Secondary Causes of Osteoporosis:
It's More Than Just Little Old Ladies

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Disclosures

- Consulting - Amgen, Radius Health
- Speaker's Bureau - Alexion, Amgen, Radius Health
- Research - Amgen, Radius Health

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Learning Objectives

(1) Review common secondary causes of bone loss.
(2) Explore some unusual causes of bone loss, including HPP, XLH, and ENPP1 deficiency.
(3) Evaluate some medications that contribute to bone loss.

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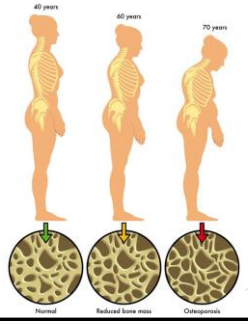

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Risk Factors

Non-Modifiable	Modifiable
Female gender	High fall risk
Menopause: Premature, Surgical, Natural	Poor health status
Small frame	Immobilization
Fracture as an adult	Cigarette smoking
Family history of osteoporosis of fractures	Lack of exercise, especially weight-bearing
Ethnicity: Caucasian, Asian	Excess alcohol intake
	Low lifetime vitamin D intake
	Low lifetime calcium intake, especially in adolescents and 20s

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Up to 30% of postmenopausal women and 50-80% of men suffer from another condition that contributes to osteoporosis !

NIH. Consensus Development Panel on Osteoporosis Prevention D Therapy. Osteoporosis prevention, diagnosis, and therapy. JAMA 2001, 285, 785-795.
Mirza, F.; Canalis, E. Management of endocrine disease: Secondary osteoporosis: Pathophysiology and management. Eur. J. Endocrinol. 2015, 173, R131-R151.

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Secondary Causes of Bone Loss

- Endocrine
- Metabolic
- Nutritional
- Gastrointestinal
- Other Conditions
- Drugs

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Endocrine and Metabolic Causes

- Acromegaly
- **Diabetes mellitus - Types 1 and 2**
- Growth hormone deficiency
- Hypercortisolism
- **Hypophosphatasia ***
- **Hyperparathyroidism**
- **Hyperthyroidism**
- Hypogonadism - most common cause of osteoporosis in men
- Porphyria
- Pregnancy
- **XLH-Linked Hypophosphatemia ***
- **ENPP1 Deficiency ***

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Hypophospha-what?

Hypophosphatemia

Low serum phosphate levels

Hypophosphatasia

Rare metabolic disease due to loss-of-function mutations in the TNSALP gene (*ALPL*), resulting in low ALP activity

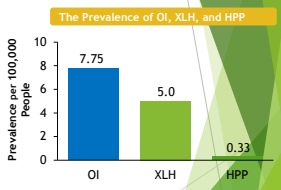
McKiernan FE et al. *J Bone Miner Res* 2014;29:1651-1660; Whyte MP. In: Genetics of Bone Biology and Skeletal Disease, 2013:337-360.

9

The Prevalence of Select Rare Bone Diseases

XLH has an estimated prevalence of 1:20,000 to 1:25,000

There are 12,000 to 16,000 patients with XLH in the US



Ruppe 2012; http://www.ncbi.nlm.nih.gov/books/NBK83985/. Accessed December 3, 2020; Beck-Nielsen et al. *Eur J Endocrinol*. 2009;160:491; Stone and Chesney. *Pediatr Radiol*. 2013;43:152; Endo et al. *Endocr J*. 2015;62:811; Carpenter. *Pediatr Clin North Am*. 1997;44:443; US Census Bureau. http://www.census.gov/popclock/?intcmp=home_pop. Accessed December 3, 2020; Orphanet website. http://www.orpha.net/consor/cgi-bin/OC_Exp.php?Expert=666. Accessed December 3, 2020; Orphanet website. http://www.orpha.net/consor/cgi-bin/OC_Exp.php?Expert=436. Accessed December 3, 2020; Barnett et al. *Am J Med*. 1964;36:222; 10. Rafaelsen et al. *Eur J Endocrinol*. 2016;174:125.

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XLH Mechanism of Disease

- Mutation in the PHEX gene (not all patients)
- FGF23 — Increased expression of FGF23
- $1,25(OH)_2D$ — Renal phosphate wasting and low 1,25(OH)2D levels
- PO_4 — Low levels of serum phosphorus
- Clinical manifestations of XLH

Carpenter et al. *J Bone Miner Res*. 2011;26:1381.

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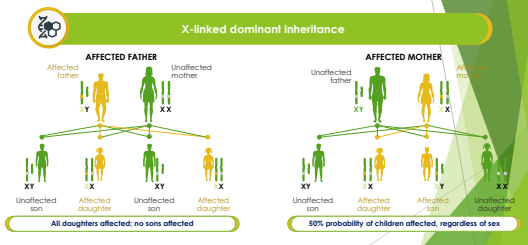
X-Linked Dominance



Ruppe 2012; http://www.ncbi.nlm.nih.gov/books/NBK83985/. Accessed December 3, 2020.

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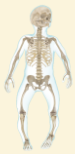
The Lifelong Impact of XLH

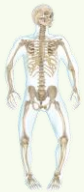
Pediatric

- Delayed and disproportionate growth
- Craniosynostosis
- Rickets
- Delayed walking



- Short stature
- Deforming of weight-bearing limbs
- Tooth abscesses
- Excessive dental caries
- Osteomalacia
- Bone and joint pain
- Joint stiffness
- Muscle pain and weakness
- Chiari malformation
- Gait abnormalities
- Diminished quality of life including psychosocial impact
- Walking device use

Adult



- Fractures
- Osteoarthritis
- Extraosseous calcifications, including:
  - Osteophytes
  - Enthesopathy
  - Spinal stenosis
- Hearing loss
- Disability that impacts ability to work

Linglart A, et al. Endocr Connect. 2014;3:R13; Linglart et al. ICCBH 2015. Poster P198; Skrinar et al. Journal of the Endocrine Society. 2019; 3:7; Carpenter T. Pediatr Clin North Am. 1997;44:443; Veilleux et al. J Clin Endocrinol Metab. 2012;97:E1492

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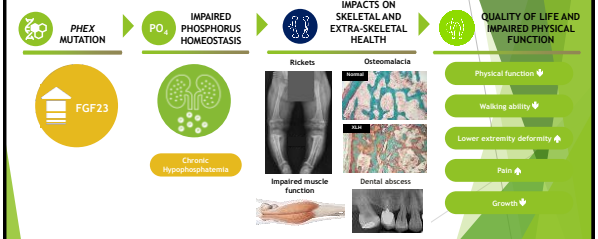
XLH in Children



Linglart et al. Endocrine Connections 2014;3: R13-R30; Jagtap et al. Indian J Endocrinol Metab. 2012;16:177-182; Econs. J Clin Endocrinol Metab. 2019;100:3622-3624; Ito et al. Eur J Endocrinol. 2016;174:325-33; Sahay and Sahay. Indian J Endocrinol Metab. 2013;17:539-544; Veilleux et al. J Clin Endocrinol Metab. 2012;97:E1492-E1498

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XLH in Peds

- Presents during first two years of life
  - With lower-extremity bowing, impaired growth, and rickets
- Clinical manifestations vary in severity
  - Ranging from isolated hypophosphatemia to severe lower-extremity bowing
- Also frequently seen: pain, gait disturbances, and impaired gross motor function

Kruppe 2012; http://www.ncbi.nlm.nih.gov/books/NBK83985/. Accessed December 3, 2020; Linglart et al. ICCBH 2015. Poster P198; Linglart et al. Endocr Connect 2014;3:R13; Veilleux et al. J Clin Endocrinol Metab. 2012;97:E1492; Carpenter. Pediatr Clin North Am. 1997;44:443.

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XLH in Peds

CRANIAL
- Chiari malformation
- Craniosynostosis

DENTAL
- Tooth abscesses
- Excessive dental caries

FUNCTIONAL LIMITATIONS AND DIMINISHED MOBILITY
- Delayed walking
- Gait abnormalities

SKELETAL
- Short stature/loss of growth potential
- Progressive skeletal deformity
- Lower-extremity deformity
- Osteomalacia
- Bone pain
- Joint pain and stiffness
- Muscle pain
- Muscle weakness
- Rickets
- Delayed growth

Kruppe 2012; http://www.ncbi.nlm.nih.gov/books/NBK83985/. Accessed December 3, 2020; Linglart et al. ICCBH 2015. Poster P198; Linglart et al. Endocr Connect 2014;3:R13; Veilleux et al. J Clin Endocrinol Metab. 2012;97:E1492; Carpenter. Pediatr Clin North Am. 1997;44:443.

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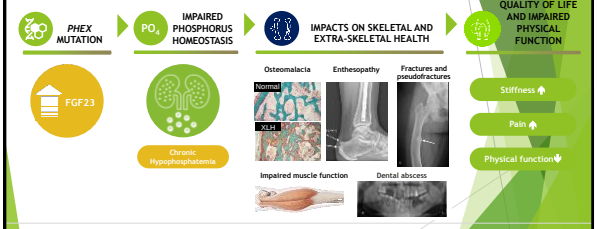
XLH in Adults



Linglart et al. Endocrine Connections 2014;3: R13-R30; Jagtap et al. Indian J Endocrinol Metab. 2012;16:177-182; Econs. J Clin Endocrinol Metab. 2015;100:3622-3624; Ito et al. Eur J Endocrinol. 2016;174:325-33; Sahay and Sahay. Indian J Endocrinol Metab. 2013;17:535-544; Skrinar et al. Journal of the Endocrine Society. 2019; 3:7. Veilleux et al. J Clin Endocrinol Metab. 2012;97:E1482-E1498; Chesher et al. J Inherit Metab Dis. 2018;41(5):865-876.

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XLH in Adults

- **Clinical manifestations in adults with XLH arise from:**
  - Unresolved complications of XLH from childhood
  - New and continuing symptoms as a result of ongoing, active disease

Skrinar et al. Journal of the Endocrine Society. 2019; 3:7. Linglart et al. ICCBH 2015. Poster P198; Linglart A, et al. Endocr Connect. 2014;3:R13; Carpenter T. Pediatr Clin North Am. 1997;44:443; Veilleux et al. J Clin Endocrinol Metab. 2012;97:E1482

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XLH in Adults

CRANIAL
- Chiari malformation
- Hearing los

DENTAL
- (Spontaneous) dental abscesses
- Excessive dental caries

FUNCTIONAL LIMITATIONS AND DIMINISHED MOBILITY
- Difficulty in walking
- Gait abnormalities
- Diminished quality of life including psychosocial impact

SKELETAL
- Short stature
- Lower-extremity deformity
- Osteomalacia
- Bone pain
- Joint pain and stiffness
- Muscle pain and weakness
- Fractures (pseudofractures and Looser zones)
- Osteoarthritis
- Extraosseous calcifications including:
  - Enthesopathy
  - Spinal stenosis

Skrinar et al. Journal of the Endocrine Society. 2019; 3:7. Linglart et al. ICCBH 2015. Poster P198; Linglart A, et al. Endocr Connect. 2014;3:R13; Carpenter T. Pediatr Clin North Am. 1997;44:443; Veilleux et al. J Clin Endocrinol Metab. 2012;97:E1462

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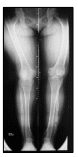
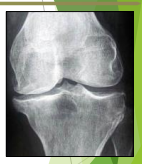
Unresolved XLH Complications From Childhood

Unresolved XLH complications from childhood may include:
- Reduced height
- Gait abnormalities
- Lower-extremity deformity
- Osteoarthritis > long-term weight-bearing on misaligned joints



Lower-extremity deformity in a young adult



Osteoarthritis of the knee in a 28-year-old woman with bone deformities after adolescence

Image 2012; http://www.ncbi.nlm.nih.gov/books/NBK83985/. Accessed December 3, 2020. Hardy et al. Radiology. 1989;171:403; Skrinar et al. Journal of the Endocrine Society. 2019; 3:7. Reid et al. Medicine (Baltimore). 1989;68:336; Linglart et al. Endocr Connect. 2014;3:R13; Beck-Nielsen, et al. Calcif Tissue Int 2014;95:87-108

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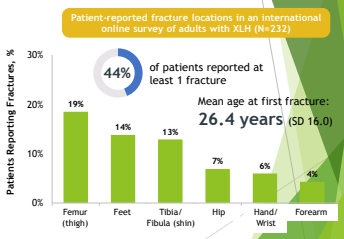
Fractures in XLH Adults

- Insufficiency fractures > long-term weight bearing on weakened bones
- Fractures of weight-bearing bones > especially the shaft of the femur or tibia



Jackson et al. *Brit Med J.* 1958;1:1269; Radiopaedia website. https://radiopaedia.org/articles/insufficiency-fracture. Accessed December 3, 2020; Radiopaedia website. https://radiopaedia.org/articles/looser-zones-1. Accessed December 3, 2020; Linglart et al. *Endocr Connect.* 2014;3:R13; Skrinar et al. *Journal of the Endocrine Society.* 2019;3:1656

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Biochemical Findings in XLH

A diagnosis of XLH is typically based on clinical and biochemical findings

Biochemical Test	XLH
Serum phosphorus	↓
TmP/GFR	↓
1,25(OH)$_2$D	↓ or inappropriately normal
25(OH)D	Normal
ALP[a]	↑
Serum calcium	Normal
Urinary calcium	↓
PTH	Normal or ↑
Serum FGF23	↑ or inappropriately normal

- Low phosphate levels and low TmP/GFR ratio are the main biochemical findings for XLH
- Alkaline phosphatase > good marker of skeletal health in children but not necessarily for adults
- FGF23 levels may be useful for establishing the diagnosis of XLH

TmP/GFR = maximal tubular reabsorption of phosphorus per glomerular filtration rate; FGF23 = fibroblast growth factor 23; TRP, tubular reabsorption of phosphate

Rugge 2012; http://www.ncbi.nlm.nih.gov/books/NBK83985/. Accessed December 3 2020; Santos et al. *Pediatr Nephrol.* 2013;28:595; Goldsweig and Carpenter. *Curr Osteoporos Rep.* 2015;13:88; Imel and Carpenter. *Endocr Dev.* 2015;28:134.

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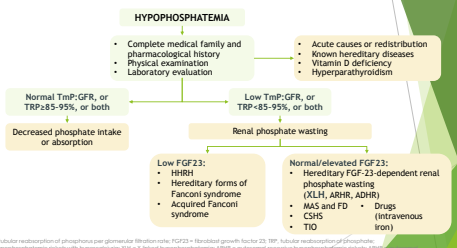
Diagnostic Algorithm for Hypophosphatemia



TmP/GFR = maximal tubular reabsorption of phosphorus per glomerular filtration rate; FGF23 = fibroblast growth factor 23; TRP, tubular reabsorption of phosphate; HHRH = Hereditary hypophosphatemic rickets with hypercalciuria; XLH = X-linked hypophosphatemia; ARHR = autosomal-recessive hypophosphatemic rickets; ADHR = autosomal-dominant hypophosphatemic rickets; MAS = McCune-Albright syndrome; FD = fibrous dysplasia; CSHS = cutaneous skeletal hypophosphatemia syndrome; TIO = tumor-induced osteomalacia. Florenzano et al. *Lancet Diabetes Endocrinol* 2020;8:163-74.

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Phosphate Reabsorption Calculation: Pediatrics

- The TmP/GFR is the ratio of renal tubular maximum reabsorption of phosphate (TmP) to glomerular filtration rate (GFR)

$$\text{TmP/GFR} = \text{serum phosphate} - \frac{\text{urine phosphate x serum creatinine}}{\text{urine creatinine}}$$

TmP/GFR = maximal tubular reabsorption of phosphorus per glomerular filtration rate.
Alon U, Hellerstein S. *Pediatr Nephrol.* 1994;8:250-251.

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Phosphate Reabsorption Calculation: Adults

- TRP is the tubular reabsorption of phosphate
- The TmP/GFR is the ratio of renal tubular maximum reabsorption of phosphate (TmP) to glomerular filtration rate (GFR)

$$TRP = 1 - \left[\frac{\text{urinary phosphate}}{\text{serum phosphate}}\right] \times \left[\frac{\text{serum creatinine}}{\text{urinary creatinine}}\right]$$

- **If TRP ≤0.86, TmP/GFR = TRP x serum phosphate**
- **If TRP >0.86, TmP/GFR = 0.3 x $\frac{TRP}{1 - (0.8 \times TRP)}$ x serum phosphate**

TRP, tubular reabsorption of phosphate; TmP/GFR = maximal tubular reabsorption of phosphorus per glomerular filtration rate.
Payne RB. Ann Clin Biochem. 1998;35:201-206.

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QR Codes for Calculations re: XLH

SCAN THE QR CODES BELOW WITH YOUR MOBILE DEVICE TO REVIEW THE RELEVANT SUBJECT*

Background on phosphate homeostasis and disorders, with information related to XLH and TmP/GFR calculation	Conversion calculator for phosphate	Automated TRP calculator (calculated values should be converted to the appropriate measurement units)	Conversion calculator for creatinine	Testing for tubular phosphate reabsorption offered by Mayo Clinic performed upon receipt of specimens

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XLH Treatment

- Treatment
  - Had been symptomatic and supportive with supplements of phosphate and high-dose calcitriol
  - Treatment approved by FDA in 2015
    - Crysvita (Burosumab)
      - Antibody that binds to excess FGF23 protein
      - Helps with the reabsorption of phosphate by the kidneys
      - Promotes bone growth by increasing the availability of phosphate in the blood

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ENPP1 Deficiency

- Genetic disorder caused by loss of function mutations in the ectonucleotide pyrophosphatase/ phosphodiesterase 1 (*ENPP1*) gene
- Challenging diagnosis as many clinical and biochemical labs similar to XLH
- The hallmark signs include:
  - Ectopic calcification of the arteries, organs, joints or ligaments
  - Pathological skeletal mineralization
  - Neointimal proliferation and vascular stenosis
- ENPP1 genetic testing should be considered in peds/adults with suspected symptoms
- Treatment under investigation

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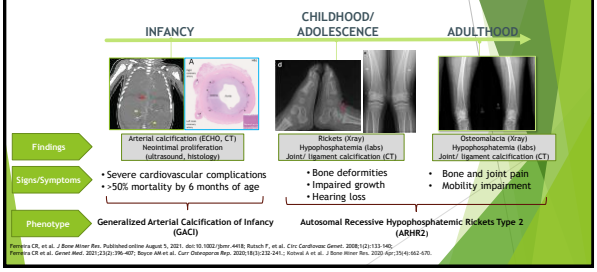
ENPP1 Deficiency



Ferreira CR, et al. *J Bone Miner Res.* Published online August 5, 2021. doi:10.1002/jbmr.4418; Rutsch F, et al. *Circ Cardiovasc Genet.* 2008;1(2):133-140; Ferreira CR et al. *Genet Med.* 2021;23(2):396-407; Boyce AM et al. *Curr Osteoporos Rep.* 2020;18(3):232-241.; Kotwal A et al. *J Bone Miner Res.* 2020 Apr;35(4):662-670.

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ENPP1 Deficiency vs XLH

Biochemical Test	ENPP1 Deficiency	XLH
FGF23	↑[a]	↑
Serum phosphorus	↓	↓
1,25$(OH)_2$D	Normal[b]	Normal[b]
25(OH)D	Normal	Normal
TmP/GFR	↓	↓
ALP	↑	↑
Serum calcium	Normal	Normal
Urinary phosphate	↑	↑
PTH	Normal/moderately high	Normal/moderately high

TmP/GFR = maximal tubular reabsorption of phosphorus per glomerular filtration rate; FGF23 = fibroblast growth factor 23

[a] FGF23 levels may be in normal range, but inappropriately high relative to serum Pi
[b] 1,25(OH)2D inappropriately low relative to serum Pi

Haffner D et al. *Nat Rev Nephrol.* 2019;15(7):435-455

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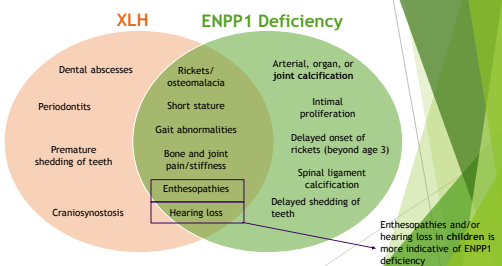
XLH vs ENPP1 Deficiency



Rutsch F, et al. *Circ Cardiovasc Genet.* 2008;1(2):133-140. Ferreira C, et al. 2021. Ectopic Calcification and Hypophosphatemic Rickets: Natural History of ENPP1 and ABCC6 Deficiencies. (unpublished). Ferreira CR, et al. *Genet Med.* 2021;23(2):396-407. Chesher D, et al. *J Inherit Metab Dis.* 2018;41(5):865-876. Thumbigere-Math V, et al. *J Dent Res.* 2018

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Low ALP levels?

Precipitously Low	Transiently Low	Persistently Low
• Multiple Myeloma or other cancers • Cardiac bypass surgery • Major trauma or surgery • Chemotherapy • Transfusions • Starvation • Sepsis/multi-organ failure	• Osteogenesis imperfecta type II • Profound hypothyroidism • Cushing disease • Bisphosphonate therapy • Adynamic renal osteodystrophy • Milk-alkali syndrome • Wilson disease • Celiac disease	• **Hypophosphatasia** • Cleidocranial dysplasia • Mseleni joint disease

Rockman-Greenberg C. Hypophosphatasia. Pediatr Endocrinol Rev. 2013; 10(suppl 2): 380-388
Whyte MP. Hypophosphatasia: natures's window on alkaline phosphatase function in humans. In: Principles of Bone Biology. 3rd ed. Academic Press; 2008:1573-1598.
Unger S, Hornet E, Mundlos S, Blaser S, Cole DE. Severe cleidocranial dysplasia can mimic hypophosphatasia. Eur J Pediatr. 2002; 161(11):623-626.

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Hypophosphatesia

- Genetic condition that causes abnormal development of the bones and teeth
  - Caused by loss-of-function mutations in the *ALPL* gene, leading to low ALP activity
    - 400 mutations identified so far
  - Autosomal dominant or recessive
- Variable presentation from infancy to adulthood
  - Frequently overlooked in childhood
  - Can be severe, moderate, mild, asymptomatic
- Cardinal lab abnormalities
  - Persistently low alkaline phosphatase level
  - High vitamin B6 level

Briot K, Roux C. Adult hypophosphatasia. Arch Pediatr. 2017;24(5S2):5S71-5S73
Mornet E. Arch Pediatr 2017;24:5S51-5S56.

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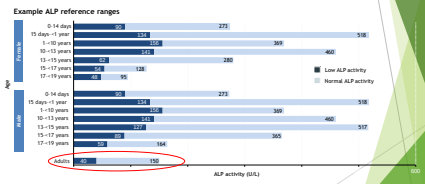
Normal ALP activity in adults and children

- Lower limit of normal ALP activity is significantly higher in infants and children than in adults
- Use appropriate age- and sex-adjusted reference ranges (labs can be different)!!!



Colantonio DA et al. Clin Chem 2012;58:854-868; Architect cSystems/Aeroset System alkaline phosphatase assay [package insert]. Abbott Laboratories. 2007;
Turan S et al. J Clin Res Pediatr Endocrinol 2011;3:7-11; Rockman-Greenberg C. Pediatr Endocrinol Rev 2013;10(suppl 2):380-388

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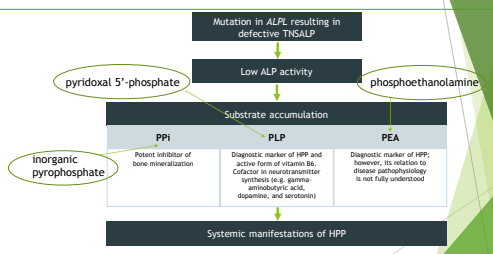
Mechanism of HPP



Rockman-Greenberg C. Pediatr Endocrinol Rev 2013;10(suppl 2):380-388; Linglart A, Biosse-Duplan M. Curr Osteoporos Rep 2016;14:95-105; Whyte MP. In: Genetics of Bone Biology and Skeletal Disease. 2013:337-360; Whyte MP. In: Principles of Bone Biology. 2008:1573-1598; Whyte MP. In: The Metabolic and Molecular Bases of Inherited

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Signs & Symptoms in Infants

Skeletal
- Underossification of cranial vault
- Rachitic chest
- Severe hypomineralization
- Non-traumatic, recurrent, non-healing fractures

Neurologic
- Vitamin B6-responsive seizures
- Craniosynostosis
- Increased intracranial pressure
- Intracranial hemorrhage
- Papilledema

Muscular/ rheumatologic
- Hypotonia
- Delayed or missed motor milestones

Renal
- Hypercalcemia
- Hypercalciuria
- Nephrocalcinosis

Respiratory
- Pulmonary hypoplasia
- Respiratory insufficiency
- Recurrent infections

Disease burden
- Poor weight gain
- Poor feeding
- Failure to thrive

Rockman-Greenberg C. Pediatr Endocrinol Rev 2013;10(suppl 2):380-388; Macica O et al. Arch Pediatr 2017;24:5S61-5S65; Whyte MP. Bone 2017;102:15-25;
Collmann H et al. Childs Nerv Syst. 2009;25:277-321; Whyte MP. Bone 2019;79:229-239; Bacchetta J. Arch Pediatr 2017;24:5S59-5S95; Mornet E. Orphanet J Rare Dis 2007;2:40

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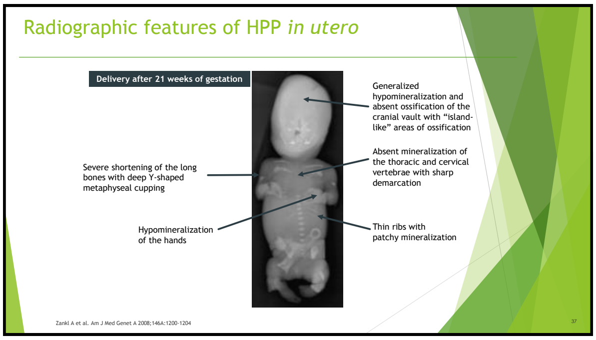
Radiographic features of HPP in utero
Delivery after 21 weeks of gestation
Generalized hypomineralization and absent ossification of the cranial vault with "island-like" areas of ossification
Severe shortening of the long bones with deep Y-shaped metaphyseal cupping
Absent mineralization of the thoracic and cervical vertebrae with sharp demarcation
Hypomineralization of the hands
Thin ribs with patchy mineralization
Zankl A et al. Am J Med Genet A 2008;146A:1200-1204
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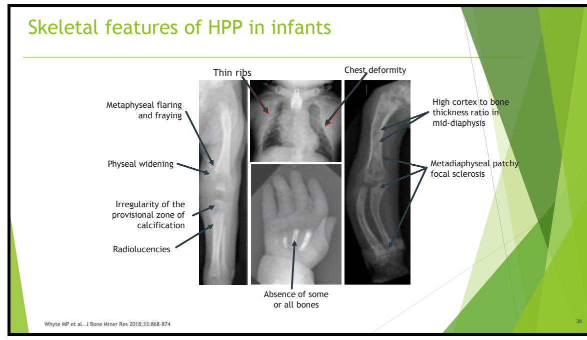
Skeletal features of HPP in infants
Thin ribs
Chest deformity
Metaphyseal flaring and fraying
High cortex to bone thickness ratio in mid-diaphysis
Physeal widening
Metadiaphyseal patchy focal sclerosis
Irregularity of the provisional zone of calcification
Radiolucencies
Absence of some or all bones
Whyte MP et al. J Bone Miner Res 2018;33:868-874
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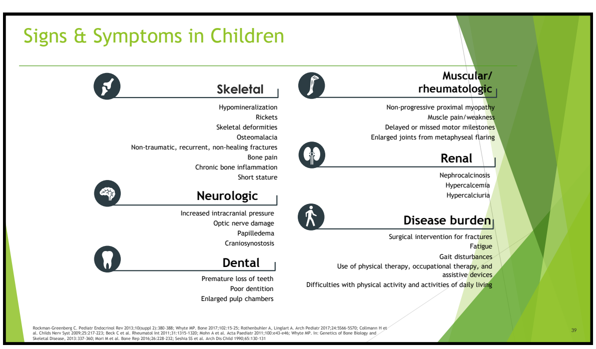
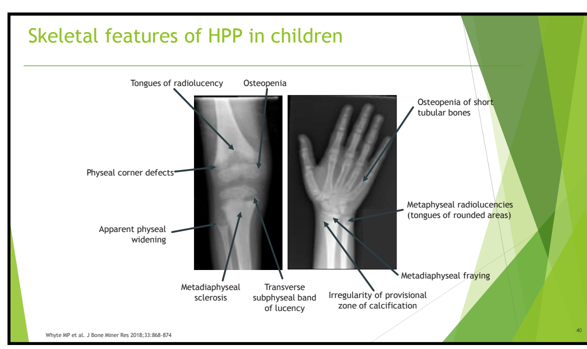

Signs & Symptoms in Children
Skeletal
Hypomineralization
Rickets
Skeletal deformities
Osteomalacia
Non-traumatic, recurrent, non-healing fractures
Bone pain
Chronic bone inflammation
Short stature
Neurologic
Increased intracranial pressure
Optic nerve damage
Papilledema
Craniosynostosis
Dental
Premature loss of teeth
Poor dentition
Enlarged pulp chambers
Muscular/ rheumatologic
Non-progressive proximal myopathy
Muscle pain/weakness
Delayed or missed motor milestones
Enlarged joints from metaphyseal flaring
Renal
Nephrocalcinosis
Hypercalcemia
Hypercalciuria
Disease burden
Surgical intervention for fractures
Fatigue
Gait disturbances
Use of physical therapy, occupational therapy, and assistive devices
Difficulties with physical activity and activities of daily living
Rockman-Greenberg C. Pediatr Endocrinol Rev 2013;10(suppl 2):380-388; Whyte MP. Bone 2017;102:15-25; Rothenbuhler A, Linglart A. Arch Pediatr 2017;24:5S66-5S70; Collmann H et al. Childs Nerv Syst 2009;25:217-223; Beck C et al. Rheumatol Int 2011;31:1315-1320; Mohn A et al. Acta Paediatr 2011;100:e43-e46; Whyte MP. In: Genetics of Bone Biology and Skeletal Disease, 2013:337-360; Mori M et al. Bone Rep 2016;26:228-232; Seshia SS et al. Arch Dis Child 1990;65:130-131
39

39


Skeletal features of HPP in children
Tongues of radiolucency
Osteopenia
Osteopenia of short tubular bones
Physeal corner defects
Metaphyseal radiolucencies (tongues of rounded areas)
Apparent physeal widening
Metaphyseal fraying
Metadiaphyseal sclerosis
Transverse subphyseal band of lucency
Irregularity of provisional zone of calcification
Whyte MP et al. J Bone Miner Res 2018;33:868-874
40

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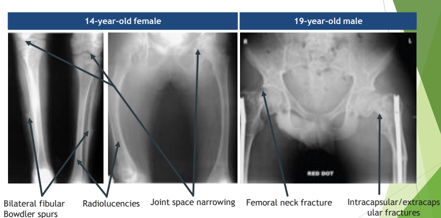
Skeletal features of HPP in adolescents



Uras I et al. Korean J Radiol 2005;6:52-54; 2. Sharma N et al. J Orthop Case Rep 2015;5:66-68

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Signs & Symptoms in Adults

Skeletal

Slow-to-heal stress fractures
Pseudofractures
Osteomalacia
Low bone mass /osteoporosis
Reduced bone mineral density
Chronic bone pain
Skeletal deformities

Renal

Nephrocalcinosis
Renal damage

Dental

History of premature loss of deciduous teeth
Adult tooth loss
Abnormal dentition
Dental caries
Periodontal disease

Muscular/ rheumatologic

Chronic muscle pain
Joint swelling
Calcium pyrophosphate deposition disease
Pseudogout
Chondrocalcinosis
Calcific periarthritis
Arthropathy

Disease burden

Limitations in activities of daily living
Significant physical function and mobility impairment
Severe pain
Mobility problems requiring assistive devices

Briot K, Roux C. Arch Pediatr 2017;24:5S71-5S73; Mornet E, Nunes ME. GeneReviews®. Available at: https://www.ncbi.nlm.nih.gov/books/NBK1150/?report=classic;
Rockman-Greenberg C. Pediatr Endocrinol Rev 2013;10(suppl 2):380-388; Whyte MP. In: Principles of Bone Biology, 2008:1573-1593; Coe JD et al. J Bone Joint Surg Am 1986;68:981-990;Weinstein RS, Whyte MP. Arch Intern Med 1981;141:727-731; Silva I et al. Acta Reumatol Port 2012;37:92-96;Barvencik F et al. Osteoporos Int 2011;22:2667-2675;
Beck C et al. Rheumatol Int 2011;31:1315-1320; Linglart A, Biosse-Duplan M. Curr Osteoporos Rep 2016;14:95-105; Chuck AJ et al. Ann Rheum Dis 1989;48:571-576;
Whyte MP et al. Am J Med 1982;72:631-641; McKiernan FE et al. J Bone Miner Res 2014;29:1651-1660; Weber TJ et al. Metabolism 2016;65:1522-1530

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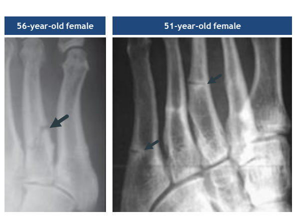
HPP in adults



Adult HPP can often manifest with slow-to-heal metatarsal stress fractures

Whyte MP et al. J Clin Endocrinol Metab 2007;92:1203-1208; Maman E et al. Joint Bone Spine 2016;83:346-348; Lawrence JE et al. Clin Cases Miner Bone Metab 2017;14:347-353

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HPP is often misdiagnosed

Misdiagnosis	Treatment/Potential Impact on Patients with HPP
Osteoporosis	• Bisphosphonates > can increase risk of atypical femoral fractures • PTH analogues > does not address the underlying cause of HPP
Nutritional Rickets	• Vitamin D & Calcium > Can lead to hypercalcemia, hypercalciuria, & nephrocalcinosis
CPPD/Pseudogout or Fibromyalgia	• Analgesics > Does not address the underlying cause of HPP
XLH	• High-dose vitamin D & phosphate > Can exacerbate hypercalcemia and hypercalciuria

Weber TJ, Sawyer EK, Moseley S, Odrljin T, Kishnani PS. Burden of disease in adult patients with hypophosphatasia: results from two patient-reported surveys. Metabolism. 2016; 65 (10): 1522-1530.
Berkseth KE, Tebben PJ, Drake MT, Heffernan TE, Jewison DE, Wermers RA. Clinical spectrum of hyposphatasia diagnosed in adults. Bone. 2013; 54(1):21-27.
Caswell AM, Whyte MP, Russell RG. Hypophosphatasis and the extracellular metabolism of inorganic pyrophosphate: clinical and laboratory aspects. Crit Rev Clin Lab Sci. 1991; 28)3_: 175-232.
Rockman-Greenberg C. Hypophosphatasia. Pediatr Endocrinol Rev. 2013; 10(suppl 2): 380-388.
Sutton RA, Mumm S, Coburn SP, Ericson KL, Whyte MP. “Atypical femoral fractures” during bisphosphonate exposure in adult hypophosphatasia. J Bone Miner Res. 2012: 27(5):987-994.
Shapiro JR, Lewiecki EM. Hyposphosphatasia in adults: clinical assessment and treatment considerations. J Bone Miner Res. 2017: 32(10):1977-1980.
Mahagna H, Amital D, Amital H. A randomized double-blind study comparing giving etoricoxib vs placebo to female patients with fibromyalgia. Int J Clin Pract. 2016;70(2): 163-170.
Guanabens H, Mumm S, Moller I, et al. Calcific periarthritis as the only clinical manifestation of hypophosphatasia in middle-aged sisters. J Bone Miner Res. 2014;29(4):929-934.
Shore RM, Chesney RW. Rickets: Part I. Pediatr Radiol. 2013;43(2):140-151.
Shore RM, Chesney RW. Rickets: Part II. Pediatr Radiol. 2013; 43(2): 152-172.

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HPP

- Treatment
  - Had been symptomatic and supportive until 2015
  - Enzyme replacement therapy approved by FDA in 2015
    - Asfotase alfa (Strensiq®)
    - Improves bone manifestations in people with childhood-onset HPP
- Important to look at age- and sex-adjusted reference ranges for children
- Look back at old ALP levels!
- Genetic testing MAY support diagnosis but negative test results do not rule out HPP
- Be aware of the possibility of this condition!
  - Studies report that 9-50% of patients diagnosed with HPP in adulthood recall symptoms occurring prior to their diagnosis!

Berkseth KE, Tebben PJ, Drake MT, Heffernan TE, Jewison DE, Wermers RA. Clinical spectrum of hypophosphatasia diagnosed in adults. Bone 2013: 54(1):21-27.
Caswell AM, Whyte MP, Russell RG. Hypophosphatasis and the extracellular metabolism of inorganic pyrophosphate: clinical and laboratory aspects. Crit Rev Clin Lab Sci. 1991; 28)3_: 175-232.
Mornet E. Molecular genetics of hypophosphatasia and phenotype-genotype correlations. Subcell Biochem. 2015:76:25-43.
Mornet E. Hypophosphatasia. Metabolism. 2018;82:142-155.

45

Diabetes

- Low bone turnover from insulinopenia in Type 1 DM
- Mechanism of bone loss not well understood in Type 2 DM
- Fracture risk increases with duration of DM and use of insulin
- Also consider inadequately treated DM issues
  - Malnutrition
  - Loss of calcium and phosphorus in urine
  - Failure to achieve peak bone mass
- Reduced BMD not always present, despite increased fracture risk
- Screen diabetics earlier !

Thong EP, Herath M, Weber DR, Ranasinha S, Ebeling PR, Milat F, Teede H. Fracture risk in young and middle-aged adults with type 1 diabetes mellitus: A systematic review and meta-analysis. Clin Endocrinol (Oxf). 2018 Sep;89(3):314-323.
Janghorbani, M., et al. (2006) Prospective study of diabetes and risk of hip fracture: The nurses' health study. Diabetes Care, 29, 1573-1578.
Nicodemus KK, Folsom AR; Iowa Women's Health Study. Type 1 and type 2 diabetes and incident hip fractures in postmenopausal women. Diabetes Care. 2001 Jul;24(7):1192-7.
Vestergaard P. Discrepancies in bone mineral density and fracture risk in patients with type 1 and type 2 diabetes—a meta-analysis Osteoporos. Int., 18 (4) (2007), pp. 427 - 444

46

Primary Hyperparathyroidism

- PHPT is very common endocrine disorders
  - 0.1-1% in postmenopausal women
  - 3 times greater in women than men
  - More common as one ages
- Increased risk of vertebral, wrist, ankle, rib and pelvic fractures with PHPT
- Mariner Captain Charles Martell >
  - Suffered with kidney stones, severe osteoporosis, hypercalcemia, heart disease

Dorairajan N, Pradeep PV. Vignette hyperparathyroidism: glimpse into its history. Int Surg. 2014 Sep-Oct;99(5):528-33. doi: 10.9738/INTSURG-D-13-00225.1. PMID: 25216416; PMCID: PMC4253919.
Spence HM. The life and death of Captain Charles Martell and kidney stone disease. J Urol. 1984 Dec;132(6):1204-7. doi: 10.1016/s0022-5347(17)50098-1. PMID: 6389906.

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PHPT > Higher morbidity & mortality!

- From a statistical standpoint, patients with hyperparathyroidism die an average of 5-6 years sooner than expected
- Incidence of several cancers is increased by 1.8 to 3-fold
  - breast, colon, kidney, and prostate
- Incidence of high blood pressure is 5.5 times higher
- Incidence of stroke is 4 times higher
- Incidence of heart disease is 2.5 times higher
- Incidence of atrial fibrillation is 8 times higher

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PHPT Clinical Presentation

- Classic presentation: bones, stones, groans, psychiatric undertones
  - Bones: osteoporosis, bone pain (particularly in the hands, feet, arms, and legs, but can be anywhere)
  - Stones: kidney stones, kidney failure, hypercalciuria
  - Groans: abdominal pain, heartburn
  - Psychiatric undertones/moans: chronic fatigue, difficulty sleeping, memory loss, poor concentration, depression, headaches
- Usually now biochemical and densitometric presentation
  - Elevation of serum calcium
  - Intact parathyroid hormone elevation
  - DXA bone density scans

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Parathyroidectomy

- When to do surgery?
  - Any patient with osteoporosis, fragility fractures, and/or evidence of vertebral compression fractures on spine imaging
  - Any patient 50 years or younger regardless of whether objective or subjective features are present or absent
  - Any patient who is unable or unwilling to comply with observation protocols
  - Any patient with neurocognitive and/or neuropsychiatric symptoms that are attributable to PHPT
- Should be conducted by surgeons with adequate training and experience in PHPT management!!!
- Cure rate is very dependent upon the experience of the surgeon
  - As high as 92% by experienced endocrine surgeons
  - As low as 80% for general surgeons who perform only a few parathyroid operations per year
- Operative management is more cost-effective than long-term observation or pharmacologic therapy
- Standard vs minimally invasive procedures
- Usually <30 minute surgery with Intraoperative PTH monitoring

Wilhelm SM, Wang TS, Ruan DT, et al. The American Association of Endocrine Surgeons Guidelines for Definitive Management of Primary Hyperparathyroidism. JAMA Surg. 2016;151(10):959-968. doi:10.1001/jamasurg.2016.2310
Bilezikian JP, Brandi ML, Eastell R, et al. Guidelines for the management of asymptomatic primary hyperparathyroidism: summary statement from the Fourth International Workshop. *J Clin Endocrinol Metab*. 2014;99(10):3561-3569.

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Medical Management Instead of Surgery

- Some long-term observational studies indicate that biochemistries and bone mineral density (BMD) may remain stable for many years in those followed non-operatively
- 15-year data suggest that BMD starts to decline at cortical sites after 10 years of observation
- 40% of patients developed one or more indications for parathyroidectomy over 15 years of follow-up
- Regular monitoring of biochemistries and of BMD with DXA is recommended for those who choose to be observed

Silverberg SJ, Shane E, Jacobs TP, Siris E, Bilezikian JP. A 10-year prospective study of primary hyperparathyroidism with or without parathyroid surgery N, Engl. J. Med. 1999; 341:1249-1255 Cope O.
The study of hyperparathyroidism at the Massachusetts General Hospital N. Engl. J. Med. 1966; 274:1174-1182. Yeh MW.
Incidence and prevalence of primary hyperparathyroidism in a racially mixed population J. Clin. Endocrinol. Metab. 2013; 98:1122-1129.
Wermers RA. Incidence of primary hyperparathyroidism in Rochester, Minnesota, 1993-2001: an update on the changing epidemiology of the disease J. Bone Miner. Res. 2006; 21:171-177.
Marcocci C, Bollerslev J, Khan AA, Shoback DM. Medical management of primary hyperparathyroidism: proceedings of the fourth International Workshop on the Management of Asymptomatic Primary Hyperparathyroidism. *J Clin Endocrinol Metab*. 2014;99(10):3607-3618.

51

Thyroid Disease

- Suppressed serum TSH and history of hyperthyroidism
  - Increased risk of hip and vertebral compression fractures
- Alendronate has reduced efficacy in postmenopausal women with osteoporosis receiving TSH-suppressive doses of levothyroxine for the management of differentiated carcinoma of the thyroid
- Concern for other drugs causing reduction in efficacy with TSH-suppressive doses of levothyroxine?
- Thyrotoxicosis
  - Increases bone turnover
  - Shortens bone remodeling cycle
  - Can cause a loss of up to 10% of mineralized bone per remodeling cycle

Parrico A, Lupoli GA, Fonderico F, Marciello F, Martinelli A, Ansante R & Lupoli G. Osteoporosis and thyrotropin-suppressive therapy: reduced effectiveness of alendronate. Thyroid 2009 19 427-442.
Bauer DC, Ettinger B, Nevitt MC, Stone KL & Study of Osteoporotic Fractures Research. Risk for fracture in women with low serum levels of thyroid-stimulating hormone. Annals of Internal Medicine 2001 134 561-568
Abrahamsen B, Jorgensen HL, Laulund AS, Nybo M, Brix TH & Hegedus L. Low Serum Thyrotropin Level and Duration of Suppression as a Determinant of Bone Osteoporotic Fracture: The OPENTHYRO Register Cohort. Journal of Bone and Mineral Research 2014 29 2045-2050

52

Nutritional/GI Conditions

- Alcoholism
- Anorexia nervosa
- Calcium deficiency
- Chronic liver disease
- Total parenteral nutrition
- Vitamin D deficiency
- **Hemochromatosis**
- Malabsorption syndromes
  - **Celiac disease**
  - Crohn's disease
  - Gastric resection
  - **Weight loss surgery**
  - Ulcerative colitis
  - Pernicious anemia

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Hemochromatosis

- Relatively common genetic disorder resulting in iron overload and iron deposition in liver/pancreas/pituitary gland
- Osteoporosis seen in one-quarter to one-third of patients
- Factors involved
  - Secondary hypogonadism
  - Liver failure
  - Vitamin D deficiency
- Iron has toxic effects on skeleton as well > increased bone resorption and decreased bone formation

Valenti L, Varenna M, Fracanzani AL, Rossi V, Fargion S, Sinigaglia L. Association between iron overload and osteoporosis in patients with hereditary hemochromatosis. Osteoporosis International. 2009; 20(549-555).
Guggenbuhl P, Brissot P, Loreal O. Miscellaneous non-inflammatory musculoskeletal conditions. Hemochromatosis: the bone and the joint. Best Practice & Research: Clinical Rheumatology. 2011; 25(649-664).

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Celiac Disease

- The presentation of celiac disease has been changing
  - More older individuals with more mild disease
  - ~1 in 100 people worldwide
- Subclinical and nonclassical cases
  - Make up 30-60% of new celiac disease cases
  - 2.5 million Americans are undiagnosed and are at risk for long-term health complications

Hujoel IA, Reilly NR, Rubio-Tapia A. Celiac Disease: Clinical Features and Diagnosis. Gastroenterol Clin North Am. 2019;48(1):19-37.
Ludvigsson JF, Murray JA. Epidemiology of Celiac Disease. Gastroenterol Clin North Am. 2019;48(1):1-18. Ganji R, Moghbeli M, Sadeghi R, Bagal G, Ganji A. Prevalence of osteoporosis and osteopenia in men and premenopausal women with celiac disease: a systematic review. Nutr J. 2019;18(1):9. Published 2019 Feb 7.

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Celiac Disease

- Untreated celiac disease > increase in fracture risk by 43%
- Diagnosis relies on serology tests
  - But confirmation with intestinal biopsies is required
- Suspected that malabsorption of micronutrients contributes to altered bone metabolism
  - Frequently vitamin D deficiency
- 40-70% prevalence of low bone mineral density in celiac patients
  - Especially in men

Zanchetta MB, Costa F, Longobardi V, et al. Significant bone microarchitecture impairment in premenopausal women with active celiac disease. Bone. 2015;76:149-157.
Zanchetta MB, Longobardi V, Costa F, et al. Impaired bone microarchitecture improves after one year on gluten-free diet: a prospective longitudinal HR-pQCT study in women with celiac disease. J Bone Miner Res. 2017;32(1):135-142.

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Weight Loss Surgery

- Higher BMI is associated with high bone mineral density and protective against fracture
- Protective effect of higher BMI may disappear in frank obesity
- Meta-analysis >> After adjustment for their higher BMD, obese women fractured more often than women with lower BMI
- Weight loss associated with loss of bone mass and increased risk of fractures

Felson D, et al. Effects of weight and body mass index on bone mineral density in men and women: The framingham study. JBMR 1993.
Cumming S, et al. Risk Factors for Hip Fracture in White Women. N Engl J Med 1995.
Johansson, et al. A Meta-Analysis of the Association of Fracture Risk and Body Mass Index in Women. JBMR 2014.

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Weight Loss Surgery

- Potential hormonal influences contribute to bone loss as studies show bone loss persists at six months despite weight stabilization
- Both Roux-en-Y gastric bypass and sleeve gastrectomy cause bone loss
- Observational study - RYGB or sleeve gastrectomy
  - Caused significant and persistent bone loss (~18% total bone mineral density lost)
- Also increased fracture rate, even 15 years out
- Surgical techniques resulting in malabsorption leads to
  - Malnutrition
  - Calcium and vitamin D deficiency with consequent secondary hyperparathyroidism

Muschitz C, Kocijan R, Marterer C, et al. Sclerostin levels and changes in bone metabolism after bariatric surgery. J Clin Endocrinol Metabol. 2015;100(3):891-901.
Nakamura KM, Haglind EGC, Clowes JA, et al. Fracture risk following bariatric surgery: a population-based study. Osteoporos Int. 2014;25(1):151-158.
Brzozowska MM, Sainsbury A, Eisman JA- Baldock PA, Center JR. Bariatric surgery, bone loss, obesity, and possible mechanisms. Obes Rev. 2013;14(1):52-67.

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Other Conditions

- **AIDS/HIV**
- Ankylosing spondylitis
- Chronic obstructive pulmonary disease
- **Gaucher disease**
- Hemophilia
- **Paget's disease of bone**
- **Hypercalciuria**
- Immobilization
- Major depression
- Ehler-Danlos syndrome
- Homocystinuria due to cystathionine deficiency
- **Renal disease**
- **Myeloma/MGUS**
- Some cancers
- Organ transplantation
- Rheumatoid arthritis
- Systemic mastocytosis
- Thalassemia
- Marfan syndrome
- Osteogenesis imperfecta

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HIV

- Multiple met-analysis > 50% higher fracture risk in HIV positive adults
- Some HIV meds also induce bone loss
  - Tenofovir disoproxil fumarate
- Other considerations that increase fracture risk:
  - Fracture history
  - Postmenopausal status
  - Co-infection with Hep C
  - Presence of AIDS-defining illness

Starup-Linde J, Rosendahl SB, Storgaard M, Langdahl B. Management of osteoporosis in patients living with HIV - a systematic review and meta-analysis. J Acquir Immune Defic Syndr. 2020;83(1):1-8.
Wettsmann, MH, Ofotokun I, Titanji K, Sharma A, Yin MT. Bone loss among women living with HIV. Curr HIV/AIDS Rep. 2016;13(6):367-373.
Marques de Menezes EG, de Paula FJ, Machado AA, de Assis PF, Barbosa Junior F, Navarro AM. Impact of antiretroviral therapy on bone metabolism markers in HIV-seropositive patients. Bone. 2013;57(1):62-67.
Triant VA, Brown TT, Lee H, Grinspoon SK. Fracture prevalence among human immunodeficiency virus-infected vs non-HIV-infected patients in a large US healthcare system. Journal of Clinical Endocrinology and Metabolism. 2008(93):3499-3504.

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Gaucher Disease

- Rare, autosomal recessive genetic disorder
- Deficiency of the lysosomal enzyme glucocerebrosidase
- Multiple types - varying degrees of symptoms
- Clinical syndrome caused by fat cells in the bone marrow/spleen/liver
  - Cytopenia
  - Splenomegaly
  - Hepatomegaly
  - Bone lesions
  - Bone pain
  - Fracture frequent
- Enzyme replacement now available

Weiss PK, Lopez G, Schiffmann R, Barton NW, Weinreb NJ, Sidransky E. Gaucher disease: Progress and ongoing challenges. *Mol Genet Metab.* 2017;120(1-2):8-21. doi:10.1016/j.ymgme.2016.11.004.
Dinnemann J, Belmatoug N, Camou F, et al. A Review of Gaucher Disease Pathophysiology, Clinical Presentation and Treatments. *Int J Mol Sci.* 2017;18(2):441. Published 2017 Feb 17. doi:10.3390/ijms18020441

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Paget's Disease of Bone

- Also known as osteitis deformans
- Not a cause of osteoporosis but often misdiagnosed as osteoporosis
- Localized disorder of bone remodeling
- Increases in bone resorption with subsequent compensatory increases in new bone formation
- Because of rapid bone turnover, affected bone becomes disorganized mosaic pattern of woven and lamellar bone
- Usually asymptomatic but can cause bone pain, deafness, nerve compression syndromes
- Can cause bowing deformities of long bones, fractures, and osteosarcoma
- Treatment > bisphosphonates

Ralston SH, Langston AL, Reid IR. Pathogenesis and management of Paget's disease of bone. Lancet. 2008;9633:155-163.
Wermers RA, Fregs TD, Atkinson EJ, et al. Morbidity and mortality associated with Paget's disease of bone: a population-based study. *JBMR.* 2008;6:819-825.

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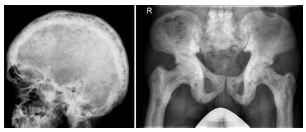
Paget's Disease of Bone



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Hypercalciuria

- Idiopathic hypercalciuria
- Characterized by
  - increased intestinal calcium absorption
  - Increased bone resorption
  - Decreased renal tubular calcium reabsorption
- Associated with low bone mineral density and increased prevalence of fractures
- Calcium excretion higher than absorption > net loss of calcium
- Treatment is thiazide diuretics which
  - Stimulate calcium reabsorption in the distal convoluted tubule
  - Stimulate osteoblast differentiation

Lauderdale DS, Thisted RA, Wen M, Fiscus MJ. Bone mineral density and fracture among prevalent kidney stone cases in the Third National Health and Nutrition Examination Survey. Journal of Bone and Mineral Research. 2001;16:1985-1898.
Heilberg IP, Weisinger JR. Bone disease in idiopathic hypercalciuria. Current Opinion in Nephrology and Hypertension. 2006;15(4):394-402.
Coe FL, Fiscus MJ, Crockett T, Strauss AL, Parks JH, Porat A, Garrel CL, Sherwood LM. Effects on low-calcium diet on urine calcium excretion, parathyroid function and serum 1, 25(OH)2D3 levels in patients with idiopathic hypercalciuria and in normal subjects. American Journal of Medicine. 1982;72(25-32.
Friedman PA and Bushinsky DA. Diuretic effects on calcium metabolism. Seminars in Nephrology. 1990;19(551-556.

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Renal Disease / Osteodystrophy

- High bone turnover
  - Classic form of osteodystrophy
  - High PTH
  - Increased activity of both osteoblasts and osteoclasts
- Low bone turnover from adynamic bone disease
  - Normal to low PTH
  - Can develop following interventions for high bone turnover
  - Complex, many factors
    - Aluminum-based phosphate binder
    - Excess use of active vit D sterols
    - Peritoneal dialysis
- Goals to maintain normal levels of PTH and phosphorus and adequate calcium absorption

Bushinsky DA. Bone disease in moderate renal failure: cause, nature and prevention. Annu Rev Med. 1997:167-176.
Sherrard JF, Hercz G, et al. The aplastic form of renal osteodystrophy. Nehpro Dial Transplant. 1996: 11(Suppl 3): 29-31.
Teiwani HC, et al. Renal osteodystrophy. J Am Acad Orthop Surg. 2006; 14:303-311.

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Renal Disease

- ?Caution in using antiresorptives in patients with osteomalacia and adynamic bone disease
- Treat CKD Stages 1-3 same as usual

- Denosumab > not cleared by the kidney, no negative effect on renal function
- Bisphosphonates' FDA warning not to use them with CrCl < 35-30 ml/min
  - Bisphosphonates are cleared by the kidney and old data using IV Pamidronate showed few patients developed ATN (all recovered)
  - IV ibandronate trials had no effect on renal function
  - IV zoledronic acid had a transient but recoverable increase in serum creatinine, but not when CrCl < 30 ml/min
- Teriparatide and abaloparatide increase renal blood flow and FDA label warning states not to use them at CrCl < 30ml/min is based on no studies

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MGUS

- 53.8% of patients with MGUS have low bone mass
- 26.2% of patients with MGUS have osteoporosis
- ~1% chance of worsening to MM each year
- Fracture risk in these patients does not depend on the immunoglobulin class of MGUS nor on the concentration of paraprotein
  - ALL patients with MGUS have an increased risk of fracture

Pepe, J.; Petrucci, M.T.; Nofroni, I.; Pasaino, V.; Diacinti, D.; Romagnoli, E.; Minisola, S. Lumbar bone mineral density as the major factor determining increased prevalence of vertebral fractures in monoclonal gammopathy of undetermined significance. Br. J. Haematol. 2006, 134, 485-490.

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MGUS Evaluation

- Referral to hematology/oncology for close follow-up
- Specific immunologic and other blood tests
  - Immunofixation - looks at types of abnormal protein
  - Serum free light chains - identifies immunoglobulin fragments which could be a myeloma variant
  - General blood tests
  - CBC - assessing for anemia
  - CMP - assessing for renal failure, hypercalcemia, albumin, total protein levels
- Additional testing
  - Tissue pathology
    - Bone marrow biopsy/aspirate - looks for clonal plasma cells (myeloma)
  - Urine tests
    - 24 hour urine collection - for protein electrophoresis and immunofixation
  - Additional serology - for staging and prognosis in myeloma
  - Radiology : PET/CT Scans or low-contrast whole body CT/MRI scan

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Drugs

- **Anti-epileptic drugs**
- Aromatase inhibitors
- Chemotherapy
- Immunosuppressants
- Medroxyprogesterone acetate
- **Glucocorticoids**
- Gonadotropin-releasing hormone agents
- Heparin
- Lithium
- **Proton pump inhibitors**
- Selective serotonin-reuptake inhibitors
- SGLT2-inhibitors
- Thiazolidinediones
- Thyroid hormone (in supraphysiologic doses)

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Anti-Epileptic Drugs

- Phenobarbital, phenytoin, primidone, valproate, carbamazepine have been associated with low bone mass
- High doses of topiramate?
- Mechanism of bone loss still uncertain
  - Multifactorial: physical activity, disabilities, access to sunlight, other meds
- Vit D metabolism accelerated leading to low 25 OH vit D levels, high bone turnover, and secondary hyperparathyroidism
- Risk increases with duration of treatment

Vestergaard P, Tigaran S, Rejnmark L, Tigaran C, Dam M, Mosekilde L. Fracture risk is increased in epilepsy. Acta Neurol Scand. 1999 May;99(5):269-75.
Fitzpatrick LA. Pathophysiology of bone loss in patients receiving anticonvulsant therapy. Epilepsy Behav. 2004 Feb;5 Suppl 2:S3-15.
Petty SJ, O'Brien TJ, Wark JD. Anti-epileptic medication and bone health. Osteoporos Int. 2007 Feb;18(2):129-42.
Petty SJ, Wilding H, Wark JD. Osteoporosis Associated with Epilepsy and the Use of Anti-Epileptics-a Review. Curr Osteoporos Rep. 2014 Apr;12(1):54-65.

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Glucocorticoid-Induced Osteoporosis

- Most common cause of secondary osteoporosis
- Glucocorticoids may be the cause of bone loss but could also be underlying disease as well
  - IBD, SLE, RA, PMR – all associated with bone loss due to systemic release of inflammatory cytokines

Van Staa TP, Leufkens HG & Cooper C. The epidemiology of corticosteroid-induced osteoporosis: a meta-analysis. Osteoporosis International 2002 13:777-787
Van Staa TP, Leufkens HG, Abenhaim L, Zhang B & Cooper C. Use of oral corticosteroids and risk of fractures. Journal of Bone and Mineral Research 2000 15:993-1000

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GIO

- Has both indirect and direct effects on bone metabolism
  - Blocks vitamin D actions on calcium absorption which causes decrease in calcium and modest increase in PTH levels
  - Glucocorticoids induce increased bone resorption and reduce bone formation through impairment of maturation of osteoblasts as well as apoptosis
- Cumulative dose and duration determines risk of fractures
- Fractures frequently in trabecular bone
- Many treatments studied to get GIO approval

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Proton Pump Inhibitors

- Very commonly used for GERD, ulcers, H.pylori treatment, Barrett's esophagus, and as gastroprotective agents
- By increasing gastric pH, may decrease calcium absorption and have negative effects on skeletal homeostasis
- **Impact on BMD and fragility fractures still very controversial**
- Remember to address adequate calcium supplementation

Fraser LA, Leslie WD, Targownik LE, Papaioannou A, Adachi JD; CaMos Research Group. The effect of proton pump inhibitors on fracture risk: report from the Canadian Multicenter Osteoporosis Study. Osteoporos Int. 2013 Apr;24(4):1161-8. doi: 10.1007/s00198-012-2112-9. Epub 2012 Aug 14. PMID: 22890365; PMCID: PMC5096922.
Solomon DH Diem SJ, Ruppert K, Lian Y, Liu CC, Wohlfart A, Greendale Ga, & Finkelstein JS. Bone Mineral Density Changes Among Women Initiating Proton Pump Inhibitors or H2 Receptor Antagonists: A SWAN Cohort Study. Journal of Bone and Mineral Research 2014 30 232-239
Gray SL, LaCroix AZ, Larson J, et al. Proton pump inhibitor use, hip fracture, and change in bone mineral density in postmenopausal women: results from the Women's Health Initiative. Archives of Internal Medicine. 2010 May;170(9):765-771. DOI: 10.1001/archinternmed.2010.94. PMID: 20458083; PMCID: PMC4240017.

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What labs should I be ordering?

- Serum protein electrophoresis
- 24 hour urine collection for calcium, sodium, and creatinine excretion
- Serum Intact PTH
- Tissue transglutaminase antibodies
- Testosterone (males only)
- Urinary free cortisol
- Complete metabolic panel
  - Calcium, phosphate, total protein, albumin, liver enzymes, alkaline phosphatase, creatinine, electrolytes
- Serum 25 OH vitamin D
- Thyroid stimulating hormone
- Complete blood count

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Take Away Points

- Secondary causes for osteoporosis and fragility fractures may FREQUENTLY be asymptomatic and require laboratory testing for detection
- Because of the high prevalence of secondary osteoporosis, laboratory testing should be considered for many patients with osteoporosis
  - Especially younger women and men younger than 70
- Many simple laboratory tests provide useful information in 40 to 85% of women who do not have clinical risk factors for bone loss
- Be comfortable referring to a bone health specialist, endocrinology, rheumatology, general or endocrine surgeon that frequently performs parathyroid surgeries, and hematology/oncology

Barzel US Recommended testing in patients with low bone density. J. Clin. Endocrinol. Metab.2003;88:1404-1405.
Tannenbaum C, Clark J, Schwartzman K et al.Yield of laboratory testing to identify secondary contributors to osteoporosis in otherwise healthy women. J.Clin.Endocrinol.Metab.2002;87:4431-4437.
Edwards BJ, Bunta AD, Simonelli C, Bolander M, Fitzpatrick LA. Prior fractures are common in patients with subsequent hip fractures. Clin Orthop Relat Res.2007;461:226-230.
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Camacho PM, Petak SM, Binkley N, Diab DL, Eldeiry LS, Farooki A, Harris ST, Hurley DL, Kelly J, Lewiecki EM, Pessah-Pollack R, McClung M, Wimalawansa SJ, Watts NB. AMERICAN ASSOCIATION OF CLINICAL ENDOCRINOLOGISTS/AMERICAN COLLEGE OF ENDOCRINOLOGY CLINICAL PRACTICE GUIDELINES FOR THE DIAGNOSIS AND TREATMENT OF POSTMENOPAUSAL OSTEOPOROSIS-2020 UPDATE. Endocr Pract. 2020 May;26(Suppl 1):1-46.

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Thank you!

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