OSTEOMALACIA UPDATE

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Nothing to Disclose
Case History

• 59 YO WM referred for evaluation of diffuse bone pain and muscle weakness

• PMHx:
  • COPD treated intermittently with glucocorticoids
  • Aseptic necrosis of L hip resulting in hip replacement
  • Low trauma hip Fx treated with alendronate but not calcium or vitamin D
  • Xrays showed osteopenia with “hot spots” on bone scan suggestive of metastases
  • W/U for cancer negative
  • Initial labs: Ca 8.5mg/dl, Pi 3.2mg/dl, Bone specific AP 187iu/l (nl <15), PTH 974 pg/ml

Case History (cont)

• PE:
  • Marked proximal muscle weakness
  • Waddling gait
  • Bone tenderness, generalized

• Repeat labs:
  • PTH and AP elevated as before but 25OHD measured at 7ng/ml
  • Double labeled iliac crest bone Bx obtained –definitive for OM

• Rx
  • High dose Vitamin D and calcium
  • Sx resolved in 2-3 mo.
Take home points

- Osteomalacia in adults may be hard to diagnose in early stages
- Evaluation frequently mistaken for osteoporosis
- Major physical findings include proximal muscle weakness and bone tenderness
- Xrays are seldom diagnostic in adults (unlike rickets in children)
- Hot spots on bone scan, representing microfractures, can be mistaken for metastases
- Laboratory generally shows low but not always out of the normal range for Ca and P, but AP and PTH are generally high and 25OHD low
- Bone biopsy following double fluorochrome labeling is definitive
The Osteomalacic Syndromes

Disorders in the vitamin D endocrine system
- Decreased bioavailability
- Insufficient sunlight exposure
- Nutritional vitamin D deficiency
- Nephrotic syndrome (urinary loss)
- Malabsorption (fungal loss)
- Ba moistur type II gastrectomy
- Sprue
- Regional enteritis
- Jejunoileal bypass
- Pancreatic insufficiency
- Cholestatic disorders
- Cholestyramine

Abnormal metabolism
- Liver disease
- Chronic renal failure
- Pseudovitamin D deficiency (CYP27B1 mutations)
- Tumoral hypophosphatemic osteomalacia
  (excess FGF23)
- X linked hypophosphatemia (mutations in PHEX with increased FGF23)
- Autosomal dominant hypophosphatemia
  (FGF23 stabilizing mutations)
- Hypoparathyroidism
- Chronic acidosis
- Anticonvulsants

Abnormal target tissue response
- Hereditary vitamin D deficient rickets (VDR mutations)
- Gastrointestinal disorders

Disorders of phosphate homeostasis
- Decreased intestinal absorption
- Malabsorption
- Antacids containing aluminum hydroxide

Increased renal loss
- X linked hypophosphatemic rickets
- Tumoral hypophosphatemic osteomalacia
- Autosomal dominant hypophosphatemia
- Fanconi syndrome

Calcium deficiency
- Dietary insufficiency
- Excessive renal loss
- Malabsorption of calcium

Primary disorders of bone matrix
- Hypophosphatasia
  - Fibrogenesis imperfecta ossium
  - Axial osteomalacia
- Inhibitors of mineralization
  - Aluminum
  - Etidronate
  - Fluoride

Classical Actions: Bone Mineral Homeostasis

The Players

Blood
- Ca, P

Bone
- 1,25(OH)2D

Kidney
- FGF23

Urine
- Ca, P

Gut
- 25 OHD

Parathyroid Glands
- PTH
Classical Actions: Bone Mineral Homeostasis

Hormonal Feedback Loops

25 OHD

1,25(OH)₂D

Bone

Kidney

Parathyroid Glands

FGF23

Classical Actions: Bone Mineral Homeostasis

Mineral Feedback Loops

Blood

Ca, P

25 OHD

1,25(OH)₂D

Parathyroid Glands

Bone

Kidney

Urine

Ca

P

Gut
Clinical Presentation of Osteomalacia

<table>
<thead>
<tr>
<th></th>
<th>Rickets</th>
<th>Osteomalacia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Presentation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>Infants, young children</td>
<td>Older adults</td>
</tr>
<tr>
<td>Asthenia</td>
<td>Common</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Muscle weakness</td>
<td>Common</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Bone pain</td>
<td>Common</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Tetanus</td>
<td>Uncommon</td>
<td>Rare</td>
</tr>
<tr>
<td>Convulsions</td>
<td>Uncommon</td>
<td>Rare</td>
</tr>
<tr>
<td>Skeletal deformity</td>
<td>Common</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Abnormal teeth</td>
<td>Common</td>
<td>Rare</td>
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</tbody>
</table>
## RADIOLOGIC FEATURES

<table>
<thead>
<tr>
<th>Radiologic changes</th>
<th>Rickets</th>
<th>Osteomalacia</th>
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</thead>
<tbody>
<tr>
<td>Decreased bone density</td>
<td>Common</td>
<td>Common</td>
</tr>
<tr>
<td>Long-bone bowing</td>
<td>Common</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Epiphyseal hypertrophy</td>
<td>Present</td>
<td>Absent</td>
</tr>
<tr>
<td>Metaphyseal flaring</td>
<td>Present</td>
<td>Absent</td>
</tr>
<tr>
<td>Pseudofractures</td>
<td>Uncommon</td>
<td>Uncommon</td>
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</tbody>
</table>
Differences between osteoporosis and osteomalacia on bone biopsy

**Osteoporosis**
- Trabecular bone volume reduced
- Mineralization lag time normal
- Osteoid maturation time normal
- Osteoid thickness normal
- Bone formation can be low, normal, or high

**Osteomalacia**
- Trabecular bone volume low, normal or high
- Mineralization lag time delayed
- Osteoid maturation time prolonged
- Osteoid thickness increased
- Bone formation is low
Comparison of osteomalacia due to vitamin D deficiency or hypophosphatemia

<table>
<thead>
<tr>
<th>Measurement</th>
<th>Vitamin D Deficiency</th>
<th>Hypophosphatemia</th>
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</thead>
<tbody>
<tr>
<td>Serum Ca</td>
<td>normal or Low</td>
<td>usually normal</td>
</tr>
<tr>
<td>Serum Pi</td>
<td>normal or Low</td>
<td>By definition &lt;2.5 mg/dl</td>
</tr>
<tr>
<td>Alkaline Pase</td>
<td>generally elevated</td>
<td>generally elevated</td>
</tr>
<tr>
<td>PTH</td>
<td>elevated</td>
<td>generally normal</td>
</tr>
<tr>
<td>25OHD</td>
<td>low</td>
<td>normal</td>
</tr>
<tr>
<td>Osteoclast surface</td>
<td>elevated</td>
<td>normal</td>
</tr>
<tr>
<td>Marrow fibrosis</td>
<td>frequent</td>
<td>seldom</td>
</tr>
<tr>
<td>Cortical thickness</td>
<td>decreased</td>
<td>decreased, normal, increased</td>
</tr>
<tr>
<td>Trabecular bone volume</td>
<td>normal or Low</td>
<td>decreased, normal, increased</td>
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</tbody>
</table>
VITAMIN D DEFICIENCY/INSUFFICIENCY IS COMMON

AND OSTEOMALACIA IS NOT RARE
when 25OHD levels fall below 12ng/ml

VITAMIN D DEFICIENCY WITH AGING

• Decreased vitamin D production in the skin
• Decreased vitamin D intake in the diet
• Decreased vitamin D absorption by intestine
• Decreased 1,25D production by the kidney
• Decreased intestinal response to 1,25D
Decreased ability of aging skin to make vitamin D


Declining Ability to Respond to PTH re 1,25D Production with Age

Decline in Intestinal Calcium Absorption in Response to 1,25D with Age

GI DISEASE A BIG CAUSE OF VITAMIN D DEFICIENCY: OFTEN UNRECOGNIZED
INCIDENCE OF BONE DISEASE IN GI DISORDERS

- Postgastrectomy: up to 70%, increases with age
- Celiac Disease: up to 80% if untreated
- Crohn’s Disease: up to 30%, affects the young
- Bariatric surgery: up to 60%, depending on procedure

Chronic Kidney Disease leads to decreased 1,25(OH)2D levels

Initial cause is increased FGF23 but subsequently to increased Pi and loss of functional tubules
Treatment for Vitamin D Deficiency
VITAMIN D SOURCES

- Natural foods
- Fortified foods
- Supplements
- Sunlight

25(OH)D RESPONSE TO ORAL D$_3$

- 66 males
- aged 38.7 yr ($\pm$ 11.2)
- dosed with vit D$_3$ from October through February

100IU D3 daily increases 25OHD3 by 1ng/ml

Heaney et al AJCN 77:204-210, 2003
D₂ vs. D₃*

- single oral dose
- 50,000 IU
- D₂ or D₃
- n = 10 in each group

*Armas et al., 2004

SUMMARY

- Osteomalacia has multiple causes but vitamin D deficiency is the most common factor
- The diagnosis of osteomalacia in the adult is not easy: 25OHD, PTH, alkPase, urine calcium are the most sensitive, and bone biopsy following tetracycline labeling is definitive
- Vitamin D deficiency/insufficiency is not rare—Vitamin D itself is the best treatment
- Osteomalacia can be prevented with 25OHD levels above 10-15ng/ml, but optimal skeletal health requires higher levels: 30-50ng/ml is safe and effective
- Vitamin D₃ has some advantages over D₂, but either should be given on a daily or weekly basis but remember if switching from D₂ to D₃, use a lower dose than when using D₂