Glucocorticoid-induced osteoporosis

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• 56 y/o postmenopausal Caucasian woman presents to her PCP with complaints of back pain.

• Pain started about 3 months ago, gradually progressing, more recently developed severe back pain after lifting heavy boxes.
• Asthma, on inhaled steroids since 2003
• Rheumatoid arthritis, on prednisone 7.5-10 mg daily since 2007, Methotrexate since 2011, and recently started on infliximab
• GERD, on Omeprazole
• HTN, well controlled on Amlodipine
Menstrual History

- Menarche at ~12 y/age. Menses have always been regular
- Has had two normal pregnancies
- Menopause at 52 y/age, no HRT use
- Has minimal menopausal symptoms
• CBC shows mild anemia
• BMP shows normal electrolytes
• Serum Calcium and albumin within normal limits
• 25-OH Vitamin D 32 ng/ml
• CRP elevated
Imaging studies
Questions

• Is the patient at increased risk for Osteoporosis
• How would you estimate patient’s fracture risk
• How can fracture risk be adjusted for the steroid use
• What are the treatment recommendations
• Would you do a bone density scan prior to any treatment decisions
GLUCOCORTICOID-INDUCED OSTEOPOROSIS

THE MOST COMMON CAUSE OF SECONDARY OSTEOPOROSIS
• “A marked osteoporosis of the skeleton was found, it being easily possible to cut the vertebral bodies with a knife, the spongy part of the bones having largely disappeared.”

  Cushing describing the effects of long-term endogenous hypercortisolism to John Hopkins Medical Society, 1932.

• 18 years later, only 1 year after the introduction of cortisone for the treatment of rheumatoid arthritis by Philip Hench and colleagues, clinicians became aware of the rapidly injurious skeletal effects of glucocorticoid administration.
Fractures Are the Most Common Serious Adverse Event

<table>
<thead>
<tr>
<th>Adverse Events</th>
<th>User (112)</th>
<th>Nonuser (112)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fracture</td>
<td>21 (19%)</td>
<td>8 (7%)</td>
</tr>
<tr>
<td>Cataract</td>
<td>17</td>
<td>5</td>
</tr>
<tr>
<td>Serious Infection</td>
<td>14</td>
<td>4</td>
</tr>
<tr>
<td>GI Bleed or Ulcer</td>
<td>11</td>
<td>4</td>
</tr>
<tr>
<td>Diabetic Complication</td>
<td>8</td>
<td>3</td>
</tr>
<tr>
<td>Herpes Zoster</td>
<td>8</td>
<td>1</td>
</tr>
<tr>
<td>Myocardial Infarction</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>Stroke</td>
<td>6</td>
<td>1</td>
</tr>
<tr>
<td>Glaucoma</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Death</td>
<td>2</td>
<td>0</td>
</tr>
</tbody>
</table>

Steroid-Induced Osteoporosis

• More than 30 million Americans are estimated to have diseases which may require long-term glucocorticoid use.
• Timely intervention is critical because glucocorticoid users can lose large amounts of bone rapidly.
  – As much as 15% in the first year of treatment alone.
• Fractures happen.
  – Osteoporotic fractures can occur in 30%-50% of patients treated chronically with glucocorticoids.
Glucocorticoid Effects On Organ Systems

- **Kidney**
  - \(\uparrow\text{Ca}^2+\text{ excretion}\)

- **Bone**
  - \(\downarrow\text{Matrix synthesis}\)
  - \(\downarrow\text{Number and function of osteoblasts}\)

- **Gut**
  - \(\downarrow\text{Ca}^2+\text{ absorption}\)

- **Pituitary**
  - \(\downarrow\text{LH/FSH}\)
  - \(\downarrow\text{Sex steroids}\)

**Consequences**
- Early \(\uparrow\text{resorption}\)
- Profound \(\downarrow\text{formation}\)
- Bone loss
Osteoblast-Osteocyte-Osteoclast
The adverse skeletal effects of glucocorticoids are primarily caused by direct actions on bone cells.
Fundamental histologic features of GIO

**Cancellous Bone**
- marked reduction in bone area, trabecular width, wall width, and osteoid area
- decreased number of osteoblasts, normal/increased number of osteoclasts, increased apoptosis of osteoblasts and osteocytes
- decreased bone interstitial fluid and blood supply

**Cortical Bone**
- increased cortical porosity
- increased osteocyte apoptosis
Postmenopausal vs Glucocorticoid-induced osteoporosis
GLUCOCORTICOID-INDUCED OSTEOPOROSIS

BONE DENSITY, BONE LOSS AND FRACTURES
Bone Loss with Initiation of Glucocorticoid Therapy

Control group from Etidronate GIO study:
74 males and females, average age 61
Prednisone $\geq 7.5$ mg/day for $\leq 3$ months.
All received Calcium 500 mg/day

GIO Patients Fracture at a Higher BMD

GLUCOCORTICOID-INDUCED OSTEOPOROSIS

Is there any chronic dose that is not harmful to the bones?
Oral Glucocorticoid Dose Strongly Correlates with Fracture Risk

### Corticosteroid Equivalency

<table>
<thead>
<tr>
<th>Corticosteroid</th>
<th>Approximate Equivalent Dose (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hydrocortisone</td>
<td>20</td>
</tr>
<tr>
<td>Prednisone/Prednisolone</td>
<td>5</td>
</tr>
<tr>
<td>Methylprednisolone</td>
<td>4</td>
</tr>
<tr>
<td>Dexamethasone</td>
<td>0.75</td>
</tr>
</tbody>
</table>

At equivalent doses, Dexamethasone causes more osteoporosis and osteonecrosis than prednisone, possibly because it is resistant to inactivation by 11β-HSD2.
GLUCOCORTICOID-INDUCED OSTEOPOROSIS

WHAT IS THE PATIENT RISK FOR OSTEOPOROSIS?
# Risk Factors for GIO

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Explanation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Advancing Age</td>
<td>The elderly have a 26-fold higher risk of vertebral fractures than youth</td>
</tr>
<tr>
<td>Low Body Mass Index</td>
<td>Risk factor for fractures and GIO</td>
</tr>
<tr>
<td>Underlying Disease</td>
<td>RA, PMR, IBD, COPD, and Transplant. are independent factors</td>
</tr>
<tr>
<td>Smoking, excessive alcohol use, family history of hip and prevalent fractures, falls</td>
<td>All are independent risk factors</td>
</tr>
<tr>
<td>Glucocorticoid Receptor Genotype</td>
<td>Polymorphisms in the gene may regulate glucocorticoid sensitivity</td>
</tr>
<tr>
<td>11β-HSD Isoenzymes</td>
<td>11β-HSD1 increases with age and use of glucocorticoid and enhances its activation</td>
</tr>
<tr>
<td>Glucocorticoid Dose</td>
<td>Greater risk of fracture with higher dose, longer duration of therapy, daily use</td>
</tr>
<tr>
<td>Low Bone Mineral Density</td>
<td>Higher fracture risk with lower BMD</td>
</tr>
</tbody>
</table>
Patient’s risk for OP Case Study

- Age, BMI, smoking, ETOH, family history of fractures, falls
- Underlying disease and Inflammatory state: Additional risk for osteoporosis?
- Immobilization
- Medications:
  - Amlodipine
  - Omeprazole (PPI)
  - Methotrexate
  - Corticosteroids (systemic and Inhaled)
  - Infliximab (TNF-α blocker)
The disease and the therapy

• Many diseases for which glucocorticoids are used are also associated with bone loss.

• The evaluation has to include the effects of the disease itself on bone as well as the use of glucocorticoids.

• Rheumatoid Arthritis, PMR, Inflammatory bowel disease, COPD and transplantation are independent risk factors.
How does Rheumatoid Arthritis affect bone?

- Periarticular bone loss
- Joint erosions
- **Generalized bone loss, fragility fractures**
  
  increased by: disease activity
  
  immobility
  
  glucocorticoid use
How does Rheumatoid Arthritis affect bone?

• RANKL is expressed by activated T and B cells

• ACPA stimulates osteoclasts and induces bone resorption

• TNF-α induces sclerostin and DKK-1 (WNT signaling antagonists) and suppresses bone formation

• TNF-α stimulates osteoclastogenesis through RANKL upregulation and directly activates osteoclasts
Inflammatory state and bone loss

- Bone loss is higher in patients with high CRP
- 107 RA patients treated with Infliximab and Methotrexate

Vis at al, *Arthritis and Rheumatism*, 2006
How Do Pulmonary Diseases Affect Bone?

• Direct effects
  – Respiratory acidosis
  – Increased cytokines (e.g. cystic fibrosis)

• Associated conditions
  – Smoking
  – Alcohol
  – Low body weight, poor nutrition
  – Decreased physical activity
  – Vitamin D deficiency (e.g. decreased sun exposure, malabsorption with cystic fibrosis)
  – Hypogonadism

• Glucocorticoid use
  • Systemic
  • Inhaled?
GIO in Patients With Asthma

% Predicted BMD vs steroid duration

Inhaled Corticosteroids and Risk of Fractures

Fractures per 1,000 patient-years

- Controls
  N=170,818

- COPD Inhaled Steroids
  N=170,818

- COPD Bronchodilators
  N=108,786

Patient’s risk for OP
Case study

- Age, BMI, smoking, ETOH, family history of fractures, falls
- Underlying diseases and Inflammatory state: Additional risk for osteoporosis?
- Immobilization
- **Medications:** Prednisone
  - Amlodipine
  - Omeprazole (PPI)
  - Methotrexate
  - Infliximab (TNF-α blocker)
Medications associated with OP/ increased Fracture Risk?

A. All patient’s meds
B. Prednisone, Amlodipine, PPI
C. Prednisone, PPI
D. Prednisone, PPI, Infliximab
E. Prednisone, Methotrexate
Medications associated with OP/ increased Fracture Risk?

A. All patient’s meds
B. Prednisone, Amlodipine, PPI
C. Prednisone, PPI
D. Prednisone, PPI, Infliximab
E. Prednisone, Methotrexate
PPIs and fracture risk

- Millions of PPI users worldwide
- PPIs have a modest risk on fractures that is dose and duration dependent
- Mechanism may be by altering Calcium metabolism or osteoclast ruffled border
- PPI plus glucocorticoid use further increase fracture risk
PPIs and fracture risk

Effect of proton pump inhibitors on fracture risk

1.12-1.43 (All)
1.28-1.65 (Hip)
1.25-2.04 (Spine)

124,655 cases
373,962 controls

(from Vestergaard et al, CTI 2006;79:76-83)
TNF-α blockers and fracture risk

- 102 RA pts on Infliximab + MTX
  significant decrease in serum RANKL level and CTX (bone resorption), slight increase in P1NP (bone formation) at 46 weeks
  - Vis et al., 2006
- Beneficial effect on markers of bone metabolism in RA pts treated with infliximab (n=10) and etanercept (n=11)
  - Seriolo et al., 2006

TNF-α blockers mainly prevent bone loss through inflammation control, (? direct effects on bone metabolism). Intensive treatment of RA prevents generalized bone loss
GLUCOCORTICOID-INDUCED OSTEOPOROSIS

HOW TO ESTIMATE PATIENT’S FRACTURE RISK?
Patient’s risk for OP Fracture
Case study

- 56 yo, nonsmoker and did not use alcohol, normal BMI
- Rheumatoid arthritis, active inflammation
- Glucocorticoids, PPI use
- Normal Calcium, creatinine, 25-OH vitamin D level
- Prevalent Compression Fracture, vertebral L1
Prior vertebral fracture is strong predictor of new vertebral fracture

<table>
<thead>
<tr>
<th>Prevalent fractures, number and location</th>
<th>Percent of all women</th>
<th>Odds ratio for ≥1 new fracture, any location</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>71.2</td>
<td>1.0 (reference)</td>
</tr>
<tr>
<td>≥1 upper (T4–10)</td>
<td>16.3</td>
<td>2.6 (1.9, 3.6)</td>
</tr>
<tr>
<td>≥1 lower (T11–L4)</td>
<td>17.6</td>
<td>2.6 (1.9, 3.6)</td>
</tr>
<tr>
<td>0</td>
<td>71.2</td>
<td>1.0 (reference)</td>
</tr>
<tr>
<td>1 upper (T4–10)</td>
<td>12.4</td>
<td>2.0 (1.3, 3.0)</td>
</tr>
<tr>
<td>≥2 upper</td>
<td>4.0</td>
<td>3.9 (2.4, 6.4)</td>
</tr>
<tr>
<td>1 lower (T11–L4)</td>
<td>13.5</td>
<td>2.1 (1.5, 3.1)</td>
</tr>
<tr>
<td>≥2 lower</td>
<td>4.1</td>
<td>3.4 (2.1, 5.5)</td>
</tr>
</tbody>
</table>

Bone Mineral Density Testing Recommendations

• BMD measurement is a valuable tool for diagnosis and fracture risk assessment

• ACR, AACE, and NOF guidelines:
  – all patients about to receive or currently receiving glucocorticoids should have a bone mineral density measurement
  – Repeat testing at 6 month intervals

• Medicolegal implications of not following guidelines
Fracture Risk Assessment tool (FRAX)
BMD Testing: Caveats

- BMD
  - inadequate for identifying patient at risk
  - useful in follow-up after intervention
- FRAX
  - underestimates the risk (does not consider the current dose, cumulative dose, and duration of therapy)
  - uses femoral neck density, but cancellous bone is major target in GIO and vertebral fractures are more common
Case Study: DEXA

- 56 yo, nonsmoker and did not use alcohol, normal BMI
- Rheumatoid arthritis, active inflammation
- Glucocorticoids PPI use
- Normal Calcium, creatinine, 25-OH vitamin D level
- Compression Fracture, vertebral L1
- **DEXA**
  - AP spine L1-L4 T-score -1.8
  - Dual Femur Total Left T-score -1.7
  - Dual Femur Total Right T-score -2.0
    - **FRAX:** Major Osteoporotic Fracture 27.6%
    - Hip Fracture 3.9%
Case Study: DEXA

Verdugo Rheumatology/ Nounce Pashinian MD
435 Arden Ave #460 Glendale CA 91203
Phone: 818 243-1187  Fax: 818 243-6182

DXA FRAX Report: Monday, September 22, 2014

Dear DR. PASHINIAN,

Your patient LEIGH MCCOLL completed a FRAX assessment on 09/22/2014 using the Lunar Prodigy Advance DXA System (analysis version: 13.60) manufactured by GE Healthcare. The following summarizes the results of our evaluation.

**PATIENT BIOGRAPHICAL:**

<table>
<thead>
<tr>
<th>Name:</th>
<th>MCCOLL, LEIGH</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient ID:</td>
<td>(not specified)</td>
</tr>
<tr>
<td>Gender:</td>
<td>Female</td>
</tr>
<tr>
<td>Ethnicity:</td>
<td>White</td>
</tr>
<tr>
<td>Birth Date:</td>
<td>04/17/1957</td>
</tr>
<tr>
<td>Age:</td>
<td>57.4</td>
</tr>
<tr>
<td>Height:</td>
<td>60.0 in.</td>
</tr>
<tr>
<td>Weight:</td>
<td>132.0 lbs.</td>
</tr>
<tr>
<td>Exam Date:</td>
<td>09/22/2014</td>
</tr>
</tbody>
</table>

**FRAX* RESULTS:** (version: 3.1)

<table>
<thead>
<tr>
<th>Major Osteoporotic Fracture</th>
<th>Hip Fracture</th>
</tr>
</thead>
<tbody>
<tr>
<td>27.6%</td>
<td>3.9%</td>
</tr>
</tbody>
</table>

Based on Femur (Right) Neck BMD

1 - The 10-year probability of fracture may be lower than reported if the patient has received treatment.
2 - Major Osteoporotic Fracture: Clinical Spine, Forearm, Hip or Shoulder

*FRAX is a trademark of the University of Sheffield Medical School's Centre for Metabolic Bone Disease, a World Health Organization (WHO) Collaborating Centre.

**ASSESSMENT:**

The probability of a major osteoporotic fracture is 27.6% within the next ten years.

The probability of a hip fracture is 3.9% within the next ten years.
GLUCOCORTICOID-INDUCED OSTEOPOROSIS

HOW TO ADJUST FRACTURE RISK FOR STEROID DOSE?
IOF Group Suggestions on FRAX Adjustment

- FRAX uses data from the UK General Practitioner Database which is based on doses of 2.5–7.5 mg of daily prednisone use or its equivalent.
- Correction factor based on dose of corticosteroids has been proposed:
  
  **Hip fracture:**
  - under 2.5 mg/day - 0.65
  - over 7.5 mg/day - 1.2

  **Major osteoporotic fracture:**
  - under 2.5 mg/day - 0.8
  - over 7.5 mg/day - 1.15

GLUCOCORTICOID-INDUCED OSTEOPOROSIS

TREATMENT RECOMMENDATIONS
Nonpharmacologic interventions
ACR 2010 Recommendations

- Minimal possible dose and duration
- Fall risk assessment, smoking and alcohol cessation
- Exercises (weight bearing) and to improve lower extremity strength and balance
- Calcium intake (dietary plus supplements) in the range of 1200 to 1500 mg /day
- Vitamin D intake 800 to 1000 IU /day or whatever is necessary to achieve “therapeutic” level of 25-OH vitamin D
Hopping against osteoporosis!
# FDA-APPROVED MEDICATIONS

<table>
<thead>
<tr>
<th>Drug</th>
<th>PMO Prevention</th>
<th>PMO Treatment</th>
<th>GIO Prevention</th>
<th>GIO Treatment</th>
<th>Men</th>
</tr>
</thead>
<tbody>
<tr>
<td>Estrogen</td>
<td>✓</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Calcitonin (Miacalcin®)</td>
<td></td>
<td>✓</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Raloxifene (Evista®)</td>
<td>✓</td>
<td>✓</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ibandronate (Boniva®)</td>
<td>✓</td>
<td>✓</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Denosumab</td>
<td></td>
<td>✓</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alendronate (Fosamax®)</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Risedronate (Actonel®)</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Zoledronate (Reclast®)</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Teriparatide (Forteo®)</td>
<td></td>
<td>✓</td>
<td></td>
<td></td>
<td>✓</td>
</tr>
</tbody>
</table>
Effects of Glucocorticoids, Bisphosphonates, and Teriparatide on Bone Cells
### ACR 2010 Guidelines for postmenopausal women and men over 50

<table>
<thead>
<tr>
<th>Drug</th>
<th>Low Risk* Pred Rx &gt; 3 mos &gt;7.5 mg Pred</th>
<th>Medium risk* Pred Rx &gt; 3 mos Any dose</th>
<th>High Risk* Pred Rx any duration Any dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alendronate (Fosamax®)</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Risedronate (Actonel®)</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Zoledronate (Reclast®)</td>
<td></td>
<td>✓ (5 mg Pred or more)</td>
<td></td>
</tr>
<tr>
<td>Teriparatide (Forteo®)</td>
<td></td>
<td></td>
<td>✓ (Pred &gt; 1 month)</td>
</tr>
</tbody>
</table>

**Low Risk- FRAX**

- <10% for 10 yr major OP fracture

**Medium Risk- FRAX**

- 10-20% for 10 yr major OP fracture

**High Risk- FRAX**

- >20% for 10 yr major OP fracture
ACR 2010 Recommendations for premenopausal women and men under 50

Counsel and assess risk factors of those starting or on prevalent GC Tx

No prevalent fragility fracture

Inadequate data for recommendation

Women (non childbearing potential) or men age <50 years

Women (childbearing potential)

Prevalent fragility fracture

GC 1-3 months
If prednisone < 5 mg/d: alendronate or risedronate OR if pred ≥7.5 mg/d: zoledronic acid

GC > 3 months
alendronate OR risedronate OR zoledronic acid OR teriparatide

GC 1-3 months
No consensus

GC >3 months
if prednisone ≥7.5 mg/d alendronate OR risedronate OR teriparatide
if pred <7.5 mg/d: no consensus

Monitor patients on prevalent GC Tx
Case Study: GIO Treatment

- Exercises as tolerated
- Counseling on Calcium and vitamin D
  - Calcium (dietary + supplement): 1,200-1,500 mg/day
  - Vitamin D: 1,000 IU/day
- Medications
  - Oral Bisphosphonates: not recommended (Pt had severe GERD)
  - Yearly IV Zoledronic Acid or daily sq Teriparatide? Started Teriparatide daily injections
- DEXA with VFA: repeat in one year
GLUCOCORTICOID-INDUCED OSTEOPOOROSIS

PRIOR FRAGILITY FRACTURE = TREATMENT
Treatment thresholds
NOGG Guideline

Without BMD test

With BMD test

Adequate calcium intake should be achieved through dietary intake if possible, with the use of supplements if necessary.

An adequate vitamin D status should be maintained, using supplements if required.

In patients treated with teriparatide, antiresorptive therapy should be considered following the permitted treatment duration of 24 months.
Thank you!

Treasure your bones!!!
Pyknodysostosis:
mutation → Cathepsin K deficiency

Henri de Toulouse Lautrec
Cathepsin K: lysosomal cysteine proteinase

Function: degrades demineralized bone: mainly type 1 collagen; acts optimally at pH 4.5-5.0
HYPEROSTOSIS

Sclerosteosis/Van Buchem’s Disease: mutations in SOST

Increased bone mass throughout skeleton.
Osteoblast
Other agents under investigation

Osteoclast targeted

- Proton pump inhibitors
- $\alpha_v\beta_3$ Integrin inhibitors
- Saracatinib (AZD0530)
- Oral recombinant Calcitonin

[Diagram showing osteoclast activity and targeted molecules]

Sealing Zone

Bone

Collagen

$\text{pH}=5$

Lysosomal Enzymes

Cathepsin K

$\alpha_v\beta_3$ integrin
Other agents under investigation

Osteoblast targeted

- PTH – oral, Td
- PTH-rel Protein
- Calcilytics (CaSR)