DISCLOSURE

Relevant Financial Relationship(s)
None

Off Label Usage
None
Metabolic Bone Disease
Basic Constructs
Metabolic Bone Diseases
Collagen Disorders

- Osteogenesis Imperfecta
- Marfan syndrome
Osteogenesis Imperfect Type III
Metabolic Bone Diseases
Mineralization Disorders

- Vitamin D deficiency
- Calcium deficiency
- Phosphate depletion
- Toxic inhibition of mineral
  - Fluoride
  - Etidronate
  - Oxalate
  - Aluminum
- Hypophosphatasia
Rickets
Metabolic Bone Diseases
Bone Remodeling Abnormalities

Oc Precursor → Osteoclast → Mononuclear Cells → Ob Precursors → Osteoblast
Resting Bone Surface “Activation” → Resorption → Reversal → Bone Formation → Mineralization

~3 WEEKS

LC = Lining Cells  CL = Cement Line  OS = Osteoid  BRU = Bone Remodeling Unit

~3 MONTHS

MAYO CLINIC
Formation > Resorption
Osteopetrosis
Resorption > Formation
Osteoporosis
Malignancy

Resorption >> Formation
Multiple Myeloma

Formation >> Resorption
Metastatic Prostate Cancer

C^{11}-choline PET = Choline-Avid Metastases
Metabolic Bone Disease
Clinical Evaluation
Evaluation of Metabolic Bone Disease History and Physical Exam

- Medical history
  Fractures, falls, other illnesses, menses, nutrition, dental history, GI surgeries, etc.
- Medications
- Physical exam
  Vital signs, general based on history with attention to teeth, spine, skin, joints, sclera, and physical performance
  One legged stance test, squat and touch floor
Some of the Causes of Rapid Bone Loss

- Medications that are “bad for the bone”
- Hypogonadism
  - Transmenopause and postmenopause
- Transplant
  - BMT and solid organ
- Malabsorption
  - Malabsorptive bariatric procedures
<table>
<thead>
<tr>
<th>Medication</th>
<th>Likely Mechanism</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glucocorticoids</td>
<td>Decrease bone formation/Increased resorption</td>
</tr>
<tr>
<td>Unfractionated heparin</td>
<td>Decrease bone formation/Increased resorption</td>
</tr>
<tr>
<td>Aromatase inhibitors</td>
<td>Reduced estrogen production</td>
</tr>
<tr>
<td>GnRH agonists</td>
<td>Hypogonadism</td>
</tr>
<tr>
<td>Medroxyprogesterone acetate (depot)</td>
<td>Reduced estrogen levels</td>
</tr>
<tr>
<td>Thyroid hormone excess</td>
<td>Increase bone resorption</td>
</tr>
<tr>
<td>Thiazolidinediones</td>
<td>Decreased bone formation</td>
</tr>
<tr>
<td>Canagliflozin</td>
<td>Unknown (? Falls due to BP lowering)</td>
</tr>
<tr>
<td>Proton pump inhibitors</td>
<td>Unknown (? Falls)</td>
</tr>
<tr>
<td>Serotonin selective reuptake inhibitors</td>
<td>Inhibition of serotonin transporter</td>
</tr>
<tr>
<td>Antiepileptics (dilantin or phenobarbitol)</td>
<td>Uncertain/Increased 25-D catabolism</td>
</tr>
<tr>
<td>Calcineurin inhibitors</td>
<td>Increased bone resorption</td>
</tr>
<tr>
<td>Antiretroviral therapy (ART) for HIV</td>
<td>Increased bone resorption</td>
</tr>
<tr>
<td>Warfarin</td>
<td>Uncertain</td>
</tr>
<tr>
<td>Voriconazole</td>
<td>Fluoride excess</td>
</tr>
</tbody>
</table>

Early Menopausal Bone Loss

Loess smoothed value of baseline normalized lumbar spine bone mineral density

Loess smoothed value of baseline normalized femoral neck bone mineral density

Evaluation of Metabolic Bone Disease Imaging

- Plain radiographs
- Bone mineral density
- Trabecular Bone Score (TBS)
- Finite element analysis (FEA)
- HRpQCT
  May be especially useful in normal DXA BMD
- Bone Scan
  Focal or diffuse?
- Computed tomography scans (CT)
- Magnetic resonance imaging (MRI)
Evaluation of Metabolic Bone Disease Lab Tests

- Systemic markers of disease
  CBC, liver and renal function, TSH, alkaline phosphatase, protein electrophoresis, and others depending on H & P
- Bone turnover markers
  Procollagen I Intact N-Terminal (P1NP), bone alkaline phosphatase, Beta-CrossLaps
- Vitamin D
  25-hydroxyvitamin D
- Calcium biomarkers
  PTH, calcium, phosphorus, albumin, magnesium, 24 hour urine calcium and creatinine
Evaluation of Metabolic Bone Disease
Bone Histomorphometry/Bone Biopsy
High Bone Mass
Case 1
Patient Presentation

- 67 year old female from Iowa referred for recent stress fractures and discrepant bone densitometry results
- Recent stress fractures from jogging
- No fragility fractures
- Mayo gastroenterologist ordered BMD and bone consultation
Past Medical History

- Gastrointestinal complaints, including chronic constipation
- Sigmoid colectomy for rectal prolapse
  Postoperative hypocalcemia and tetany due to phosphorus-containing laxative
- Ileal and cecal resections for ischemia due to intussusception
Past Medical History (Cont.)

- Anorexia Nervosa with decreased oral intake and weight concerns
- Menopause in early 40s without hormone replacement therapy
- Unable to tolerate calcium supplements (bloating/gas)
History (Continued)

- **Medications**
  - Tegaserod Maleate
  - Omeprazole
  - Docusate sodium
  - Metronidazole cream

- **Social History**
  - No current tobacco (25 pack years)
  - 2-3 ounces of alcohol per week

- **Family History**
  - Sister with osteoporosis and height loss
  - Mother with fracture at age 90
Physical Exam

- BMI 15.189 (weight 38.4 Kg, height 159 cm)
- BP 104/53, Pulse 65 and regular
- Thin woman, No scoliosis or kyphosis
- Rest unremarkable
BMD: 1.47g/cm² L2-4

T score of +2.3
Z score of +4.7
BMD: 0.77g/cm² (total)

T score of -1.7
Z score +0.4
<table>
<thead>
<tr>
<th>Date</th>
<th>Femur Neck</th>
<th>T score</th>
<th>Z score</th>
<th>% change</th>
<th>Type of scanner</th>
</tr>
</thead>
<tbody>
<tr>
<td>7-13-98</td>
<td>0.673 g/cm²</td>
<td>-1.6</td>
<td></td>
<td></td>
<td>Hologic</td>
</tr>
<tr>
<td>9-13-2000</td>
<td>0.700 g/cm²</td>
<td>-1.3</td>
<td>+0.1</td>
<td>4.0%</td>
<td>Hologic</td>
</tr>
<tr>
<td>7-12-2004</td>
<td>0.77 g/cm²</td>
<td>-1.7</td>
<td>+0.4</td>
<td></td>
<td>Lunar</td>
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<tr>
<td>L-spine (L2-4)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>7-13-98</td>
<td>1.139 g/cm²</td>
<td>+0.5</td>
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<td></td>
<td>Hologic</td>
</tr>
<tr>
<td>9-13-2000</td>
<td>1.204 g/cm²</td>
<td>+1.1</td>
<td>+2.9</td>
<td>+5.7 % *</td>
<td>Hologic</td>
</tr>
<tr>
<td>7-12-2004</td>
<td>1.47 g/cm²</td>
<td>+2.3</td>
<td>+4.7</td>
<td></td>
<td>Lunar</td>
</tr>
</tbody>
</table>

* indicates significant change
Question 1: Which of the following best summarizes your initial recommendations to the patient?

A. You have a superb BMD and are at low risk for future fracture.
B. We need to do more tests. Let’s start with some x-rays of your spine.
C. We need to do some lab work to further characterize your BMD findings.
D. We need to further characterize your family members BMD.
E. All the above.
Case 2
History

- A 76 year old is referred for a marked change in her BMD of the hip.
- 5 years earlier she was told that her hip BMD was well above average and that she did not need to worry about osteoporosis (T score +3).
- A repeat spine and hip BMD at this time shows that she has osteoporosis.
- She is complaining of left hip pain that has been present the last 4-5 years.
Left Femur Bone Density

Reference: Total

<table>
<thead>
<tr>
<th>BMD (g/cm²)</th>
<th>Young-Adult T-Score</th>
<th>Age-Matched Z-Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neck</td>
<td>1.409</td>
<td>2.7</td>
</tr>
<tr>
<td>Troch</td>
<td>1.238</td>
<td>3.4</td>
</tr>
<tr>
<td>Total</td>
<td>1.433</td>
<td>3.4</td>
</tr>
</tbody>
</table>

Trend: Total

%Change vs Baseline
Question 1: Which of the following is indicated?

A. Work up for malignancy  
B. X-ray of the left hip  
C. Initiation of oral bisphosphonates  
D. Skeletal survey  
E. Hepatitis C serologies
Hypercalcemia
Case 3 History

- 38 year old from OK referred for persistent PHPT
- Hypercalcemia on lab – Sept. 2007
  Fibromyalgia – “hurting all over”
- Parathyroid scan nonlocalizing
- Parathyroid exploration 10/07
  Left inferior excised – benign lymph node
  Left and right identified and left in tact
- Post-op calcium 11.6 mg/dL, PTH 62 pg/ml
History (continued)

- Repeat parathyroid scan negative
- CT neck asymmetric uptake right thyroid
- Repeat surgery 1/25/08
  Right hemithyroidectomy
  Numerous areas of possible parathyroid adenomas excised
  All benign fat or lymph nodes
- Post-op calcium 11.8 mg/dL, PTH – 46 pg/mL
History (continued)

• No history of head or neck radiation
• No history of lithium or thiazides
• No family history MEN/Jaw Tumor
• Father with hypercalcemia – details not known
• No calcium or vitamin D supplements
• History of Ebstein’s anomaly
  Asymptomatic
Case 3 Medications

- Levothyroxine 112 mcg daily
- Pregabalin 50 mg TID
- Midrin 1-2 prn headache
- Oxymorphone ER 20 mg 1-2 tablets every 8 hours
Case 3 Physical Examination

- VS – 160 cm; 90 kg; BMI 35.156 kg/m$^2$
- Well healed collar scar
- Holosystolic murmur best heard in 2$^{nd}$ ICS
- Abdominal obesity
- Numerous trigger points c/w fibromyalgia and pain over right trochanteric bursa
Question 1: What is the next most important test to order?

A. Repeat subtraction parathyroid scan and neck ultrasound
B. Search for non-PTH causes of hypercalcemia to include PTHrP, 1,25-dihydroxyvitamin D, Vitamin A, SPEP/UPEP
C. Bone mineral density of hip, spine, and wrist and assessment for kidney stones
D. 24 hour urine calcium and creatinine
E. Venous sampling for PTH
Case 4
Case 4

- 48 year old female from Minnesota
- Breast cancer treated ≈ 5 years ago with wide local excision after breast conservation surgery followed by radiation, chemotherapy, and tamoxifen (2 years)

Invasive ductal carcinoma

T1 (1.5 cm), N0, M0 (ER - PR + HER2/neu -)

No history of recurrence on aromatase inhibitor now with menopause (2 ½ years)
Lab Results – Serum Calcium

10.4 mg/dL (2.6 mmol/L)
Laboratory Results (Cont.)

• Maximal serum calcium - 11.1 mg/dL (2.78 mmol/L) 3 years prior.
• PTH - 30 pg/mL (nl, 15-50)
• Phosphorus – 4 mg/dL (1.29 mmol/L)
• 24 hour urine calcium – 152 mg
• Normal tests: TSH, 25-hydroxyvitamin D (31 ng/mL; 77.38 nmol/L), CBC, creatinine, AST, and alkaline phosphatase.
Complications History (Cont.)

- No kidney stones
- No adult fractures
  
  BMD – FN T-score = -0.5; LS T-score = -0.9
  
  Decline of 7.2% at LS - started on risedronate 1 year ago.

- No symptoms
History (Cont.)

- Limited calcium intake – dietary 600-800 mg/day with sporadic use of a supplement (none recently).
- FH negative for hypercalcemia or MEN
- No specific head or neck radiation treatment
- No prior lithium use
Medications

- Metoprolol tartrate 50 mg one half pill daily
- Venlafaxine 37.5 mg one pill twice daily
- Anastrozole 1 mg one pill daily
- Levothyroxine 75 mcg one pill daily
- Risedronate 35 mg one pill weekly
Physical Exam

• Unremarkable
Question 1: What would you recommend next?

A. Observation with follow-up calcium, phosphorus, and PTH in 1 year
B. Parathyroid scan and consultation with a skilled parathyroid surgeon
C. Further work-up of her hypercalcemia including 1,25-dihydroxyvitamin D, vitamin A, and PTHrP
D. Discontinuation of anastrozole
E. None of the above
Case 5

- 60 year old male from New Mexico
- Age 20-23 (1973-1976)
  Passed 30 kidney stones
  Intermittent hypercalcemia with low to normal PTH
  Parathyroid surgery – no parathyroid adenoma
- Recurrent nephrolithiasis – 2009/2011
  Complicated by urethral strictures
- 2013 – vitamin D3 5000 IU daily recommended
  Recurrent nephrolithiasis x 4
Case 5 (continued)

- January 2014 – more stones, urethroplasty
- 2 childhood fractures only
  DEXA BMD FN T-score -1.6
- March 2014 – Rochester visit
Case 5
Past Medical History

- Nephrolithiasis
- Type 2 diabetes
- Gout
- Hypertension
- Hyperlipidemia
- Depression
- OSA
Case 5
Medications

- Aspirin 81 mg one tablet daily
- Citalopram 20 mg one tablet daily
- Tamsulosin 0.4 mg one tablet daily
- Insulin detemir 10 units daily SQ
- Atorvastatin 10 mg one tablet daily
- Fish Oil one capsule daily
- Glipizide ER 2.5 mg one tablet daily
Case 5
Family History

• 6/8 siblings, nephew, niece with chronic urinary calculi, mild intermittent hypercalcemia, hypercalciuria, low PTH

• Brother died from recurrent kidney stones and ESRD
Laboratories

• Outside
  Calcium – 10.5 mg/dL (albumin 4.0 4 g/dL);  
  PTH – 13 pg/mL; 25-hydroxyvitamin D – 38 ng/mL; 1,25-dihydroxyvitamin D – 98 pg/mL

• Mayo
  Calcium – 10.6 mg/dL; phosphorus – 3.5 mg/dL;  
  PTH 14 pg/mL; albumin – 4.3 g/dL; creatinine – 1.5 mg/dL; vitamin A – 83.5 mcg/dL (nl, 32.5-78);  
  24 urine calcium – 207 mg (diet restricted in calcium); 25-hydroxyvitamin D – 69 ng/mL;  
  1,25-dihydroxyvitamin D – 70 pg/mL

Normal – SPEP; CBC; TSH; magnesium
Case 5
Physical Exam

• Vital signs
  Height – 178.8 cm; weight – 87.8 kg; BMI – 27.49; BP – 90/55

• Rest unremarkable
Which of the following is the best next diagnostic plan?

A. 24,25-hydroxyvitamin D
B. Call pharmacy to assess medications and bring in all medications to office
C. PTHrP
D. Bone marrow biopsy
E. Chest radiograph, PPD, and fungal serologies
Low Bone Mass
Case 6

History

• 34 year old female from MN referred for osteopenia
• Rt foot fracture stepping over coffee table
  Complicated by DVT → PE after immobilization while on transdermal ERT
  No other fractures
• Prior TAH BSO for endometriosis 7 years prior
  On ERT since
Case 6 (cont)

- DEXA BMD 1 year prior
  Hip Z-score -1.9 (T-2.0)
  Spine Z-score -1.9 (T-1.9)
- Additional risk factors
  Coumadin for 6 months after DVT otherwise completely unremarkable
Case 6 (cont)

- Medications
  Citracal 3 tablets daily
  Prilosec → History ulcer NSAIDS
- FH
  No fractures
  Brother with autoimmune hepatitis
Case 6
Physical Examination

- No blue sclera
- Dentition unremarkable
- No joint hyperextensibility
- No signs of Cushing’s
Case 6
Lab Results

- Serum calcium – 10.7 mg/dL
  Repeat calcium 10.2 mg/dL, phosphorus – 3.8 mg/dL, and PTH 36 pg/mL
- Normal serum creatinine
- 24 hour urine calcium – 199 mg
- 25-hydroxyvitamin D – 33 ng/mL
- Bone alkaline phosphatase 5.1 µ/L (premenopausal < 14 µ/L)
Question 1: Which one of the following would you recommend next?

A. More lab work
B. Estrogen Replacement Therapy
C. Bisphosphonate Therapy
D. Review of medical records
E. Parathyroid scan