IBD and Bone Health in Adults and Children

Francisco A. Sylvester, MD
Associate Professor of Pediatrics
Goals

• To review basic bone biology

• To understand the principles of DXA and its pitfalls

• To examine how IBD subverts normal bone function

• To review therapeutic options to increase BMD in patients with IBD
Bone And IBD

• Decreased bone mineral density
  – Males = Females
  – CD = UC (?)

• Fracture risk?
  – Vertebral fractures

Bernstein CN et al. Gastroenterology 2003;124:795
Semeao EJ et al. Gastroenterology 1997;112:1710
Vertebral Fractures - IBD

Goal

To review basic bone biology
Compact Bone

80% Bone Mass
Trabecular Bone

80% Bone Metabolic Activity
Osteoclasts

Sylvester FA, E Canalis 2006
Osteoblasts
Bone Remodeling

- Osteoclasts followed by osteoblasts
- Act on the same bone surface

http://www.umich.edu/news/Releases/2005/Feb05/img/bone.jpg
Abnormal Bone Remodeling: Osteoporosis

- Reduced bone mass
- Architectural deterioration of the skeleton
- Increased risk of fracture
Bone Mass and Age

Areal BMD

Growth

Ageing

Modeling Remodeling

Remodeling

Males

Females

Seeman E JCEM 2001;86:4576-84
Modeling Changes Bone Shape

Leonard, MB Pediatrics 2007;119:S166-74
Determinants of Bone Mass

- Endocrine Disorders
- Inflammation
- Genetics
- Medications
- Poor Nutrition
- Inactivity
- Chronic Illness
Goal

To understand the principles of DXA and its pitfalls
DXA Technology

**Detector** *(detects 2 tissue types - bone and soft tissue)*

**Patient**

**X-ray Source** *(produces 2 photon energies with different attenuation profiles)*

**Photons**
DXA: Size Matters!

Areal Projection Of Bone

Emerging photons

Bone

Scanning path

Incident photons

Different Size
But…. Same Material Density (in g/cm$^3$)
DXA: Size Matters!

Different “Areal” Density (in g/cm²)

“More Dense”

“Less Dense”
Reporting DXA
T- scores vs. Z-scores

\[ \text{Z-score} = \frac{\text{BMD (Observed} \ - \ \text{Normal for Age/Sex)}}{\text{SD}} \]

\[ \text{T-score} = \frac{\text{BMD (Observed} \ - \ \text{Normal for Young Adult)}}{\text{SD}} \]
Definition of Osteoporosis

• WHO definitions (2000) based on T-score
  – $\geq -1 = $ Normal
  – $< -1$ but $\geq -2.5 = $ Osteopenia
  – $< -2.5 = $ Osteoporosis

• *Only* applicable to post-menopausal women

• Not intended as thresholds for treatment

• Not validated in patients with IBD
Fracture Risk Gradient – T-Score

Relative Risk for Fracture

Bone Density (T-score)
Bone Density & Age vs. Fracture Risk

10-Year Fracture Probability (%)

Femoral Neck T-score

Age

Probability of first fracture of hip, distal forearm, proximal humerus, and symptomatic vertebral fracture in women of Malmö, Sweden.

Who Should Have DXA?

- Pre-existing fragility fracture
- > 65 years of age
- Patients with risk factors for low BMD/fracture
- Exposure to glucocorticoids ≥ 3 months
- Consider repeating in 6 – 12 months

Lichtenstein GR et al. Inflamm Bowel Dis 2006;12:797-813
Vertebral Fractures – Crohn Disease

• Cross-sectional prevalence of vertebral fractures
• 224 patients
  – 70 (36%) normal BMD
  – 123 (51%) osteopenia
  – 31 (13%) osteoporosis
• Mean age 38.7± 11.8 y
• 45 patients – 88 fractures
  – 16 with normal BMD

Goal

To examine how IBD subverts normal bone function
IBD - Bone

- Malnutrition
- Malabsorption
- Decreased physical activity
- Delayed puberty
- Medications
- Inflammation
Hypothesis

IBD: A Gut – Bone Axis?
Gut – Bone Axis Candidates

• Immunological factors
  – Soluble factors
  – Cells (circulating/local)

• Nutritional deficiencies
  – Direct effects
  – Indirect effects
    • Body composition
    • Hormonal axes
Infliximab – Bone Biomarkers

Luminal Crohn

Fistulizing Crohn

Franchimont N et al. *Aliment Pharmacol Ther* 2004;20:607
Pediatric Bone ≠ Adult Bone!
Effect of Infliximab
REACH Study

BSAP (U/L)

Baseline  
Week 10

% Change 109 ± 97
P<0.001

CTX (μg/μmol Cr)

Baseline  
Week 10

% Change 43 ± 78
P<0.001

IBD - Infliximab – Bone

- Increased markers of bone formation
- No effect on resorptive markers in adults
- Increased bone turnover in children
- Improved BMD

Osteoclasts

Sylvester FA, E Canalis 2006
Osteoclast Development

Exposure to signals such as prostaglandin E2, parathyroid hormone, and 1,25-dihydroxyvitamin D

Expression of osteoclast differentiation factor by osteoblasts or stromal cells

Binding of osteoclast differentiation factor to osteoprotegerin prevents differentiation and activation

Macrophage colony-stimulating factor

Osteoclast precursor

RANK

Osteoblasts

RANK

Osteoclastic

Osteoprotegerin

IBD – RANKL – OPG

• Modest increases in serum OPG/sRANKL

• OPG and BMD inversely correlated

• In mice OPG increases BMD/treats colitis

• OPG is a regulator of intestinal immune responses

• Vidal K et al. Am J Physiol Gastrointest Liver Physiol 2004;287:G836-44
• Bernstein CN et al. Inflamm Bowel Dis 2005;11:325-30
• Moschen AR et al. Gut 2005;54:479-87
OPG/RANKL in Children with IBD

The Colon: A Source of OPG

Gut – Bone Axis: Indirect Effects?
Effect of Lean Body Mass

- Muscle strain drives bone formation
- LBM deficits present at diagnosis in IBD
- Persist despite weight gain/symptom improvement

Sylvester FA et al. DDW 2007
Gut – Bone Axis – Indirect Effects

• Growth stunting

• Nutrient intake/absorption/utilization
  – Calcium
  – Vitamin D
  – Vitamin K
  – Zinc
Immune Factors
- T cells (INF-γ, RANKL)
- Cytokines (TNF-α, IL-6)
- OPG

Nutrition
- Calcium, vitamin D
- Caloric/Protein intake
- Vitamin K/Others
- Hypogonadism
  - ↓IGF-I
  - Inactivity
  - ↓Lean tissue mass
  - Medications

Inactivity
- ↓Lean tissue mass

Medications

↑Osteoclasts

↓Bone Mass

↓Osteoblasts
Bone and IBD - Unknowns

• Disease duration?
• Activity of disease?
• Site of IBD involvement?
• Small bowel surgery?
• Diagnosis in childhood?
• Skeletal site susceptibility?
• Effect of remission?
Goal

To review therapeutic options to increase BMD in patients with IBD
Risk Factors – Fracture
Modifiable

- Lifestyle factors
- Low BMI
- Risk of falling
- Lifelong low Ca intake
- Vitamin D deficiency/insufficiency
- Use of glucocorticoids
- Concurrent medical conditions
## Calcium

- **Women**
  - Pregnant and nursing: 1200 mg
  - 25-50 y: 1000 mg
  - > 65 y: 1500 mg

- **Men**
  - 25-65 y: 1000 mg
  - > 65 y: 1500 mg
## Vitamin D<sub>2</sub> vs. Vitamin D<sub>3</sub>

<table>
<thead>
<tr>
<th>D&lt;sub&gt;2&lt;/sub&gt;</th>
<th>D&lt;sub&gt;3&lt;/sub&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ergocalciferol</td>
<td>Cholecalciferol</td>
</tr>
<tr>
<td>Derived from fungal/plant sources</td>
<td>Produced in the skin</td>
</tr>
<tr>
<td>Drisdol, Chewable vitamins</td>
<td>Poly-Vi-Sol, Delta-D</td>
</tr>
<tr>
<td>Both equally effective to increase vitamin D levels (Some studies show D&lt;sub&gt;3&lt;/sub&gt; &gt; D&lt;sub&gt;2&lt;/sub&gt;)</td>
<td></td>
</tr>
</tbody>
</table>
## Dietary Sources of Vitamin D

<table>
<thead>
<tr>
<th>Source</th>
<th>Serving Size</th>
<th>Vitamin D (IU)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Milk</td>
<td>1 cup</td>
<td>98</td>
</tr>
<tr>
<td>Baked herring</td>
<td>3 oz.</td>
<td>1,775</td>
</tr>
<tr>
<td>Baked salmon</td>
<td>3 oz.</td>
<td>238</td>
</tr>
<tr>
<td>Canned tuna</td>
<td>3 oz.</td>
<td>136</td>
</tr>
<tr>
<td>Sardines</td>
<td>1 oz.</td>
<td>77</td>
</tr>
<tr>
<td>Raisin bran cereal</td>
<td>¾ cup</td>
<td>42</td>
</tr>
<tr>
<td>Pork sausage</td>
<td>1 oz.</td>
<td>31</td>
</tr>
<tr>
<td>Egg yolk</td>
<td>1</td>
<td>25</td>
</tr>
</tbody>
</table>

USDA 2002
Bisphosphononates
Take Home Points

• Bone mass deficits occur in patients with IBD

• Risk of fractures mildly increased
  – Vertebral fracture prevalence?

• Multifactorial pathogenesis
Take Home Points

• Bone mass can be measured by DXA
  – Be aware of pitfalls

• Identify and address modifiable risk factors

• Control of inflammation, calcium/vitamin D, activity may increase bone mass
Acknowledgements

• NIH grant R01-DK-066303
• Donaghue Foundation
• CCMC
• Dr. Ernesto Canalis (Saint Francis Hospital & Medical Center)