Pathophysiology of Postmenopausal & Glucocorticoid Induced Osteoporosis

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Bone ECHO
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Review: normal bone formation
Bone Modeling

Diagram showing bone modeling processes:

- Osteoblast
- Mineralization
- Bone-lining cells
- Bone formation
- Bone resorption
- Normal shape modification

Cells and processes involved in bone modeling.
Remodeling

- MDGFs
- Clastokines
- Osteoblast bone formation
- New bone
- Lining cell
- Normal
Peak Bone Mass

• Maximum bone mass achieved in life
• Usually in the 3rd decade of life
• 60 -80% peak bone mass has genetic determinants (ethnicity, sex, body size)
• variability related to environmental factors (diet, exercise, habits, diseases, medications)
• Chronic diseases during childhood
Cellular Components
10% of bone volume

Osteoprogenitor cells
(mesenchymal stem cells)
• Osteoblasts
• Bone lining cells
• Osteocytes

Hematopoietic stem cells
• Osteoclasts
Osteoblasts
Extracellular Components
Collagen – Type 1
Extracellular Components
Inorganic Matrix

A

B

C

D
Bone Lining Cells
Osteocytes
Osteoclast
Postmenopausal Osteoporosis
Postmenopausal Bone Loss

Cellular / molecular level

Estrogen promotes:
• mesenchymal stem cell differentiation to osteoblast lineage
• Preosteoblast to osteoblast differentiation
• Limits osteocyte and osteoblast apoptosis
• Estrogen increases:
  - Osteoblast production of growth factors (IGF1, TGF beta) and procollagen synthesis
Postmenopausal Bone Loss

Cellular / molecular level

Estrogen promotes:

• Reduces serum and bone marrow levels of Sclerostin (potent inhibitor of Wnt signaling)

• Estrogens effects on osteoclasts:
  - Reduces production of RANKL (central molecule in osteoclast development)
  - Increases production of OPG (soluble RANKL decoy receptor)
Postmenopausal Bone Loss

• Prior to menopause
  bone formation = resorption rates

• Declining estrogen levels
  - increase BMU activation frequency
  - extension of resorption phase

• Bone resorption increases by 90%
  Bone formation by 45%
Postmenopausal Bone Loss

With accelerated bone loss:
- Efflux of calcium into extracellular fluid
- Compensatory mechanisms – limit hypercalcemia:
  * Increased renal calcium clearance
  * Decreased intestinal calcium absorption
  * Partial suppression of PTH secretion
Postmenopausal Bone Loss

Declining estrogen:

increased RANKL and decreases OPG – increased osteoclast development/ activity

• cytokines produced by osteoblasts, now rise including IL1, IL6, TNF alpha, MCSF (macrophage colony stimulating factor) all of which play a role in mediating bone resorption

• Loss impact on promoting apoptosis of osteoclast lineage cells and of mature osteoclasts
Summary

Estrogen deficiency
• Increased renal calcium clearance
• Decreased intestinal calcium absorption
• Partial suppression of PTH secretion

• Increases osteoclast recruitment, differentiation, and survival
• Osteoblast activity and differentiation declines. Increase in premature apoptosis
• T cell generated cytokines increase that promote bone resorption (IL1, IL6, TNF alpha)
Glucocorticoid Induced Osteoporosis
Glucocorticoid Induced Osteoporosis

- 2\textsuperscript{nd} most common kind of osteoporosis
- Most common iatrogenic form of the disease
- Fractures may occur in 30-50% of patients on chronic glucocorticoid therapy
- Often asymptomatic prevalent vertebral fractures
- Increase risk of future vertebral fractures independent of BMD
Glucocorticoid Induced Osteoporosis

• Reduction in BMD biphasic:
  - 6-12 % loss in the 1st year followed by
  - Slower annual loss of about 3%

• Risk of fracture escalates as much as 75% in 1st 3 months before significant decline in BMD

• Pts steroids various disorders pred 10mg/day > 90 days – 7 fold increase in hip fractures and 17 fold increase in vertebral fractures
  (Steinbuch, et al 2004 OI 15:323-328)
Glucocorticoid Induced Osteoporosis

• GIOP diffuse. Effects cortical and trabecular bone. Predilection for fractures in sites of predominately trabecular (cancellous)

Architectural changes

• Loss of trabecular connectivity
• Impact of loss of horizontal trabeculae
<table>
<thead>
<tr>
<th>Effects of corticosteroid use</th>
<th>Result</th>
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<tbody>
<tr>
<td>Inhibition of vitamin D–mediated calcium absorption, hypercalciuria</td>
<td>Secondary hyperparathyroidism</td>
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<tr>
<td>Inhibition of gonadotrophin secretion, decreased gonadal hormone secretion</td>
<td>Hypogonadism</td>
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<tr>
<td>Bone cell aging and death</td>
<td>Early aging and death of osteocytes and osteoblasts, impaired formation and function</td>
</tr>
<tr>
<td>Bone cell longevity and function</td>
<td>Osteoclastic longevity, bone destruction</td>
</tr>
<tr>
<td>Changes in bone quality: trabecular thinning and perforations</td>
<td>Microarchitectural destruction, loss of strength, increased fracture risk</td>
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Glucocorticoid-induced Osteoporosis

- Reduced Calcium absorption
- Hypercalciuria + secondary hyperparathyroidism
- Reduced gonadotropin secretion
- Reduced matrix protein synthesis
- Enhanced Osteoclastic activity
- Reduced Osteoblast function
Summary

• Reduced calcium absorption
• Hypercalcuria
• Decrease in gonadotropins
• Osteoclasts increased longevity - early
• Osteoblasts / Osteocytes
  - Reduced formation/function
  - Early aging /death