Recognizing When It's Not Osteoporosis After All

AMERICAN ORTHOPAEDIC ASSOCIATION
OWN THE BONE

May 21, 2021

E. Michael Lewiecki, MD, FACP, FACE
Director, New Mexico Clinical Research & Osteoporosis Center
Director, Bone Health TeleECHO
University of New Mexico Health Sciences Center
Albuquerque, New Mexico, USA

Disclosure

- No direct compensation from potentially conflicting entities
- Employed by New Mexico Clinical Research & Osteoporosis Center, which has received the following in the past one year:
  - Research grant support from Amgen, Radius, Mereo
  - Consulting and scientific advisory board fees from Amgen, Radius, Alexion, Sandoz
  - Honoraria for service with speakers' bureaus of Alexion, Radius
  - Support for project development with University of New Mexico
- Board positions with the ISCD, NOF, OFNM
- Guideline committees with ISCD, NOF, AACE, NAMS

Objectives

- Define criteria for diagnosing osteoporosis
- Describe the evaluation of patients with osteoporosis
- Identify patients who appear to have osteoporosis, but they actually have other skeletal disorders

3 Ways to Diagnose Osteoporosis

Criteria that are **consistent** with osteoporosis

- **Bone mineral density (BMD)**
  - T-score ≤ -2.5 at LS, TH, FN, or 33%R
  - Assumption: other causes of low BMD have been excluded
- **Fragility fracture**
  - Hip fracture regardless of T-score
  - Fracture of spine, proximal humerus, pelvis, or in some cases, distal forearm, and T-score between -1.0 and -2.5
  - Assumption: other causes of fracture have been excluded
- **FRAX**
  - T-score between -1.0 and -2.5 and fracture probability exceeds country-specific treatment thresholds [US: MOF ≥ 20% or HF ≥ 3%]
  - Assumption: FRAX provides a reasonably accurate estimate of fracture risk

National Bone Health Alliance. Osteoporos Int. 2014;25:1439-1443.

Beyond T-score

- T-score ≤ -2.5 is not always osteoporosis
  - Osteomalacia
  - CKD-Mineral and Bone Disorder
  - Osteogenesis imperfecta
  - Many other disorders
- T-score > -2.5 may be osteoporosis
  - Fragility fracture
  - High fracture probability

Many Causes of Low BMD

Inherited	**Nutritional**	**Endocrine**	**Drugs**	**Other**
OI	Malabsorption	Hypogonadism	Glucocorticoids	MM
Homocystinuria	Chronic liver dis.	Hyperthyroidism	Anticonvulsants	RA
Marfan's syndrome	Alcoholism	Cushing's syndrome	Excess thyroid	Mastocytosis
	Ca^{++} deficiency	Hyperparathyroidism	Depo-Provera	Immobilization
	Vitamin D deficiency	Eating disorder	Aromatase inhibitors	TIO
	Low phosphorus		Androgen deprivation	XLH
			Chemotherapy	
			Immunosuppressives	
			Tobacco	
			Lithium	
			Aluminum	
			Long term heparin	
			Thiazolidinediones (TZDs)	
			Tenofovir	

How do we know it’s osteoporosis and not something else?

Evaluation

Focused history

- Prior fractures
- Family history of fractures
- Childhood development
- Falls
- Medications, supplements
- Osteoporosis treatments
- Historical max. height
- Lifestyle
- Surgery
- Diet
- Review of systems
- More

Physical exam

- Height (stadiometer)
- Falls risk assessment
- Gait
- Sclerae
- Kyphosis
- Rib-pelvis space
- Skeletal deformity
- Rash
- Tremor
- Hepatomegaly
- Flexibility
- More

Lab for all

- CBC
- Blood chemistries (CMP+P)
  - Calcium
  - Albumin
  - ALP
  - eGFR
  - LFTs
  - Phosphorus
- 25-OH-vitamin D
- 24-hour urine for calcium, sodium

Lab for some

- TSH
- Celiac antibodies
- Bone turnover markers
- Urinalysis
- sIFE, kappa/lambda light chain ratio
- Intact PTH
- Overnight dexamethasone suppression
- TRP
- FGF23
- Bone biopsy

Osteomalacia

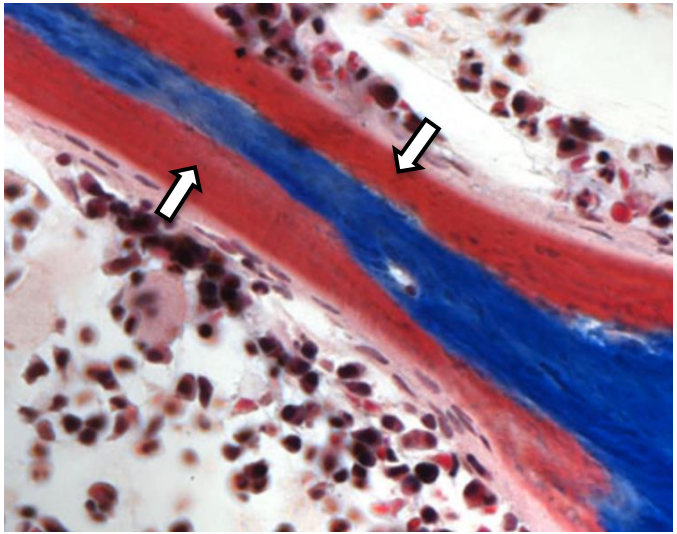
"Soft Bones"

Disorders and conditions characterized by defective bone mineralization

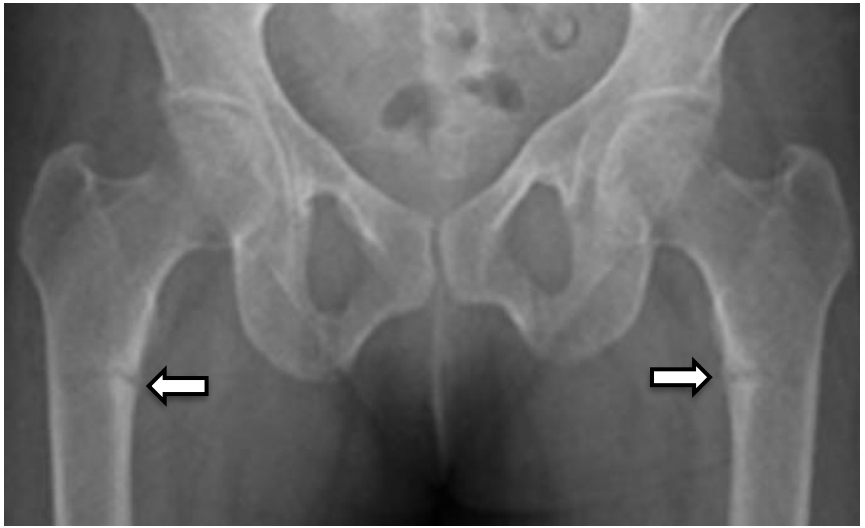
Prevalence of bone mineralization defects (OV/BV > 2%) was 26% on bone biopsies in 675 Europeans with association with low vitamin D levels *

* Priemel M et al. J Bone Miner Res. 2010;25:305-312.

Osteomalacia



Photomicrograph of Bone Biopsy
Red = unmineralized osteoid
Blue = mineralized osteoid



Pseudofractures
(Looser zones, Milkman's syndrome)

https://www.endocrinologyadvisor.com/home/decision-support-in-medicine/endocrinology-metabolism/osteomalacia-2/

It is important to recognize osteomalacia because . . .

- Treatment is different than for osteoporosis
- Osteoporosis treatments may be harmful
- Your patient will be very happy
- You will be a hero

When to Suspect Osteomalacia

- Generalized bone pain
- Proximal muscle weakness
- Waddling gait
- Bone tenderness
- Fractures
- Pseudofractures
- Abnormal ALP
- Low phosphorus
- Skeletal deformities (rickets in children)

DXA cannot distinguish osteomalacia from osteoporosis

Examples of Osteomalacia

- Acquired
  - Nutritional/Malabsorption – vit D deficiency, GI surgery, CD
  - Medications - some anticonvulsants, antiretroviral therapy
  - Tumor Induced Osteomalacia (TIO)
  - Chronic Kidney Disease-Mineral and Bone Disorder (CKD-MBD)
- Inherited
  - Hypophosphatasia (HPP)
  - X-Linked Hypophosphatemia (XLH)

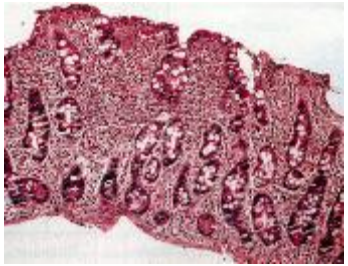
Woman with Recent Wrist Fracture

- Healthy and active 52 y/o postmenopausal woman
- After a recent wrist fracture from a fall, her first ever DXA → L1-L4 T-score = -3.9, LFN T-score = -3.1
- ROS unremarkable
- No family hx of skeletal diseases
- Weight 110 lbs, height 63 inches
- Exam unremarkable except for slight tenderness of anterior tibia and slow rising from a squatting position
- What do you do next?

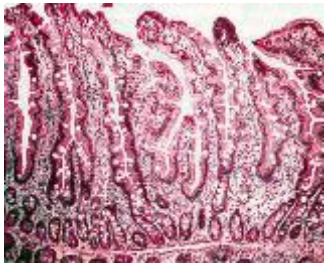
- **Serum calcium = Normal**
  9.1 (Nl. 8.4-10.4)
- **Serum phosphorus = Normal**
  2.6 (Nl. 2.4-5.0)
- **Serum 25-OH-D = Very low**
  9 (Nl. 30-30)
- **ALP = High**
  180 (Nl. 44-147)
- **iPTH = High**
  176 (Nl. 12-72)
- **24-hour urine calcium = Very low**
  8 mg (Nl. > 50-100)

- Celiac antibodies → high titer endomysial IgA antibodies

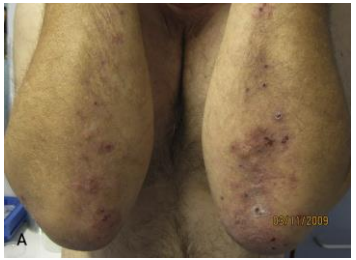
Diagnosis: Celiac Disease



Celiac Disease



Normal



Dermatitis Herpetiformis

- Findings consistent with osteomalacia as well as osteoporosis
- Treatment was gluten free diet to resolve malabsorption and correct osteomalacia before considering osteoporosis therapy
- 12% LS BMD increase over 2 years with gluten free diet alone in this patient
- Giving osteoporosis medications first could be harmful as well as ineffective

Farrell RJ et al. NEJM. 2002;346:180-188.
Oxentenko AS. Mayo Clin Proc. 2019;94:2556-2571.

Woman with Chronic Fatigue and Pain

- 75 y/o woman has not felt well for about 8 months, with progressive fatigue, weakness, and difficulty walking
- Right foot pain 8 months ago: stress fracture diagnosed by X-ray
- Right hip pain 5 months ago: stress fracture right femoral head diagnosed by nuclear bone scan
- Long-standing HIV infection controlled with medications
- Currently taking abacavir, raltegravir, tenofovir, pantoprazole, and pancreatic enzymes
- Exam: unstable gait, using walker, difficulty rising from chair

- DXA: L1-L4 T-score = -3.2
- Serum calcium = 8.9 (Nl. 8.4-10.4)
- Serum phosphorus = 2.2 (Nl. 2.3-5.6)
- Serum 25-OH-D = 98 (Nl. 30-30)
- ALP = 223 (Nl. 38-150)
- iPTH = 52 (Nl. 12-72)
- eGFR = 39
- Celiac antibodies normal
- CTX = 1409
- 24-hour urine calcium = 291 mg (Nl. > 50-100)

- TRP = 29% (Nl. > 80%)
- FGF23 = < 50 (Nl)

Diagnosis: Hypophosphatemic Osteomalacia Secondary to Tenofovir

- Warnings and Precautions
  - New or worsening renal impairment
  - Fanconi syndrome*
  - Decreases in BMD
- Reports of hypophosphatemia with osteomalacia documented by bone biopsy and pseudofractures on bone scans

- Treated with K-Phos Neutral 500 mg QID and stopping tenofovir
- Slow resolution of symptoms
- Giving osteoporosis medications first could be harmful as well as ineffective

* Syndrome of inadequate reabsorption of small molecules in the proximal renal tubules

Man with Pain, Weakness, Fractures

- 48 y/o man is hospitalized with a hip fracture from a fall and consultation was requested
- He was healthy until about 2 years earlier, then progressive pain in buttocks, low back, arms, and legs
- 1 year ago started having difficulty rising from a chair, eventually needing a walker and then a W/C
- Extensive work-up by many specialists unremarkable except for low D (18) and high ALP (205)
- DXA: L2-L4 T-score = -3.0
- Treated with ZOL

- Phosphorus = 1.5 (2.4-5.0)
- Renal tubular reabsorption of P = 40% (Nl. > 80%)
- FGF23 = 262 (Nl. <180)
- Diagnosed with tumor-induced osteomalacia
- Octreotide scan shows intense uptake in right mandible
- Oral surgeon excised benign fibroma
- Several months later, patient was walking and metabolic studies returned to normal

Lewiecki EM et al. Arthritis Rheum. 2008;58:773-777.

Tumor-Induced Osteomalacia

- Rare paraneoplastic syndrome resulting in osteomalacia
- Usually from small slow growing benign mesenchymal tumor
- Excess FGF23 causes hypophosphatemia due to renal phosphate wasting and ↓ production of 1,25-$(OH)_2$-D
- Typical patient has low P, low TRP, high FGF23, low/low nl. 1,25-$(OH)_2$-D, nl. Ca, nl. PTH
- Treatment is resection of tumor
- Burosumab is a fully human monoclonal antibody to FGF23, approved for XLH in 2018 and TIO in 2020
- Indication: “The treatment of FGF23-related hypophosphatemia in tumor-induced osteomalacia (TIO) associated with phosphaturic mesenchymal tumors that cannot be curatively resected or localized in adult and pediatric patients 2 years of age and older.”

Burosumab package insert.

Woman with Recurrent Poorly Healing Fractures

- 63 y/o woman is referred by orthopedist for management of “severe osteoporosis”
- Prior treatment with alendronate from age 49 to age 54
- DXA: L33%R T-score = -4.2 (spine and hip not valid)
- Multiple low trauma fractures, often with delayed healing
  - Age 42+ - recurrent metatarsal stress fractures
  - Age 47 - left femur shaft, fall
  - Age 59 - right femur shaft, fall
  - Age 62 - left mid-tibia

Childhood and family history:

- Multiple episodes respiratory failure requiring hospitalization before age 18
- Chronic bone pain beginning in childhood
- Delayed childhood motor development with waddling gait, difficulty walking and running, failure to keep up with peers
- Brother with similar symptoms and early loss of deciduous teeth

Exam and Lab

- Exam
  - Height 62.4 in., weight 210 lbs.
  - Slow unstable gait
  - Using wheeled walker
  - Valgus (knock-kneed) deformity
  - Difficulty getting on exam table
- Lab
  - Normal CBC, calcium, phosphorus, 25-OH-D, GFR, LFTs, K/L light chains, 24-hr urinary calcium
  - ALP = 21 U/L (Nl. 38-150)
  - Differential diagnosis of low ALP . . .

- Common causes of low ALP
  - Denosumab
  - Bisphosphonates
  - Wrong reference range
  - Improper specimen collection
  - Glucocorticoids
  - Chemotherapy
  - Tamoxifen
  - Clofibrates
- Uncommon causes
  - Hypophosphatasia
  - Milk-alkali syndrome
  - Massive blood transfusion
  - Vitamin D toxicity
  - Vitamin C deficiency
  - Mg or Zn deficiency

Adapted from Whyte MP. Bone. 2017;102:15-25.

Diagnosis: Juvenile Onset Hypophosphatasia

- B6 = 298 nmol/L (Nl. 20-125)

- Confirmatory genetic testing: ALPL heterozygous pathogenic variant consistent with dominant form of hypophosphatasia

Hypophosphatasia (HPP)

- Rare inherited disorder caused by inactivating mutations of *ALPL* gene that encodes for TNSALP resulting in poor bone mineralization (rickets, osteomalacia) – autosomal dominant and autosomal recessive
- Prevalence
  - ~ 1/100,000 for severe perinatal and infantile forms
  - ~ 1/2500 Mennonites in Manitoba (1 in 25 are carriers)
  - Unknown for mild forms [probably more common than we thought]
    - ~1/6370 in one European study (Mornet E et al. Ann Hum Genet. 2011;75:439-445.)
- Manifestations and severity highly variable
  - Perinatal, infantile, childhood, adult, odonto-hypophosphatasia
  - Adults may present with recurrent poorly healing fractures, atypical femur fractures, or seem to have osteoporosis

Bianchi ML. Osteoporos Int. 2015;26:2743–2757.

Summary

- Patients with skeletal deformities or recurrent fractures should be thoroughly evaluated for contributing factors
- **Measure phosphorus** and **pay attention to ALP** in all patients with skeletal diseases
- If you don't feel comfortable evaluating and treating, refer to someone who does, and . . .
- If you want to learn more about rare bone diseases, consider participating in Rare Bone Disease TeleECHO (OI Foundation)