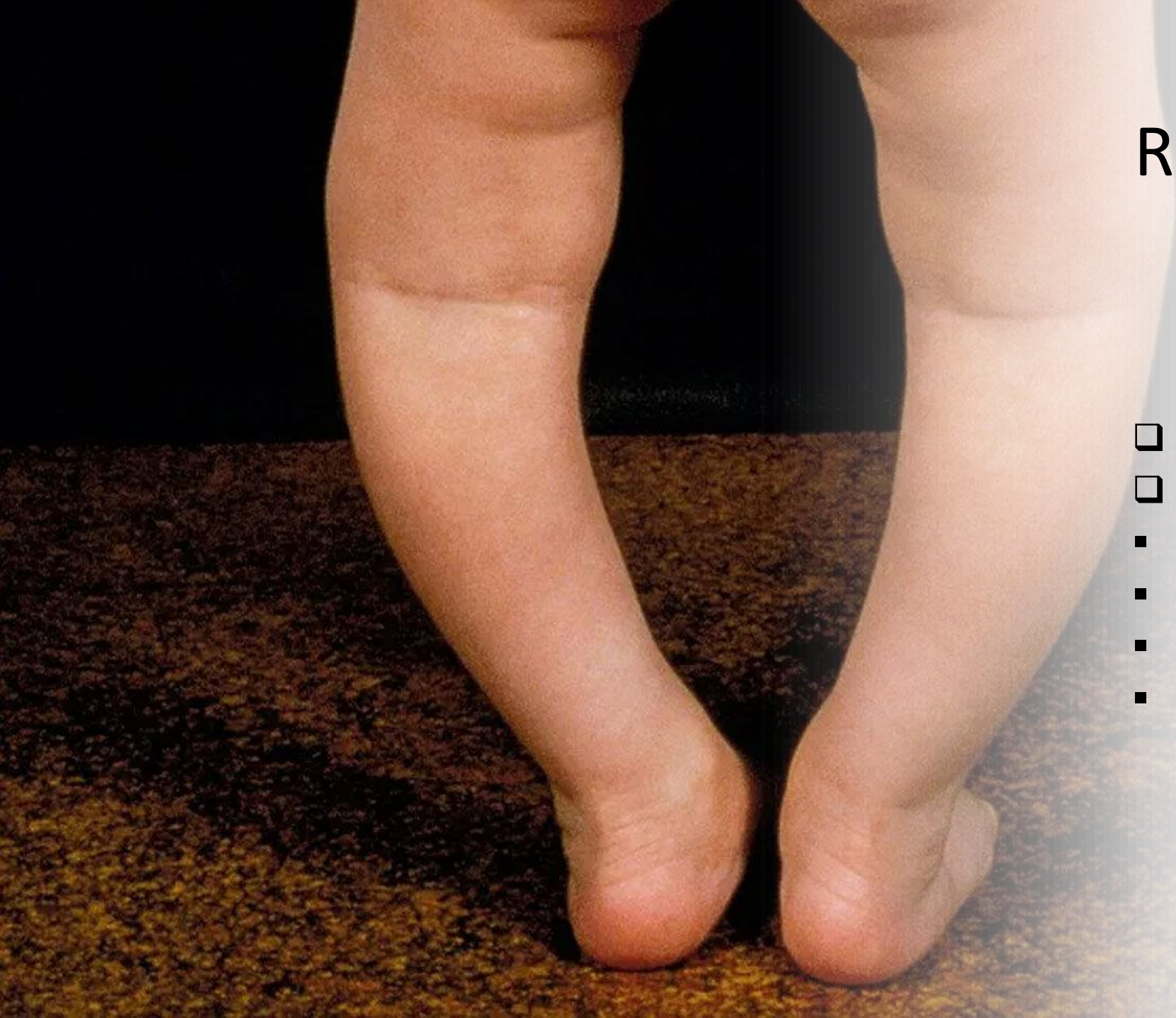


Rickets Disease

- ***Supervised by: Dr. Doaa Qaoud***
- ***Done by:***
  - ***Soud Talal***
  - ***Dana Sawalha***
  - ***Sawsan Sweilmeen***
  - ***Orayb Siam***

RICKETS

***Definition :

- **Rickets is a common bone disease worldwide that is associated with disturbances in calcium and phosphate homeostasis and can lead to short stature and joint deformities.**

- **It results from abnormalities of the growth plate cartilage predominantly affecting longer bones and leads to poor bone growth, defective mineralization, and bony deformities, such as bow-legs and knock-knees. This is usually secondary to deficiencies of calcium or phosphorus because they are essential for normal bone growth and mineralization**

- **Bones consist of cells that have various specific roles during the bone formation process:**

1. Osteoblasts

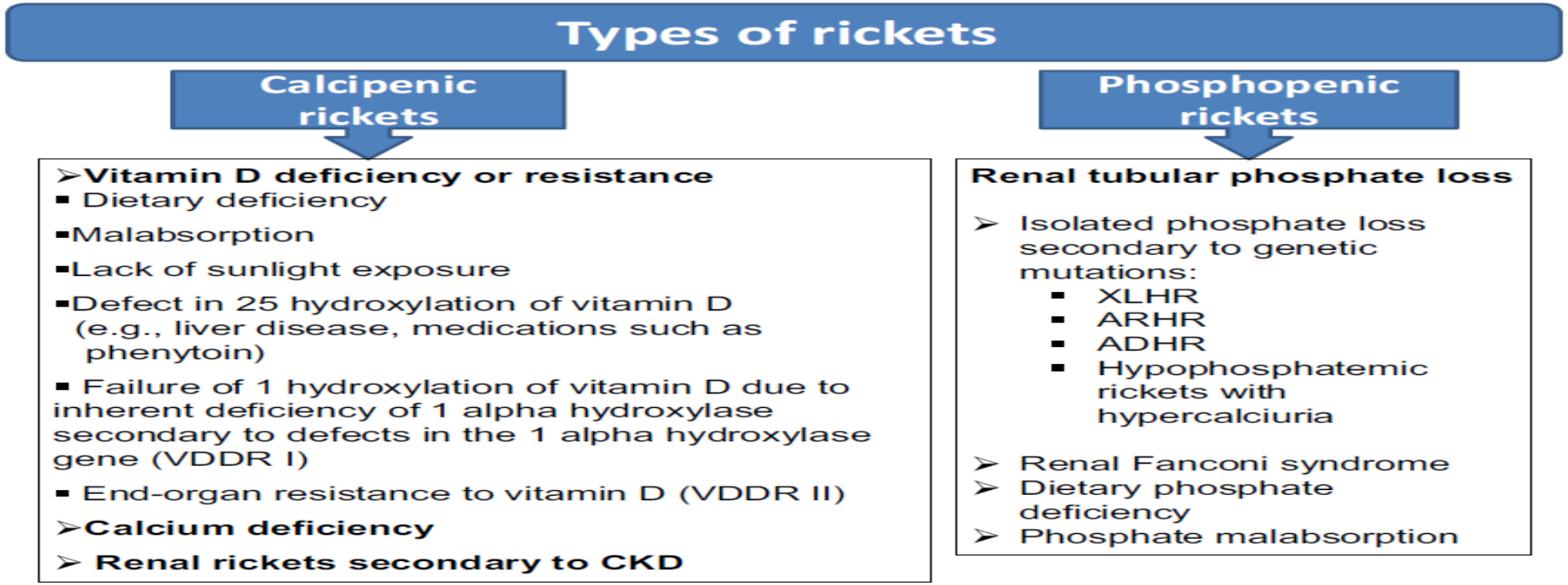
Are bone-forming cells that secrete the extracellular matrix and mineralize the osteoid.

2. Osteoclasts

Break down the bone matrix during the stage of remodeling or aging.

For bone maturation, the organic component of the bone matrix, the osteoid, must be mineralized by calcium salts. In rickets, this process is hampered and results in amassing of osteoid beneath the growth plate leading to softness in the bone over a gradual period of time

- classified into 2 major groups based on phosphate or calcium levels: phosphopenic and calcipenic



- **<u>There are other subtypes of rickets, such as:</u>**

-vitamin D–dependent type 1 rickets

-vitamin D–dependent type 2 rickets

-renal rickets

-hypophosphatemic rickets

Because growth plate cartilage and osteoid continue to expand but mineralization is inadequate ;

-The growth plate thickens.

-There is an increase in the circumference of the growth plate and the metaphysis, **increasing bone width at the location of the growth plates** and causing some of the **classic clinical manifestations**, such as **widening of the wrists and ankles**.

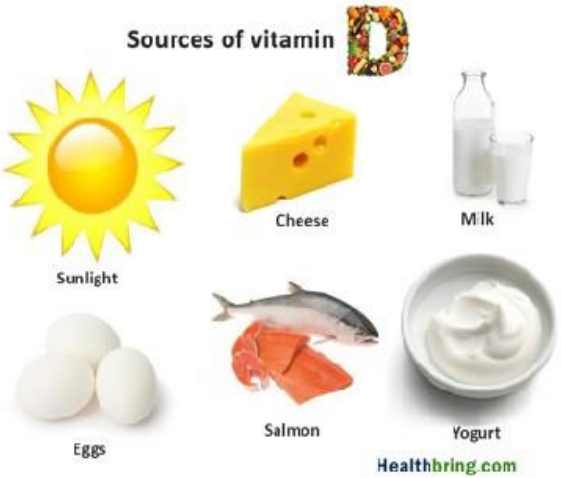
-There is a general softening of the bones that causes them to bend easily when subject to forces such as weight bearing or muscle pull

—>**This softening leads to a variety of bone deformities.**

Table 51-2 Causes of Rickets

VITAMIN D DISORDERS
Nutritional vitamin D deficiency Congenital vitamin D deficiency Secondary vitamin D deficiency Malabsorption
Increased degradation Decreased liver 25- hydroxylase Vitamin D–dependent rickets type 1 A and B Vitamin D–dependent rickets type 2 A and B Chronic kidney disease
CALCIUM DEFICIENCY
Low intake Diet Premature infants (rickets of prematurity) Malabsorption Primary disease Dietary inhibitors of calcium absorption
PHOSPHORUS DEFICIENCY
Inadequate intake Premature infants (rickets of prematurity) Aluminum-containing antacids
RENAL LOSSES
X-linked hypophosphatemic rickets* Autosomal dominant hypophosphatemic rickets* Autosomal recessive hypophosphatemic rickets (1 and 2)* Hereditary hypophosphatemic rickets with hypercalciuria Overproduction of fibroblast growth factor-23 Tumor-induced rickets* McCune-Albright syndrome* Epidermal nevus syndrome* Neurofibromatosis* Fanconi syndrome Dent disease Distal renal tubular acidosis

Types of Vitamin D :



There are 2 forms of Vitamin D :

1.Vitamin D2 (Ergocalciferol): it's an **exogenous vitamin, Plant-sourced food**, and **poorly absorbed.**

2.Vitamin D3 (Cholecalciferol): it can be **produced by exposure to sun by the skin (endogenous)** or **exogenous animal-sourced food**

Vitamin D physiology

Step 1: Skin

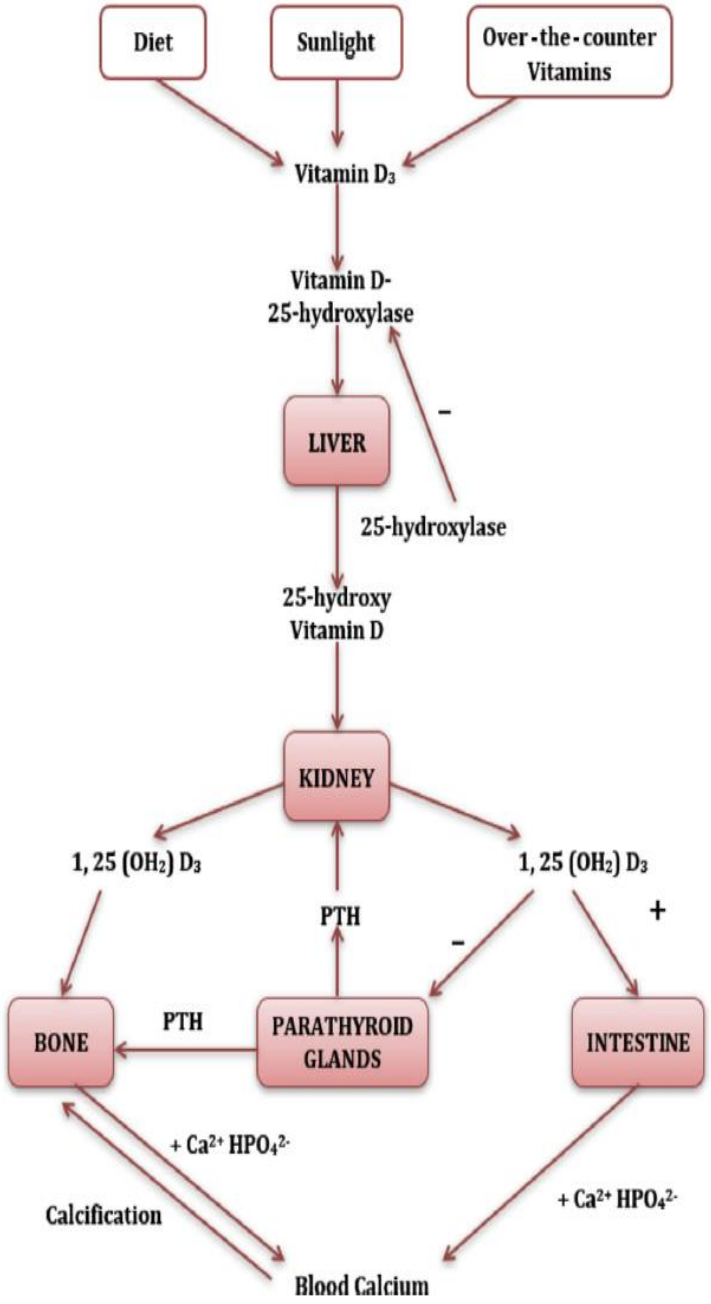
Using energy from the ultraviolet light, skin modifies a metabolite of cholesterol to form cholecalciferol (D_3). D_3 can also be directly absorbed form the GI System if ingested.

Step 2: Liver

Cholecalciferol (D_3) is converted to **25-hydroxycholecalciferol ($25(OH)D_3$)** in the liver.

Step 3: Kidney

25-hydroxycholecalciferol ($25(OH)D_3$) is converted to fully active, **1,25- dihydroxycholecalciferol ($(1,25(OH)_2D_3$)** in the proximal tubule



- The Exogenous Source: it contains both VitD2,D3 and taken from our diets ,vitamin D2 and D3 are absorbed from upper small intestine and bile is essential

- Mechanism: vitamin D3 and D2 form mixed micelles by combining with bile salts (micelles)

1. Mixed micelles are presented to mucosal cells
2. Absorption occurs by passive transport

Transport

Vitamin D binding globulin: vitamin D is transported from intestine to the liver by binding to vitamin D binding globulin

- 25 – Hydroxy D3 and 1,25 – dihydroxy D3 are also transported in the blood by binding to vitamin D binding globulin

Storage:

25 – hydroxycholecalciferol is the major storage and circulatory form of vitamin D

Metabolism

Synthesis of 1,25 – Dihydroxycholecalciferol

the active form of vitamin D is 1,25 – Dihydroxycholecalciferol and is also called as calcitriol

Cholecalciferol is first hydroxylated to 25 – hydroxycholecalciferol by a specific **hydroxylase** enzyme present in liver

1-alpha hydroxylase in the kidney hydroxylates 25 – hydroxycholecalciferol 1,25 – Dihydroxycholecalciferol

Both hydroxylase enzymes (of liver and kidney) require cytochrome P450, NADPH and molecular oxygen for hydroxylation process

1 α – hydroxylase activity is increased by hypocalcemia (stimulates PTH secretion) and it's activity may be **feedback** inhibited by 1,25 – DHCC

Functions of Vitamin D

Intestine :

Promotes absorption of Calcium and Phosphorus.

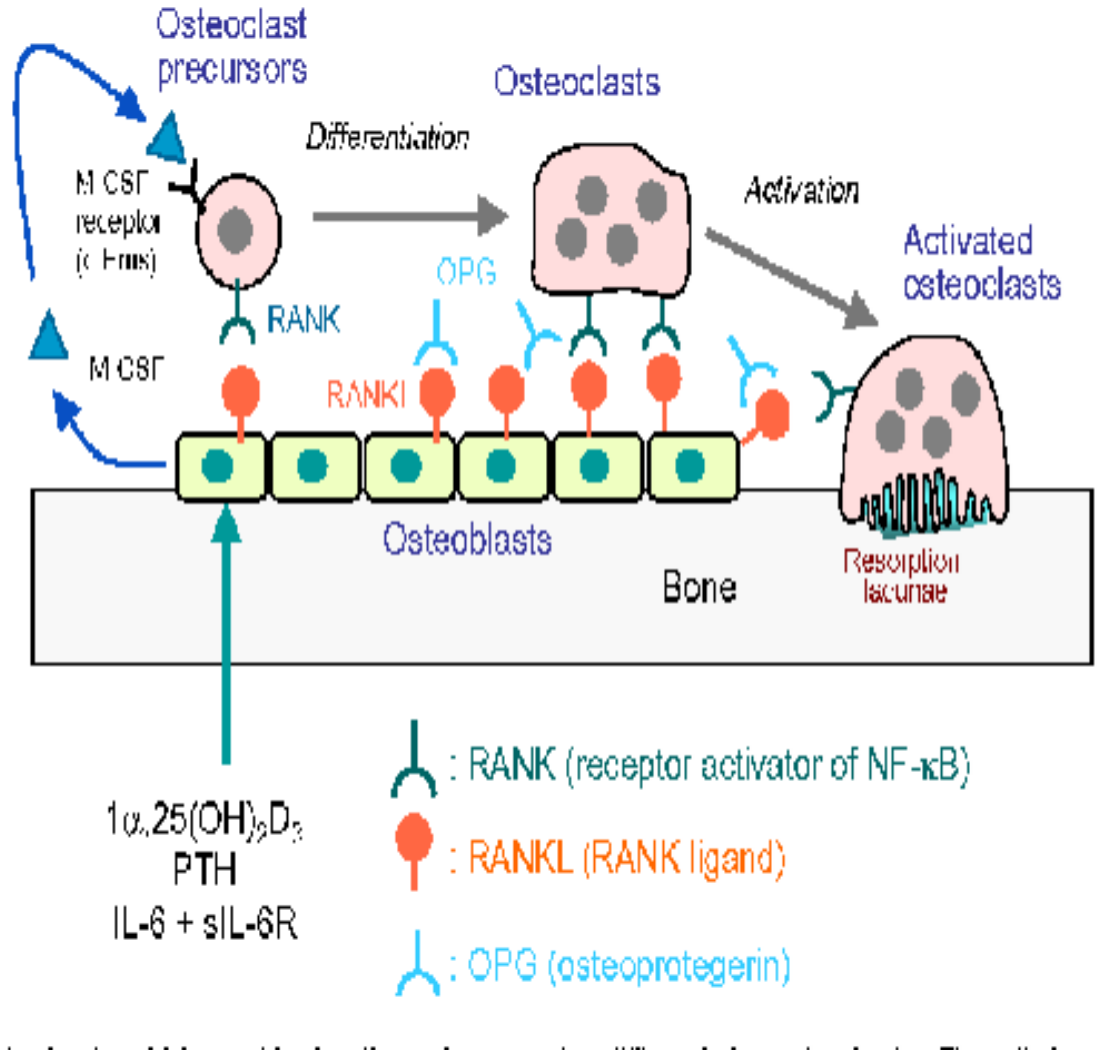
in the intestinal cells, calcitriol binds with a cytosolic receptor to form a **calcitriol-receptor complex** —>This complex interacts with a specific DNA leading to the synthesis of a specific calcium binding protein, This protein increases calcium uptake by intestine

The Kidneys:

Calcitriol is also involved in minimizing the excretion of calcium and phosphate through the kidney by **decreasing their excretion and enhancing reabsorption.**

Bones :

1.25-DihydroxyVitD + PTH will stimulate the expression of **RANKL**(Receptor Activator of Nuclear Factor kappa B Ligand) on **osteoblasts and the RANK receptor is on the preosteoclasts** which will results in **differentiation of preosteoclasts to mature osteoclasts which will secrete HCL and activate enzymes like proteases which will dissolve Calcium and Phosphorus** from the bones and deliver it to the plasma.



Mineralization of bone:

Vitamin D contributes to the mineralization of **osteoid matrix and epiphyseal cartilage** in the formation of both flat and long bones in the skeleton.

-it stimulate **osteoblasts** to synthesize calcium binding protein, **osteocalcin**, involved in the deposition of calcium during bone development.

-**Calcitriol** also **stimulates osteoblasts** which **secrete alkaline phosphatase**. Due to this enzyme, **the local concentration of phosphate is increased.** The **ionic product of calcium and phosphorus increases**, leading to mineralization.

Role in Neuromuscular transmission:

-**vitamin D**

plays a direct role as it is involved in calcium hemostasis and calcium plays a role in neuromuscular transmission.

-when the **extracellular fluid concentration of calcium ions falls** below normal, the **nervous system** becomes more **excitable**, because this causes **increased neuronal membrane permeability to sodium ions**, allows **easy initiation of action potentials.**

-When the level of **calcium** in the body fluids **rises above normal**, the **nervous system becomes depressed and reflex activities of CNS are sluggish**

Function of VitD

- ✓ THE MAJOR BIOLOGICAL FUNCTION OF VitD is Maintenance of plasma Calcium and Phosphate.

- ✓ Aids in the intestinal absorption of Calcium and Phosphate.
- ✓ Role in bone mineralization.
- ✓ Neuromuscular transmission.
- ✓ Renin-angiotesnion regulation (decrease risk of hypertension)
- ✓ Diabetes control (regulation of insulin secretion)
- ✓ Promotes cell growth
- ✓ Regulation of the immune function
- ✓ Anti-inflammatory
- ✓ Role in cancer prevention

Vitamin D disorders :

1. Nutritional vit D deficiency
2. Congenital vit D deficiency
2. Secondary vit D deficiency
3. Inherited vit D deficiency

Nutritional vit D deficiency :

- Nutritional rickets is the most common form of bone disease, primarily affecting infants and young children. Although primarily caused by vitamin D deficiency, calcium and phosphate deficiencies also play a significant role

- The primary cause of vitamin D deficiency usually involves interplay of nutritional inadequacy and lack of sunlight exposure with overlapping contributions by cultural, environmental, and genetic factors .
- An infant's vitamin D status depends upon the amount of vitamin D transferred from the mother prenatally and upon the amount of vitamin D ingested or produced by the skin during exposure to ultraviolet light postnatally .
- Transplacental transport of vitamin D, mostly 25-D, typically provides enough vitamin D for the 1st 2 months of life unless there is severe maternal vitamin D deficiency.
- Infants who receive formula receive adequate vitamin D, even without cutaneous synthesis.**BUT** Because of the low vitamin D content of breast milk, breastfed infants rely on cutaneous synthesis or vitamin supplements.

***Clinical features:

Both skeletal and extra-skeletal manifestations are present in patients with nutritional rickets.

- Skeletal symptoms include swollen wrists and ankles, delayed tooth eruption, leg deformity, rachitic rosary, frontal bossing, craniotabes, and bone pain.

- Extraskeletal findings include muscle weakness and hypocalcemic seizures

- Nutritional/medical history, biochemical testing, and radiographs are used to diagnose nutritional rickets. Along with low level of 25 (OH) vitamin D, laboratory findings are also helpful in its diagnosis as well as in differentiating it from other causes of rickets

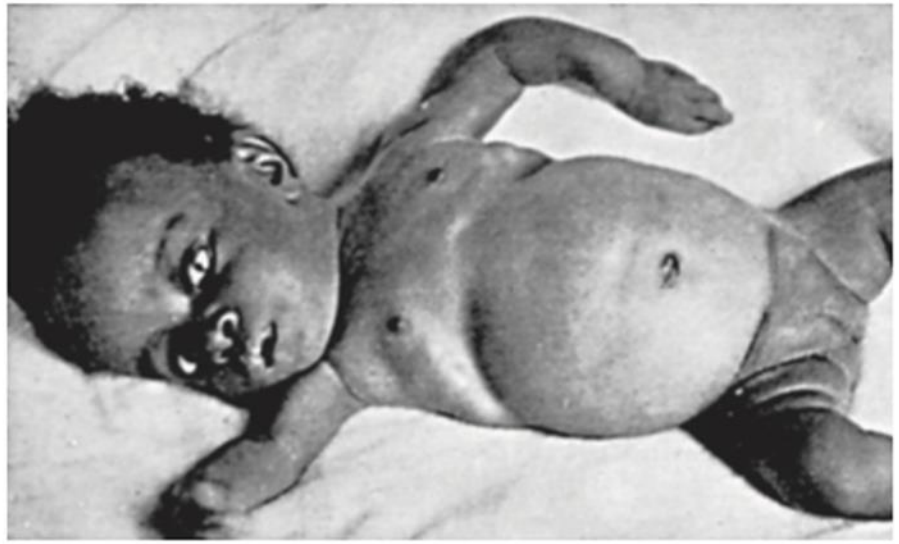


Figure 48-2 Deformities in rickets showing curvature of the limbs, potbelly, and Harrison groove.

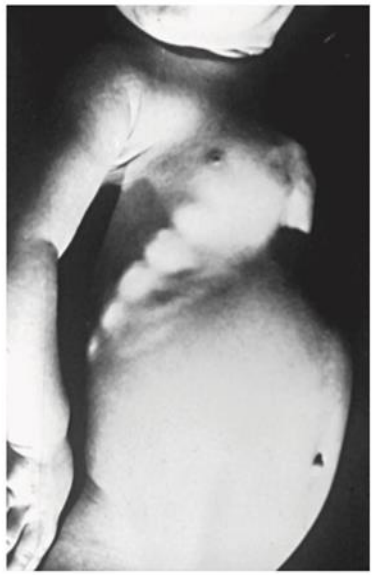
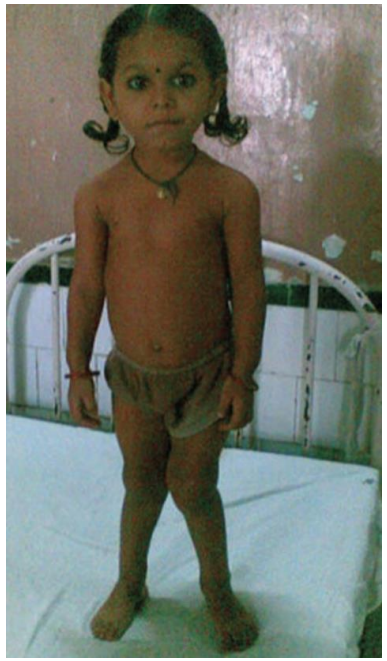
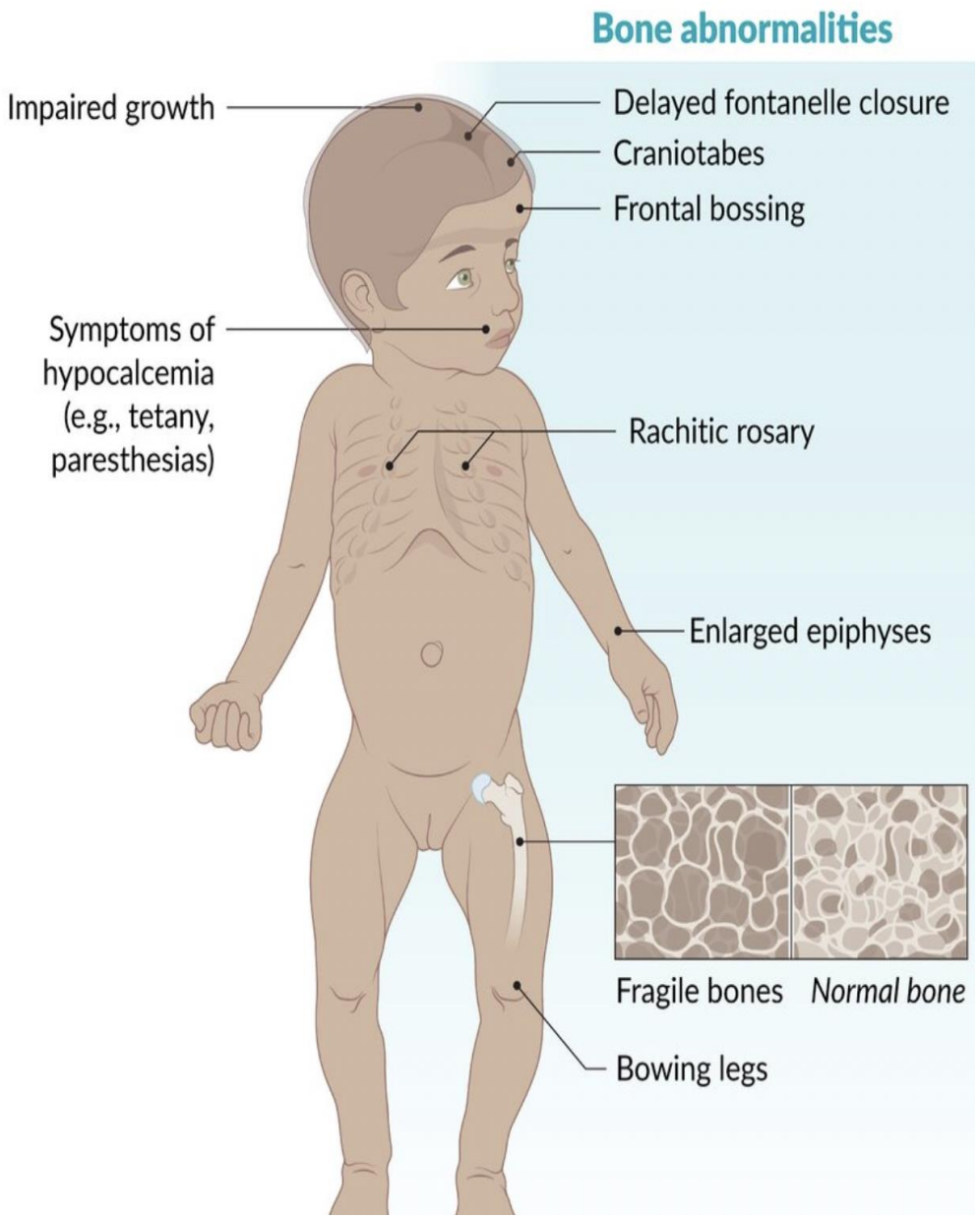


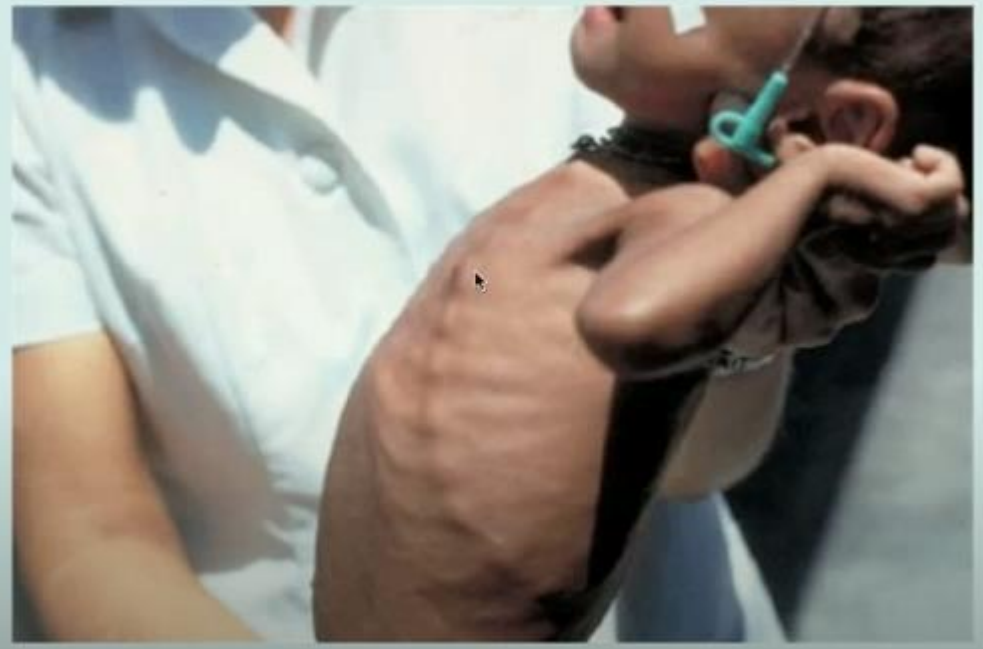
Figure 48-1 Rachitic rosary in a young infant.





Rickets: Harrison's groove

Rickets: Rachitic rosary



***Risk factors for Nutritional vitamin D deficiency rickets :

1) Exclusive breastfeeding

2) Maternal vitamin D deficiency during pregnancy her offspring can have signs of rickets at birth or during the first three months of life.

3) Skin pigmentation and low sun exposure – Dark skin Mother is an additional risk factor for developing rickets in breastfed infants .

4) Vitamin D defeciency can also be secondary to unconventional dietary practices, such as vegan diets that use unfortified soy milk or rice milk

5) Cutaneous synthesis can be limited because of the inefectiveness of the winter sun in stimulating vitamin D synthesis; avoidance of sunlight because of concerns about cancer, neighborhood safety, or cultural practices;

***TREATMENT :

The treatment of nutritional vitamin D deficiency with **cholecalciferol** consists of an intensive phase followed by a maintenance phase.

The National Osteoporosis Society in the United Kingdom recommends 3000 IU (in infants <6 months old), 6000 IU (6 months– 12 years old), and 10,000 IU (12–18 years old) of cholecalciferol per day in the intensive phase followed by 400 to 600 IU/d in the maintenance phase.

The U.S. Endocrine Society recommends 2000 IU/d cholecalciferol for 6 weeks for all age groups in the intensive phase followed by 400 to 1000 IU/d in the maintenance phase.

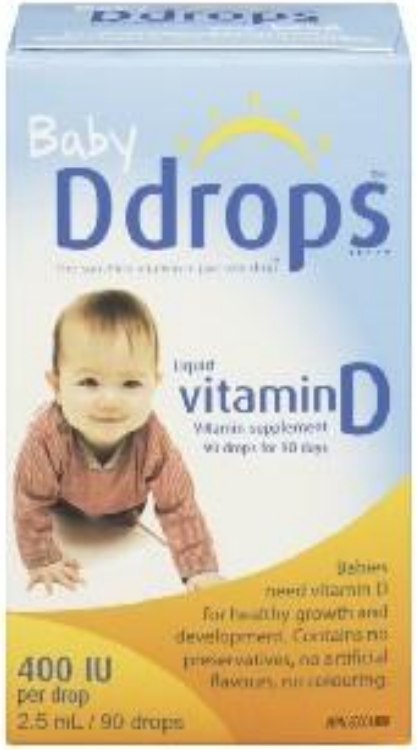
***Prevention :

Most cases of nutritional rickets can be prevented by universal administration of 400 IU of vitamin D to infants who are breastfed. Older children should receive 600 IU/day. Vitamin D may be administered as a component of a multivitamin or as a vitamin D supplement.

***Prognosis :

Most children have an excellent response to treatment, with radiologic healing occurring within a few months.

Laboratory test results should also normalize rapidly. Many of the bone malformations improve dramatically, but children **with severe disease can have permanent deformities and short stature.**



Inherited Vitamin D deficiency

Vitamin D–Dependent Rickets, Type 1

- Occurring generally during the first year of life, (VDDR I) is a rare autosomal recessive disorder, have mutations in the gene encoding renal 1*α*-hydroxylase, preventing conversion of 25-D into 1,25-D.
- There is an inactivating mutations in the CYP27B1 gene on chromosome 12 , which encodes the enzyme.
- Clinical manifestations include typical features of rickets including symptomatic hypocalcemia.
- They have normal levels of 25-D, but low levels of 1,25-D. Occasionally, 1,25-D levels are at the lower limit of normal, inappropriately low given the high PTH and low serum phosphorus levels, both of which should increase the activity of renal 1α-hydroxylase and cause elevated levels of 1,25-D.
- As in nutritional vitamin D deficiency, renal tubular dysfunction can cause a metabolic acidosis and generalized aminoaciduria.

- As expected, these children will not respond to high doses of cholecalciferol but respond to physiologic doses of calcitriol or 1a-hydroxyvitamin D (1–2 mg daily).
- Adequate intake of dietary calcium (30–75 mg/ kg per day of elemental calcium) should be maintained.

Vitamin D–Dependent Rickets, Type 2

- Hereditary resistance to vitamin D ,is a rare autosomal recessive disease caused by a defect in the calcitriol vitamin D receptor and is characterized by end-organ resistance to vitamin D .

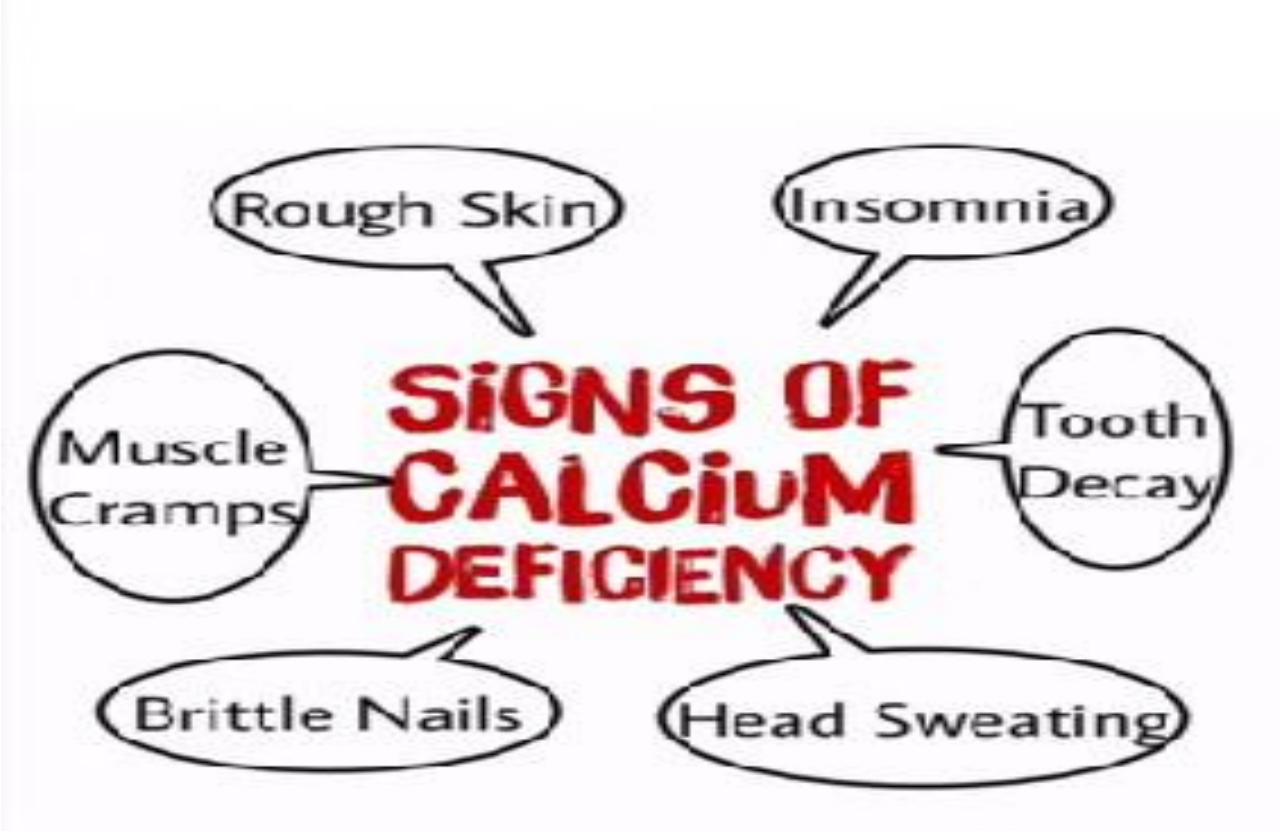
- Patients with vitamin D–dependent rickets type 2 have mutations in the gene encoding the vitamin D receptor, preventing a normal physiologic response to 1,25-D.
- Levels of 1,25-D are extremely elevated . Most patients present during infancy, although rickets in less severely affected patients might not be diagnosed until adulthood. Less-severe disease is associated with a partially functional vitamin D receptor.
- Alopecia also occurs in two-thirds of cases due to a lack of vitamin D receptor activity within keratinocytes and is a marker of disease severity.
- Because VDDR II is a hereditary disease resistant to 1,25-dihydroxyvitamin D, no completely proven treatment is available.

Renal Rickets

- The term renal rickets is usually restricted to those with chronic kidney disease.there is decreased activity of 1α-hydroxylase in the kidney, leading to diminished production of 1,25-D.

- Laboratory findings usually show low calcitriol levels, but 25-hydroxyvitamin D levels may even be normal. The most characteristic finding is the elevated phosphate level secondary to poor renal function of chronic kidney disease. Because patients with chronic kidney disease cannot convert the calcidiol into the active form calcitriol, vitamin D supplementation alone is therefore ineffective for renal rickets. Instead, a low-phosphate diet, dietary phosphate binders, and oral administration of 1 alfacalcidol or calcitriol is advised, along with maintaining normal 25-hydroxyvitamin D level

Calcium deficiency



- **Calcium** is the most abundant major mineral.
- 90% of calcium is in the skeleton; the remaining 1% is in extracellular fluids, intracellular compartments, and cell membranes.
- Calcium intake can come from a variety of sources, with dairy products providing the most common and concentrate source.

***Calcium physiology :

The 3 primary hormones that plays a role in calcium regulation:

1.parathyroid hormone (PTH)

The primary function of PTH is to control calcium concentration in the extracellular fluid, which it does by affecting the rate of transfer of calcium into and out of bone, resorption in the kidneys, and absorption from the GI tract. The effect on the kidneys is the most rapid, causing reabsorption of calcium and excretion of phosphorus. On bone is to mobilize calcium from the bone to the extracellular fluid;

PTH does not directly affect calcium absorption from the gut. Its effect is mediated indirectly by regulation of synthesis of the active metabolite of vitamin D.

2.1,25-dihydroxyvitamin D-3 (Vitamin D3)

3.calcitonin

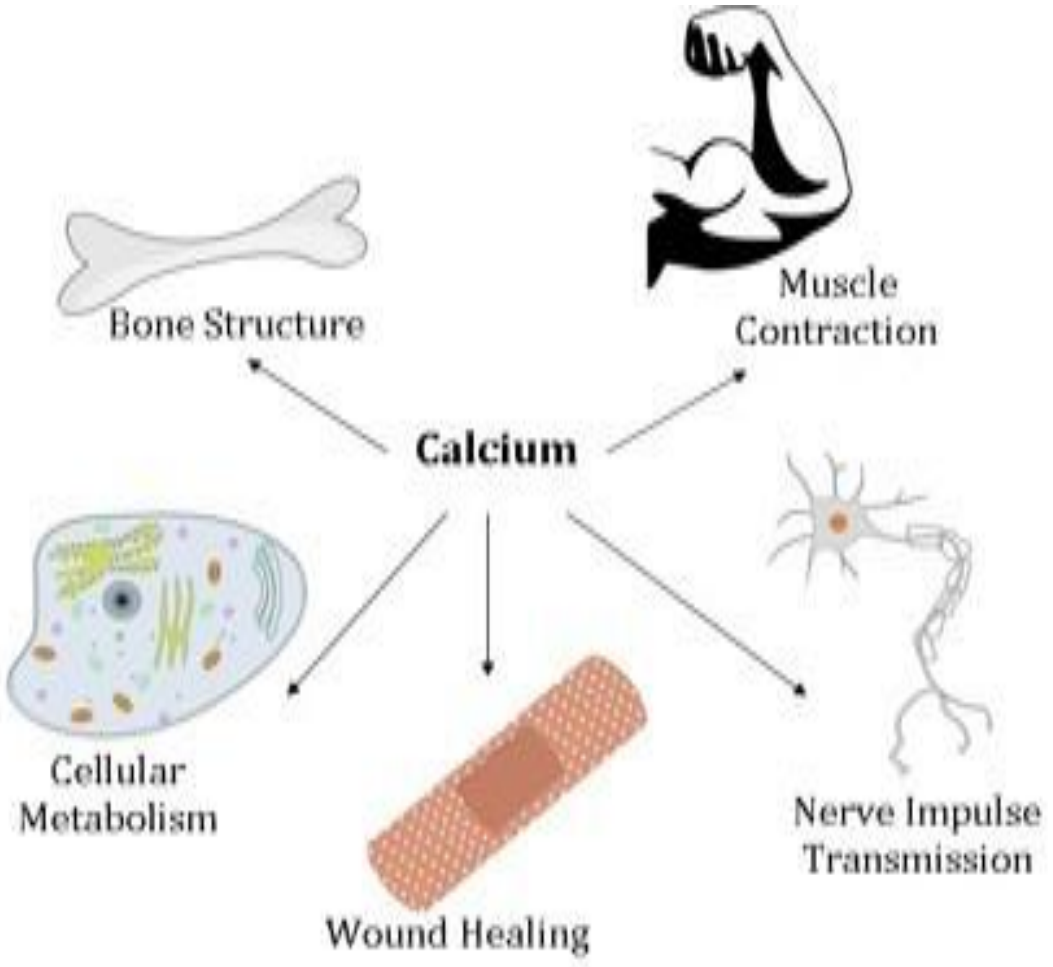
counteracts parathyroid hormone (PTH) and vitamin D.

More specifically, calcitonin lowers blood Ca^{2+} levels in two ways:

- Major effect: Inhibits osteoclast activity in bones, which break down the bone
- Minor effect: Inhibits renal tubular cell reabsorption of Ca^{2+} and phosphate, allowing them to be excreted in the urine

Calcium function

- **Ionized calcium plays an important function in muscle contraction.**
- **Ionized calcium also serves many microbiological functions, including activating protein kinases, enzyme phosphorylation, and mediating cell response to hormones such as epinephrine, glucagon, vasopressin (ADH), secretin, and cholecystokinin.**



CALCIUM DEFICIENCY

Rickets secondary to inadequate dietary calcium is a significant problem in some countries in Africa, although there are cases in other regions of the world, including industrialized countries.

❖ **Causes :**

I. after weaning from breast milk and formula since breast milk and formula are excellent sources of calcium, this form of rickets develops more likely to occur in children who are weaned early.

II. low calcium content in diet , ca <200 mg/day

III. grains and green leafy vegetables high in phytate , oxalate and phosphate (decrease absorption of ca).

IV. in children getting IV nutrition without adequate calcium .

V. malabsorption of calcium (celiac disease , intestinal abetalipoprotenemia ,after small bowel resection)

❖ Prevention :

1. **discouraging early cessation of breastfeeding.**
2. **Increase dietary intake of calcium.**

Phosphorus deficiency

- Abundant in all tissues of the body, phosphorus is a vital structural component for mineralization of bone.

- Both calcium and phosphorus keep the bone in a healthy, functional state. In phosphopenic/hypophosphatemic rickets, the defect usually results from increased renal excretion of phosphate. Urinary loss of phosphate can be either as a part of generalized tubular dysfunction as seen in Fanconi syndrome, or secondary to either increased synthesis/ reduced catabolism of the FGF-23, or inactivating mutations in genes encoding for sodium-dependent phosphate transporters in the proximal renal tubule

Sources of phosphorus:

- The food rich in calcium is also rich in phosphorous, i.e. milk, cheese, beans, eggs, cereals, fish and meat

Functions of Phosphorus:

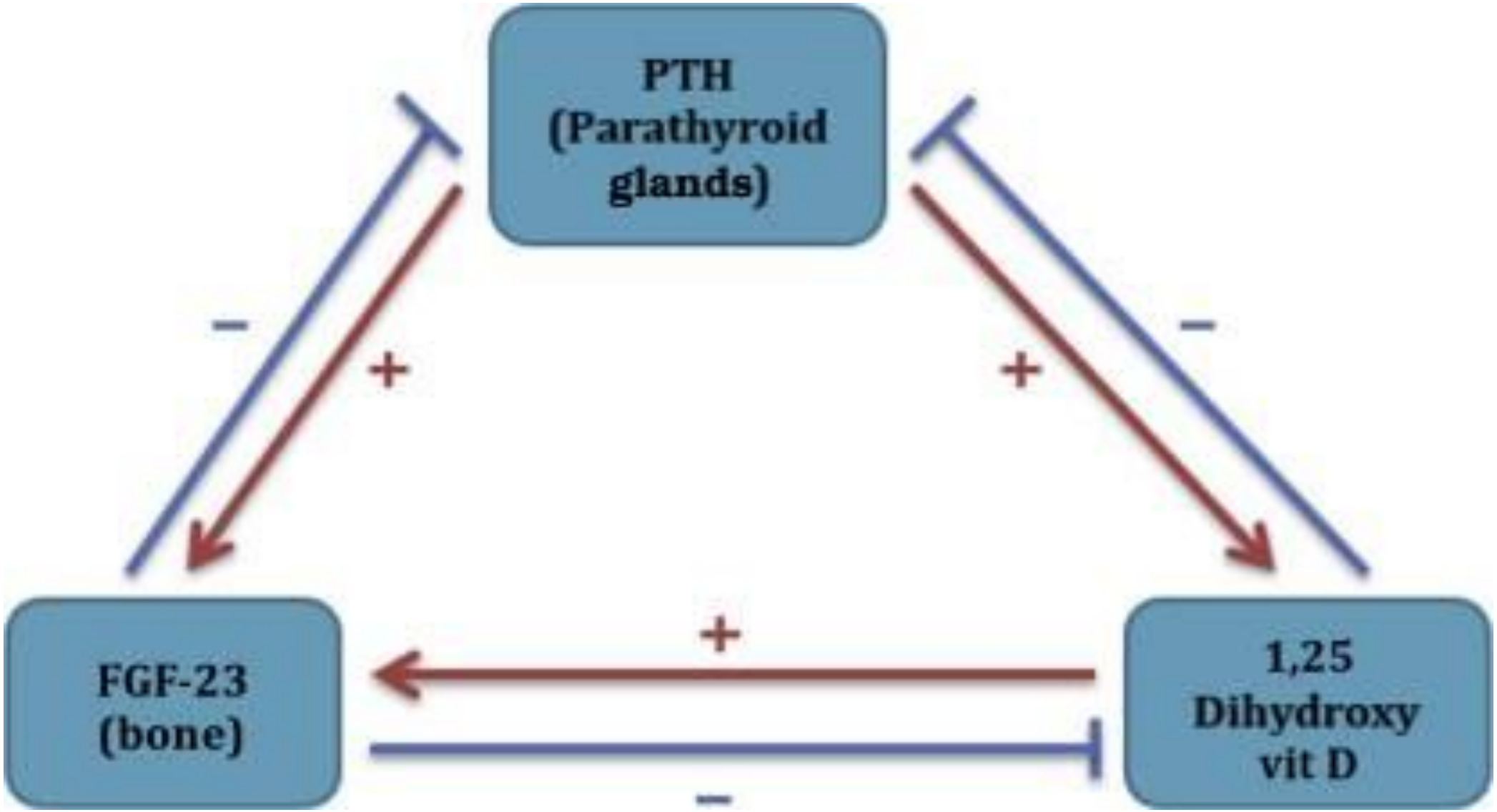
- Component of cell membranes & walls (Phospholipids)
- Structural & functional roles in body
- Component of Nucleic acids and ATP
- Acid-base balance
- High energy phosphate compounds
- Protein synthesis
- important in energy metabolism and Energy transfer
- Maintenance of blood pH

PHOSPHOROUS DEFICIENCY:

With the exception of starvation or severe anorexia, it is almost impossible to have a diet that is deficient in phosphorus, because phosphorus is present in most foods.

*Decreased phosphorus absorption can occur in diseases associated with malabsorption (celiac disease, cystic fibrosis, cholestatic liver disease), but if rickets develops, the primary problem is usually malabsorption of vitamin D and/or calcium.

Isolated malabsorption of phosphorus occurs in patients with long-term use of **aluminum-containing antacids**, These compounds are very effective at chelating phosphate in the GI tract, leading to decreased absorption. This entity responds to discontinuation of the antacid and short-term phosphorus supplementation.


PTH
(Parathyroid
glands)
−
+
+
−
FGF-23
(bone)
+
−
1,25
Dihydroxy
vit D

Regulation of phosphate homeostasis

- The amount of renal phosphate reabsorption is tightly regulated by dietary Pi intake, parathyroid hormone (PTH) and fibroblast growth factor 23 (FGF23).

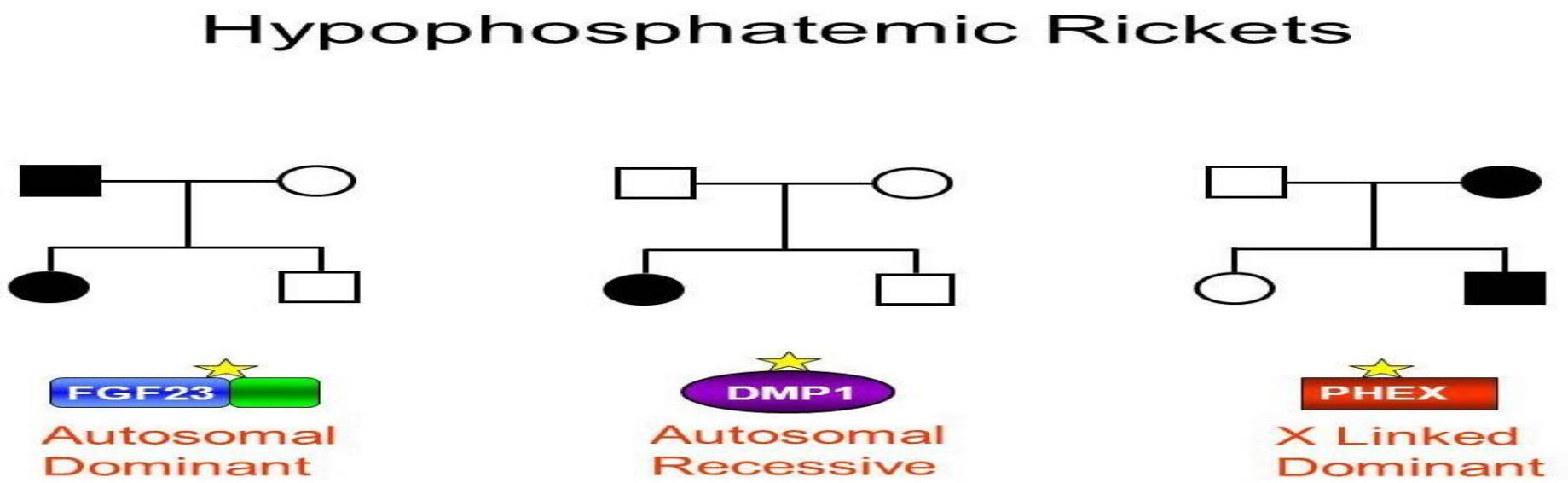
1. PTH ; increase phosphaturia by reducing renal tubular phosphate reabsorption via inhibiting the sodium-phosphate co-transporters (NaPi IIa/IIc).
2. Fibroblast growth factor-23 (FGF- 23) is a humoral mediator that **decreases renal tubular reabsorption of phosphate** and therefore decreases serum phosphorus. FGF-23, synthesized by osteocytes, also **decreases the activity of renal 1α-hydroxylase**, resulting in a decrease in the production of 1,25-D.
3. 1,25(OH)2D increases the intestinal absorption of dietary phosphorus via upregulating NaPi Iib and activates FGF23 production

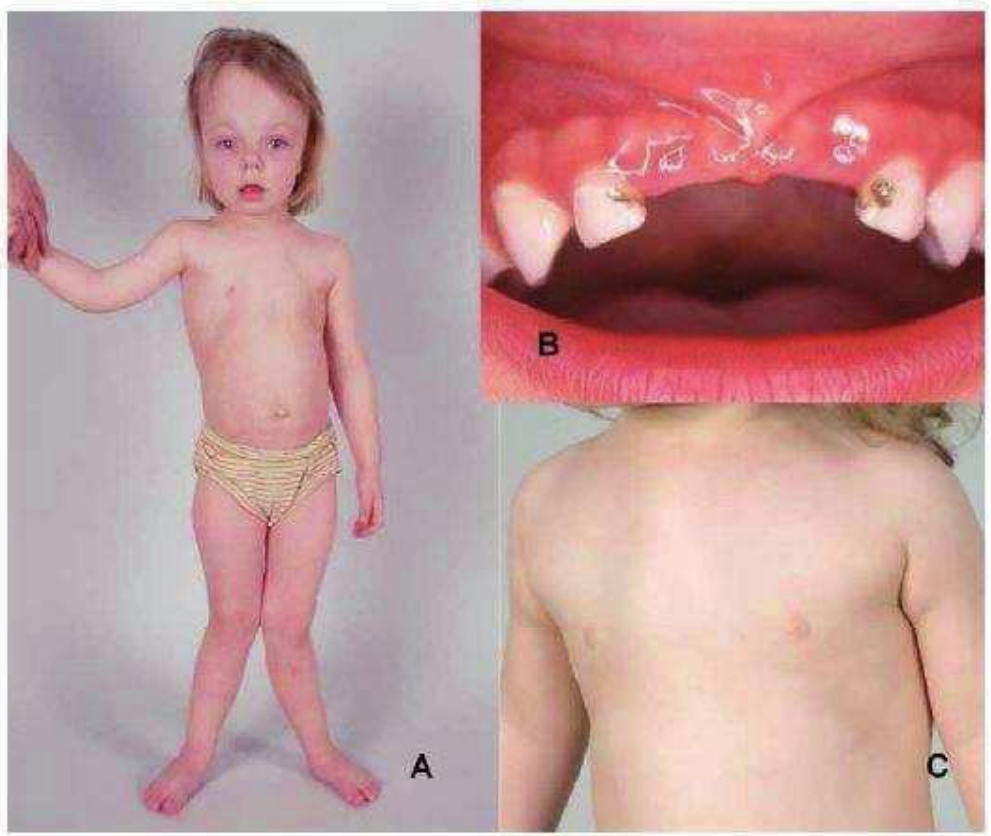
Hypophosphatemic Rickets:

The main defect in these forms of rickets is the increased loss of phosphate through the urine.

Hereditary causes occur due to **genetic mutations** involving:

- Phosphate-regulating neutral endopeptidase (PHEX) – (X-linked dominant)
- Dentin matrix acidic phosphoprotein 1 (DMP1) – (Autosomal recessive)
- FGF-23 – (Autosomal dominant)





Hypophosphatesia is a rare inborn error of metabolism due to the dysfunction of the tissue nonspecific alkaline phosphatase enzyme. Childhood hypophosphatesia has onset of symptoms between 6 months and 18 years and can present as rickets, reduced mobility, fractures, and poor growth. It is characterized by low alkaline phosphatase levels.

Hypophosphatemic rickets should not be confused with hypophosphatesia as it is characterized by low alkaline phosphatase levels, which is paradoxical because other forms of rickets are associated with high alkaline phosphatase levels.

X-Linked Hypophosphatemic Rickets

It is the most common genetic form of hypo-phosphatemia, with an incidence of 1:20,000.47 The disease results from mutations of the phosphate-regulating gene on the X chromosome (PHEX gene), which impairs the inactivation of FGF-23 by an ill-understood mechanism.

Increased FGF-23 level results in renal wasting of phosphorus at the proximal tubule level, which results in hypophosphatemia.

Increased FGF-23 level also results in low calcitriol levels due to inhibition of renal 1^{α}-hydroxylase.

Clinical findings:

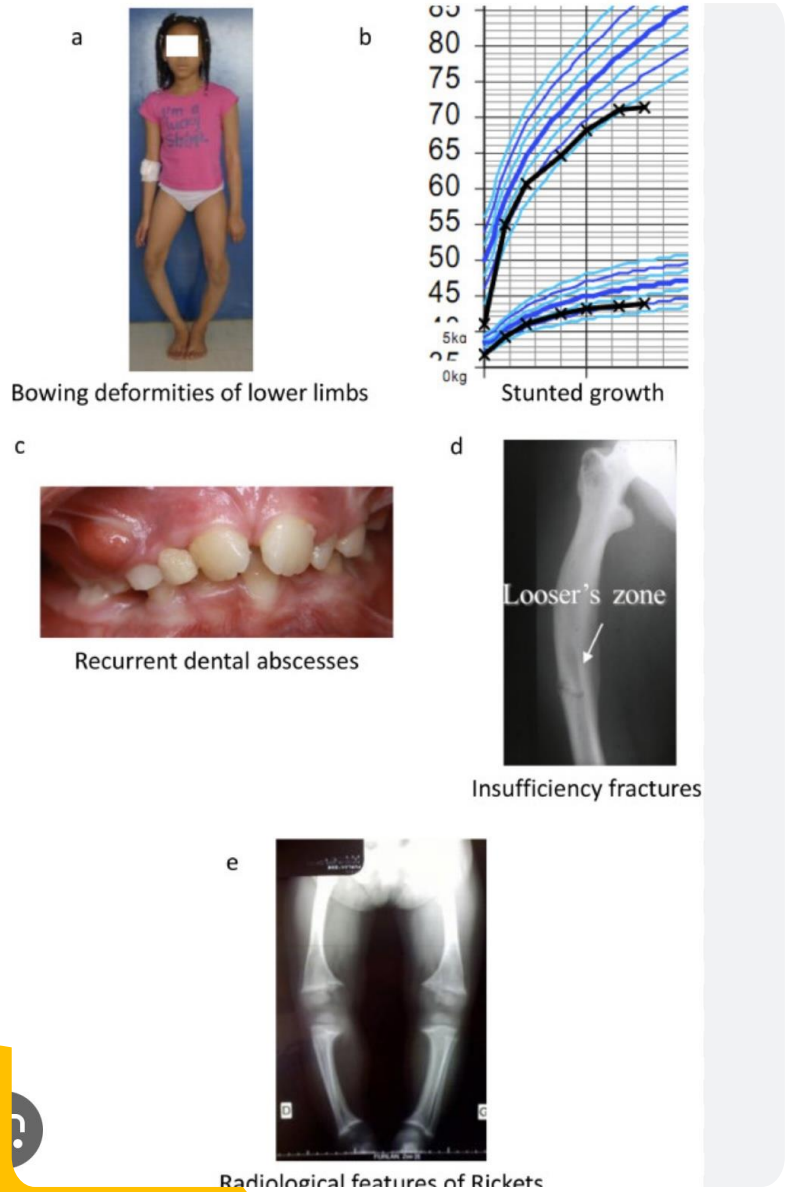
- Unlike vitamin D deficiency, craniotabes and rachitic rosary are not common.

1) One of the initial clinical findings is **frontal bossing**, which may appear as early as 6 months of age.

2) As the child starts walking, progressive limb deformities become evident, leading to **disproportionate short stature with shorter limbs**. Lower limbs are more affected, leading to coxa vara, genu valgum, or genu varum.

3) **Dental abnormalities** are common and may often be the presenting complaints. These abnormalities include abscessed noncarious teeth, enamel defects, and enlarged pulp chambers.

4) Recent studies have shown higher incidence of **cranio-vertebral and cranial vault anomalies**, especially early closure of the cranial sutures (craniosynostosis) and Chiari type 1 malformation.



Treatment:

Combination of oral phosphorus and 1,25-D (Calcitriol)

Daily: 1-3 g of elemental phosphorus divided into 4-5 doses.

Prognosis:

The response to therapy is usually good, although frequent dosing can lead to problems with compliance.

Girls generally have less-severe disease than boys, probably because of the X-linked inheritance.

Short stature can persist despite healing of the rickets.

Autosomal Dominant Hypophosphatemic Rickets

Autosomal dominant hypophosphatemic rickets has a variable age of onset and an incomplete penetrance. The defect being an activating mutation in FGF-23 leading to phosphaturia.

The actions of FGF-23 include decreased reabsorption of phosphate in the renal proximal tubule, which results in hypophosphatemia, and inhibition of the 1α-hydroxylase in the kidney, causing a decrease in 1,25-D synthesis.

- Elevated levels of FGF-23 and hypophosphatemia were observed with iron deficiency in humans and mice with autosomal dominant hypophosphatemic rickets mutation.

- Based on the age of presentation, there are 2 subgroups:

1) Presents during childhood and mimics X-linked dominant hypophosphatemic rickets.
2) presents during adolescence or adulthood with bone pain, weakness, and pseudo fractures but no deformity.

Autosomal Recessive Hypophosphatemic Rickets

ARHR type 1 occurs due to loss of function mutations in DMP 1, a noncollagenous bone matrix protein expressed in osteoblasts and osteocytes.

DMP1 has a role in osteocyte proliferation and in the down-regulation of FGF-23.

ARHR type 2 occurs due to loss of function mutations in ectonucleotide pyro-phosphatase/phosphodiesterase 1. Loss of function mutations in this protein can lead to generalized arterial calcification of infancy.

- Clinical manifestations and biochemical findings of patients with ARHR are similar to those with X-linked dominant hypophosphatemic rickets.

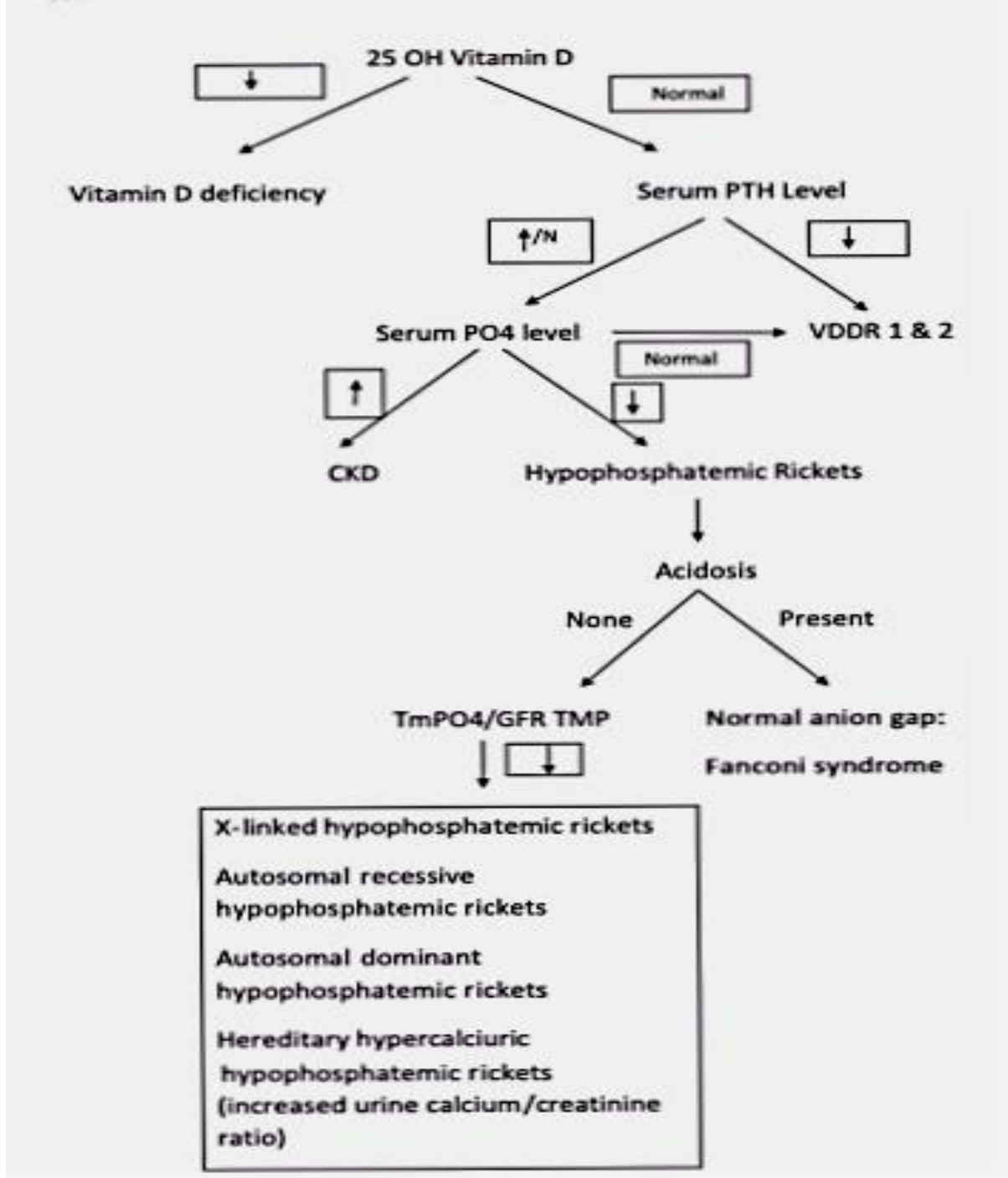
Hereditary Hypophosphatemic Rickets With Hypercalciuria

This particular variant of inherited hypophosphatemic rickets results from a genetic defect wherein there is loss of function mutation in the gene SLC34A3 disrupting its key role in maintaining phosphate homeostasis.

- Bone pain, muscle weakness, and pseudo fractures are the common presenting complaints, but dental abnormalities are not usually reported.

- In contrast to other variants of inherited hypohosphatemic rickets, FGF-23 level is normal and 1,25-dihydroxy vitamin D levels are elevated for low phosphorus levels.

- These patients also exhibit hypercalciuria, which predisposes them to nephrolithiasis.


25 OH Vitamin D
↓
Normal
Vitamin D deficiency
Serum PTH Level
↑/N
↓
Serum PO4 level
VDDR 1 & 2
Normal
↑
↓
CKD
Hypophosphatemic Rickets
Acidosis
None
Present
TmPO4/GFR TMP
↓
Normal anion gap:
Fanconi syndrome
X-linked hypophosphatemic rickets
Autosomal recessive hypophosphatemic rickets
Autosomal dominant hypophosphatemic rickets
Hereditary hypercalciuric hypophosphatemic rickets (increased urine calcium/creatinine ratio)

Management of Hypophosphatemic Rickets:

- **Phosphate supplementation** (elemental phosphorus in 3 to 5 doses of 20 to 60 mg/kg per day) remains the cornerstone of management.
- Most of them also benefit from **calcitriol supplementation** (20–30 ng/kg per day) or alfacalcidol 30 to 50 ng/kg per day, as the FGF-23 suppresses formation of 1,25 dihydroxy cholecalciferol.
- If supplemented by **calcitriol** (In the exception of hereditary hypophosphatemic rickets with hypercalciuria as it might worsen the case), urinary calcium should be monitored closely to avoid nephrocalcinosis.
- For hereditary hypophosphatemic rickets with hypercalciuria supplementation with **phosphate** forms the mainstay of its treatment.

- Evaluation and treatment of iron deficiency is important in children with autosomal dominant hypophosphatemic rickets, as iron deficiency causes increased expression of the FGF-23 gene.

- In the management of X-linked hypophosphatemia, secondary hyperparathyroidism results from the persistent stimulation of parathyroid cells by FGF-23 and phosphate supplements, and also from the suppression of 1,25 dihydroxy vitamin D by FGF-23 in children not managed with active vitamin D.

This secondary hyperparathyroidism leads to increased phosphaturia and bone resorption.

In contrast, excessive vitamin D treatment and/or inadequate phosphate intake suppresses PTH levels and results in reduced bone turnover, jeopardizing the healing process of rickets and growth.

Which necessitates the adjustment of therapies and monitoring of PTH levels to keep within normal limits (10–65 pg/ml).

Fanconi Syndrome

There is an underlying proximal tubulopathy results in glycosuria, hypokalemia, proximal renal tubular acidosis, hyperuricosuria, and generalized aminoaciduria

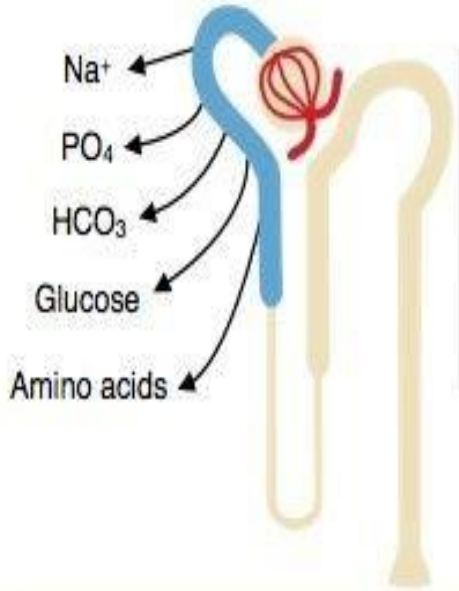
also, can have significant urinary phosphate loss resulting in hypophosphatemic rickets.

It may be primary or secondary to other conditions.

Management includes any specific therapy for the underlying disorder if identified along with phosphate supplementation and acidosis correction.

Fanconi Syndrome

↳ Global **proximal tubule dysfunction**



Phosphaturia
Renal glycosuria
Aminoaciduria
Tubular proteinuria
Proximal renal tubular acidosis

Etiology

- Genetic diseases (Dent, Cystinosis, Wilson, Galactosemia)
- Acquired (Cisplatin, Heavy metals)

Clinical

- Growth failure
- Hypovolemia
- Persistent acidosis
- Rickets and osteomalacia (hypophosphatemia)
- Constipation and weakness (hypokalemia)

Type	Calcium	Phosphorus	Alkaline phosphatase	PTH	25 (OH)D	1,25 $(OH)_2$ D
Calcipenic rickets						
Vitamin D deficiency	↓ or N	↓ or N	↑ or ↑↑	↑	↓	Variable
Vitamin D–dependent rickets type I	↓	↓ or N	↑↑	↑	N	↓
Vitamin D–dependent rickets type II	↓	↓ or N	↑↑	↑	N	N or ↓
Phosphenic rickets						
Nutritional phosphate deficiency	↑ or N	↓	↑ or ↑↑	↓ or N	N	↑
X-linked hypophosphatemic rickets	N	↓	↑	N or slightly ↑	N	N or ↓
Autosomal dominant hypophosphatemic rickets	N	↓	↑	N	N	↓
Autosomal recessive hypophosphatemic rickets	N	↓	↑	N	N	↓
Hereditary hypophosphatemic rickets with hypercalciuria	N	↓	↑	N or ↓	N	↑

25 (OH)D, 25-hydroxy vitamin D; 1,25 (OH)2 D, 1,25 dihydroxy vitamin D; N, normal levels; PTH, parathyroid hormone; ↑, increased levels; ↓, decreased levels.

Case discussion

Leyla is a 5-year-old girl, born by Caesarean section for fetal macrosomia (birth weight 4520 g), without any perinatal problems. She was exclusively breast fed until 6 months of age, then switched to formula milk.

Since the age of 2 years Leyla has been complaining of recurrent hip pain and the mother reports that the baby does not walk normally. The orthopedist prescribes corrective insoles as he noticed valgism of the knees and foot pronation. Due to the persistence of these signs, the girl undergoes a radiological examination which shows bone deformations and osteopenia. A diagnosis of rickets due to vitamin D deficiency is made and supplementation with vitamin D 400 IU/day is started.

After 2 years a deflection in the growth curve is noted and the child is sent to your specialist outpatient clinic. She is sent without any radiological or laboratory documentation. Upon clinical examination you notice a prominent forehead, valgism of the knees and brevity of the limbs.

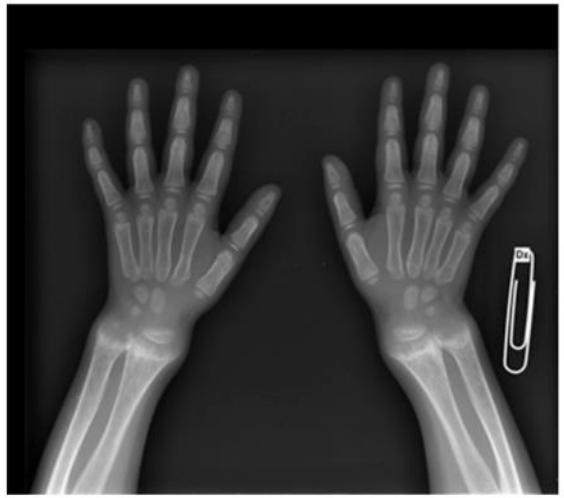
- **Which tests would you need to confirm or exclude the diagnosis of rickets?**

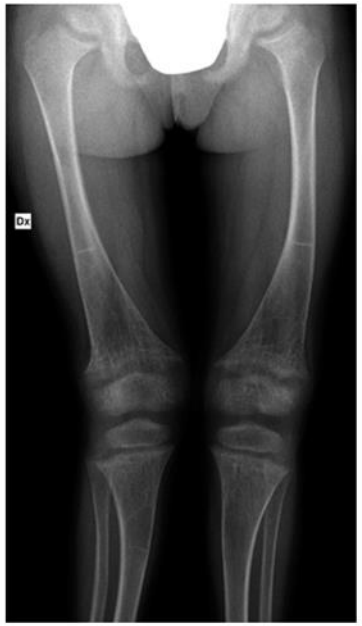
Rickets is a radiological diagnosis. Usually x-ray images of the hands and limbs are obtained.

These are Leyla's x-rays.

Hand X-Ray: Marked widening of radial and ulnar metaphysis, swelling of periarticular soft tissue. Marked osteopenia of radial and ulnar diaphysis.

Limb X-Ray: Cup-shaped enlargement of distal femoral and proximal distal metaphases of the tibia. Curved deformity of the femoral and tibial diaphysis. Marked osteopenia.





- **Based on the patient history and the X ray findings, what are possible etiologies of the patient's condition?**

1) Rickets due to vitamin D deficiency.
2) Renal osteodystrophy.
3) Rickets associated with Fanconi syndrome.
4) Rickets of genetic origin.

All answers are correct.

- **What are the appropriate first-line laboratory tests to narrow down the differential diagnoses?**

Serum and urine electrolytes

Alkaline phosphatase

PTH

Vitamin D level

Serum creatinine

Urinary glucose

Urinary amino acids

Leyla's lab results

- **The tests show:**

Low serum phosphorus
Elevated alkaline phosphatase and PTH
High normal urinary phosphorus concentration
Normal vitamin D level, serum calcium and creatinine
Absent glucosuria and aminoaciduria

- Normal vitamin D levels exclude vitamin D deficiency.
- Absent glucosuria and aminoaciduria exclude Fanconi syndrome.
- Normal serum creatinine rules out CKD-associated osteodystrophy.

- Urine phosphorus concentration is within the normal range. **So, Is there a better way to diagnose an inadequately high urinary phosphorus excretion?**

1) 24-hour phosphorus excretion.

2) Urinary phosphorus/creatinine ratio.

3) TMP/GFR.

4) Urinary/serum phosphorus ratio.

- Urine phosphorus concentrations may be normal despite impaired tubular reabsorption in the presence of low serum phosphorus levels.
- Renal phosphorus loss can be reliably evaluated by the tubular transport maximum of phosphorus relative to glomerular filtration rate **(Tmp/GFR):**

TmP/GFR = Pp - (Up x Pcr/Ucr)

where Pp, Up, Pcr and Ucr refer to plasma and urine concentration of phosphate and creatinine, respectively. All values must be expressed in the same units.

- **The normal range of TmP/GFR** is 1.2 to 2.6 mmol/l in infants and young children (0.5-6 years) and 0.6 to 1.7 mmol/l in adults.

- **The TmP/GFR of our patient is 0.8 mmol/l, i.e. markedly low for her age.**

Diagnosis

- **What is the most likely diagnosis?**

1) Rickets due to Vitamin D deficiency.
2) Renal osteodystrophy.
3) Rickets associated with Fanconi syndrome.
4) Rickets of genetic origin.

- We can exclude rickets due to Vitamin D deficiency (Vit D in normal range, disease manifestation already at 1 year of life).
- We can exclude renal osteodystrophy (the patient has normal renal function).
- We can exclude Fanconi syndrome (absence of glycosuria of aminoaciduria).

- At this point the answer is **Rickets of genetic origin.**

Next step

- **So now as we are suspecting a familial form of rickets, which is our next diagnostic step?**

1) Radiological examination of mother.
2) Radiological examination of father.
3) Laboratory examination of mother.
4) Bone biopsy.
5) Genetic testing in affected child.

- We should order **genetic screening for inherited forms** of hypophosphatemic rickets.
- The radiological examination of the parents can reveal whether the patient's parents are also affected by the disease (in case the disease is inherited by X-linked or autosomal dominant transmission) but it does not allow us to make a definitive diagnosis.
- Bone biopsy will not clarify the etiology of the disease.

Genetic result interpretation

- From the genetic test you learn that Layla carries a heterozygous point mutation in the PHEX gene leading to an amino acid exchange (c.501G>A, p.(Trp167).

- Exploring the family history in more detail, you learn that the parents never experienced any bone pain or other bone symptoms and had a completely normal development. The patient's mother is only short in stature.

- **How is it possible that Leyla is affected by an X-chromosomal disease although none of the parents are clinically affected?**

1) The defect is recessive and was transmitted from both mother and father to Leyla.

2) She carries a de novo mutation.

3) The mutation is transmitted as an X-linked dominant trait with complete penetrance, but variable expressivity.

4) Mother’s short stature suggests that she is mildly affected and transmitted the disease to her daughter.

5) The genetic test has to be repeated, for sure there is a mistake.

- **X-linked hypophosphatemic rickets is the most common genetic form of rickets**. It is characterized by short stature, bone pain, radiological signs of rickets, increased fractional phosphate excretion, and low levels of 1.25-OH-vitamin D.
- The incidence is estimated 1:20.000.

- It is caused by the mutation in the **"Phosphate regulating gene with Homology to Endopeptidases"(PHEX)** located on the X chromosome. PHEX encodes an endopeptidase expressed predominantly in bone and teeth that regulates fibroblast growth factor 23 (FGF-23) turnover.

- PHEX mutations lead to increased circulating levels of FGF-23, a phosphate regulating hormone (phosphatonin) that leads to reduced renal tubular phosphate reabsorption and consequently decreased bone mineralization.

- PHEX mutations are transmitted as an X-linked dominant trait with complete penetrance but variable expressivity. This disease seriously affects male subjects (46 XY) and may affect female subjects with variable grade of expressivity (46 XX).

- In Leyla's case her father cannot be the carrier of the mutation as he would be expected to have a severe disease phenotype.
- **The mutation may have been transmitted by her mother or it may have occurred de novo.**

Management

- **What treatment will you initiate for the child ?**

1) Oral phosphorus supplementation.

2) Vitamin D supplementation.

3) Non-steroidal anti-inflammatory drugs.

4) Burosumab (anti-FGF23 antibody).

5) Infliximab (anti-TNF antibody).

- For more than 40 years, treatment for X-linked hypophosphatemia has consisted of multiple daily doses of oral phosphate salts and active vitamin D. The drawbacks of this conventional therapy include poor tolerability and compliance, mineralization of tissues outside bone, especially the kidneys (nephrocalcinosis), and secondary hyperparathyroidism.
- In addition, conventional therapy does not completely correct bone deformities and impaired growth.

- **Burosumab (Crysvita®),** a fully human IgG1 monoclonal antibody directed at fibroblast growth factor 23 (FGF23), directly addresses the excessive FGF23 activity present in most genetic forms of rickets by binding to FGF23 and inhibiting its signaling. This leads to normalized gastrointestinal phosphate absorption and renal phosphate reabsorption, thereby **improving serum phosphate levels and consequently bone mineralization**.

- In clinical trials, two-weekly subcutaneous Burosumab administration increased serum phosphorus levels in pediatric and adult patients with XLH. In children rickets was markedly improved, and adults reported reduced pain and stiffness, improved physical functioning, and markedly accelerated healing of fractures/pseudofractures. Burosumab is well tolerated by children and adults. **Currently the drug is approved only for children**.

Summary

- The precise diagnosis of the cause of rickets is fundamental for the correct therapy and prognosis.
- Late rickets is always genetic rickets.
- The most common genetic form of rickets is X-linked hypophosphatemic rickets.
- Burosumab (Crysvita®), a fully human IgG1 monoclonal antibody directed at fibroblast growth factor 23 (FGF23), is the treatment of choice for X-linked hypophosphatemia (XLH).

Reference

- https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7335963/