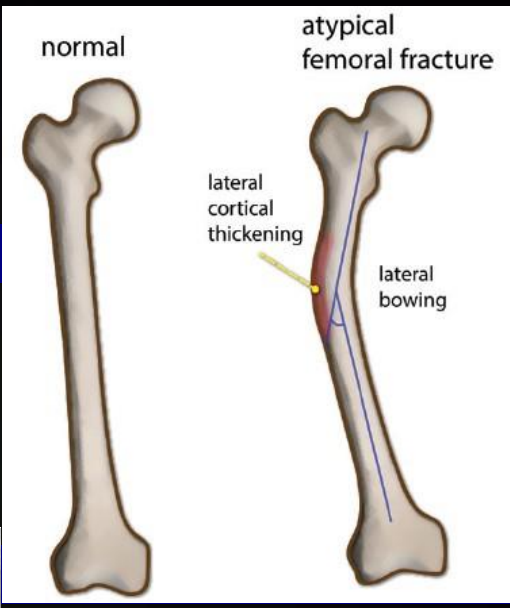


SFH

Cheung AM, McKenna MJ, van de Laarschot DM, et al. J Clin Densitom. 2019;22(4):506-516
Petraszko A, Siegal D, Flynn M, et al. Skeletal Radiol 2016; 45:615–623
Meier RP, Perneger TV, Stern R, et al. Arch Intern Med 2012; 172:930–936

AFF - Treatment

- When an AFF is identified, Screening of the Contralateral Hip & entire Femur is recommended with AP & Lateral radiographs, because up to 44% of patients demonstrate a fracture in the Contralateral femur either at the time of the fracture or in subsequent years.
- Bone scanning or MRI should be favored whenever the patient presents with clinical features associated with AFF, such as thigh or groin pain.
- Conservative treatment can be considered, in patients with Incomplete AFF with minimal or absent groin or thigh pain.
- Other Imaging features, that may raise the risk of Progression & Suggest the need for possible Surgical treatment are:
  - (a) The presence of a Radiolucent line in the Lateral Cortex,
  - (b) Fracture in the Subtrochanteric location,
  - (c) Deformity or Bowing of the femur,
  - (d) The presence of a Current or Prior Contralateral AFF,
  - (e) The Absence of Healing, at short-interval follow-up imaging



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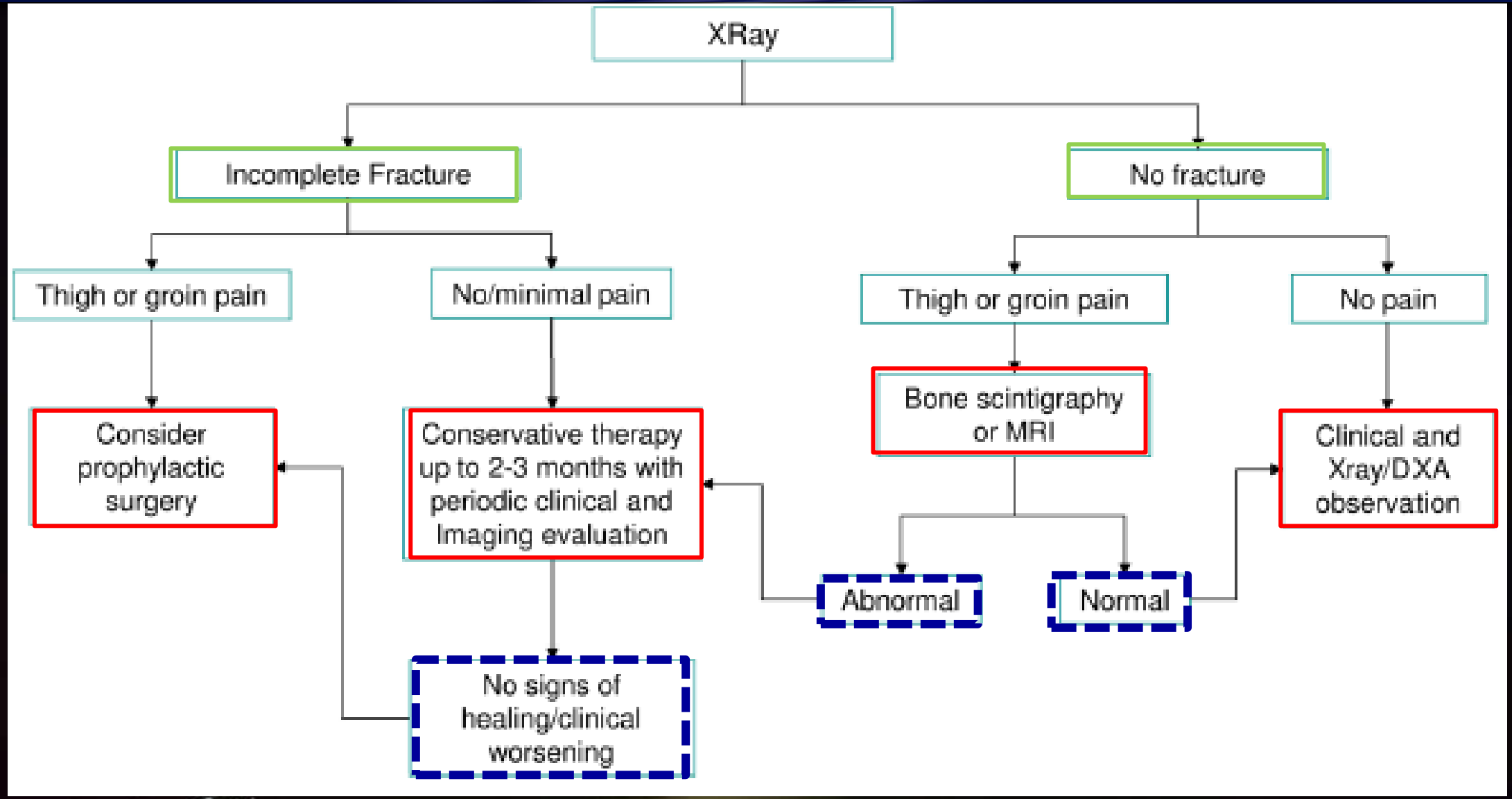
Evaluation of the Contralateral femur



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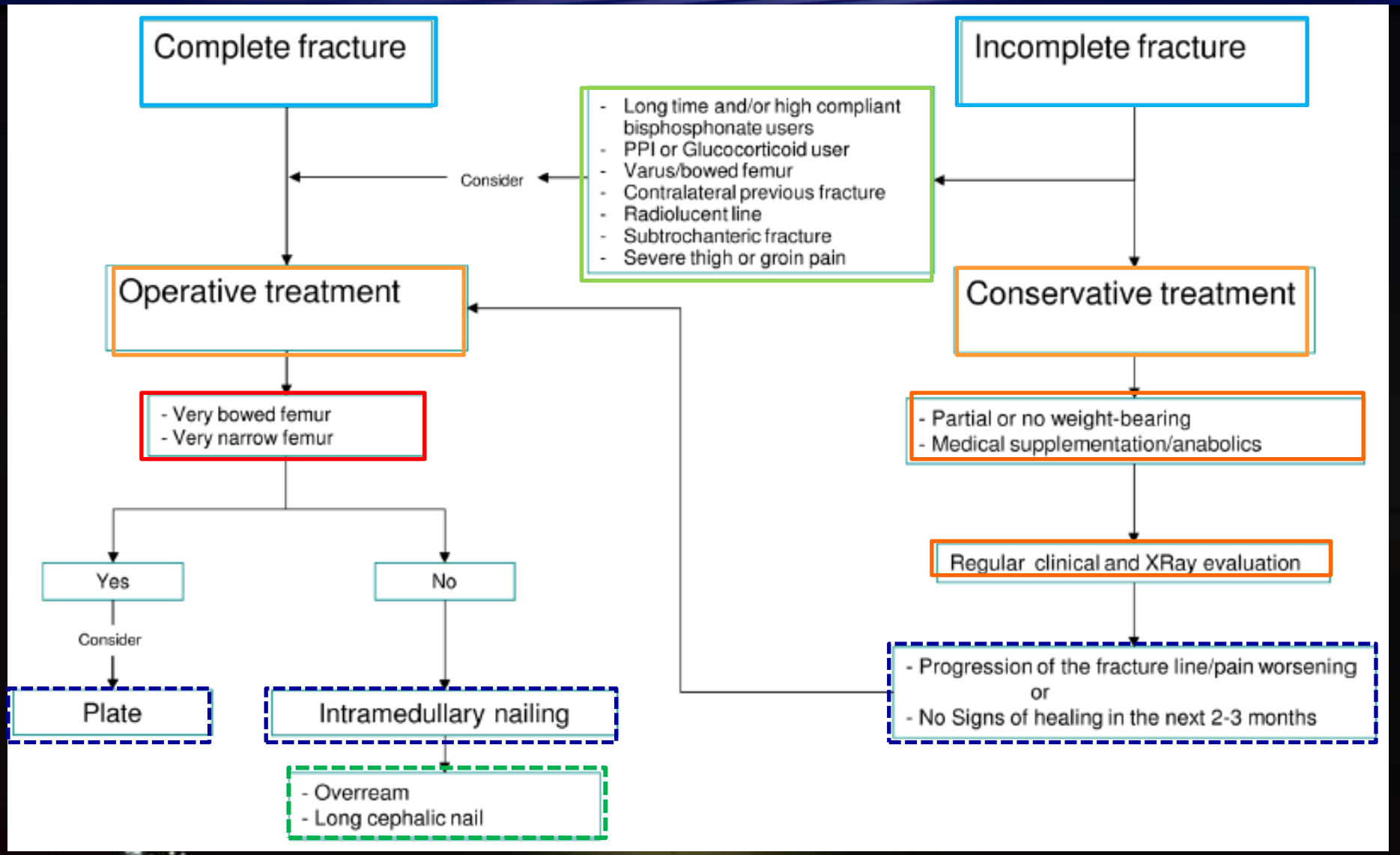
AFF: Fracture Treatment decision-making



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AFF - Surgical Strategy

- *Surgical Management of BP's associated AFF, should be approached with Cautious & Thoughtful Planning.*
- *The Primary Surgical Goal is: Restoration of Length, Alignment, & Rotation of the femur.*
- *Additional steps including: Open reduction, Fracture bed preparation, Interfragmentary compression & Bone grafting or other Biologic Augmentation, may be taken to Enhance fracture healing.*
- *Canal diameter, Location, & Size of the IM Sclerotic pedestal, Presence of existing implants & Femoral geometry…… will Influence Implant choice & Surgical strategy.*
- *Cephalomedullary nails (γ-nail) are preferred over Standard nails, to prophylactically protect the femoral neck from future fracture.*
- *Short IM nails should not be used (Long γ-nails).*

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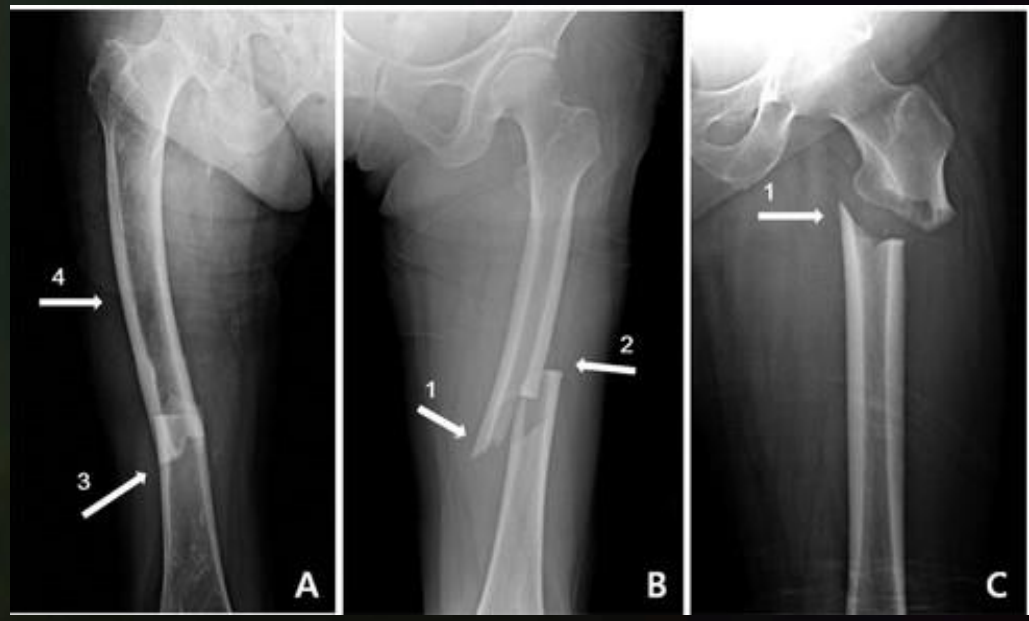
AFF – Surgical Treatment Guidelines

- *The decision to proceed to Prophylactic Surgery for an Incomplete fracture should depend on several factors including:*
  - *>> The presence of Bilateral disease,*
  - *>> Persistent pain & a Previous fracture on the Opposite side.*
  - *>> If a patient is Asymptomatic, Prophylactic surgery may not be justified.*
- *The presence of a Radiolucent line, is important to differentiate between Symptomatic Incomplete fractures, that do or do not respond to non-operative treatment.*
- *If Pain is minimal, for an Incomplete femoral fracture, without a Radiolucent fracture line, non-operative management with Anabolic agent (TPTD), can be tried initially.*



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Prevention of AFF - Drug holiday

- *Both the Swedish & Kaiser Permanente Southern California studies showed 70% & 44%–80% Reduction respectively in AFF risk, 1–4y after Cessation of BP's.*
- *The ASBMR Task Force, Recommends Risk Reassessment after 3y of IV BP & 5y of oral BP use.*
- *Nevertheless, during 'Drug Holiday', there should be ongoing risk assessment, for both AFF & Osteoporotic fractures.*
- *In general, Indications for Continued use of BP's, should be reviewed at every clinical follow-up & at minimum every 2y, when patient undergoes BMD assessment.*

Would you benefit from a drug holiday?

To prepare for a visit with your doctor, weigh the following factors.

How long have you been on treatment?	0-2 yrs	3-4 yrs	5+ yrs
What was your fracture risk before you started taking the drug?	Low	Moderate	High
What is your fracture risk now?	Low	Moderate	High
What is your bone density?	Normal	Low bone mass	Osteoporosis
Have you broken a bone?	No		Yes

Should you take a holiday?	Yes	Maybe	No

*More answers in the **GREEN**: You could probably benefit from a drug holiday.*
*More answers in the **RED**: You probably should stay on treatment.*
*More answers in the **YELLOW**: You'll want to discuss carefully with your doctor.*

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Treatment of Osteoporosis in patients with AFF

- *Long-term treatment of Osteoporosis in patients diagnosed with AFF is particularly challenging, because of Limited options to treat osteoporosis after discontinuation of BP's.*
- *Anabolic agent (TPTD) is the Recommended Treatment of Choice, but Osteoanabolic use is approved only for 2y & requires bridging with Antiresorptive after 2y.*
- *However, the use of BP's or Dmab, in a patient with AFF, few years after initial discontinuation of these drugs, has not been studied yet.*
- *Serum bone turnover markers (BTM) around the time of AFF, are susceptible to misinterpretation, because of expected increase in bone turnover.*
  The role of BTM in Resuming treatment for osteoporosis, after complete healing of AFF, is debatable, although an increase in BTM might be used in this decision-making.
- *The Combined Assessment of BMD & BTM may be used to guide decision-making.*
  There is no evidence to inform, how the use of any of these medications following AFF, relate to Future fractures, Functional outcomes or Survival rates.

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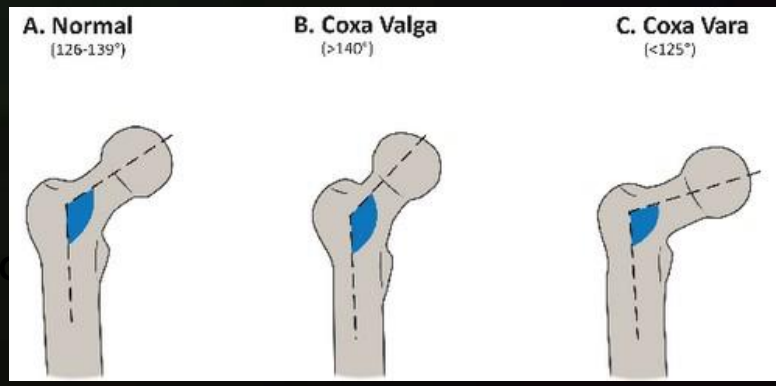
CONCLUSIONS(I)

- *AFFs have been associated with BP's & other Osteoporosis medications, but they also occur in Treatment-naive patients.*
  They are Rare, particularly compared with the HF & other FF, that BP's can prevent.
- *AFFs is perhaps the Largest Factor responsible, for the Large Decrease in use of BP's & other Antiresorptive medications since 2007 (creating the Osteoporosis "Treatment Gap").*
- *The diagnosis of AFF should be made, according to ASBMR criteria.*
- *It is generally Recommended that when Incomplete AFF are visualized, Antiresorptive medications should be stopped & in more serious cases, Prophylactic surgery should be considered.*
- *Complete AFF should be treated with Stable fixation, Avoiding fracture gaps & Restoration of Anatomical neck-shaft angle.*



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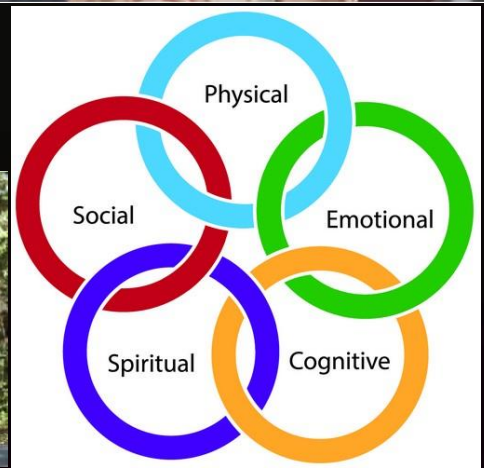
CONCLUSIONS(II)

- *Temporary "Drug Holidays" after 3-5y of therapy, are Appropriate for BP's, especially for ALN after 5y & Zoledronic acid after 3y, in patients at Low risk of AFF.*
- *There are some data showing that discontinuation Decreases AFF risk, & thus use of "Drug Holidays" could likely Enhance the benefit/risk balance, for a longer-term Treatment course, for Osteoporotic patients.*
- *However, Discontinuation for other Antiresorptive medications, (including Dmab, RAL or Estrogen), Results in Rapid Loss of benefits & should be followed by some sort of Continued therapy.*
- *Anabolic therapy is Approved for up to 2y & should be followed by an Antiresorptive drug, to Retain benefits.*
  More Research about the Impact of Temporary "BP Drug Holidays" on AFF risk is needed…….
- *In conclusion, AFFs are Rare, but remain a Catastrophic event for some patients. The benefit/risk ratio, is clearly in favour of BP's & Other Treatments, in patients at High FF risk.*

The Age Gap / Global average



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Thank you for your attention