Glucocorticoid Induced Osteoporosis
A Translational Journey
From the bedside to the bench and
Back to the bedside

Nancy Lane M.D.
Distinguished Professor of Medicine and
Rheumatology and Aging
Director, Center for Musculoskeletal Health
University of California at Davis
Sacramento, California
Glucocorticoid-Induced Osteoporosis

- Most common form of secondary osteoporosis
- Occurs at any age, in both sexes and across ethnic groups
- Approximately 30-50% of patients sustain osteoporotic fractures
- Common long-term uses:
  - Pulmonary and Rheumatologic disorders
  - Inflammatory bowel disease
  - Organ transplantation
  - Neurological diseases
  - Skin diseases

Graded Fracture Risk Associated with Increasing Doses of Corticosteroids

MRI of L4 Vertebral Body of Biconcave Fracture of 40 y.o. woman on Glucocorticoids for SLE
Glucocorticoid-Induced Osteoporosis

“The greatly compressed bodies of the vertebrae...were so soft they could be cut with a knife.”

– Harvey Cushing, 1932
Rapid BMD Decline Due to Glucocorticoids in Rheumatoid Arthritis

Laan, Ann Int Med 1993;119:996
Bone Structure in GIOP

Normal

GIOP

Courtesy: Dr. David Dempster
Fracture Incidence is Higher in GC users than GC Nonusers at any given BMD

GC Excess In Mice Rapidly Induces Osteopenia
GC Excess Induces Rapid Increases in Gene Expression Associated with Osteoclast Activation and Bone Resorption
Chronic GC Excess Is Associated With Prolonged Suppression Of Bone Formation

*P < 0.05 vs. PL
GC Excess Increases Expression Of Wnt Signaling Inhibitors
Elements of Wnt/β-catenin Signaling

Summary

GC excess
1. Rapid increases in gene expression for osteoclast activation and bone resorption
2. Prolonged suppression of bone formation and it appears associated with increased expression of Wnt inhibitors (Dkk1, Wif1)
3. Rapid trabecular bone loss
Clinical observation

• Patients with GC excess fracture at higher BMD that postmenopausal osteoporosis patients
GC Excess Increases Osteocytic Gene Expression that is Associated with Reduced Mineralization
GC Excess Decreases Elastic Modulus Around The Osteocytes

PL

GC

OVX

Measured by SPM
Glucocorticoid Treatment results in a Reduction in Elastic Modulus and mineral around the Osteocyte Lacunae from iliac crest biopsy specimen

Scanning Probe Microscopy

Atomic Force Microscopy
Do Osteocytes Contribute to Bone Mineral Homeostasis?
Osteocytic Osteolysis Revisited

• Osteocytes are buried in matrix
• Osteocytes lacunae change in size with clinical calcium deficit
  (hypophosphotemic rickets, glucocorticoids, during lactation, prolonged estrogen deficiency)
• The osteoclast surface may not be sufficient to maintain calcium balance
• There is evidence that osteocytes can express MMPs, and secrete them, and contribute to calcium and phosphorus homeostasis
Osteocyte Lacunar Size Increases with Lactation

John Wysolmerski and Lynda Bonewald

Cortical bone

Trabecular bone

Width of Canaliculi
Possible Explanation for Transient and Permanent Changes in Osteocyte Lacunae size that may alter bone quality in the presence of Glucocorticoids

Teti & Zallone
Bone
2008
H vessels in the distal femoral metaphysis stained with anti-CD31 changed with GC treatment and appeared to recover after discontinuation of GC treatment.
Gene Pathways influenced by GC and GC+ PTH

• GCs reduced gene expression of both angiogenic and nitric oxide pathways compared to placebo treated mice.
• GC+PTH treatment increased gene expression of both angiogenic and nitric oxide pathways compared to GC alone.
• These data suggest that GC + PTH may maintain blood flow, bone vascularity and maintain bone hydration which may reduce the GC induced bone fragility.
Bound water measurements of mouse femurs by NMR

Data from J. Nyman, Vanderbilt
Bending strength vs. bound water

Peak moment (N·mm)

Bound water (%)

Veh.-120d
GC-120d
Recovery
Combined
Veh.-60d
GC-60d

$R^2 = 0.3881$

$p < 0.0001$
Hydration measured by NMR and Standardized beta coefficients (with $p$-value) for selected predictors of ultimate moment as determined by boot-strapped general linear models

<table>
<thead>
<tr>
<th>Predictors</th>
<th>$I_{\text{min}}/c_{\text{min}}$</th>
<th>Different covariates</th>
<th>Ct.Th</th>
<th>Adj-$R^2$</th>
</tr>
</thead>
<tbody>
<tr>
<td>$I_{\text{min}}/c_{\text{min}}$</td>
<td>$\beta=0.594$ ($p&lt;0.0001$)</td>
<td>–</td>
<td>–</td>
<td>0.342</td>
</tr>
<tr>
<td>$I_{\text{min}}/c_{\text{min}}$+Ct.Th</td>
<td>$\beta=0.363$ ($p=0.001$)</td>
<td>–</td>
<td>$\beta=0.476$ ($p&lt;0.0001$)</td>
<td>0.509</td>
</tr>
<tr>
<td>$I_{\text{min}}/c_{\text{min}}$+Ct.TMD</td>
<td>$\beta=0.592$ ($p&lt;0.0001$)</td>
<td>($p=0.718$)</td>
<td>–</td>
<td>0.332</td>
</tr>
<tr>
<td>$I_{\text{min}}/c_{\text{min}}$+Ct.Po</td>
<td>$\beta=0.533$ ($p&lt;0.0001$)</td>
<td>$\beta=0.313$ ($p=0.001$)</td>
<td>–</td>
<td>0.428</td>
</tr>
<tr>
<td>$I_{\text{min}}/c_{\text{min}}$+PW</td>
<td>$\beta=0.470$ ($p=0.001$)</td>
<td>$\beta=0.252$ ($p=0.012$)</td>
<td>–</td>
<td>0.380</td>
</tr>
<tr>
<td>$I_{\text{min}}/c_{\text{min}}$+BW</td>
<td>$\beta=0.343$ ($p=0.015$)</td>
<td>$\beta=0.416$ ($p&lt;0.0001$)</td>
<td>–</td>
<td>0.441</td>
</tr>
<tr>
<td>$I_{\text{min}}/c_{\text{min}}$+Ct.TMD+Ct.Th</td>
<td>$\beta=0.325$ ($p=0.002$)</td>
<td>$\beta=0.175$ ($p=0.066$)</td>
<td>$\beta=0.536$ ($p&lt;0.0001$)</td>
<td>0.530</td>
</tr>
<tr>
<td>$I_{\text{min}}/c_{\text{min}}$+Ct.Po+Ct.Th</td>
<td>$\beta=0.371$ ($p=0.001$)</td>
<td>(p=0.699)</td>
<td>$\beta=0.439$ ($p=0.005$)</td>
<td>0.502</td>
</tr>
<tr>
<td>$I_{\text{min}}/c_{\text{min}}$+BW+Ct.Th</td>
<td>$\beta=0.266$ ($p=0.015$)</td>
<td>$\beta=0.235$ ($p=0.065$)</td>
<td>$\beta=0.383$ ($p=0.001$)</td>
<td>0.531</td>
</tr>
<tr>
<td>$I_{\text{min}}/c_{\text{min}}$+PW+Ct.Th</td>
<td>$\beta=0.349$ ($p=0.001$)</td>
<td>(p=0.657)</td>
<td>$\beta=0.454$ ($p&lt;0.0001$)</td>
<td>0.502</td>
</tr>
</tbody>
</table>

$I_{\text{min}}/c_{\text{min}}$ – section modulus of the femur mid-shaft

Ct.Th – cortical thickness of femur mid-shaft

Ct.TMD – cortical tissue mineral density of femur mid-shaft

Ct.Po – cortical porosity of femur mid-shaft

PW – percent volume fraction of pore water

BW – percent volume fraction of bound water

Data unpublished from Jeff Nyman, PhD
Both PTH And RIS Restored GC-induced Bone Loss

a. Trabecular bone volume of the DFM (% changes from day 0)

b. Three-dimensional images from DFM taken at day 56

c. 8th-LVB Bone Volume (%)

d. Three-dimensional images from the LVB at day 56
a. Effects on select Wnt-signaling inhibitory gene expressions

b. Effects on select genes that inhibit mineralization

a = p<0.05 from PL
b = p<0.05 from GC
Perceptions of GIOP Prevention

• Proportion of physicians rating osteoporosis “one of the top 3 side effects” of high dose glucocorticoids:
  – 75% for post-menopausal women
  – 25% for 45 year old woman
  – 8% for 45 year old man

Buckley, J Rheum.
Pathophysiology of Glucocorticoid-Induced Osteoporosis

Glucocorticoids

- Osteoblast bone formation: ↓ Apoptosis, ↓ Lifespan, ↓ Function
- Osteoclast bone resorption: ↓ Glucocorticoids

- Glucocorticoids:
  - ↓ Osteoblast bone formation
  - ↓ Estrogen
  - ↓ Testosterone
  - ↓ Adrenal androgens
  - ↓ GI calcium absorption
  - ↓ Urinary calcium excretion

- Osteoporosis:
  - ↑ hPTH 1-84
  - ↓ Calcium
Calcium and Vitamin D

Selected Bisphosphonate Prevention Studies: BMD of Lumbar Spine

*P < 0.05 difference between groups.
Selected Bisphosphonate Treatment Studies: BMD of Lumbar Spine

% Change in BMD From Baseline

- Placebo
- Bisphosphonate

Risedronate
Devogelaer (1 yr) (n = 290)

Alendronate
Saag (1 yr) (n = 194)

Etidronate
Pitt (2 yr) (n = 49)

Alendronate
Saag (2 yr) (n = 76)

*P < 0.05 difference between groups.
GIOP Bisphosphonate Trials: Fracture Rate

**Fracture Rate (%)**

- **1 year (Adachi 97)**
  - Etidronate 400 mg Cyclical: 40% risk reduction
  - Placebo: 70%* risk reduction

- **1 year (Reid 98 - Abstract)**
  - Etidronate 400 mg Cyclical: 40% risk reduction

- **1 year (Saag 98)**
  - Etidronate 400 mg Cyclical: 70%* risk reduction

- **2 year (Saag 98 - Abstract)**
  - Etidronate Ext 2.5 mg, 5 mg, 10 mg: 90%* risk reduction

**Etidronate** 400 mg Cyclical
**Risedronate** 5 mg
**Alendronate** 5 mg, 10 mg
**Alendronate Ext** 2.5 mg, 5 mg, 10 mg

*P < 0.05
Human parathyroid hormone
1-34 and 1-84
Role of PTH in Treatment of GIOP

• Glucocorticoids
  • shorten osteoblast and lifespan
  • inhibit osteoblast activity

• PTH
  • prolongs osteoblast lifespan
  • stimulates bone formation

• PTH represents a pathophysiology-based approach to treat GIOP
Changes in Bone Turnover Markers in GIOp patients treated with PTH

Lane et al., JBMR, 2001
Effect of 1 year of PTH+HRT vs. HRT alone for Glucocorticoid-Induced Osteoporosis

% change in BMD

-10 0 10 20 30 40

Spine QCT
Spine DXA
Hip
Radius

35 9.8 1.3 -0.3

Lane, JCI 1998;102:1627
Percent Change in Bone Mineral Density at the Lumbar Spine and Total Hip from Baseline to 18 Months

Percent Change in Markers of Bone Formation and Resorption

A  N-Terminal Propeptide of Type I Collagen

![Graph showing change in N-Terminal Propeptide of Type I Collagen over time for Teriparatide and Alendronate]

No. at Risk
Alendronate 100 99 85 76
Teriparatide 99 98 86 77

B  C-Telopeptide of Type I Collagen

![Graph showing change in C-Telopeptide of Type I Collagen over time for Teriparatide and Alendronate]

No. at Risk
Alendronate 91 79 75 71
Teriparatide 85 71 66 64
### Incident Fracture Data at 18 months of the Study

<table>
<thead>
<tr>
<th>Site</th>
<th>Alendronate</th>
<th>rhPTH 1-34</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vertebral</td>
<td>10/165</td>
<td>1/171</td>
</tr>
<tr>
<td></td>
<td>(6.1%)</td>
<td>(0.6)</td>
</tr>
</tbody>
</table>

**P value**

0.004

Change in BMD at total hip, the lumbar spine with Denosumab vs. Residronate.

Saag et al Lancet. 2018
Percentage change in CTX (A) and P1NP (B) from baseline to 12 months

Saag et al Lancet. 2018
SUMMARY

• Denosumab is effective in both preventing and treating GC induced bone loss
• However, no difference in fractures incidence between Denosumab and Risedronate
• Please remember that if a patient discontinues Denosumab, even if no longer on GCs, may still need anti-resorptive treatments.
Adults ≥40 Years at Moderate Risk of Major Fracture

• Treat with oral BP over calcium and vitamin D alone
• Treat with oral BP over IV BP, teriparatide, denosumab, or raloxifene
  • Oral BPs preferred for safety and cost, and because of lack of evidence of superior antifracture benefits from other OP medications. Other therapies, if oral BPs are not appropriate, in order of preference:
    • IV BP
      • Higher risk profile for IV infusion over oral BP therapy
    • Teriparatide
      • Cost and burden of therapy with daily injections

Summary of Glucocorticoid Osteoporosis and Osteonecrosis

1. GCs induce ON and OP

2. Prevention and treatment of GC induces osteoporosis and osteonecrosis. ON may require either maintenance or regeneration of the bone vasculature.

3. Additional studies are needed to determine if the changes in bone cell viability in the presence of GCs results from direct toxicity to the cells and or from compromised vasculature.
Thank You to My Collaborators and Research Funding Support

UCSF/UCD
Wei Yao
Guive Balooch
Mehdi Balooch
Thomas Bruenig
Kuo Lian
Ravi Nalla
Claude Arnaud
Abhijit Chaudhari
Alanna Dobrovsky
Jia Jiang

LLNL/UCSF
John Kinney
David Haupt

Proctor and Gamble
Roger Phipps
Merck and Co
Donald Kimmel
Univ of Missouri at KC
Lynda Bonewald
UC Berkeley
Robert Ritchie, Joel Ager
Southwest Research Institute
Daniel Nicolella

NIAMS/NIH
ORWH/NIH, CIRM
THANK YOU

On behalf of IOF, we thank you for your participation in this webinar