Atypical Femoral Fractures
Insights and Enigmas

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Abreviations used

- TFF- Typical femoral fractures
- AFF- Atypical femoral fractures
- BPO- Bisphosphonate
- PMO- Postmenopausal osteoporosis
- FX- Fracture
- Bx- Biopsy
- HR- Hazard Ratio
Need for discussion

- Widespread use of BPO, millions of patient years of exposure over 4 decades
- Substantial reduction (30–50 percent) in “Typical osteoporotic fractures”
- Long standing concern about diminished bone turnover/diminished bone strength. “Frozen bone concept”—ONJ, microcracks
- Reports only since 2005 on “Atypical Femoral FX”
  - Is it a new entity or rare osteoporotic fracture, should we be concerned?
Sites of Femur fracture

- Femoral neck
- Intertrochanteric
- Subtrochanteric
- Femoral shaft or diaphysis
## Fractures in PMO-Differential features

<table>
<thead>
<tr>
<th>Typical femoral fracture</th>
<th>Atypical femoral fracture</th>
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<tbody>
<tr>
<td>Associated with fall- 95 %</td>
<td>No fall</td>
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<tr>
<td>No prodrome</td>
<td>Prodromal thigh pain</td>
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<tr>
<td>Reduction( 30-50% ) with effective BPO therapy</td>
<td>Often associated with BPO/Steroid use</td>
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<tr>
<td>Located at or above the trochanter -95 %, Can be comminuted, 5% diaphyseal</td>
<td>Below the intertrochanteric line, prox. Shaft of the femur, non-comminuted</td>
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<td>Generally spiral, could be transverse</td>
<td>Transverse with a medial spike</td>
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<td>Generally unilateral</td>
<td>U/L or B/L</td>
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<tr>
<td></td>
<td>Increased femoral cortical thickness</td>
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</tbody>
</table>
Typical intertrochanteric fracture
Typical Femoral neck fracture
Typical Communityed femoral shaft fracture
Atypical B/L Transverse Femoral fracture with cortical hypertrophy
Atypical Transverse Femoral midshaft fracture

diffuse periosteal new bone formation
focal cortical thickening
AFF
Diagnostic Modalities

Plain x-ray

Radionuclide scanning

MRI

Dexa Scan
Body of evidence for AFF

- Small, not based on prospective randomized clinical trials
- Histomorphometric data
- Retrospective Analysis from BPO clinical trials
- Analysis from register based national Cohort study
Histomorphometry

- Iliac crest bone biopsies
- No significant biopsy data available from actual fracture site
- Conflicting bone biopsy reports
Histomorphometry

- Odvina et al-2005,
  - Bone bx reports on 9 pts with unusual fracture
  - Fosamax for 3-8 yrs
  - Delayed healing in 5
  - 3 on concomitant estrogen and 2 on steroids
  - Predominant feature of marked decrease of bone formation with reduced or absent osteoblastic surface
  - Supported "frozen bone concept"
Histomorphometry

Visekruna et al - 2008

- Bx reports on 2 pts
- 5, 10 yrs of fosamax exposure respectively
- Both also on steroids
- Both had increased osteoclast nos. One had decreased osteoblasts, other increased
- *No definite conclusions*
Histomorphometry

- Somford et al- 2009
  - 1 Pt. With RA
  - Multiple DMARDS, Steroids
  - Left AFF, 9 months later - Rt AFF
  - Bx from iliac crest and Rt femur 1 cm above Fx
  - Osteoblast suppression at Crest/cancellous bone
  - Osteoclast induction at Shaft/ cortical bone
  - ? Diff. mechanisms at 2 sites perhaps due to genetic and morphological differences
Histomorphometry, Denosumab data

- Inhibitor of RANK ligand, inhibits osteoclast differentiation and function
- Most potent antiresorptive agent
- Recently approved for use of postmenopausal osteoporosis
- Effects on bone histomorphometry, and relationship with AFF analyzed by Reid et al in 2010, with hypothesis it should increase risk of AFF by severe suppression of bone turnover
**Histomorphometry, Denosumab data**

- Iliac crest biopsies in subset of placebo and Denosumab treated women at 24 and 36 months in *Freedom study*.
- Double labeling present only in 19% of denosumab versus 94% of placebo bones indicating significantly lower bone turnover with drug.
- Bone markers did not distinguish denosumab treated patients with double labels (high turnover) from those with absent labels (low turnover).
- Osteoclasts absent in more than 50% of Denosumab treated patients.
Histomorphometry, Denosumab data

- STAND study.
  - Biopsies performed at 24 and 36 months on patients continually treated with Fosamax versus switch to Denosumab after 24 months of Fosamax treatment.

- Absent or single labeling in 80% of Denosumab biopsies versus 10% of the Fosamax biopsies --confirms strong inhibition of bone turnover by Denosumab.

- Surprisingly markedly reduced fracture incidence Over 3 years and the absence of any AFF in Denosumab treated patients.
  - Does not support “frozen bone” concept.

- Could future data from longer duration of treatment be different?
Data from clinical trials

- Black et al. 2010.
  - Secondary analysis of results of 3 large RCT of BPO, 14,000 PTS
  - 2 on Fosamax- (FIT and FLEX), 1 on Reclast (HORIZON PFT)
  - 284 Femur FX records reviewed
  - Only 12 AFF, rate of 2.3 per 10,000 pt yrs. Hazard ratio of 1.03 on BPO compared with placebo

*Increase in risk was not significant, but patients on low dose of Fosamax and on less than 4 years of treatment
Data from registries

- Possible coding mistakes constitute inherent limitation, can confound data

- Relative infrequency of AFF
  - 10% of all femoral fractures are subtrochanteric and diaphyseal and
  - out of those only 10% atypical

- Danish registry, cross section exam of hospital discharge records of 12000 patients between 1997 through 2005 period compared AFF vs TFF
Data from Danish registry

- Only 7% of patients with AFF exposed to Fosamax, 15% exposed to glucocorticoids
- Hazard ratio between Fosamax users versus non-Fosamax users only 1.46
- BPO Exposure
  - HR for AFF was 1.46
  - HR for TFF was 1.45
  - No sig. diff. between two types of Fx, after adjustment for comorbidities was made
- Greater adherence to BPO reduced risk of both AFF and TFF.

*Conclusion – Both FX should be considered as osteoporotic fx as similar epidemiology*
Data from other registries

- Risk for AFF was higher in patients exposed to BPO vs placebo but the risk for AFF was higher than placebo even before exposure - Is underlying bone disease the cause?
- Duration of exposure was studied, overall risk was found to be the same in patients treated for 9 years versus those treated for 3 months, also 25% of fractures seen in BPO exposure of less than 3 years.
Data from other registries

- Analysis of age-adjusted data from hospital admission rates, medical claims and incidence of all types of fractures shows that for every 100 TFF prevented by BPO use, only 1 AFF fracture noted.

- Increasing adherence rates with BPO medications was associated with decreased AFF incidence, 3.75% in MPR values more than 80% versus 5.1% in MPR of less than 50%, supporting these were possibly a subset of TFF.
Data from other skeletal disorders

- AFF seen in uncommon conditions like Paget’s disease of the bone, osteopetrosis, adult hypophosphatasia, X-linked hypophosphatemia
- Marked abnormalities in bone structure are noted leading to fragility of bone and radiological abnormalities, indicating other pathogenetic mechanisms apart from decreased bone turnover
AFF with distinctive features are rare events in patients with PMO

Lot of publicity regarding BPO therapy and AFF but larger studies do not support the hypothesis that the drugs caused the fracture

Increased cortical thickness associated with AFF but no data concerning the appearance of femurs prior to BPO exposure

Biochemical markers of bone turnover do not provide useful predictive data

Identification of comorbidities like rheumatoid arthritis, COPD, asthma, diabetes in 10% systemic glucocorticoid therapy in 25%, PPI use in about 33% of the patients
**Insights/Enigmas**

- AFF higher in BPO users versus non-BPO users but also occurred in significant number of non-BPO users and medical conditions other than osteoporosis

- Overall benefits from BPO far exceeds the risk of AFF, remember 100:1

*Association with BPO use and AFF established but Cause and effect relationship not established*

*Are they a separate entity or are they a subset of typical osteoporotic fractures, not answered*
Report of Task Force Of the American Society for Bone and Mineral Research

- Established the definition
- Reviewed what is known and what is not known about AFF and a potential relationship with BPO usage
- Epidemiology of AFF
- *Working on specific diagnostic and procedural codes and establishment of international registries*
- Treatments
- *Research directions*
Treatment of AFF

- Should BPO therapy be stopped?
- Most experts would probably answer yes
- Should patients be treated with Forteo? Some data suggests might be a good idea, helps with wound healing
- Future studies of bone biopsies closer to the fracture site would aid in selection of surgical intervention
Take home points

- Evidence does not suggest changing your prescription habits but
- Do not deny BPO *out of fear* to patients who really need it
- Do not prescribe BPO to patients who do not need it, use calculation tools like FRAX to select appropriate patients
- Assess comorbidities like diabetes, rheumatoid arthritis, steroid use. If significant, consider non-BPO pharmaceutical agents
- Educate patients about clinical symptoms of AFF
- Drug holidays after 5-6 years of BPO should be considered, as no strong evidence for ongoing benefit, reeval in 2-3 yrs
- Individualize treatment
References


