Calcium Nephrolithiasis and Bone Health

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Objectives:
- Diagram the roles of vitamin D and Parathyroid hormone in calcium homeostasis
- Describe the contribution of androgens and estrogens on osteoporosis and fractures in stone formers.
- List 3 dietary interventions for stone formers with osteoporosis
- Identify key pharmaceutical management of bone loss in stone formers including roles of thiazide diuretics and bisphosphonates
Kidney Stones and Bone Health

- Noah S. Schenkman, MD
- University of Virginia School of Medicine
190 mg Calcium/ 100 gm serving Turnip greens
Are kidney stones an annoying episodic problem or manifestation of chronic metabolic disease?

Are kidney stones deadly?

How do hormones play into this?

What is the role of diet?

Does giving dietary calcium to patients with calcium stones make sense?
Osteoporosis

- Most common bone disorder affecting humans
  - compromised bone strength
  - increased risk of fracture

![Bone Comparison](image-url)
Osteoporosis

- Peak bone mass: age 30 y/o in women
- Slow decline until menopause, then decline hastens.
- At age 80, women have lost 30% of their bone mass
  - 1st indication of disease is usually a fall with non-vertebral fracture
  - Marked height loss over the years may be sign of underlying vertebral compression fracture.
Osteoporosis

- White American women age 50:
  - risk of osteoporotic fracture is 40%
  - 2/3 of fx occur after age 75.

- Hip fx: average age - 82 y/o:
  - 25% increase in mortality in following year
  - 25% of women require long term care, 50% have long term loss of mobility

- Avg. 3.8 yr. follow up
  - RR for mortality was 6.7 for hip fx.
  - 8.64 for vertebral fx.
Osteoporosis

- Goal: reduce fracture risk
  - Slow or stop bone loss or improve bone architecture and strength
  - 13-18% of American women >50 y/o have osteoporosis of the hip (less than 2.5 SD below the mean BMD of healthy, young, white women)
  - 4% in age 50-59, 52% in age 80 or older
  - Osteoporosis responsible for 90% of hip and spine fx in white women age 65-84
Risk factors for osteoporosis

- Age (50 to 90 years)
- Sex
- Weight$^a$
- Height$^a$
- Low femoral neck BMD
- Prior fragility fracture
- Parental history of hip fracture
- Current tobacco smoking
- Long-term use of glucocorticoids
- Rheumatoid arthritis
- Other causes of secondary osteoporosis
- Alcohol intake of more than two units daily

$^a$Body mass index is automatically computed from height and weight. Adapted from World Health Organization Collaborating Centre for Metabolic Bone Diseases.$^{28}$

Idiopathic Hypercalciuria!
Bone Mineral Density

- **BMD**: Factor of peak bone mineralization (age 30) and subsequent mineral loss
- **T score** most useful for postmenopausal women:
  - compare current BMD to mean BMD of normal, young adult population of same gender
## Osteoporosis

### BMD-based definitions of bone density

<table>
<thead>
<tr>
<th>Category</th>
<th>T-score Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>T-score above (ie, better than) or equal to −1.0</td>
</tr>
<tr>
<td>Low bone mass</td>
<td>T-score between −1.0 and −2.5</td>
</tr>
<tr>
<td>Osteoporosis</td>
<td>T-score below (ie, worse than) or equal to −2.5</td>
</tr>
<tr>
<td>Osteopenia</td>
<td></td>
</tr>
</tbody>
</table>

*From the World Health Organization.*

Calcium Homeostasis
Calcium Homeostasis

Food
600–1200 mg/day

GIT
300–1000 mg/day
feces

1.25(OH)₂D₃
300–400 mg/d
100–200 mg/d

ECF
1–2 g
(8.5–10.5 mg/dL)

PTH
4.9–9.7 g/d
5–10 g/d

25(OH)D₃
↓ PTH
1:25(OH)₂D₃

Kidneys
100–300 mg/day
urine

Bones
1000 to 2000 g

PTH,
1:25(OH)₂D₃

250–500 mg
250–500 mg

Pars
1:25(OH)₂D₃

250–500 mg

300–400 mg/d
Parathyroid Hormone

- Regulates: kidney, bone, intestinal mucosa (indirect)
  - Stimulated by decreases in serum calcium
  - Inhibited by high serum calcium, elevated vit. D3
- Effects in kidney:
  - stimulates activation of vitamin D3
  - promotes calcium reabsorption
  - suppresses tubular reabsorption of phosphate
- Effect on bone:
  - stimulates osteoclasts to breakdown apatite, releasing calcium and phosphorus
Hyperparathyroid

- May be responsible for stones in 2-8% of calcium stone formers
- Hypercalcemia is hallmark of the disease
  - Increased mobilization of calcium from bone leads to osteoporosis
  - Increased absorption from gut (PTH stimulated 1,25 OH D3 production)
  - Increased tubular resorption of calcium in kidney
Hyperparathyroid: Renal Effects

- Renal manifestations: hypercalciuria, hyperphosphaturia, nephrocalcinosis, hyperchloremic acidosis, and distal RTA
- Incidence of stones: 20%
- calcium oxalate or calcium phosphate stones
  - nephrocalcinosis due to high levels of calcium and phosphate in urine.
Stimulated by PTH and low serum phosphate. Also by estrogen, growth hormone
Vitamin D

- Acts to increase serum calcium and phosphate levels to enhance bone mineralization
  - Increases calcium and phosphate absorption from brush border of intestine
- Hypervitaminosis D usually due to overdose.
  - May have hypercalcemia. Rarely have urolithiasis
Estrogen

- Direct effects on stone formation are not known, generally thought to be protective
- Women generally have lower rates of stone formation than men
- Post-menopausal women have higher urine calcium levels than premenopausal
- Epidemiological evidence for increased incidence of stones in menopausal women
Hypercalciuria and Bone disease

- Epidemiologic evidence of 4 x increased vertebral fracture risk in stone formers*
- Decreased femoral neck BMD in pts with idiopathic hypercalciuria
- BMD correlates inversely with urinary calcium excretion in stone formers, but not in non-stone formers
- No strong data showing increased risk femoral neck fractures in stone formers

Heilberg & Weisinger, Curr Opin.Nephr. & HTN, 2006
Cumulative incidence of vertebral fracture among Rochester, Minnesota, residents following an initial episode of symptomatic nephrolithiasis

Melton, et al, Kidney Int. 1998
Hypercalciuria and Bone disease

- Decreased BMD in cortical and trabecular bone
  - some studies show increased markers of bone resorption
- Most studies confirm low bone formation and severe mineralization defect
- Normal serum calcium, phosphorus, parathyroid and vitamin D
The Stone Patient paradox

- “Common wisdom” is to restrict calcium intake in patients to prevent kidney stones.
- How does one treat the risk factors for calcium lithiasis while preventing potentially fatal ( ) osteoporotic fractures?
Dietary calcium and stones

- 120 men with recurrent calcium oxalate stones and hypercalciuria
- Normal calcium, low animal protein, low salt diet vs. low calcium diet
- Stone recurrence: 23/60 in low calcium group, 1/60 in normal calcium group
- Lower chance of stone recurrence with normal calcium diet RR = 0.49

Borghi, et al, NEJM, 2002
Influence of calcium intake on stones

**Figure 2.** Kaplan–Meier Estimates of the Cumulative Incidence of Recurrent Stones, According to the Assigned Diet.

The relative risk of a recurrence in the group assigned to the normal-calcium, low-protein, low-salt diet, as compared with the group assigned to the low-calcium diet, was 0.49 (95 percent confidence interval, 0.24 to 0.98; P=0.04).

Borghi, et al, NEJM, 2002
Thiazide and Osteoporosis

- Many observational studies note that thiazide diuretic use is associated with:
  - Higher BMD
  - Decreased bone loss
  - 30% risk of fracture reduction
- Supported by two RCT’s showing modest improvement in BMD
Thiazide and Osteoporosis

- Thiazides reduce renal calcium excretion
- 122 women completed 4 year randomized controlled trial:
  - HCTZ 50 mg/d vs. placebo
- 31% reduction in fractures and small positive benefit in bone density, sustained over 4 years

Bolland, et al., Osteoporosis Int, 2007
Thiazide and Osteoporosis

- 320 men and women age 60-79
- Randomize to placebo, 12.5 mg or 25 mg HCTZ
- Modest dose related improvement (1%) in spine and hip BMD at 3 yrs.

The effect of thiazide/indapamide and K-Cit on BMD of the L2–L4 spine, femoral neck, and radial shaft of hypercalciuric kidney stone formers

Data are expressed as percentage of normal, matched for age and gender (Z-score). **Indicates $P = 0.001$, †indicates $P < 0.001$. Bars above the blocks represent mean±s.d. Figure reprinted with permission by Pak et al.136 BMD, bone mineral density; K-Cit, potassium citrate.

Treatment

- Group 1: 35 Ca stone formers on alendronate 70 mg/wk
- Grp2: 35 Ca Stone formers on alendronate + HCTZ 50 mg/d
- At 2 yrs, both groups improved in bone markers, BMD, and decrease in calciuria, but HCTZ had statistically significant improvement over Grp 1.
Strategies to Effective treatment: Medication

- Pursue metabolic work-up in stone formers in both sexes
  - Young women may be at particular risk for osteoporotic fractures in later life
  - If hypercalciuria is found, treat with thiazide and potassium citrate to prevent bone loss
  - Post menopausal women with IHC probably benefit from thiazide and bisphosphonate therapy
Strategies to Effective treatment: Diet

- Stone formers should be on normal calcium diet (1000-1200 mg/d)
  - Low sodium, low animal protein diet
  - Dietary calcium more protective than supplements for stone prevention
- For Supplemental Calcium: Risk of stone recurrence vs. hip fracture in terms of morbidity and mortality
Future

- Screen all stone formers with BMD?
  - Not supported by insurance
  - Need better data
Questions ?