Medication Associated Osteoporosis

*Drugs that are bad for the bones*

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Director UCSF Rheumatoid Arthritis Clinic

Outline of Today’s Talk

- Other medications that induce osteoporosis
  - Cancer therapies (anti-hormonal therapies)
  - Diabetic therapy: thiazolidinediones
  - Heparin
  - (Not included in talk: barbituates, PPIs, etc…)

Necessary Therapies

Preventable Consequences

- Prednisone
- Arimidex
- Lupron
- thiazolidinediones
- Heparin

Actual SFGH Case in 2007

- VIP UCSF physician admitted after suffering multiple severe spinal and hip fractures from a fall.
- The fractures were so severe and unstable, he was transferred from UCSF to SFGH for special handling by the trauma and neurosurgery services.
- His past medical history was notable for cardiac disease and prostate cancer.
- His x-rays, in addition to demonstrating multiple severe and unstable hip and spinal fractures showed profound osteopenia.

- Other history:
  - The patient had received many years of lupron therapy for prostate CA
  - Had never received a DXA
  - Had never been offered any osteoporosis prevention or therapy (not even calcium and vitamin D)
Osteoporosis (OP) and Prostate Cancer

- High incidence of OP in men with prostate cancer even before ADT (10-25%)
- May be due to advanced age, hypogonadism, and diminished vitamin D
- Risk of OP in androgen deprivation therapy (ADT) patients is markedly increased, and doesn’t depend upon the regimen used

Androgen Deprivation Therapy – Effects on Bone Mineral Density

- In one prospective trial of 62 patients, BMD decreased 7.6% at two years with surgical or chemical castration (+/- antiandrogen therapy)
- Most studies concur in showing declining BMD post Androgen Deprivation Therapy

Comparing Surgical and Chemical Orchietomy, Effects on BMD

Daniels et al.

Chemical Castration  Surgical Castration

Medical castration is very effective!!

Incidence of First OP fracture after Orchietomy

Daniels et al.

- Incidence of first fracture is 15% at 4 years in castrated patients vs. 1.5% in prostate ca patients without ADT
- Rises to 50% vs. 8% At 9 years!!!!
Fracture Free Survival over Time
Retrospective study of 50,000 patients with prostate cancer 1992-97
Diminishes with increasing dosages of ADT.

At 9 years, only 50% patients receiving 9 doses of therapy remained fracture free!

Number of Patients needed to harm to cause a fracture: Synergistic effects of Age and cumulative ADT dose

Table 4. Estimated Number Needed to Harm for the Occurrence of Any Fracture within 12 to 50 Months after Diagnosis, According to Age and Extent of Androgen Deprivation.*

<table>
<thead>
<tr>
<th>Age</th>
<th>1-4 doses</th>
<th>5-8 doses</th>
<th>≥9 doses</th>
<th>Needed to harm (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>66-69 y</td>
<td>74 (16-146)</td>
<td>42 (29-73)</td>
<td>18 (16-24)</td>
<td>15 (13-18)</td>
</tr>
<tr>
<td>70-74 y</td>
<td>60 (46-146)</td>
<td>69 (37-71)</td>
<td>27 (13-36)</td>
<td>14 (12-17)</td>
</tr>
<tr>
<td>75-79 y</td>
<td>61 (41-123)</td>
<td>34 (14-61)</td>
<td>15 (14-37)</td>
<td>15 (11-11)</td>
</tr>
<tr>
<td>≥80 y</td>
<td>46 (13-91)</td>
<td>26 (10-45)</td>
<td>13 (8-21)</td>
<td></td>
</tr>
</tbody>
</table>

* Estimates were calculated on the basis of adjusted rates of fracture five years after diagnosis from a Cox model with any fracture as the outcome. Doses of a gonadotropin-releasing hormone agonist were grouped according to the number of doses received within the 12 months after diagnosis. CI denotes confidence interval.

Treatment of ADT Osteoporosis
- Treatment initiation is recommended for both iatrogenic and naturally occurring hypogonadism in males
- In cases involving Prostate CA – androgen replacement therapy not an option!
- Therefore, recommendations of the American Cancer society and other organizations:
  - Screen patients initiating and continuing ADT therapy
  - Treat with appropriate therapy

How Good are We with Following the Guidelines: An Assessment of Quality

Canadian retrospective cohort study
149 patients with non-metastatic prostate cancer who received at least one dose ADT
2008-2009 Tertiary care center
Evidence Supporting Bisphosphonate in ADT

- Meta-analysis of 15 studies with 2,634 patients
- Multiple different agents included

### Meta-analysis of Bisphosphonate in ADT

**Fracture Reduction**

- All fracture risk reduction: 0.80 (0.69, 0.94)
- Z = 2.8 (p = 0.005)
- NNT (14-166) depending upon agent and type of fracture

**Reduction in Osteoporosis**

- Risk reduction: 0.39 (0.28, 0.55)
- NNT (2.49-3.06) depending upon agent studied

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**Table 1: Characteristics of all studies included in the meta-analysis**

<table>
<thead>
<tr>
<th>Study</th>
<th>Type</th>
<th>Patients</th>
<th>Intervention</th>
<th>Comparator</th>
<th>Duration</th>
<th>Fracture Risk Reduction</th>
<th>Z-Value</th>
<th>p-Value</th>
<th>NNT (95% CI)</th>
<th>Type of Fracture</th>
</tr>
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<tbody>
<tr>
<td>Pelosi et al.</td>
<td>Paclitaxel, Docetaxel</td>
<td>156</td>
<td>80 vs 76</td>
<td>Bisphosphonate vs Placebo</td>
<td>24 months</td>
<td>0.79 (0.64-0.97)</td>
<td>2.08</td>
<td>0.04</td>
<td>13 (9-21)</td>
<td>Fracture type: 12.8</td>
</tr>
<tr>
<td>Charpentier et al.</td>
<td>Paclitaxel, Docetaxel</td>
<td>150</td>
<td>76 vs 74</td>
<td>Bisphosphonate vs Placebo</td>
<td>24 months</td>
<td>0.80 (0.69-0.94)</td>
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<td>0.005</td>
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**Figure 1:** Risk for fracture relative to placebo in patients with prostate cancer and multiple risk factors by agent

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**Figure 2:** Bisphosphonate increases BMD up to 36 months. Smith et al. NEJM 2009; 361 (8)
Donosumab lowers rate of vertebral fractures at 12, 24, and 36 months.

*Smith et al. NEJM 2009; 361 (8)*

### Androgen Deprivation Therapy

**Take Home Points**
- ADT is very bad for the bones
  - RAPID, Dramatic loss in BMD
  - BMD and fracture incidence worse with advancing age and cumulative ADT dose
  - Surgical or chemical castration the same
  - Close monitoring of BMD (at least 1-2 years)
  - Bisphosphonates recommended, especially in lower BMD individuals
- Denosumab: FDA approved to increase bone mass in patients receiving ADT

### Aromatase Inhibitors

- **Breast Cancer and Osteoporosis**
  - Chemotherapy causes gonadal ablation, premature menopause and premature osteoporosis
  - May be possible direct anti-metabolic effects of chemotherapy on bone *(Greep et al. Am J Medicine 2003;114:653-9)*
  - Increasing use of Aromatase inhibitors
  - Use of 3rd generation non-steroidal: anastrozole and letrozole cause 96-99% aromatase inhibition – very effective
  - Used more widely for metastatic or high risk disease because of superiority vs. tamoxifen

### Clinical Trials of Tamoxifen vs. AIs: Different effects on Fracture Risk

Fracture rate as high as 11% over 5.5 years in AI rx’d pts.
REBBBeCa: Risedronate Effect on Bone Loss in Breast Cancer  

- Randomized double blinded placebo controlled trial
- 12 months follow up with 12 month extension
- 87 newly post-menopausal women after chemotherapy for breast cancer
- Risedronate weekly vs. placebo
- Primary outcome: changes in hip and spine BMD

Patient Characteristics

| Dietary calcium (mg/d) | 691 ± 347 | 758 ± 513 | 0.50 |
| History of adult fractures (n, %) | 7 (15.9) | 23 (39.2) | 0.13 |
| Breast cancer treatment (n, %) | 44 (100) | 45 (100) | NA |
| Lumpectomy | 27 (61.4) | 26 (57.8) | 0.50 |
| Mastectomy | 17 (38.6) | 19 (42.2) | 0.50 |
| Radiation therapy | 10 (22.2) | 9 (19.6) | 0.66 |
| Tamoxifen | 30 (66.7) | 30 (66.7) | 0.66 |

Aromatase inhibitor

| Bone mineral density (BMD) | T12 (g/cm²) | 0.91 ± 0.16 | 0.92 ± 0.14 | 0.57 |
| Calcium (mg/d) | 0.885 ± 0.017 | 0.868 ± 0.016 | 0.30 |
| 25-Hydroxyvitamin D (ng/ml) | 12.3 ± 4.4 | 12.3 ± 4.4 | 0.86 |
| PTH (ng/ml) | 68.0 ± 20.0 | 52.4 ± 23.9 | 0.14 |
| LBM (g/cm²) | 6.4 ± 1.5 | 5.0 ± 1.5 | 0.24 |
| Lateral lumbar spine (L2-L4) | 0.716 ± 0.054 | 0.716 ± 0.054 | 0.50 |
| Total hip | 0.801 ± 0.103 | 0.801 ± 0.084 | 0.50 |
| Femoral neck | 0.786 ± 0.099 | 0.786 ± 0.105 | 0.50 |
| Trochanter | 0.666 ± 0.086 | 0.666 ± 0.081 | 0.50 |
| Triceps (cm) | 0.65 ± 1.5 | 0.65 ± 1.5 | 0.50 |
| FA (joint) | 0.7 ± 0.1 | 0.7 ± 0.1 | 0.50 |
| FA (joint) | 0.67 ± 0.1 | 0.67 ± 0.1 | 0.50 |

FIG. 2. Mean (SEM) percent change in bone mineral density from baseline to 12 months

Use of Bisphosphonates to Prevent Bone Loss in Breast Cancer Treated with AI’s  
Greenspan et al. J Clinical Oncology June 2008

- Since publication of trial, standard of care has shifted away from tamoxifen and towards aromatase inhibitors
- 12 month extension of REBBBeCa to 24 months (roughly 10% drop out in both arms)
- Use of AI’s increased from less than 20% to 44% in second year
  - Allowed for subgroup analysis of patients on AI’s
Zo-Fast (not to be confused with Z-fast)
Bundred et al. Cancer July 2008

Nearly identically designed study looking at BMD in 931 patients

Z-Fast: Zoledronic Acid and AI’s
Brufsky et al. J Clinical Oncology 2007

- Open label, randomized, unblinded study
- Patients receiving letrozole received either A. upfront or B. delayed Z.A. (if their t-score dropped <2.0)

Donosumab and Bone Mass in Patients on Aromatase Inhibitor Therapy

- 2008 Randomized double blinded placebo controlled trial
- N=125 placebo; N=127 60 mg Donosumab q 6m.
- All women with low bone mass but not osteoporosis
- Stratified by duration of AI therapy (< = 6 months)
- Follow up at 12 and 24 months

Fig 2. Mean (SEM) percent change in bone mineral density of the lumbar spine and the total hip at months 6 and 12 in women with early-stage breast cancer administered upfront or delayed zoledronate

Fig 4. (A) Mean (SE) percent change in bone mineral density from baseline to 24 months

Statistically significant increases in BMD at 12 (5.5%) and 24 (7.6%) months

Not affected by duration of AI use

FDA approval of Donosumab to increase bone mass in breast cancer patients receiving adjuvant AI therapy

Diabetic therapy: Thiazolidinediones (Glitizones)

- Peroxisome proliferator-activated receptor-γ protein agonist
- Ppar-γ helps regulate bone formation
- Decreased IGF-1 expression
  - Decreased bone formation
- Decreased osteoblastogenesis
- Promote osteoclast differentiation through increased Rank-L

Glitazones: Effects on BMD

- Schwartz AV, Sellmeyer DE, et al. 2006
  - Observational: Health, aging, and body composition
  - Postmenopausal women with 0.61% bone loss/yr

- Glintborg et al. 2008
  - Prospective trial in women with PCOD
  - 16 week follow up: -1.1% BMD spine; -1.4% femoral neck

- Grey et al. 2007
  - Prospective trial of BMD in postmenopausal women
  - 14 week follow up with decline BMD Hip -1.9%

Glitazones: Effect on Fracture Risk

- ADOPT Trial
  - 1840 women, 2511 Men
  - Compared rosiglitazone, metformin, and glyburide
  - Follow up 4 years
  - Vertebral fractures not assessed
  - Cumulative fracture risk no different in men
  - Women, 2X cumulative Fx rate (seen in pre and post-menopausal women):
    - Rosiglitazone 15%
    - Metformin 7.3%
    - Glyburide 7.7%
**UK General Practice Research Database (GPRD)**


- Observational study of older individuals
- TZD therapy and its duration are associated with sig increase in nonvertebral fractures

<table>
<thead>
<tr>
<th>Fracture Site</th>
<th>OR</th>
</tr>
</thead>
<tbody>
<tr>
<td>hip/femur</td>
<td>4.54</td>
</tr>
<tr>
<td>humerus</td>
<td>2.12</td>
</tr>
<tr>
<td>Forearm</td>
<td>2.90</td>
</tr>
</tbody>
</table>

**And the Evidence Keeps Growing…**

- Jones SG. Am J Manag Care 2009, 15:491–496.
  - Claims database
  - TZD doubles risk limb fracture in women

  - Meta-analyses of 10 trials (n=13,715) and two observational studies (n=31,769)
  - TZD double fracture risk in women/ not men

**More Evidence!**

  - Retrospective (N=84,339)
  - Men and women at increased risk of fracture
  - Fracture risk increases with cumulative exposure

  Medicare beneficiaries over 65
  - Compared TZD, sulfonylureas and metformin
  - TZD monotherapy is associated with increased risk of peripheral fractures regardless of sex and type

**Journal of Diabetes Mellitus**

"Oral bisphosphonates improve the bone mineral density in men with diabetes with or without thiazolidinediones"

Subhashini Yathur, Jared Davis

**Table 2. Changes in Bone mineral density at follow up**

<table>
<thead>
<tr>
<th>Fracture Site</th>
<th>T2D+H (23)</th>
<th>T2D (22)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AP (g/cm²)</td>
<td>0.848</td>
<td>0.848</td>
</tr>
<tr>
<td>Neck (g/cm²)</td>
<td>1.340</td>
<td>1.340</td>
</tr>
<tr>
<td>Total BMD (g/cm²)</td>
<td>2.06</td>
<td>2.06</td>
</tr>
<tr>
<td>Radius (g/cm²)</td>
<td>1.50</td>
<td>1.50</td>
</tr>
</tbody>
</table>

**Retrospective Review of EMR**

- No specified agent. HgA1c and vit D levels comparable
- Average follow up (BP=2.56 yrs; no BP 1.47 yrs)
What to do?

- Meager data: No randomized trials of anti-resorptive agents (e.g. bisphosphonates)
- Avoid use of TZD in patients at high risk for fracture
- Use lower doses of TZD or in combination
  - TZD-metformin combinations exist
  - Or incretins (some evidence that they promote bone formation)

Heparin: An old friend
Griffith et al. JAMA 1965;193(2):91-94

- Long term use of un-fractionated heparin is well-established cause of bone loss and fracture
- 117 patients studied
- 107 Patients on doses <10,000 U/day: no fractures after 1-15 yrs
- 10 patients 15-30,000 U/day: 6/10 vertebral fracture (> 6 months)

Unfractionated Heparin

- Loss in BMD dose and duration dependant
- Mechanism not entirely understood
  - Animal studies suggest decreased osteoblast activity (less bone formation)
  - Decreased OPG decoy leads to increased RANK-RANKL and osteoclast (increased bone resorption)

Heparin: clinical effects

- Most studies of long term use (> 6 months) in pregnancy
- Up to 1/3 patients significant loss in BMD
- 2.2-5% incidence of fracture (mostly vertebral)
- Indications for long-term heparin increasing
Summary of clinical trials: Unfractionated heparin

<table>
<thead>
<tr>
<th>Drug</th>
<th>Patient number</th>
<th>Treatment</th>
<th>Results</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>UFH</td>
<td>184</td>
<td>13,000 IU/d for 25 weeks</td>
<td>4/184 (2.2%) decrease in bone mineral density as determined by radiography</td>
<td>Dahlman et al., 1993 [6]</td>
</tr>
<tr>
<td>UFH</td>
<td>39</td>
<td>8,000 IU/d for 28 weeks</td>
<td>4/39 (10.3%) decrease in bone mineral density as determined by ultrasound absorptiometry</td>
<td>Dahlman et al., 1994 [6]</td>
</tr>
<tr>
<td>UFH</td>
<td>14</td>
<td>12,000 IU/d for 9 months</td>
<td>5/14 (35.7%) decrease in bone mineral density as determined by ultrasound absorptiometry</td>
<td>Barbour et al., 1994 [7]</td>
</tr>
<tr>
<td>UFH</td>
<td>25</td>
<td>Mean 25,382 IU/d for 162 days</td>
<td>7% decrease in bone mineral density when compared to UFH</td>
<td>Dussek et al., 1996 [11]</td>
</tr>
</tbody>
</table>

LMWH: Effects on BMD

- LMWH shown to lower BMD in many studies
- Loss appears to be less than with UFH, although not compared head to head

LMWH vs. UFH: Risk of fracture head to head

- Monreal et al. 1994 and Pettit et al. 1999

LMWH appears to be associated with decreased fracture rates compared to UFH
**Heparin: summary**

- Long term UFH likely associated with rapid, significant, and potentially partially irreversible loss of BMD
- Adverse effect is proportionate to dose and duration
- Up to 1/3 of patients who receive long term heparin suffer significant loss of BMD
- Long term UFH likely associated with excess risk for vertebral and hip fracture (2.2-5% incidence in pregnant women)

**LMWH: summary**

- LMWH effects on BMD controversial. Most studies favor loss of BMD
- Losses in BMD appear less for LMWH than UFH, although few head to head studies
- Fracture risk appears greater in patients receiving UFH v. LMWH in head to head studies
- Long term effects (reversibility) of LMWH unknown - larger clinical trials needed

**LMWH: ? No effect on BMD**

LMWH vs. oral Vit.K antagonist

- Secondary prophylaxis for VTE
- Women and men (not pregnant)
- Greater loss of BMD with LMWH