Metabolic Bone Diseases with Focus on Hypophosphatasia in children & adolescents

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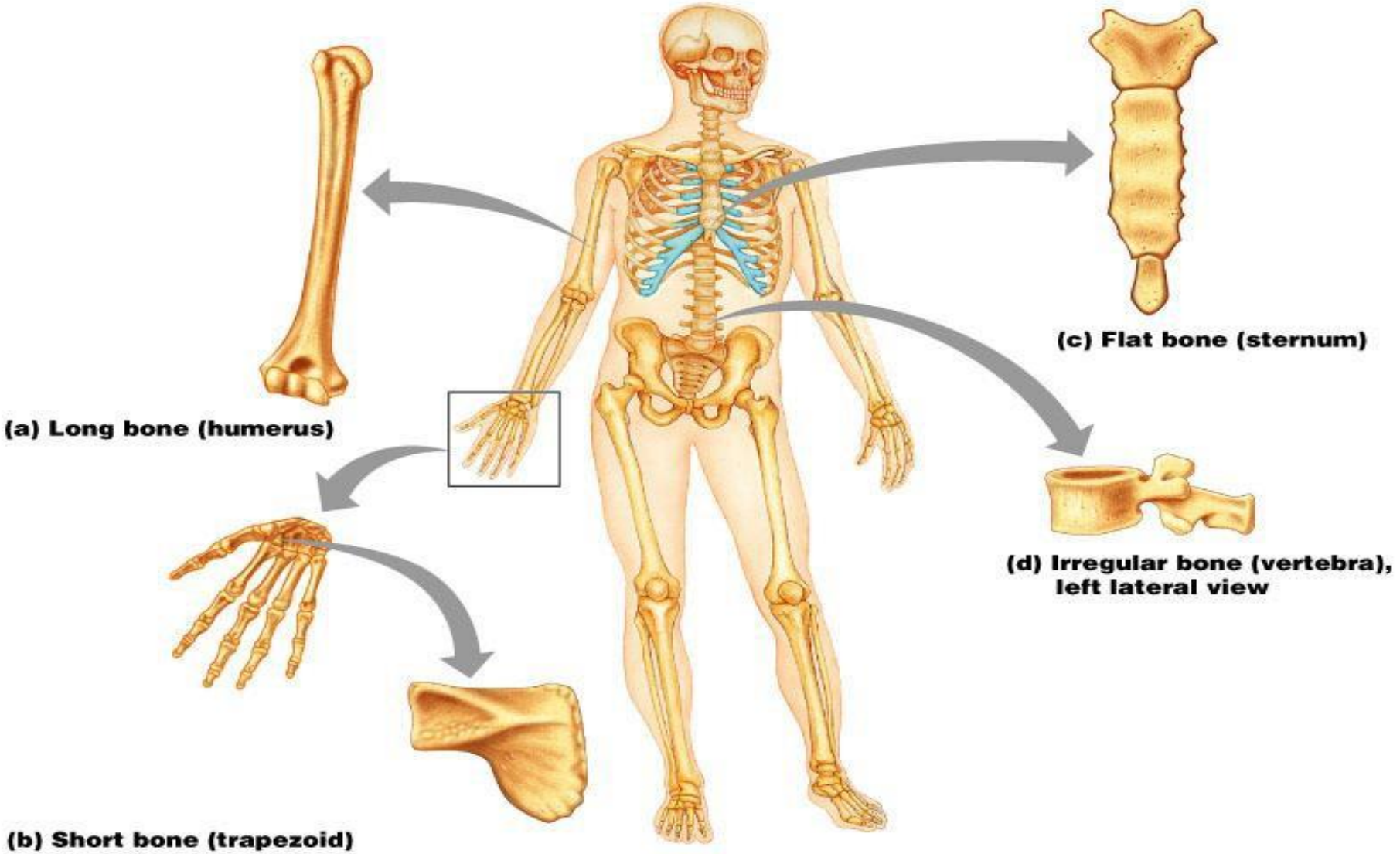
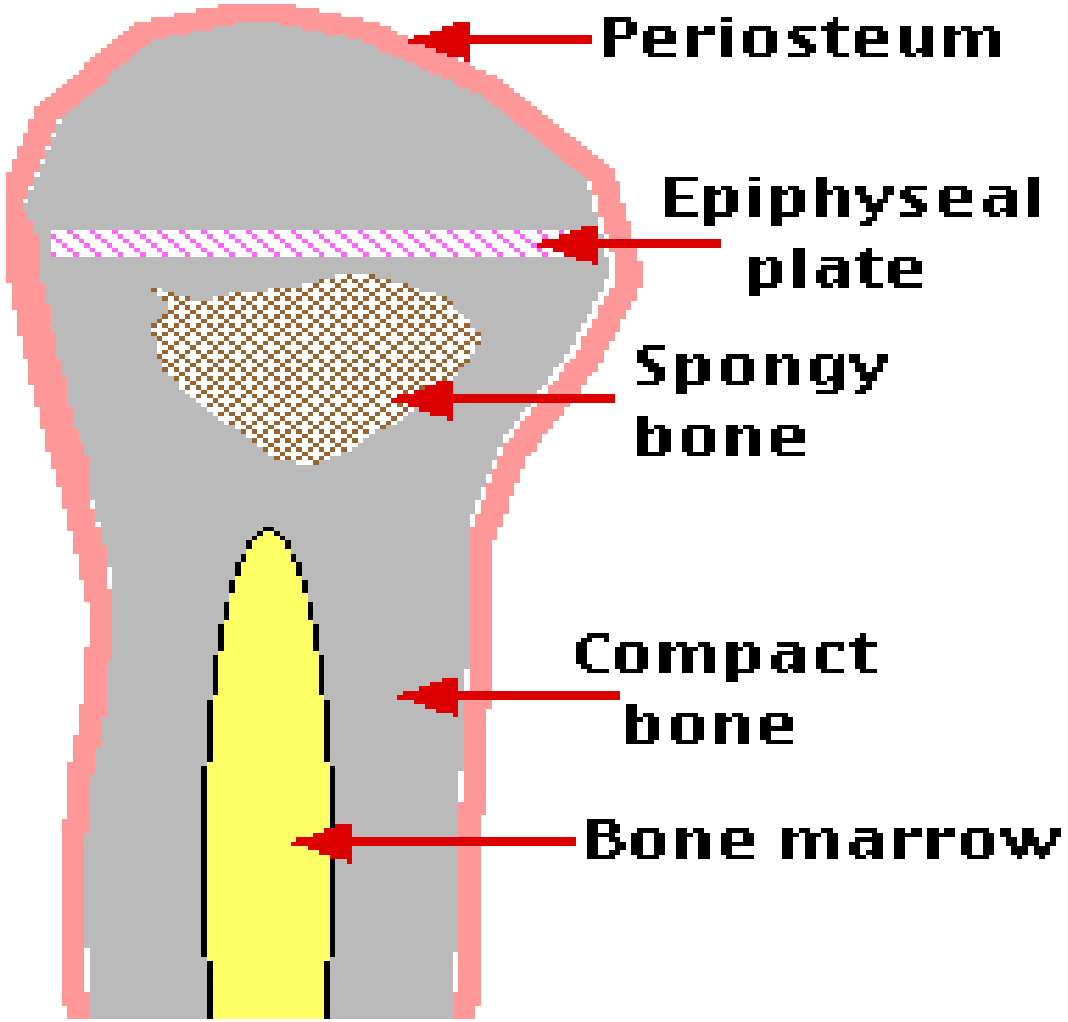
Objectives

- Bone structure.
- Components of the bone.
- Factors affecting Bone health.
  - Intrinsic & Extrinsic factors.
- Rickets/ Osteomalacia.
- Osteoporosis
  - Osteogenesis imperfecta.
- Hypophosphatasia
  - Types.
  - Clinical features.
  - Management.
- Summary.

CLASSIFICATION OF BONE



Bone Structure



Components of bone

- Calcified matrix (90%)
  - composed of collagen fibers (type-1),
  - Glycosaaminoglycan containing spindle shaped crystals of hydroxyapatite
- Mineral Element
  - Crystals of Calcium and Phosphate are arranged either amorphously or as Hydroxyapatite Ca_{10} $(PO4)_6$ $(OH)_2$
- Non Collagenous Components (Proteins)
  - Osteocalcin: protein produced by the Osteoblasts
  - α2 HS- glycoprotein: produced by the liver and absorbed by the bone matrix
  - Amino Acids: about one fourth of amino acids present in collagen are proline and hydroxproline.

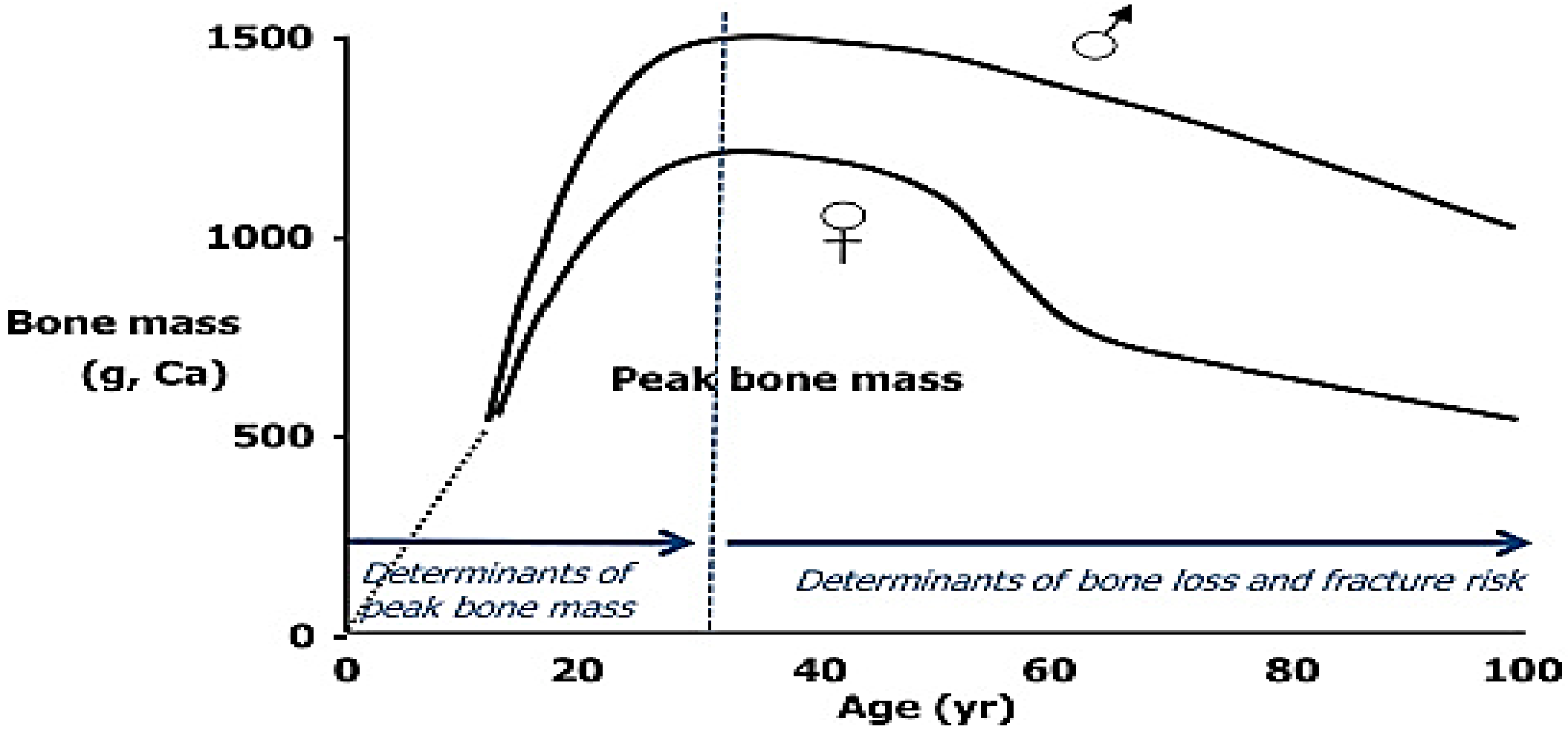
Skeleton is solid but dynamic!

- Skeleton is not static structure, but in continuous "modeling - remodeling process".
- Bone is continually remodeled throughout life because bones sustain recurring micro-trauma.
- The hallmark of Rickets/ Osteomalacia is decreased bone mineralization (calcium/phosphate or both).
- The hallmark of osteoporosis is reduction in skeletal mass caused by imbalance between bone resorption & bone formation.

Factors influencing bone density

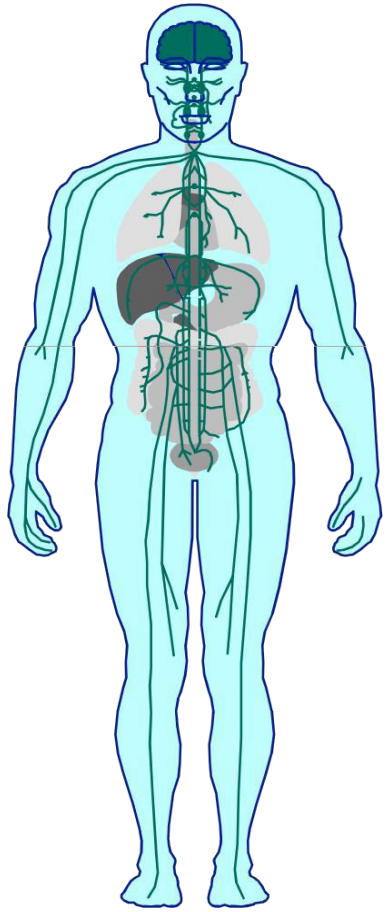
- Heredity “genetic potentials”.
- Ethnicity (blacks stronger bone density than whites).
- Gender (male’s BMD higher than females).
- Diet (calcium & vitamin D).
- Physical activity (sedentary life is associated with low BMD).
- Pubertal status (strong effects of sex hormones on BMD).
- Hormonal factors.
- Body mass (higher BMI has lower BMD).
- Medications (corticosteroids).
- Sporadic risk factors (cigarette smoking, alcohol, soft drinks & excessive caffeine).

BMD throughout lifespan



Hormonal factors

- Corticosteroid: Negative.
- Growth hormone: Positive.
- Pituitary hormones : Positive.
- PTH: Negative.
- Testosterone : Positive.
- Estrogen: Positive.
- Thyroxin : Negative.
- Vitamin D : Positive.



Metabolic Bone Diseases

Common manifestations of various metabolic bone diseases

- Recurrent fractures.
- Bone deformities.
- Recurrent bone pains.
- Short stature.
- Dental problems.
- Recurrent chest infections.
- Delayed walking and gross motor milestones.
- Generalized hypomineralization in bone x-ray.

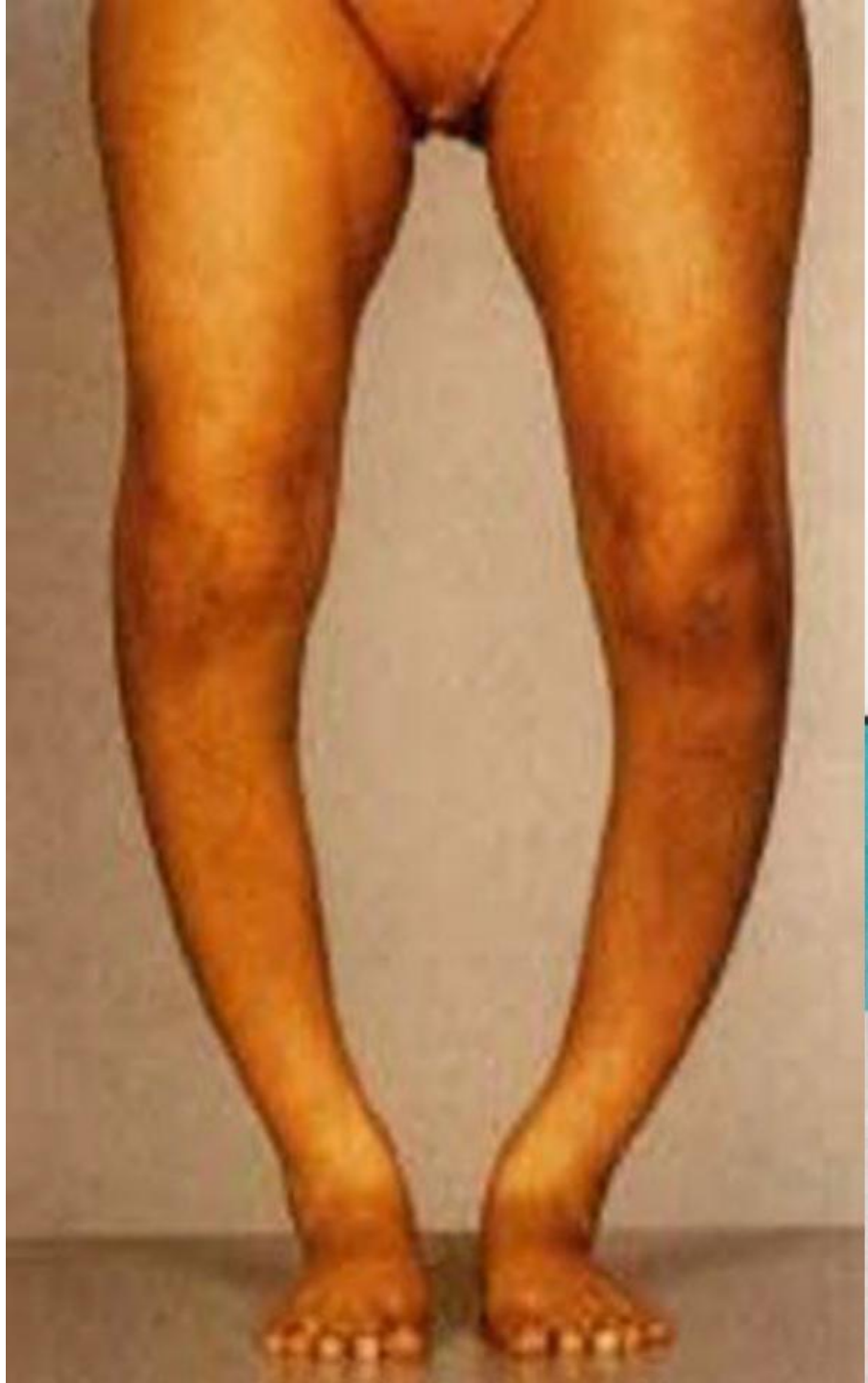
Rickets

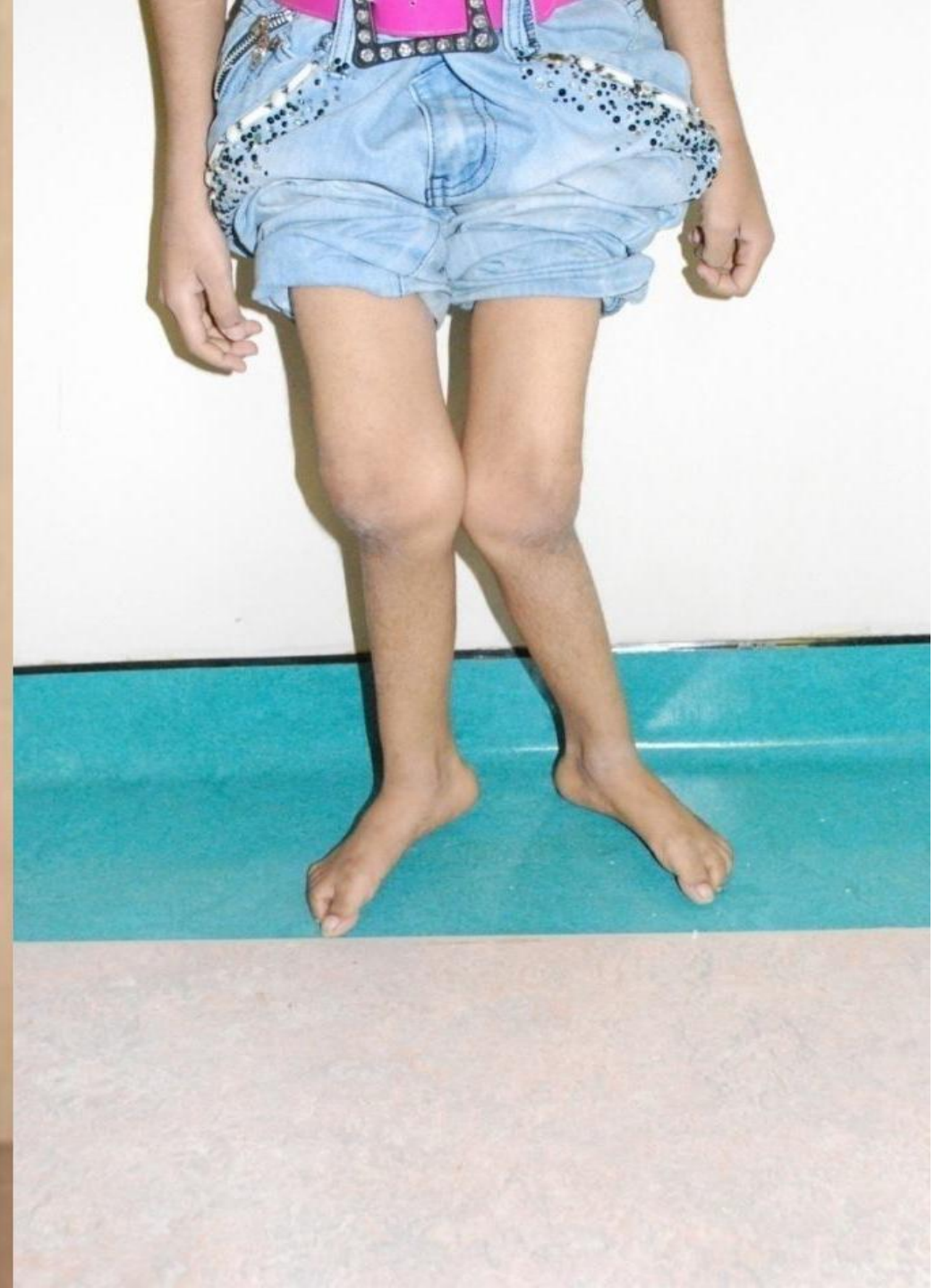
- Rickets is a disease of the growing bones in which defective mineralization occurs in both bone & cartilage of the epiphyseal growth plates.
- Is associated with growth retardation & skeletal deformities.

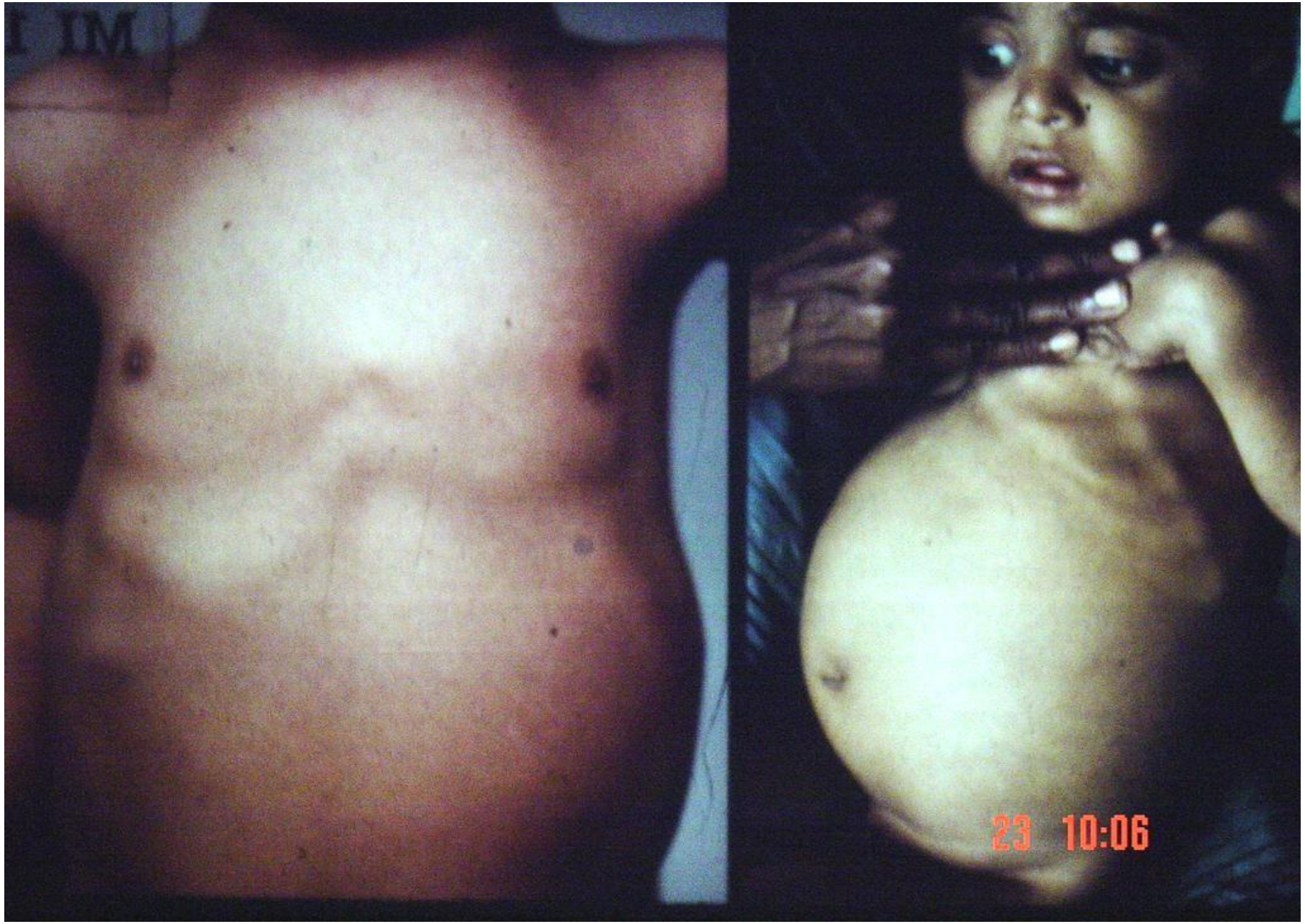
Types

- Hypocalcaemic Rickets (commonest type).
- Hypophosphatemic Rickets (not common).
- Combined Rickets (combination of hypocalcemia & hypophosphatemia).

Clinical manifestation of Rickets



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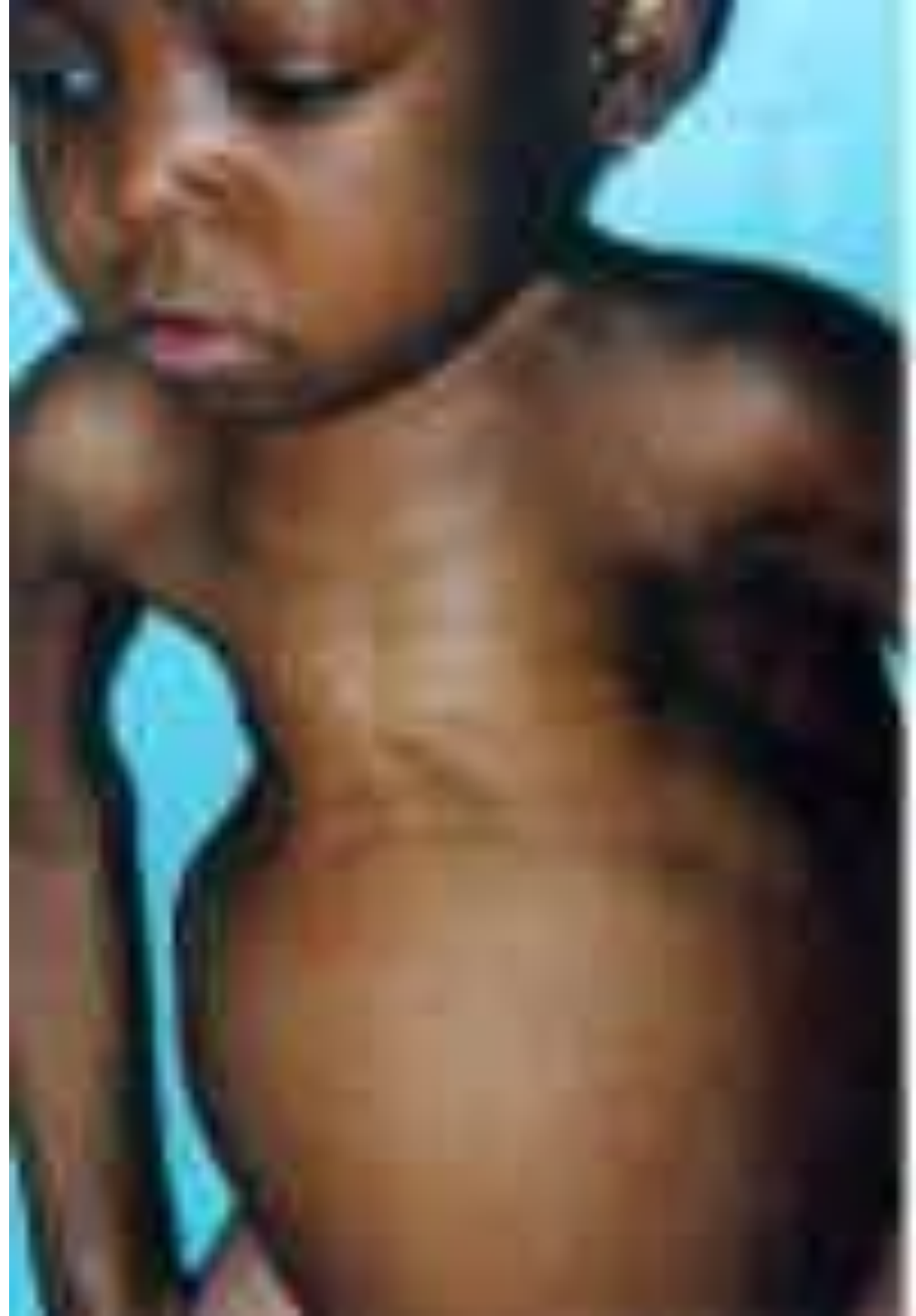


Hereditary Rickets

- Hypophosphatemic rickets.
- Vitamin D resistant rickets.

Vitamin D dependent rickets

Type 1

- Rare, autosomal recessive.
- Lack of 1 α hydroxylase enzyme.
- It appears early months of life.

Type 2

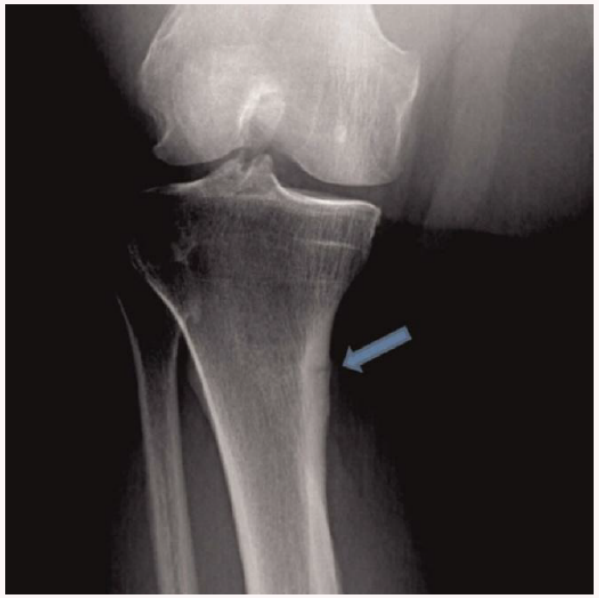
- Rare autosomal recessive disorder.
- 1 α hydroxylase enzyme is present.
- Lack of Calcitriol receptors.
- Common in Arabs.
- Baldness.
- Severely affected individuals.
- Unresponsive to vitamin D therapy.

XLH

- XLH is a type of rickets characterized by excessive loss of phosphate unrelated to calcium levels
  - Caused by a mutation in the phosphate-regulating gene (PHEX)
  - Leads to impaired renal tubular reabsorption of phosphate

Clinical Manifestations:

- Growth retardation (short stature)
- Bowed legs
- Lower extremity insufficiency fractures
- Arthritis and Osteomalacia (adults)
- Low blood phosphate and vitamin D
- Raised urine phosphate
- Raised serum ALP in children
- Normal serum calcium



XLH is treated with Vitamin D metabolites (calcitriol) and phosphate

Osteoprosis

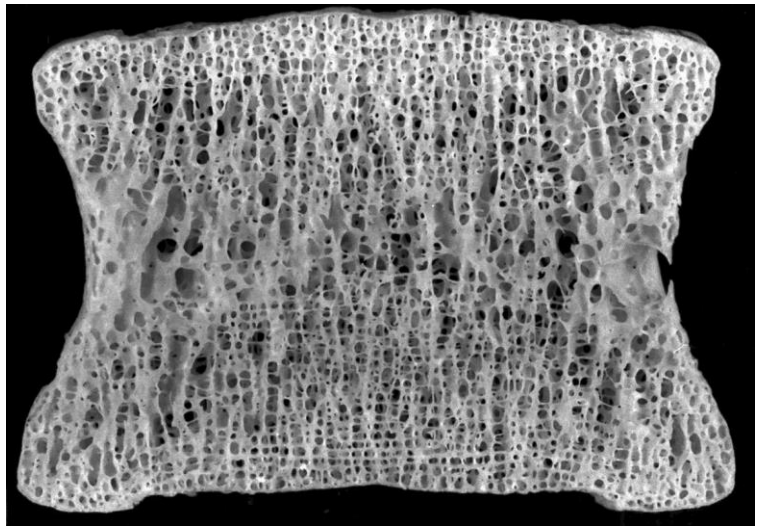
When to suspect??

- Recurrent bone pain (variable in severity).
- Easy bone fractures (Low/ No trauma).
- Decreased mobility & impaired daily life activities.

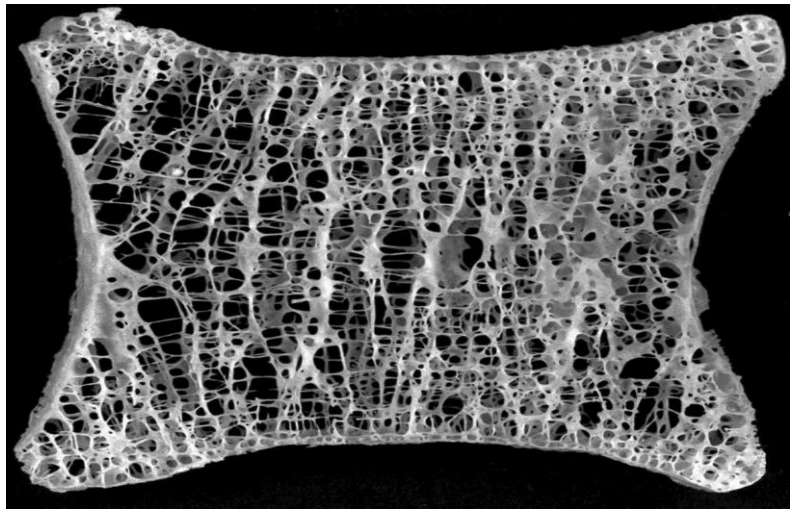
Normal biochemistry including (normal calcium, phosphate, ALP, vitamin D and PTH)

Osteoporosis in children

- No WHO definitions in children & adolescents.
- Universal agreed definition for children:
  - BMD Z-score by DXA ≤ -2.0 SD
  - Osteopenia, if Z-score between -1.0 and -2.0



Normal bone



Osteoporosis

Causes of Osteoporosis In Children

- Primary
  - Heritability of bone loss.
    - Osteogenesis imperfecta.
    - Idiopathic juvenile osteoporosis.

Causes of secondary osteoporosis

- Endocrine / Metabolic diseases:
  - Estrogen deficiency.
  - Testosterone deficiency.
  - Cushing’s syndrome.
  - Primary hyperparathyroidism.
  - Thyrotoxicosis.
  - GH deficiency.
  - Gaucher’s disease.
- Malabsorption diseases:
  - Gastrectomy.
  - Celiac disease.
  - Small bowel resection.
  - Crohn’s disease.
  - Cystic fibrosis.

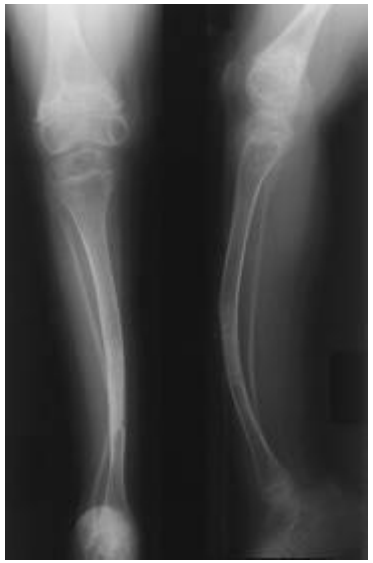
Causes of secondary osteoporosis

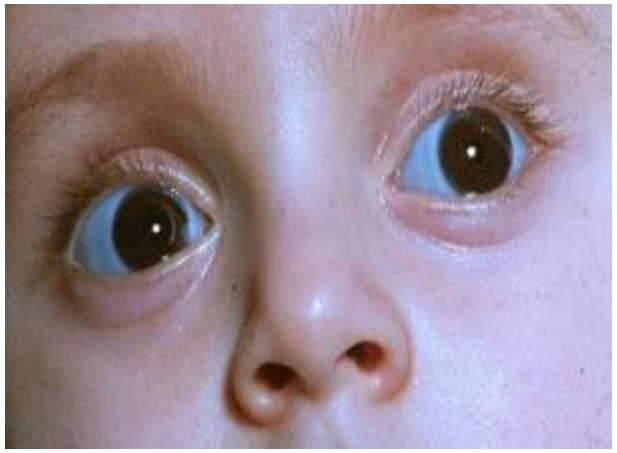
- Malignancies
- Autoimmune disorders
  - Rheumatoid arthritis, Lupus erythematosis
- Immobilization
  - CP/ Neuromuscular disorders
- Drugs
  - Corticosteroids, loop diuretics, anticonvulsants, GnRH agonist, chemotherapy (Methotrexate), heparin.

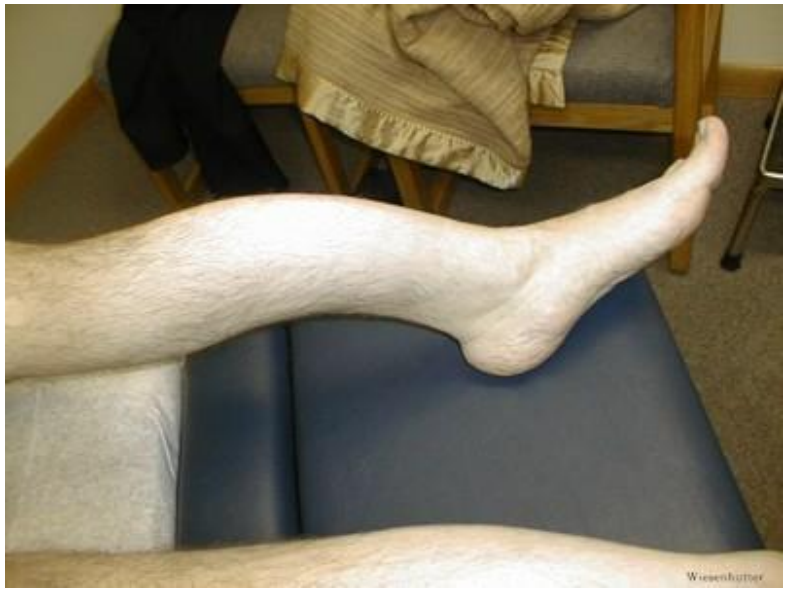
Osteogenesis Imperfecta (OI)

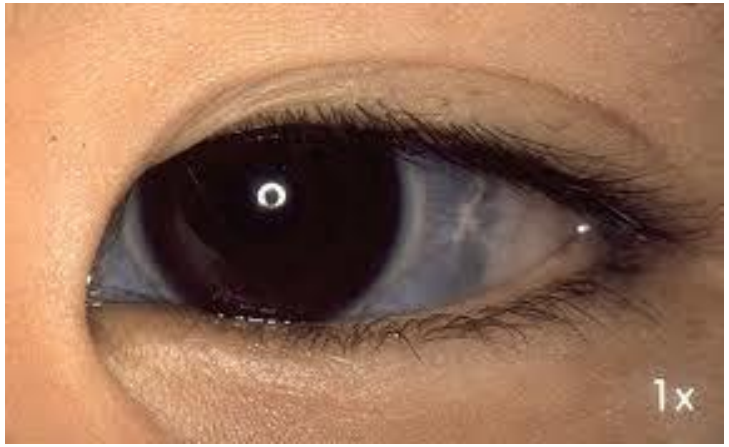
- Incidence 1 : 20,000 live births.
- Inherited disorder of collagen 1 deficiency.
- At least 8 distinct forms of OI.
- Variation in severity from one person to another.
- Pathologic changes seen in all tissues in which type 1 collagen is an important constituent (e.g., bone, ligament, dentin, and sclera).
- Equally common in males & females.
- Family history , but most cases due to new mutations.
- Commonly present with fractures after minor trauma.
- Short stature, bone deformities and dental problems.

Osteogenesis Imperfecta





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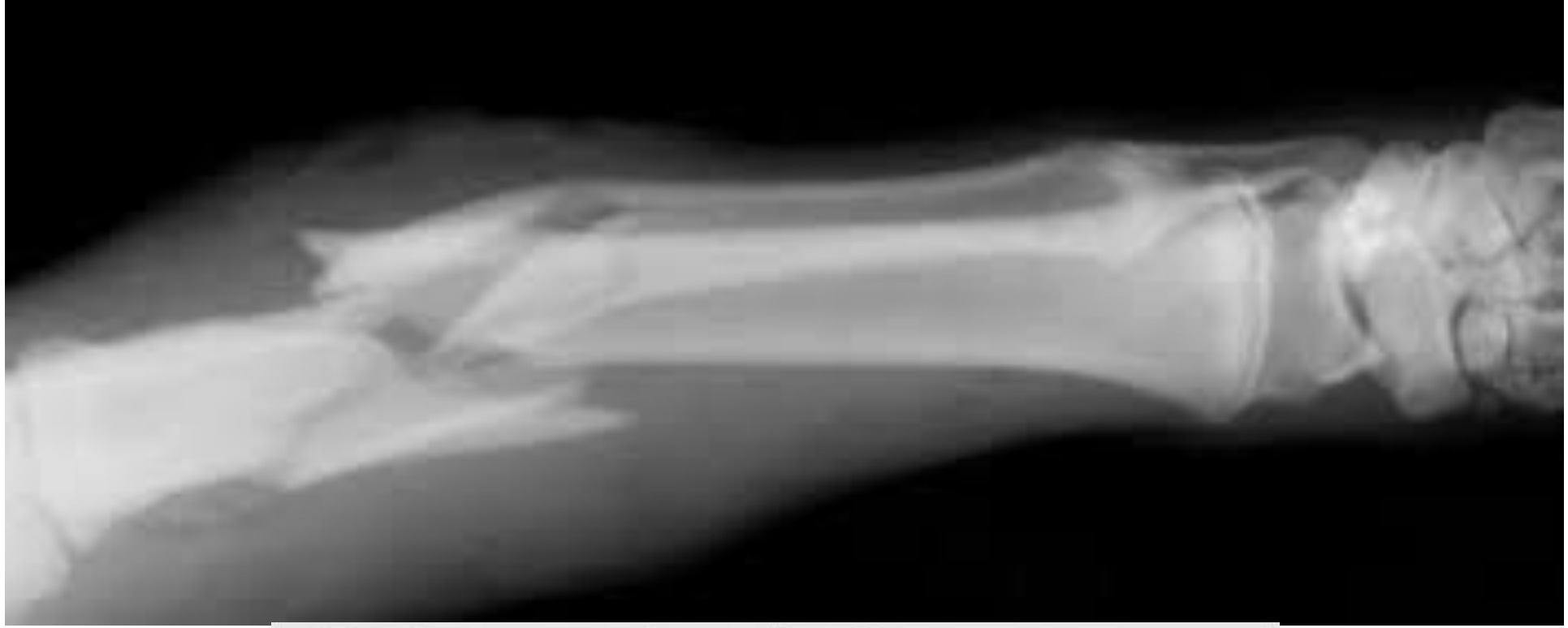

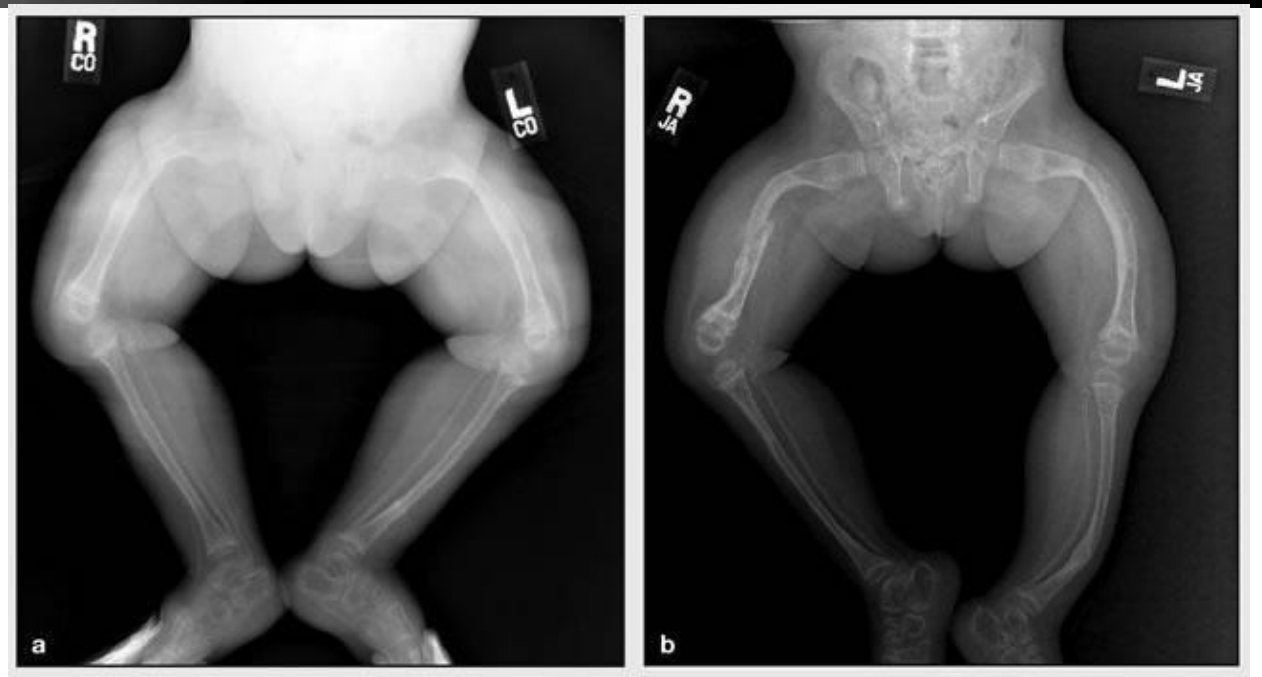
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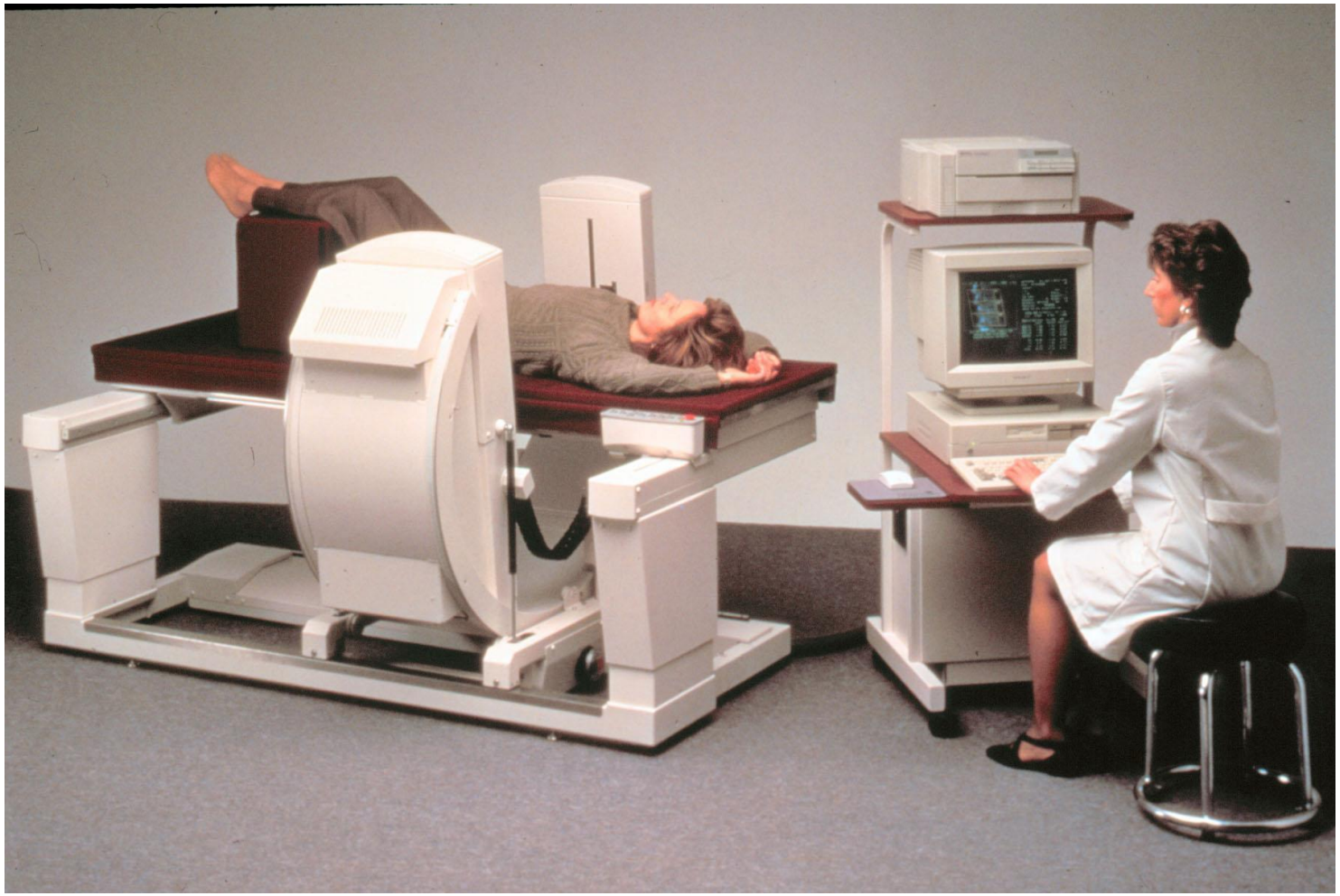
DXA scanner – open configuration



Hypophosphatasia (HPP)

- Hypophosphatasia (HPP) is a ultra rare, life-threatening, progressive, systemic, inherited metabolic disorder.
- Caused by loss-of-function mutations in the ALPL gene, which encodes tissue-nonspecific alkaline phosphatase (TNSALP).
- (TNSALP) deficiency in osteoblasts & chondrocytes impairs bone mineralization, leading to rickets or osteomalacia.

HPP is highly variable in its clinical expression

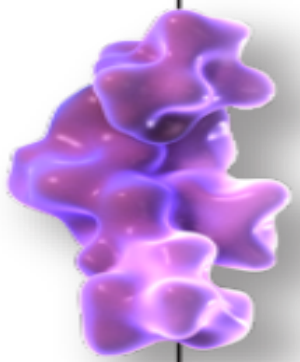
- 4 subtypes based on age at onset.

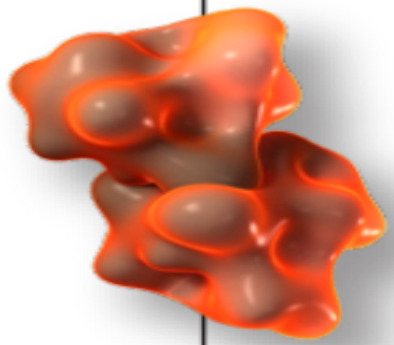
HPP subtype	Onset of first signs/symptoms
Perinatal-onset	In utero and at birth
Infantile-onset	< 6 months of age
Juvenile-onset	≥ 6 months to 18 years of age
Adult-onset	≥ 18 years of age with no evidence of disease in childhood

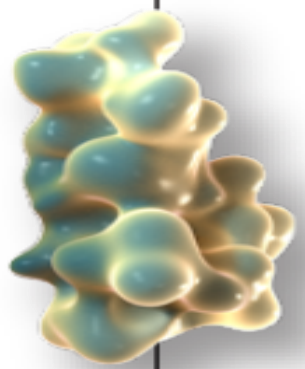
- Odontohypophosphatasia (odontoHPP), Pre/Peri-natal benign,
- Pseudohypophosphatasia (pseudoHPP)

1. Rockman-Greenberg C. *Pediatr Endocrinol Rev*. 2013;10 Suppl 2:380-388. **2.** Mornet E, Nunes ME. Hypophosphatasia. GeneReviews. Updated 2011. University of Washington. Available at:http://www.ncbi.nlm.nih.gov/books/NBK1150/. Accessed November 5, 2013. **3.**. Whyte MP, et al. *Bone*. 2015;75:229-39.

Low ALP







Pyridoxal 5′-phosphate

PLP (vitamin B_6)

Low ALP activity impairs PLP (vitamin B_6) transport across the plasma membrane into the CNS, which can lead to vitamin B_6–responsive seizures.[1,4,5]

Inorganic pyrophosphate

PPi

PPi is a known inhibitor of bone mineralization and impairs calcium/phosphate homeostasis, which can lead to systemic damage.[1,4]

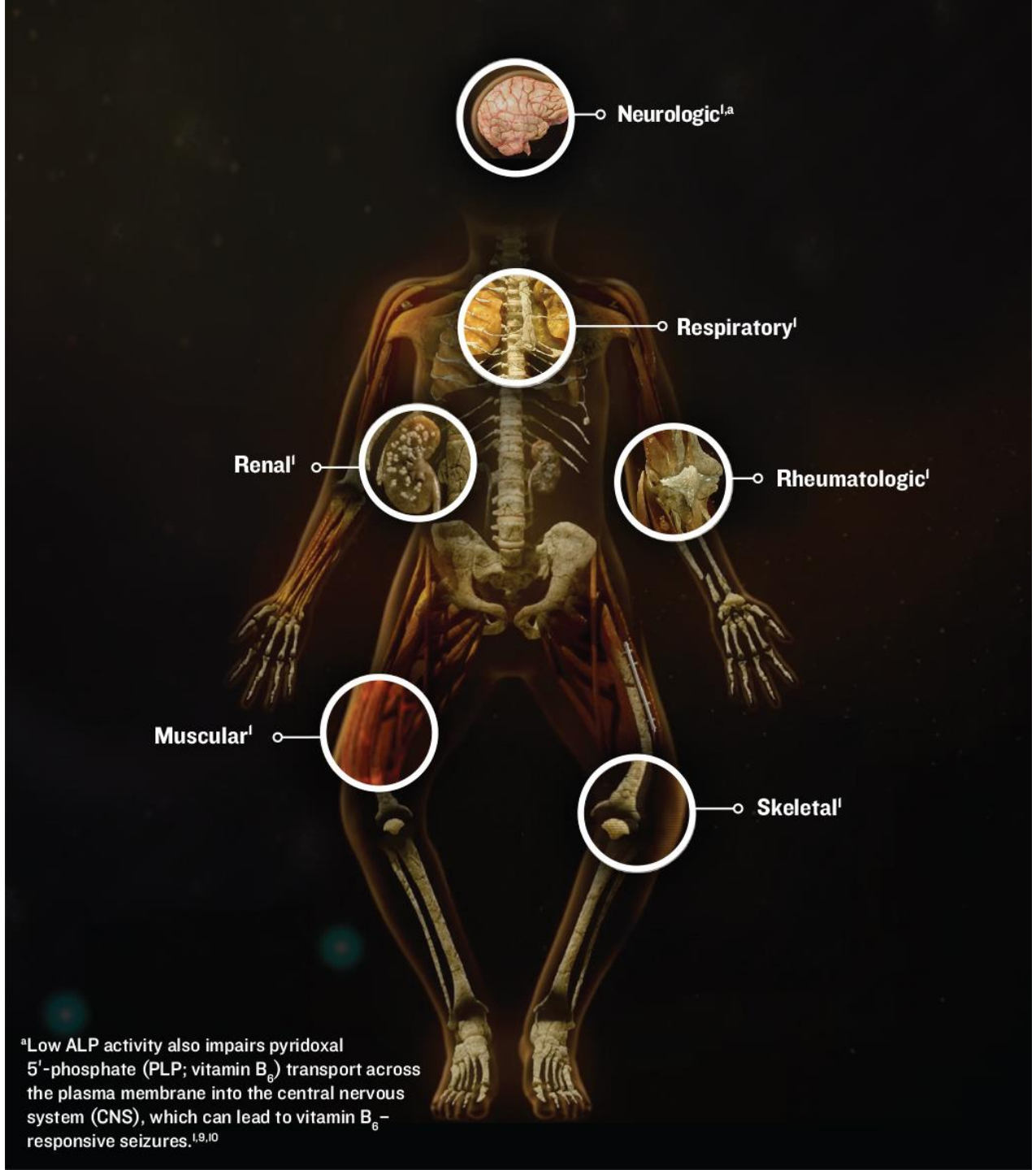
Phosphoethanolamine

PEA

PEA is a diagnostic marker of HPP, but its relation to disease pathophysiology is not fully understood.[4,5]

- NEUROLOGIC
- DENTAL
- SKELETAL
- MUSCULAR/ RHEUMATOLOGIC
- RESPIRATORY
- RENAL

HPP is a Lifelong Disease with Systemic Consequences

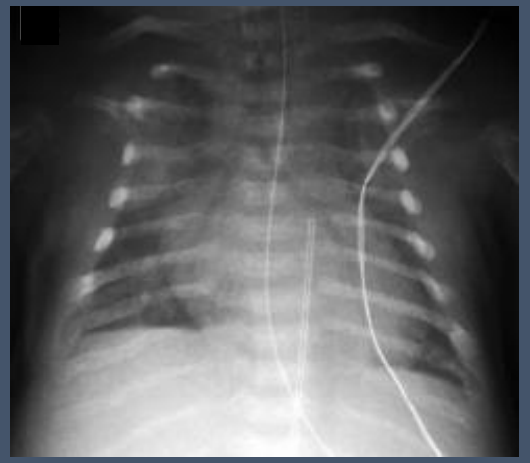


[a]Low ALP activity also impairs pyridoxal 5′-phosphate (PLP; vitamin B_6) transport across the plasma membrane into the central nervous system (CNS), which can lead to vitamin B_6–responsive seizures.[1,9,10]

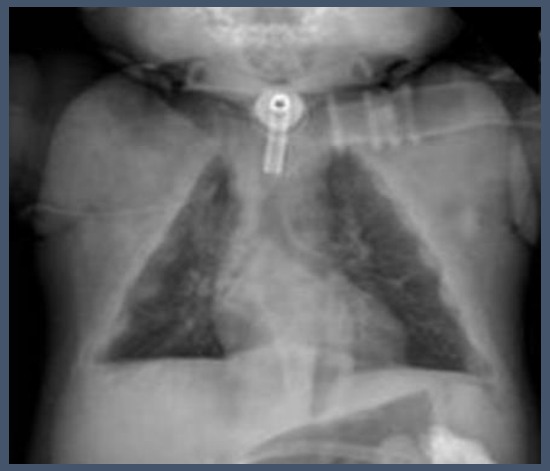
Pulmonary Manifestations

Pulmonary Manifestations of HPP

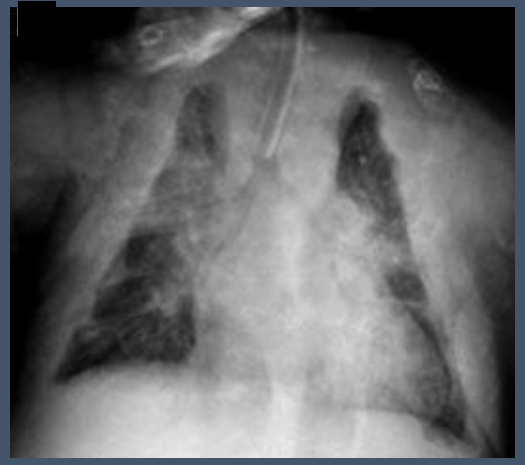
Severe rib cage hypomineralization leading to chest deformity and decreased thoracic volume can occur in newborn and infant patients with HPP[1-4]:



Bell-shaped chest deformity in a patient aged 12 days[3,a]



Undermineralized ribs and bell-shaped chest deformity in a patient aged 33 months[3,a]



Deformities and poor mineralization in a patient aged 32 months[3,a]

Respiratory complications are the most common cause of death in patients with HPP[5]

HPP, hypophosphatasia.

[a]Images are from different patients. Images reproduced from Whyte et al. *N Engl J Med.* 2012;366:904-913. With permission from Massachusetts Medical Society.

1. Linglart and Biosse-Duplan. *Curr Osteoporos Rep.* 2016;14:95-105. **2.** Rockman-Greenberg. *Pediatr Endocrinol Rev.* 2013;10(suppl 2):380-388. **3.** Whyte et al. *N Engl J Med.* 2012;366:904-913. **4.** Silver et al. *Pediatr Pathol.* 1988;8:483-493. **5.** Whyte et al. *J Pediatr*. 2019;pii: S0022-3476(19)30139-8 [Epub].

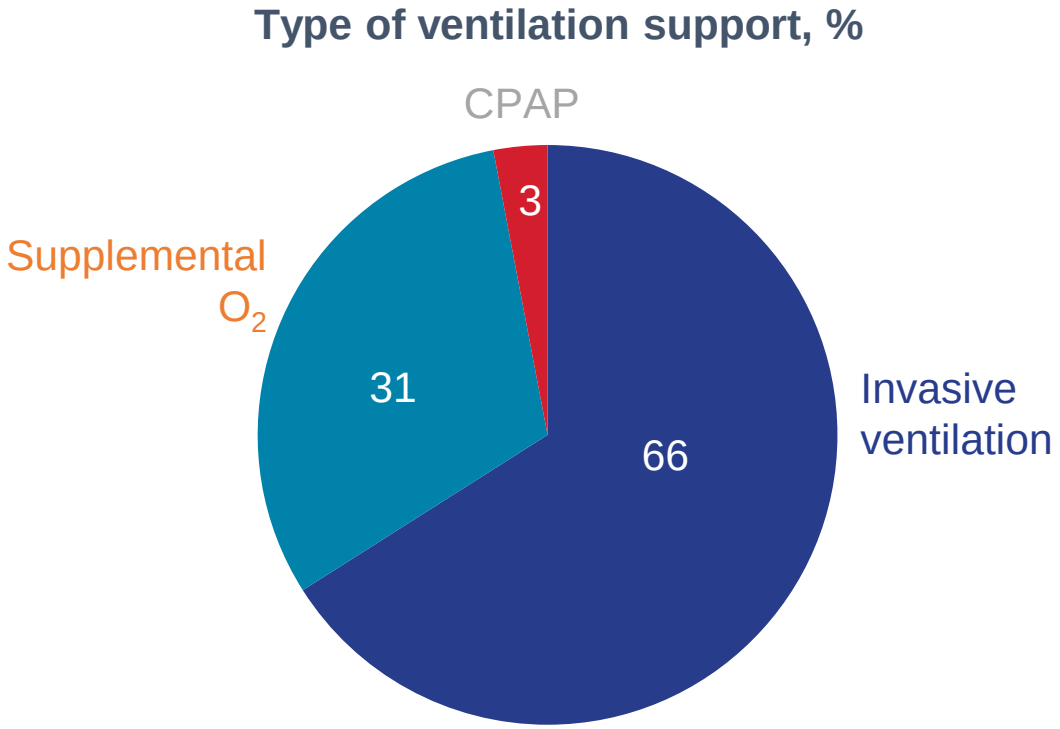
Burden of Pulmonary Manifestations

Rib cage hypomineralization may lead to:

- Chest deformity[1]
- Pulmonary hypoplasia[2]
- Respiratory insufficiency[1,3,4]
- Respiratory compromise and failure[2,4]
- Need for prolonged and invasive/ noninvasive ventilator support[1,3]
- Respiratory complications, including repeated pneumonia[5]

CPAP, continuous positive airway pressure; HPP, hypophosphatasia.
[a]Mechanical ventilation via intubation or tracheostomy.
1. Rockman-Greenberg. *Pediatr Endocrinol Rev*. 2013;10(suppl 2):380-388. **2.** Orimo. *Ther Clin Risk Mgmt*. 2016;12:777-786. **3.** Kitaoka et al. *Clin Endocrinol.* 2017;87:10-19. **4.** Phillips et al. *Mol Genet Metab*. 2016;119:14-19. **5.** Whyte. *Nat Rev Endocrinol.* 2016;12:233-246. **6.** Whyte et al. *J Pediatr.* 2019;pii: S0022-3476(19)30139-8 [Epub].

In a retrospective chart review of 48 untreated patients with perinatal- or infantile-onset HPP, 64% (29/45) required respiratory support[6]



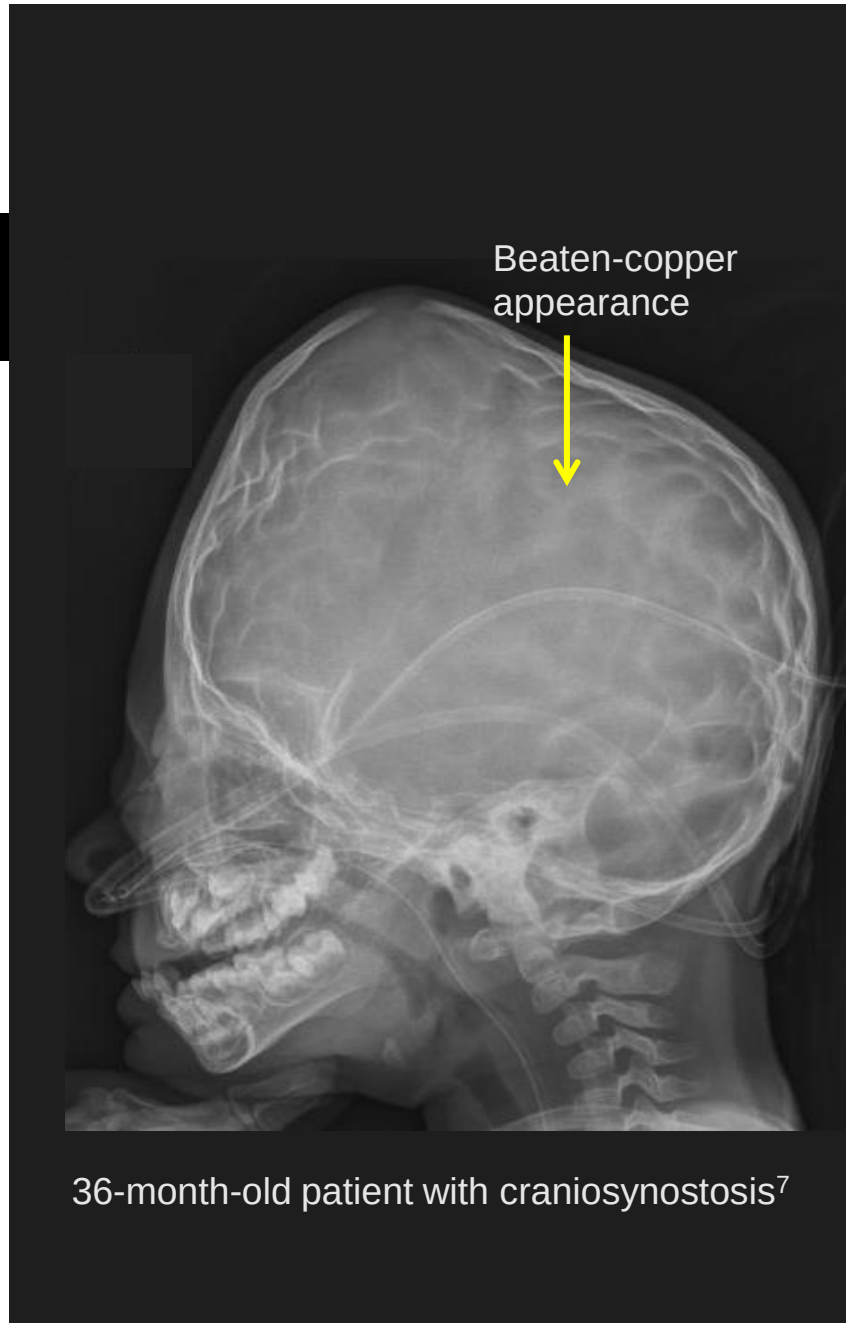
95% (18/19) of the patients who required invasive ventilation died[6,a]

Neurologic Manifestations

Neurologic Burden of HPP

Neurologic manifestations occur in patients with HPP because of low vitamin B_6 and complications from craniosynostosis

- **Neonates and infants with HPP can experience:**
- **Vitamin B_6–responsive seizures[1,2]**
  - **These seizures are a fatal prognostic indicator[1]**
- **Intracranial hypertension and hemorrhage[3]**
- **Encephalopathy[3]**
- **Conductive deafness[4-6]**
- **Brainstem or cerebral cortex damage[4]**
- **Craniosynostosis[3]**



36-month-old patient with craniosynostosis[7]

HPP, hypophosphatasia.
Image reproduced from Whyte et al. *N Engl J Med.* 2012;366:904-913. With permission from Massachusetts Medical Society.

1. Baumgartner-Sigl et al. *Bone*. 2007;40:1655-1661. **2.** Rockman-Greenberg. *Pediatr Endocrinol Rev*. 2013;10(suppl 2):380-388. **3.** Collmann et al. *Childs Nerv Syst*. 2009;25:217-223. **4.** Taketani et al. *Arch Dis Child.* 2014;99:211-215. **5.** Kitaoka et al. *Clin Endocrinol*. 2017;87:10-19. **6.** Whyte et al. *Lancet Diabetes Endocrinol*. 2019;7:93-105. **7.** Whyte et al. *N Engl J Med*. 2012;366:904-913.

Burden of Craniosynostosis and Associated Neurological Complications in HPP

Alterations in skull formation are common in HPP,[1] resulting in

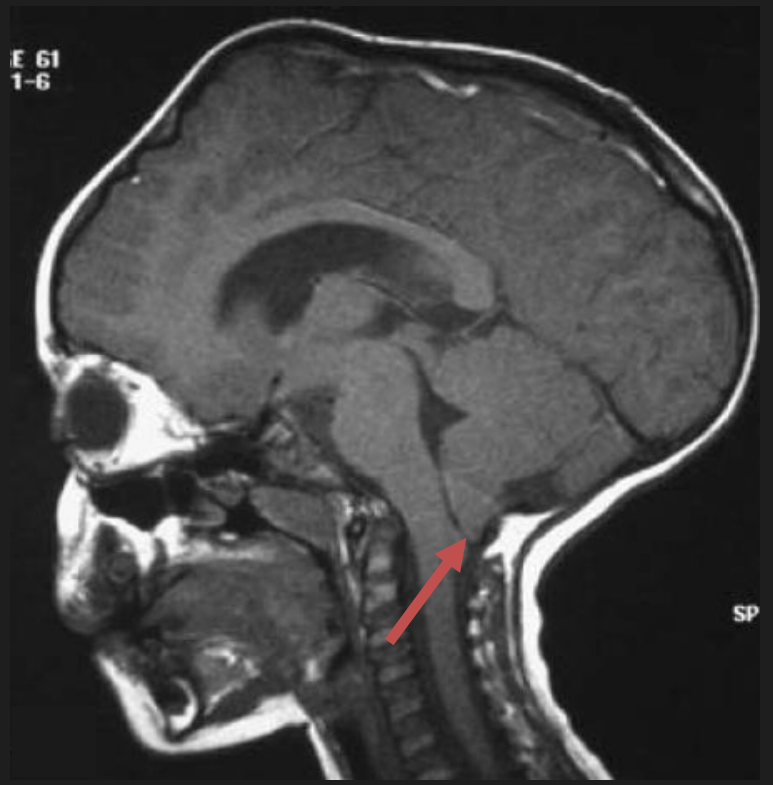
- Functional craniosynostosis, often before the true bony craniosynostosis[1]
- Premature fusion of the cranial sutures[1]

Sequelae of craniosynostosis May include[1-3]:

- Intracranial hypertension
- Hydrosyringomyelia
- Papilledema, proptosis, hypertelorism
- Optic nerve damage
- Herniation of the cerebellar tonsils
- Repetitive cranial surgeries

Increased intracranial pressure is a dangerous complication of craniosynostosis and can cause a broad range of neurologic manifestations in patients with HPP[4]

In a chart review of patients ≤5 years of age, 61% (19/31) of patients with HPP had craniosynostosis[5]



HPP patient aged 6.6 years with craniosynostosis and protrusion of the cerebellar tonsils below the foramen magnum (herniated cerebellar tonsils)[1]

HPP, hypophosphatasia.

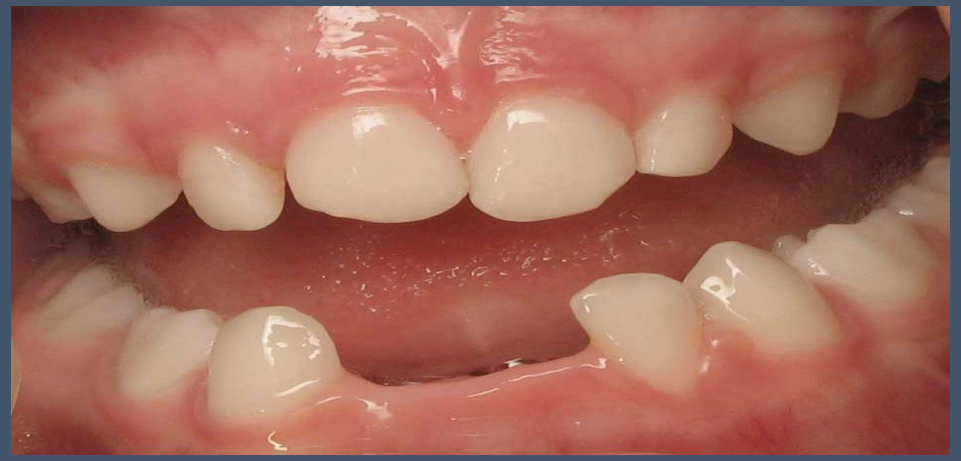
Image reproduced from Collmann et al. *Childs Nerv Syst*. 2009;25:217-223. With permission from Springer Nature.

1. Collmann et al. *Childs Nerv Syst*. 2009;25:217-223. **2**. Rockman-Greenberg. *Pediatr Endocrinol Rev*. 2013;10(suppl 2):380-388. **3**. Linglart and Biosse-Duplan. *Curr Osteoporos Rep.* 2016;14:95-105. **4.** Weber et al. *Metabolism*. 2016;65:1522-1530. **5.** Whyte et al. *J Pediatr*. 2019;pii: S0022-3476(19)30139-8 [Epub].

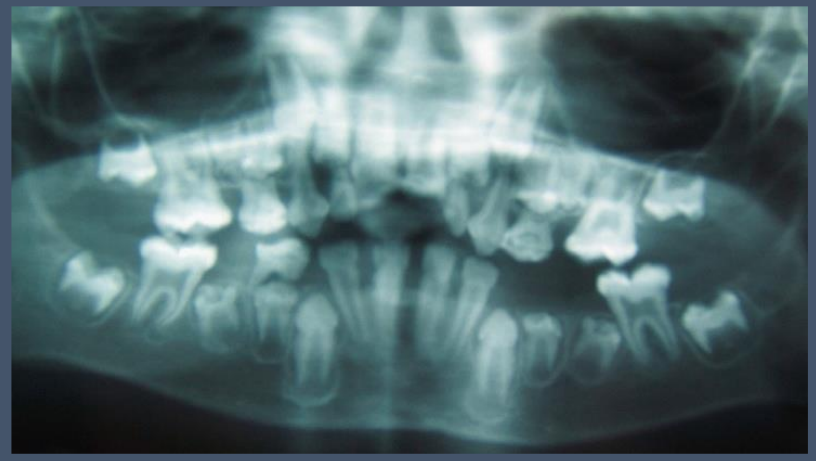
Dental Manifestations

Dental Manifestations of HPP in Children

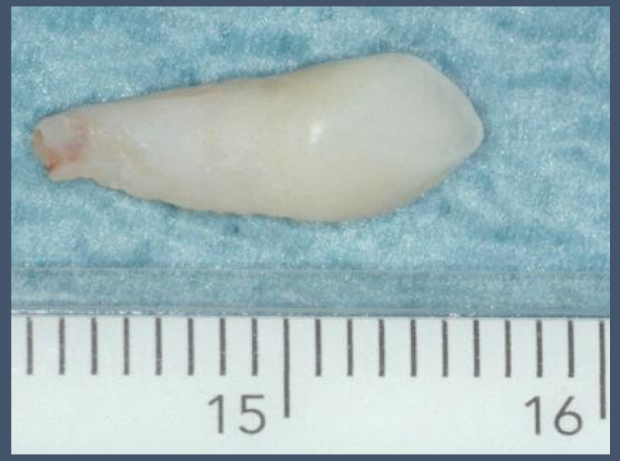
Anterior deciduous teeth (incisors) are most commonly affected, but all teeth may be involved



2.5-year-old patient with spontaneous loss of the lower incisors



panoramic radiograph revealing enlarged pulp chambers and abnormalities of the shape of the crowns



Clinical view of the exfoliated mandibular right cuspid in 4-year-old patient with intact root

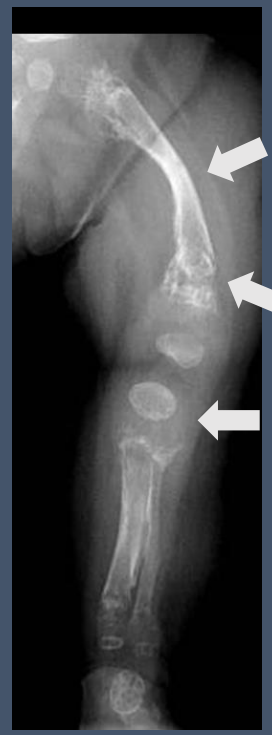
HPP, hypophosphatasia.
Reibel et al. *Orphanet J Rare Dis*. 2009;4:6. Images used with permission from BioMed Central.

Skeletal Manifestations

Burden of Skeletal Manifestations of HPP

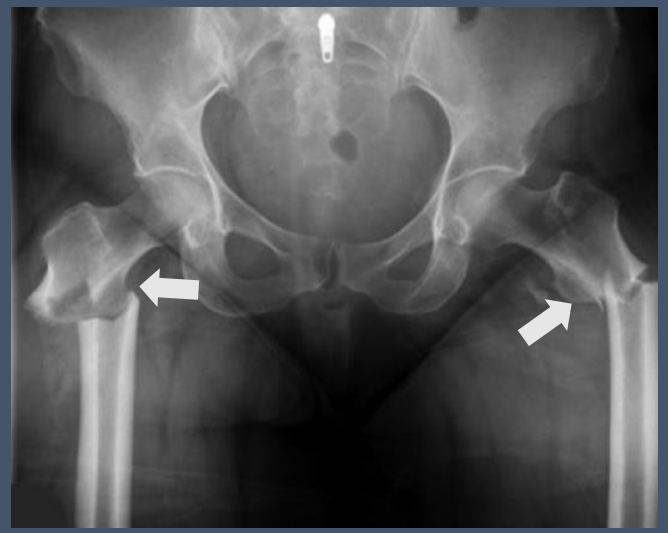
Patients with HPP may experience

7 months of age[1]



- Skeletal deformities (eg, bowing of long bones)[2]
- Short stature[3]
- Delayed walking and waddling gait[4]

Bilateral acute subtrochanteric femoral fractures in adult with HPP[5]



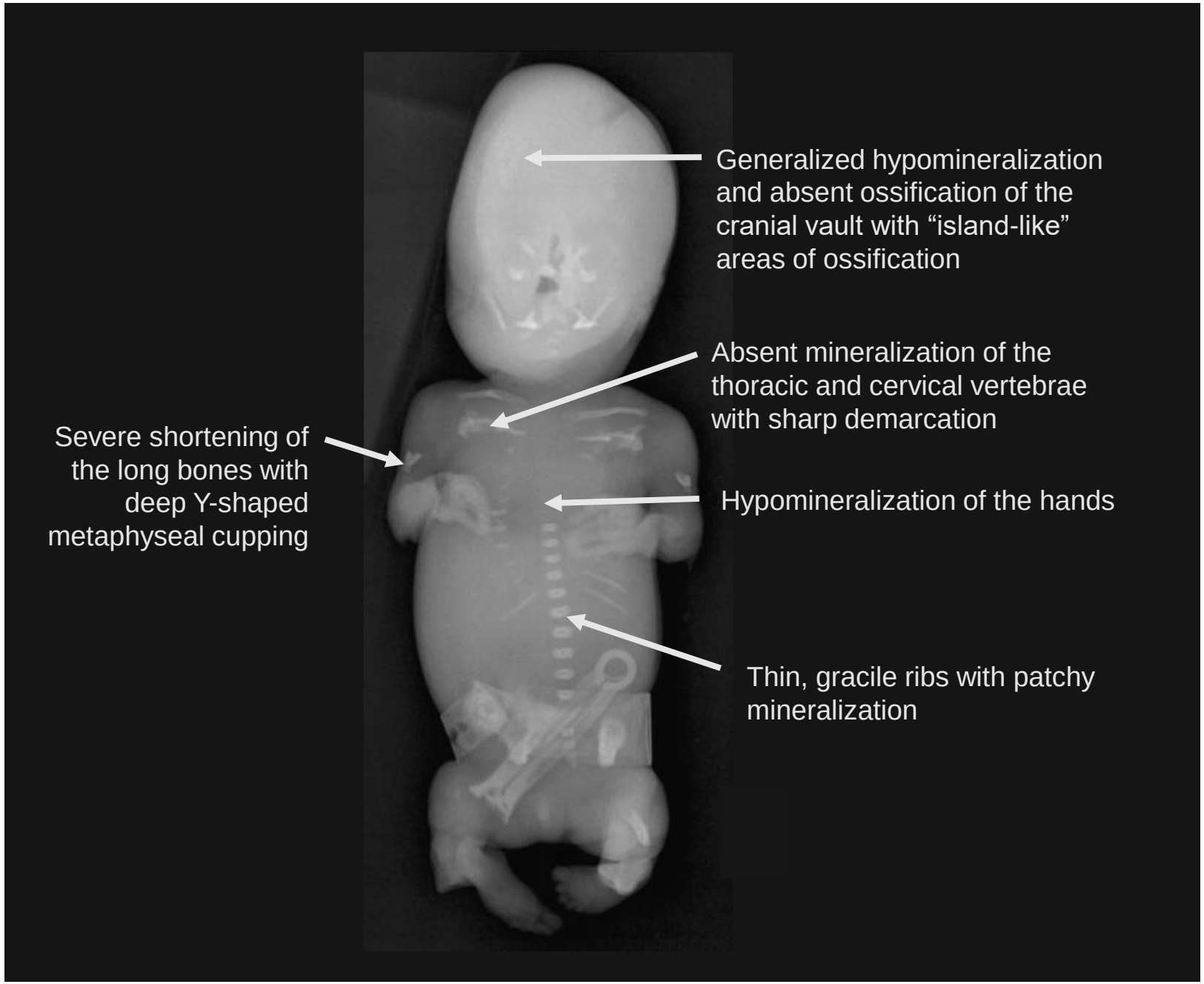
- Bone pain[6]
- Osteomalacia[2,7]
- Osteoporosis[2,7]
- Fractures[6]
  - Frequent
  - Poorly healing/nonhealing
  - Nontraumatic
  - Recurrent
- Multiple surgical interventions[6]

HPP, hypophosphatasia.

Images reproduced from Whyte et al. *N Engl J Med.* 2012;366:904-913. With permission from Massachusetts Medical Society.

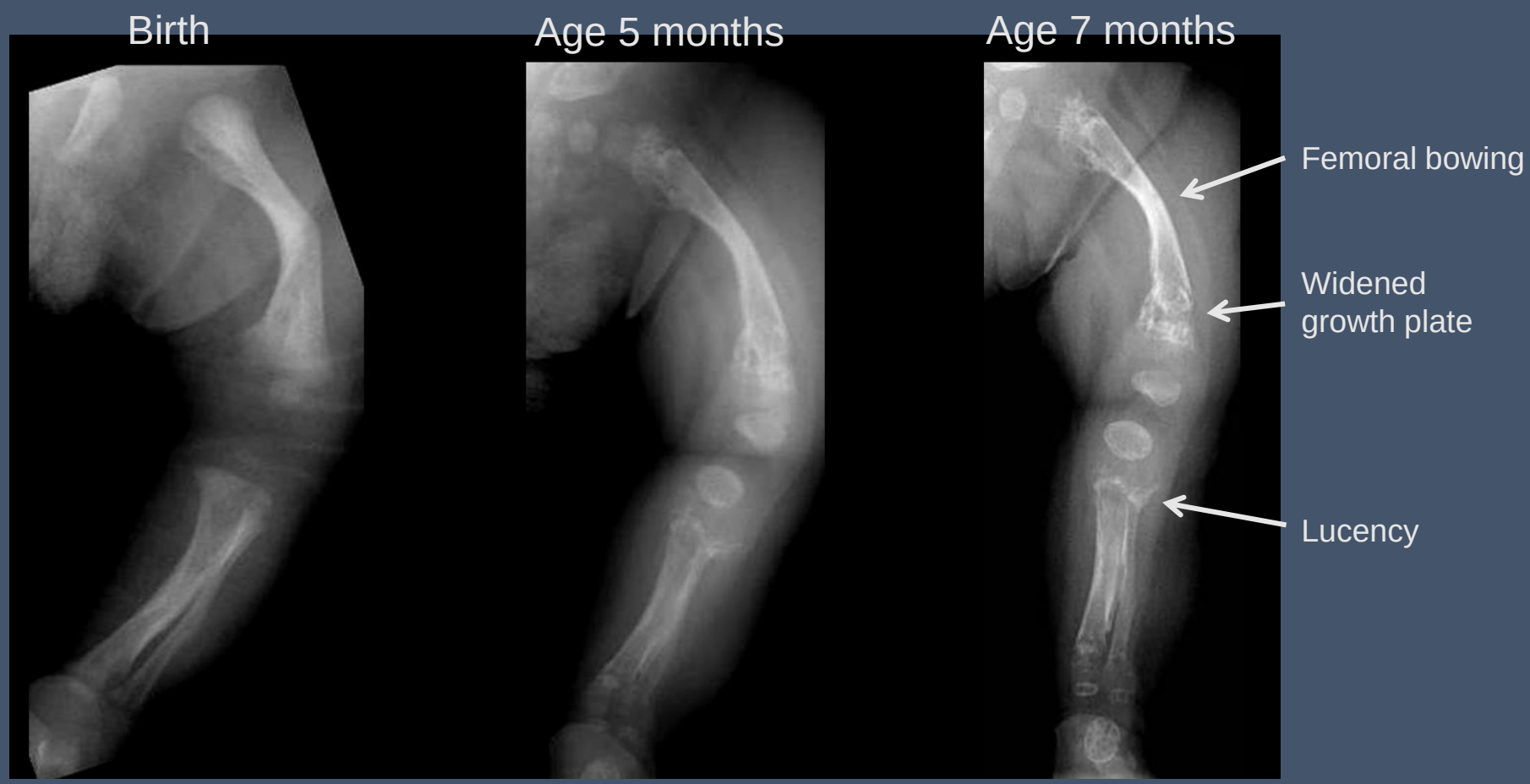
1. Whyte et al. *N Engl J Med.* 2012;366:904-913. **2.** Rauch et al. Poster presented at: American Society for Bone and Mineral Research Annual Meeting; September 16-20, 2011; San Diego, CA. Poster MO0193. **3.** Rockman-Greenberg. *Pediatr Endocrinol Rev*. 2013;10(suppl 2):380-388. **4.** Bishop et al. *Arch Dis Child*. 2016;101:514-515. **5.** Sutton et al. *J Bone Miner Res.* 2012;27:987-994. **6.** Weber et al. *Metabolism*. 2016;65:1522-1530. **7.** Nordin et al. In: *The Physiological Basis of Metabolic Bone Disease*. 2014:201-209.

Radiographic Features of HPP in -utero



HPP, hypophosphatasia.

Progressive Skeletal Bowing & Demineralization



Images reproduced from Whyte et al. *N Engl J Med.* 2012;366:904-913. With permission from Massachusetts Medical Society.

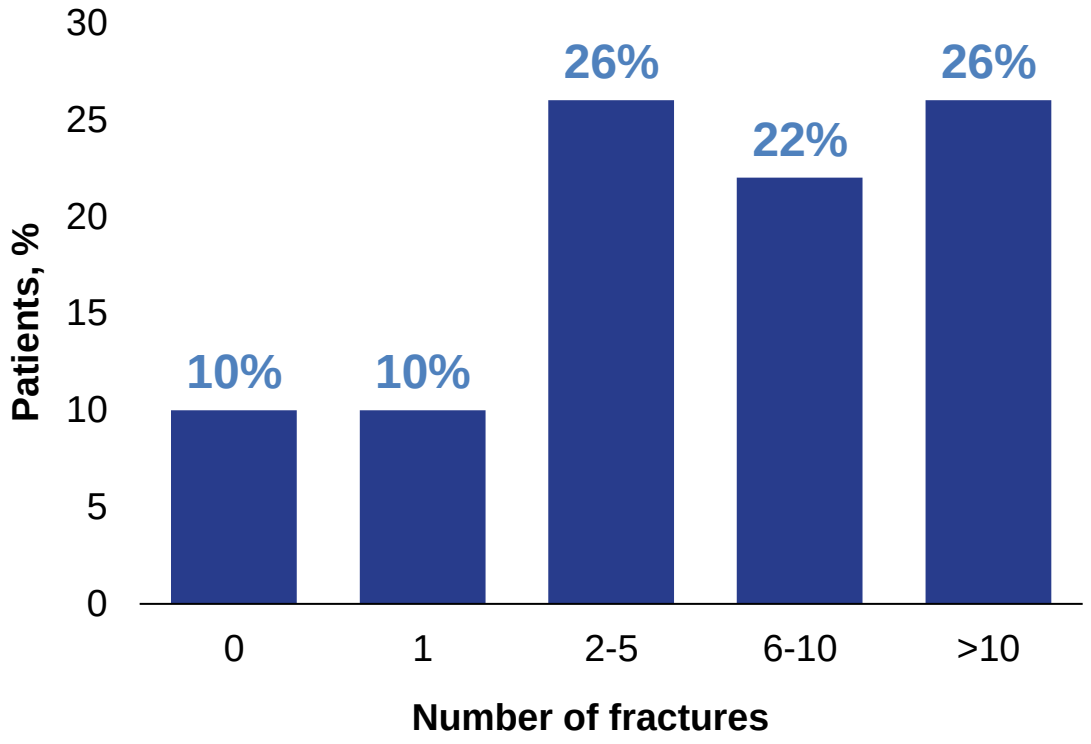
HPP is Associated with a High Risk of Multiple Fractures

- 23% (7/30) of infants and young children experienced at least one fracture (chart review)[1,a]
- 34% (11/32) of pediatric patients (5-15 years of age) experienced fractures (chart review)[2,b]
- 86% (108/125) of adults with HPP experienced at least one fracture (survey)[3,c]
- Adults with HPP experience a large number of fractures (12.9 [mean] fractures [range, 1-100]; survey)[3,c]

HPP, hypophosphatasia.
[a]Data from a noninterventional, retrospective chart review study designed to understand the natural history of 48 patients with perinatal- and infantile-onset HPP ≤5 years of age.[1] [b]Data from a retrospective, multinational, noninterventional chart review study of childhood HPP (N=32, age 5-15 years).[2] [c]HPP Impact Survey/HPP Outcomes Survey Telephone (HIPS/HOST) combined data from an Internet questionnaire and telephone survey that queried demographics, HPP-related illness history, disease progression, and health-related quality of life. One hundred eighty-four patients participated (59 children, 125 adults).[3]

1. Whyte et al. *J Pediatr.* 2019;pii: S0022-3476(19)30139-8 [Epub]. **2.** Whyte et al. Slides presented at: Endocrine Society Annual Meeting & Expo; March 5-8, 2015; San Diego, CA. Abstract LB-OR01-4. **3.** Weber et al. *Metabolism.* 2016;65:1522-1530.

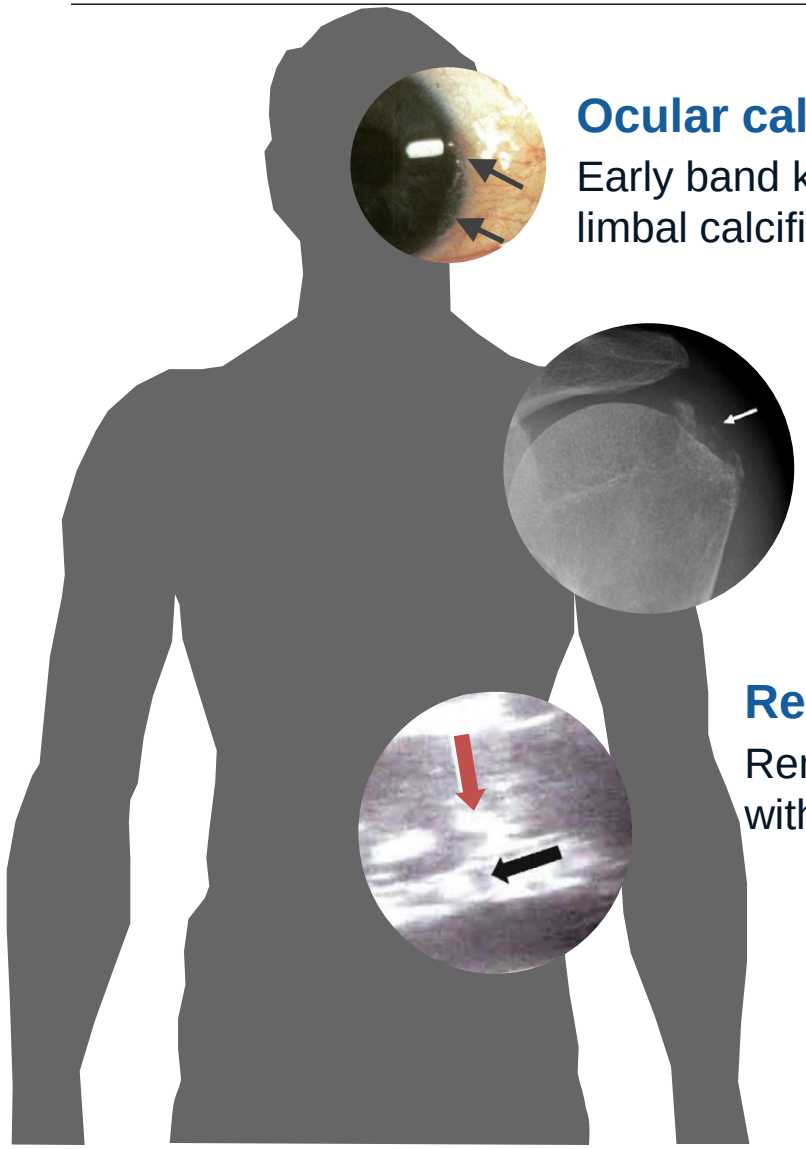
Total fractures sustained throughout life reported by adult patients with HPP (n=125)[3,c]



Fractures can be frequent, poorly healing/ nonhealing, nontraumatic, or recurrent and may require multiple surgical interventions[3]

Ectopic Calcifications

Examples of Ectopic Calcifications



Ocular calcification[a]

Early band keratopathy with white limbal calcification (arrows)[1]

CPPD crystal deposition

Radiograph of right shoulder with large area of periarticular calcium (arrow) deposition adjacent to the greater tuberosity of the humerus[2]

Renal calcification

Renal ultrasound revealing a calcification spot (red arrow) with posterior acoustic shadowing (black arrow)[3]

CPPD, calcium pyrophosphate dihydrate; HPP, hypophosphatasia.
[a]Image is from patient diagnosed with renal failure and hyperparathyroidism.

1. Klaassen-Broekema and van Bijsterveld. *Br J Ophthalmol*. 1993;77:569-571. Image reproduced with permission from BMJ Publishing Group. **2.** Guanabens et al. *J Bone Miner Res*. 2014;29:929-934. Image reproduced with permission from American Society for Bone and Mineral Research. **3.** Barvencik et al. *Osteoporos Int*. 2011;22:2667-2675. Image reproduced with permission from Springer Nature.

Functional Impairment

The manifestations of HPP that can lead to mobility issues can include:

- Pain
- Loss of physical function
- Muscle weakness
- Recurrent fractures leading to repeated surgeries
- Unusual gait and impaired mobility

HPP, hypophosphatasia.
Weber et al. *Metabolism*. 2016;65:1522-1530.

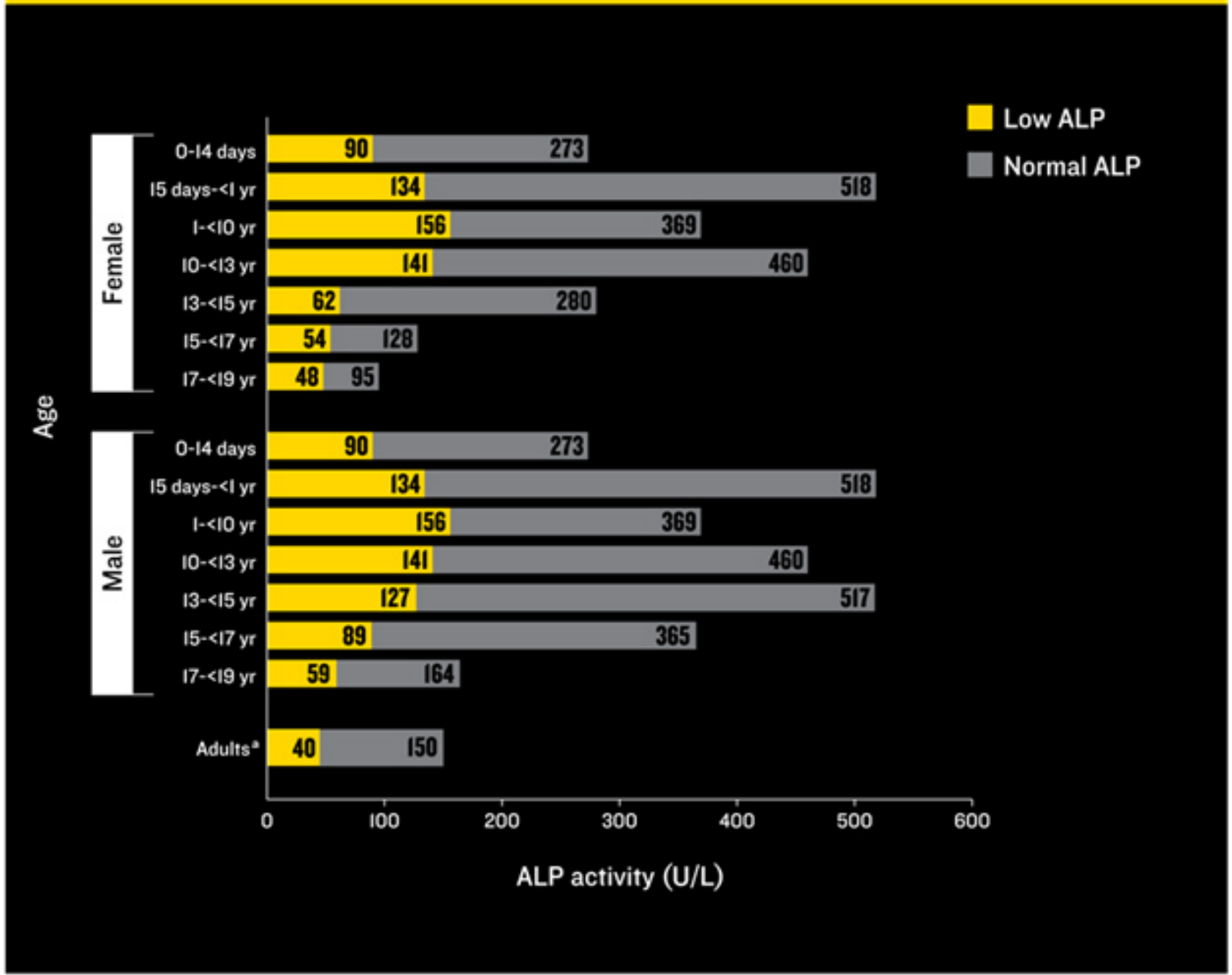
Burden of Misdiagnosis in HPP

Diagnostic delay can potentially lead to[1-4]

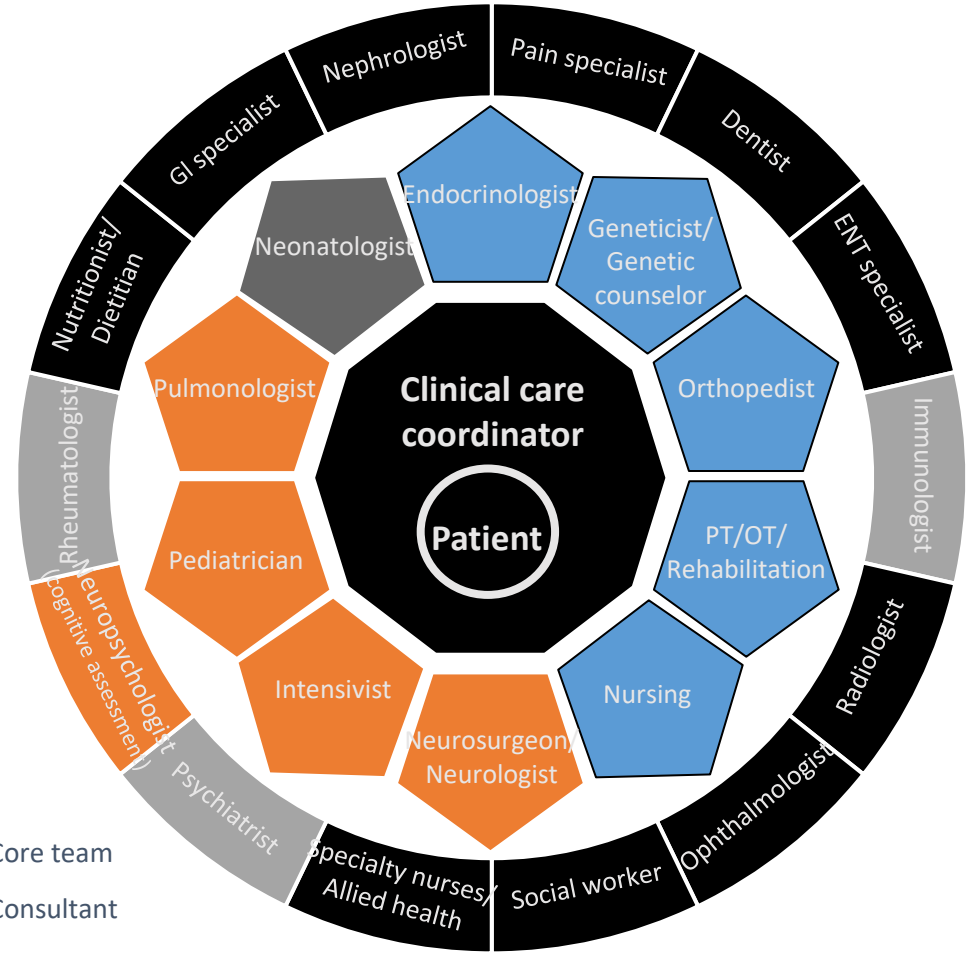
HPP, hypophosphatasia.

1. Rockman-Greenberg. *Pediatr Endocrinol Rev*. 2013;10(suppl 2):380-388. **2.** Sutton et al. *J Bone Miner Res.* 2012;27:987-994.
3. Weber et al. *Metabolism*. 2016;65:1522-1530. **4.** Mornet. *Orphanet J Rare Dis*. 2007;2:40.

AGE- AND GENDER-ADJUSTED ALP REFERENCE INTERVALS (U/L) [8,10]



Multidisciplinary Management is Essential for Patients with HPP



The core team[a] involved in treatment evolves as the patient ages

Infants and children with HPP

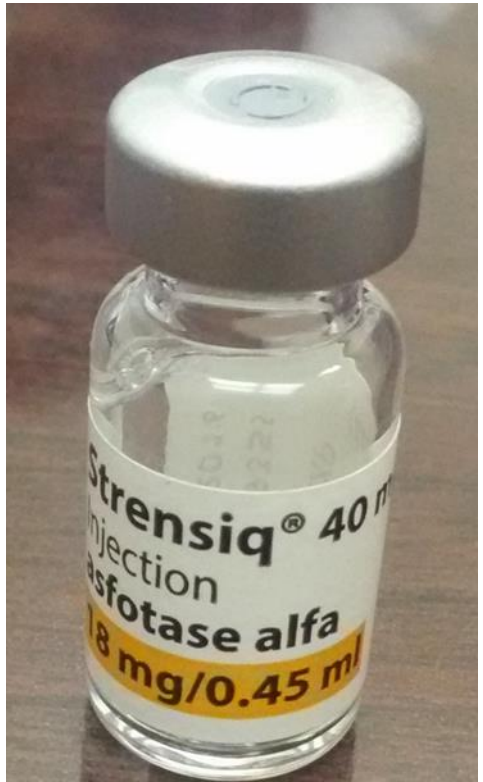
- Endocrinologist
- Medical geneticist
- Pediatrician
- Other pediatric metabolic bone disorder specialists and clinical care coordinators

ENT, ear, nose, and throat; GI, gastrointestinal; HPP, hypophosphatasia; OT, occupational therapy; PT, physical therapy.
[a]Coordination may vary by country.
Kishani et al. *Mol Genet Metab.* 2017;122:4-17.

Medical Therapy

Asfotase Alfa (Strensiq)

S/C injection 3 or 6 times a week.



Conclusions

- Bone health has many contributing intrinsic & extrinsic factors.
- Physicians & health workers should be aware of various pathological causes of the bone and be able to differentiate between them.
- Rickets / vitamin D deficiency is a common bone health condition encountered in Saudi Arabia.
- Vitamin D prophylaxis and or sun exposure should be mandatory to all ages in this country.
- Awareness of various causes of Osteoporosis in children is of highly importance.
- screening for Osteoporosis is important to prevent children suffering from this disease.

Conclusion

- HPP is a rare, inherited metabolic disorder with lifelong, systemic clinical manifestations.
- The burden of HPP is characterized by a variety of painful, disabling symptoms that can occur at any age.
- Skeletal and non skeletal manifestations can lead to mortality in babies and infants and dental problems, poorly healing/nonhealing fractures, bone deformities, muscle and joint weakness, pain, and possible renal failure in surviving children and adults.
- These manifestations can result in impairment of daily activities and decreased quality of life.
- Timely and accurate diagnosis of HPP is critical because misdiagnosis can lead to ineffective management that can potentially worsen the burden of symptoms.
- A multidisciplinary team is necessary for the optimal management of patient symptoms.

Thank You