Michigan – AACE 2012 Annual Meeting

Does Hypercalciuria Cause Osteoporosis?

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Potential Conflict of Interest

CVS/Caremark, education consultant
Calcium Oxalate Crystals in Idiopathic Hypercalciuria

Calcium oxalate dihydrate  Calcium oxalate monohydrate

Treatment Trials of Thiazides
Definition of Hypercalciuria

- Men: >300 mg calcium per 24 hr
- Women: >250 mg calcium per 24 hr
- >4.0 mg calcium/Kg body weight
- >140 mg calcium/g urine creatinine

Effect of Calcium, Protein, and Sodium Intake on Recurrent Calcium Oxalate Stones

From Borghi et al NEJM 2002
Reversal of Low BMD in 57 year old Woman

- Sudden onset of severe back pain
- Menopause age 52 years
- Alendronate since age 53 years
- Mother had vertebral fractures

57 Year-Old Woman

- Lateral Vertebral Assessment (LVA)
- Kyphosis
- T11 total collapse
Laboratory Tests

- Serum Ca 9.6 mg/dL
- Serum 25-OH-vitamin D 42 ng/mL
- Parathyroid hormone 38 pg/mL
- eGFR 88 mL/min
- Urine Ca 321 mg/24 hr

Treatment of Hypercalciuria

- Chlorthalidone 25 mg daily
- CaI at 900 mg from foods
- UCa from 321 to 209 mg/24 hr
- Increase in spine (shown) and femoral neck BMDs
57 Year Old Woman with Low Bone Mineral Density

Since starting CTD:
UCa to 209 mg/24 hr
BMD increased 6%

Causes of Low Bone Density in Postmenopausal Osteoporosis

- Hypogonadal states
- Endocrine disorders
- Nutritional disorders
- Gastrointestinal diseases
- Rheumatologic disorders
- Hematologic disorders and malignancies
- Selected inherited disorders
- Immobilization
- Scoliosis
- Sarcoidosis
- Drug-induced
- Family history
- Alcoholism
- Low calcium intake
- Recurrent falls
- Frailty
- Low body weight
Prevalence of Hypercalciuria in Patients with Osteoporosis

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Prevalence</th>
</tr>
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<tbody>
<tr>
<td>Tannenbaum</td>
<td>2002</td>
<td>9.8%</td>
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<tr>
<td>Deutschmann</td>
<td>2002</td>
<td>10.3%</td>
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<tr>
<td>Peris</td>
<td>2002</td>
<td>21%</td>
</tr>
<tr>
<td>Giannini</td>
<td>2003</td>
<td>19%</td>
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</table>

Idiopathic Hypercalciuria

- Hypercalciuria in the absence of other causes
- Ca-stone formers (10%)
- Normal serum Calcium, PTH
- Increased intestinal Ca absorption
- Normal or increased 1,25D
- Defective renal tubule Ca reabsorption
- Low bone mass and increased fracture risk
- Elevated peripheral blood monocyte VDR
Pathogenesis of IH Bone Disease

- Is the bone disease inherited or acquired?
- Relationship of hypercalciuria and low bone mass
- Osteoclastic and/or osteoblastic dysfunction?

<table>
<thead>
<tr>
<th>TABLE</th>
<th>Hypercalciuric Stone-Forming (IH) Humans</th>
<th>Genetic Hypercalciuric Stone-Forming (GHS) rats</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urine Ca Excretion</td>
<td>Increased (by definition)</td>
<td>Increased</td>
</tr>
<tr>
<td>Intestinal Ca Absorption</td>
<td>Increased in most patients</td>
<td>Increased</td>
</tr>
<tr>
<td>Renal Tubular Ca Reabsorption</td>
<td>Decreased in many patients</td>
<td>Decreased</td>
</tr>
<tr>
<td>Bone Resorption</td>
<td>Increased in most patients – as evidenced by markers of bone resorption</td>
<td>Increased</td>
</tr>
<tr>
<td>Bone Mineral Density</td>
<td>Decreased in most patients</td>
<td>Decreased</td>
</tr>
<tr>
<td>Serum PTH</td>
<td>Normal to reduced or Elevated</td>
<td>Reduced</td>
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<tr>
<td>Serum 1,25(OH)<em>{2}D</em>{3}</td>
<td>Normal to elevated</td>
<td>Normal to elevated</td>
</tr>
<tr>
<td>Vitamin D Receptor</td>
<td>Increased number or no increase Gene polymorphism</td>
<td>Increased number</td>
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<tr>
<td>Ca Receptor</td>
<td>Changes in number not reported Activating and inactivating mutations associated with hyper- and hypo-calciuria, respectively Gene polymorphism</td>
<td>Increased number Treatment with cinacalcet activates the receptor – associated with increased UCa in SD but not GHS rats</td>
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<tr>
<td>Stone formation</td>
<td>Consequence of hypercalciuria</td>
<td>Present</td>
</tr>
</tbody>
</table>

Bushinsky et al, 2011
Intestinal Calcium Absorption and 1,25(OH)₂D
In Idiopathic Hypercalciuria


Calcium Balance in Idiopathic Hypercalciuria

Coe, Favus, Asplin The Kidney 2004
Effect of Low Ca Intake on Urine Ca in IH and Normals


BMD of Femur (Cortical) and Vertebrae (Trabecular) Bone

Bushinsky et al JBMR 2009
Bone Disease in Idiopathic Hypercalciuria

- Bone mineral density reduced
  - 15 studies, >600 patients
  - SPA, DPA, DXA, QCT
  - Lumbar spine BMD low in 11% to 92% of cases
  - Femoral neck BMD normal or low
  - Distal radius BMD normal

Hip and Spine BMD and Urine Ca in IH

Asplin et al 2003
Urine Ca Excretion and BMD

Asplin et al, 2006

Relationship of Urine Ammonium Excretion in IH Stone-Formers

Asplin et al, KI, 1999
Cumulative Incidence of Vertebral Fractures Following Initial Stone Episode

Melton et al, KI, 1998

Bone Histomorphometric Parameters in Idiopathic Hypercalciuria and other Metabolic Bone Diseases

- **Parameter**
  - Formation
  - Miner. apposition rate
  - Miner. Lag time
  - Osteoid vol
  - Osteoblastic activity
  - Resorption

<table>
<thead>
<tr>
<th>Parameter</th>
<th>IH</th>
<th>PMO</th>
<th>HMO</th>
<th>GIO</th>
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<tr>
<td>Formation</td>
<td>D</td>
<td>I</td>
<td>D</td>
<td>D</td>
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<tr>
<td>Miner. apposition rate</td>
<td>D</td>
<td>I</td>
<td>D</td>
<td>D</td>
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<tr>
<td>Miner. Lag time</td>
<td>Pr</td>
<td>Red</td>
<td>N</td>
<td>N</td>
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<tr>
<td>Osteoid vol</td>
<td>N-I</td>
<td>N</td>
<td>N</td>
<td>N</td>
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<tr>
<td>Osteoblastic activity</td>
<td>D</td>
<td>I</td>
<td>D</td>
<td>D</td>
</tr>
<tr>
<td>Resorption</td>
<td>N-I</td>
<td>I</td>
<td>I</td>
<td>I</td>
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</table>

D=decreased; I=increased; N=normal; Pr=prolonged; Red=reduced; Mineral=mineralization
Effect of Chlorthalidone on Calcium Balance in Idiopathic Hypercalciuria

Lauderdale et al, J Bone Miner Res 16:1893, 2001

Bushinsky et al, KI, 1988
Response of Hypercalciuric Men to Hydrochlorothiazide

Adams et al, Ann Int Med, 1999

Familial Patterns of Idiopathic Hypercalciuria

Coe et al
NEJM, 1979
Conclusions

- IH is a common cause of low bone mass in SF and non-SF
- Low BMDs increase fracture risk
- Treatment targets reduction of hypercalciuria
- Unresolved bone cell dysfunction

QUESTIONS?
<table>
<thead>
<tr>
<th>Accession Number</th>
<th>Fold Change (Log2)</th>
<th>P value</th>
<th>Gene Symbol</th>
<th>Pathway</th>
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<tr>
<td>NM_012854</td>
<td>5.6</td>
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<td>Inflammatory response</td>
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<td>NM_031531</td>
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<td>NM_010926</td>
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<td>TNFRSF1b</td>
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<td>XM_001074265</td>
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<td>0.33E-01</td>
<td>CSF-2 (GM-CSF)</td>
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<td>NM_013134</td>
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<tr>
<td>NM_013322</td>
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<td>TNFRSF11 (RANKL)</td>
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<tr>
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<td>NM_012601</td>
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<td>NM_012758</td>
<td>0.5</td>
<td>1.87E-06</td>
<td>Bmp2</td>
<td>TGF-beta</td>
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</table>

Model for immune system actions in osteoclast functions (Clowes et al).