Glucocorticoid Associated Osteoporosis

Prevention and Treatment

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Traditional rheumatology practice

I found part of the problem. These little white pills were jammed in the disc drive.

That's prednisone - I figured it works for everything else!
Bone loss in GIO is bimodal and occurs rapidly in an early phase (weeks) and more gradually in a later phase. Which one of the following primarily occurs in the early/rapid phase?

A. Increased osteoblast apoptosis (cell death)
B. Increased osteoclast activity
C. Decreased osteoblast activation
D. Combination of A,B,C
Glucocorticoids: Some toxicities

- Diabetes
- Cataracts
- HTN
- Weight gain
- Fluid retention
- PUD
- Myopathy
- Psychiatric
- OSTEOPOROSIS & OSTEONECROSIS

50% of patients

Fracture risk increases with AGE, GENDER, and Dose

Van Staa et al, JBMR, 1998
Glucocorticoid Effects of Bone
Weinstein R. NEJM 2011;365:62-70

Increased apoptosis of osteocytes (bone quality decreased before BMD)

Prolonged osteoclast survival and decreased osteoclastogenesis

Increased Osteoclast bone resorption

Decreased osteoblastogenesis and increased apoptosis

Multiple pathways affected!!!! Increased bone resorption relative to decreased bone formation and decreased overall bone quality:

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**GLUCOCORTICOIDS: “Double Whammy to Bones”**

Biophasic effect: Osteoclast effects are early and osteoblast are late

- **Osteoclast /Pro-resorptive effects (early)**
  - Decrease OPG
  - Increase RANK-L → osteoclast #,
    activity, lifespan

- **Anti bone-formation effects (late)**
  - Decrease osteoblast and osteoclast formation
  - Decrease osteoblast lifespan
  - Enhance apoptosis in osteocytes
GLUCOCORTICOID - INDUCED OSTEOPOROSIS

- **Early phase** of rapid bone loss (Pro-resorption)
  - As early as **2 mos** into therapy
  - Resorption markers elevated
  - Pts on high dose prednisone can lose 15-20% of trabecular bone (spine) in 5-7 mos

- **Slower phase** of bone loss (Anti-Formation)
  - Continues indefinitely
  - Trabecular bone especially vulnerable

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**Glucocorticoid Effects on Remodeling/Strength**

A= osteocyte apoptosis leading to deterioration of bone quality
B= fast bone loss due to a "relative" increase in resorption without corresponding formation in pre-existing BMUs
C= gradual accumulation of unrepaired defects due to suppressed remodeling
D= fast repair of defects by resurgent remodeling
E= restoration of osteocyte network leading to improved bone quality

Manolagas, *JBMR*, 2000
Relative Rate (± 95% CI) of Non-vertebral Fractures: D/C Steroids (5 years) - REVERSAL

Question #2

What is the minimum dose of daily prednisone associated with a significant increase in hip fracture risk?
(Ave. dose for acute COPD flare 50-60 mg/day)

A. <2.5 mg
B. 2.5-5mg
C. 7.5mg-12.5 mg
D. >12.5 mg
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**SUMMARY**

- Relatively low doses of po GCs (2.5-7.5 mg Pred) increase fracture risk.
- Increase in risk is **quick** -- within 3 mos of starting therapy.
- Vulnerable population: postmenopausal women, elderly pts.
- Fracture risk decreases if stop therapy.
- **More falls in steroid-treated patients** (frailty, less mobility, less activity).

van Staa et al, *JBMR*, 2000

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**Summary of professional organization guidelines**

Weinstein R. *NEJM* 2011;365:62-70

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<table>
<thead>
<tr>
<th>Variable</th>
<th>American College of Rheumatology(^a)</th>
<th>National Osteoporosis Foundation(^b)</th>
<th>Royal College of Physicians of London(^c)</th>
<th>Belgian Bone Club(^d)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dose and duration of glucocorticoid treatment warranting pharmacologic intervention</td>
<td>≥7.5 mg/day for at least 3 months, but patients at increased risk require treatment with any dose or duration</td>
<td>≥3 mg/day for at least 3 months</td>
<td>T score ≥ −2.5, unless patient is at high risk on the basis of a modified FRAX model</td>
<td>≥3 mg/day for at least 3 months</td>
</tr>
<tr>
<td>BMD threshold for treatment if dose and duration qualify</td>
<td>Threshold to be based on the FRAX algorithm in addition to higher daily and cumulative dose, intravenous usage, and declining BMD(^d)</td>
<td>T score ≤ −1.5</td>
<td>T score ≤ −1.0 to −1.5</td>
<td>T score ≤ −1.0 to −1.5</td>
</tr>
<tr>
<td>Yearly BMD testing recommended</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Prevalent vertebral fractures as justification for pharmacologic intervention</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Calcium and vitamin D supplementation</td>
<td>1200–1500 mg of calcium per day and 800–1000 units of vitamin D per day for all patients</td>
<td>1200 mg of calcium per day and 2000 units of vitamin D per day for all patients</td>
<td>Only for patients with low calcium intake (&lt;1 g/day) or vitamin D deficiency (not defined)</td>
<td>For all patients</td>
</tr>
<tr>
<td>Pharmacologic intervention</td>
<td>Bisphosphonates; teriparatide reserved for patients at highest risk</td>
<td>Bisphosphonates; teriparatide only for patients at high risk</td>
<td>Bisphosphonates as first-line options, followed by teriparatide</td>
<td>Bisphosphonates</td>
</tr>
</tbody>
</table>
2017 American College of Rheumatology Guidelines on GIOP

Systematic literature review summarizes evidence for risks/benefit of GIOP 1) Risk Assessment 2) treatment and 3) Follow up using G.R.A.D.E. methodology

- Adults
- Women of childbearing potential
- Adults requiring very high doses of glucocorticoids
- Adults with organ transplants
- Children ages 4-17

Principles Reflected in ACR 2017 guidelines

- GIO does not occur in a vacuum but interacts with risk factors other than corticosteroids
- Guided by risk/benefit assessment: risk assessed using FRAX score risk or other risk calculator PLUS correction/adjustment for prednisone dosage
- Risk calculators stratifying GC use as low/high (<7.5 mg/day) underestimate risk associated with higher daily GC doses
- Observational data suggest risk to young women and children receiving high dose GC’s
I. Clinical fracture risk assessment

- Risk assessment should be undertaken within 6 months of starting therapy.

- Periodic reassessment of risk:
  - Every 1-3 years for adults not on therapy.
  - 2-3 years (BMD) for high risk adults (>40) on therapy, adults who've completed OP treatment, and higher risk younger adults.

Initial risk assessment workflow
GIO, fracture risk, & effect of other factors: Glucocorticoids are not given in a vacuum
ACR 2017 Guidelines definition of risk:

Recommendations are conditional for moderate risk & strong for high risk

<table>
<thead>
<tr>
<th>Moderate/High Risk</th>
<th>Moderate/High Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age &lt; 40 Years</strong></td>
<td><strong>Age ≥ 40 Years</strong></td>
</tr>
<tr>
<td>1. History of OP fracture(s) OR</td>
<td>1. History OP fracture(s) OR</td>
</tr>
<tr>
<td>2. Z score &lt; −3 at hip or spine and prednisone ≥ 7.5 mg per day OR</td>
<td>2. Men ≥ 50 years and PMP women with a BMD T score ≤ -2.5 at the hip or spine OR</td>
</tr>
<tr>
<td>3. &gt; 10%/year loss of BMD at hip or spine and prednisone ≥ 7.5 mg per day OR</td>
<td>3. FRAX (GC-adjusted) 10-year risk for major osteoporotic fracture ≥ 10% OR</td>
</tr>
<tr>
<td>4. Very high dose GCs and ≥ 30 years</td>
<td>4. FRAX (GC-adjusted) 10-year risk for hip fracture &gt; 1% OR</td>
</tr>
<tr>
<td>5. Very high dose GCs</td>
<td>5. Very high dose GCs</td>
</tr>
</tbody>
</table>

II. Treatment: Moderate/high risk

Women not of childbearing potential and men: (order of preference)

1. Oral bisphosphonate
2. IV bisphosphonate
3. Teriparatide
4. Denosumab
5. Raloxifene (PMP women as last resort)
Treatment: Moderate/high risk

Women of childbearing potential (conditional): (order of preference)

1. Oral bisphosphonate
2. Teriparatide
3. IV bisphosphonate (high risk only)
4. Denosumab (high risk only)

Treatment: High dose GCs

Adults ≥ 30 years

Initial prednisone dose > 30 mg/day or cumulative dose > 5 grams in 1 year

1. Oral bisphosphonate
2. IV bisphosphonate
3. Teriparatide
4. Denosumab
5. Raloxifene (PMP women as last resort)
III: Follow up

- After 5 years of treatment:
  – Continue therapy if still assessed at mod/high risk.

- After discontinuing GC treatment
  – Mod/high risk: continue treatment
  – Low risk: discontinue treatment

- What about therapeutic “failures?”

Question #3

True or False:
There have been no head to head comparative effectiveness studies of bisphosphonates for GIO:

A. True
B. False
Question #3

True or False:
There have been no head to head comparative effectiveness studies of bisphosphonates for GIO:

A. True
B. False

What about Zoledronic Acid? Better than other bisphosphonates?: Horizon
Reid et al. Lancet. 2009 Apr 11;373(9671):1253-63

- 1 year randomized double blind, double dummy, non-inferiority
- 833 patients
  - Subdivided into treatment groups based on duration of steroid therapy (>3 months)
- IV ZA 5mg vs. PO Risedronate 5mg
- Primary endpoint: BMD LS spine
Horizon Demographics: A representative population

Majority of patients were on more than 7.5mg prednisone a day!

Majority of patients had rheumatoid arthritis or SLE

Higher risk patients studied – in order to maximize potential effect size

Horizon Results

Figure 2. Change in mean bone mineral density of lumbar spine and femoral neck for (A) treatment and (B) prevention subgroups Error bars=95% CI. *p=0.0005. †p=0.0001. ‡p=0.0050. §p<0.0001. ¶p=0.0156. p=0.0049.
**PTH vs. bisphosphonates:**

**Beneficial for GIO? (2008)**

Saag et al. NEJM 2007;357:2028-39

- 36 Month randomized double blinded controlled
- 18 month interim analysis
- 428 patients studied
  - 22-89 years of age
  - Treated with GC’s for at least three months
  - Prednisone equivalent of 5 mg/day or more
  - 20 mcg/d PTH vs. 10 mg/d alendronate
  - Everyone continued Ca/VitD

**Who were the Patients?**

- BMD<-2.0 or <1.0 + fragility fracture (Higher risk patients)
- Exclusions: Standard for PTH Use
- Two treatment groups similar (n=214 both)

<table>
<thead>
<tr>
<th></th>
<th>Alendronate</th>
<th>PTH</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>57.3</td>
<td>56.1</td>
</tr>
<tr>
<td>Prednisone dose</td>
<td>7.8</td>
<td>7.5</td>
</tr>
<tr>
<td>Non Vert Frag Fx</td>
<td>20.1%</td>
<td>19.6%</td>
</tr>
<tr>
<td>BMD T score LS Spine</td>
<td>-2.6</td>
<td>-2.5</td>
</tr>
<tr>
<td>BMD T score Hip</td>
<td>-1.9</td>
<td>-2.0</td>
</tr>
</tbody>
</table>
Patients’ Underlying Disease

Table 1. (Continued.)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Aleendronate</th>
<th>Teriparatide</th>
</tr>
</thead>
<tbody>
<tr>
<td>Underlying glucocorticoid-requiring disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rheumatologic disorders — no. (%)</td>
<td>161 (75.2)</td>
<td>161 (75.2)</td>
</tr>
<tr>
<td>Rheumatoid arthritis</td>
<td>111 (51.9)</td>
<td>96 (45.8)</td>
</tr>
<tr>
<td>Systemic lupus erythematosus</td>
<td>21 (9.8)</td>
<td>28 (13.1)</td>
</tr>
<tr>
<td>Polymyalgia rheumatica</td>
<td>8 (3.7)</td>
<td>10 (4.7)</td>
</tr>
<tr>
<td>Vasculitis</td>
<td>3 (1.4)</td>
<td>5 (2.3)</td>
</tr>
<tr>
<td>Other rheumatic disorders</td>
<td>18 (8.4)</td>
<td>20 (9.3)</td>
</tr>
<tr>
<td>Respiratory disorders</td>
<td>31 (14.5)</td>
<td>29 (13.6)</td>
</tr>
<tr>
<td>Inflammatory bowel disease</td>
<td>4 (1.9)</td>
<td>3 (1.4)</td>
</tr>
<tr>
<td>Other conditions</td>
<td>18 (8.4)</td>
<td>21 (9.8)</td>
</tr>
</tbody>
</table>

High risk for fx: higher prednisone dose, lower BMD, and RA/SLE diagnosis

PTH vs. Alendronate

More than 25% attrition rate in both arms
**PTH vs. Alendronate: Fracture Results**

**Table 2. Summary of New Fractures and Clinically Relevant Adverse Events.**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Alendronate (N=214)</th>
<th>Teriparatide (N=224)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vertebral — no./total no. (%)*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Radiographic evidence</td>
<td>10/165 (6.1)</td>
<td>1/171 (0.6)</td>
<td>0.004</td>
</tr>
<tr>
<td>Clinical evidence</td>
<td>3/165 (1.8)</td>
<td>0</td>
<td>0.07</td>
</tr>
<tr>
<td>Nonvertebral — no. (%)‡</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any</td>
<td>8 (3.7)</td>
<td>12 (5.6)</td>
<td>0.36</td>
</tr>
<tr>
<td>Nonvertebral fragility</td>
<td>3 (1.4)</td>
<td>5 (2.3)</td>
<td>0.46</td>
</tr>
</tbody>
</table>

*Saag et al. Arthritis Rheum. 2009 Nov;60(11):3346-55*

**PTH vs. Alendronate 36 month Follow Up: BMD results**

*Saag et al. Arthritis Rheum. 2009 Nov;60(11):3346-55*
**PTH vs. Alendronate: 36 month fracture follow up**

*Saag et al. Arthritis Rheum. 2009 Nov;60(11):3346-55*

At 36 months, statistically significant reduction in both radiographic and clinical vertebral fractures.

No significant differences in non-vertebral fractures.

**Table 2. Incident vertebral and nonvertebral fractures in subjects with glucocorticoid-induced osteoporosis**

<table>
<thead>
<tr>
<th>Fracture type</th>
<th>Subjects taking alendronate (n = 214)</th>
<th>Subjects taking teriparadine (n = 214)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥1 radiographic vertebral†</td>
<td>13 (7.7)</td>
<td>3 (1.7)</td>
<td>0.007</td>
</tr>
<tr>
<td>≥1 clinical vertebral‡</td>
<td>4 (2.4)</td>
<td>0</td>
<td>0.003</td>
</tr>
<tr>
<td>≥1 nonvertebral</td>
<td>45 (2.0)</td>
<td>16 (7.5)</td>
<td>0.443</td>
</tr>
<tr>
<td>≥1 nonvertebral fragility</td>
<td>5 (2.3)</td>
<td>9 (4.2)</td>
<td>0.256</td>
</tr>
</tbody>
</table>

*Values are in the number (%).
†Subjects with baseline and postbaseline spinal radiographs (n = 190 subjects in the alendronate group and 173 subjects in the teriparadine group).
‡A clinical vertebral fracture (assessed in 190 subjects in the alendronate group and 173 subjects in the teriparadine group) was a new radiographically confirmed fracture that was associated with symptoms such as back pain.

**PTH for GC induced Osteoporosis: Summary**

- **PTH appears to improve BMD in GC assoc. osteoporosis**
  - Evidence suggests superior increases in BMD vs. alendronate at hip, femoral neck, and LS spine.

- However, high attrition rate in this study
  - Nearly 50% drop out in both arms by 36 months.
  - Appears to be of benefit both for clinical and radiographically defined fractures at 36 months.
  - BUT....overall rate of clinical fracture is low in both groups.

- Decrease in fractures limited to vertebral fractures but non-significant for non-vertebral fractures.
Follow Up Treatment: Treatment “failures”

For adults > 40:
- Fracture > 18 months on treatment
- Loss of BMD > 10% year

- Teriparatide or denosumab
- IV bisphosphonate if failure thought due to non-compliance or oral absorption