Rickets

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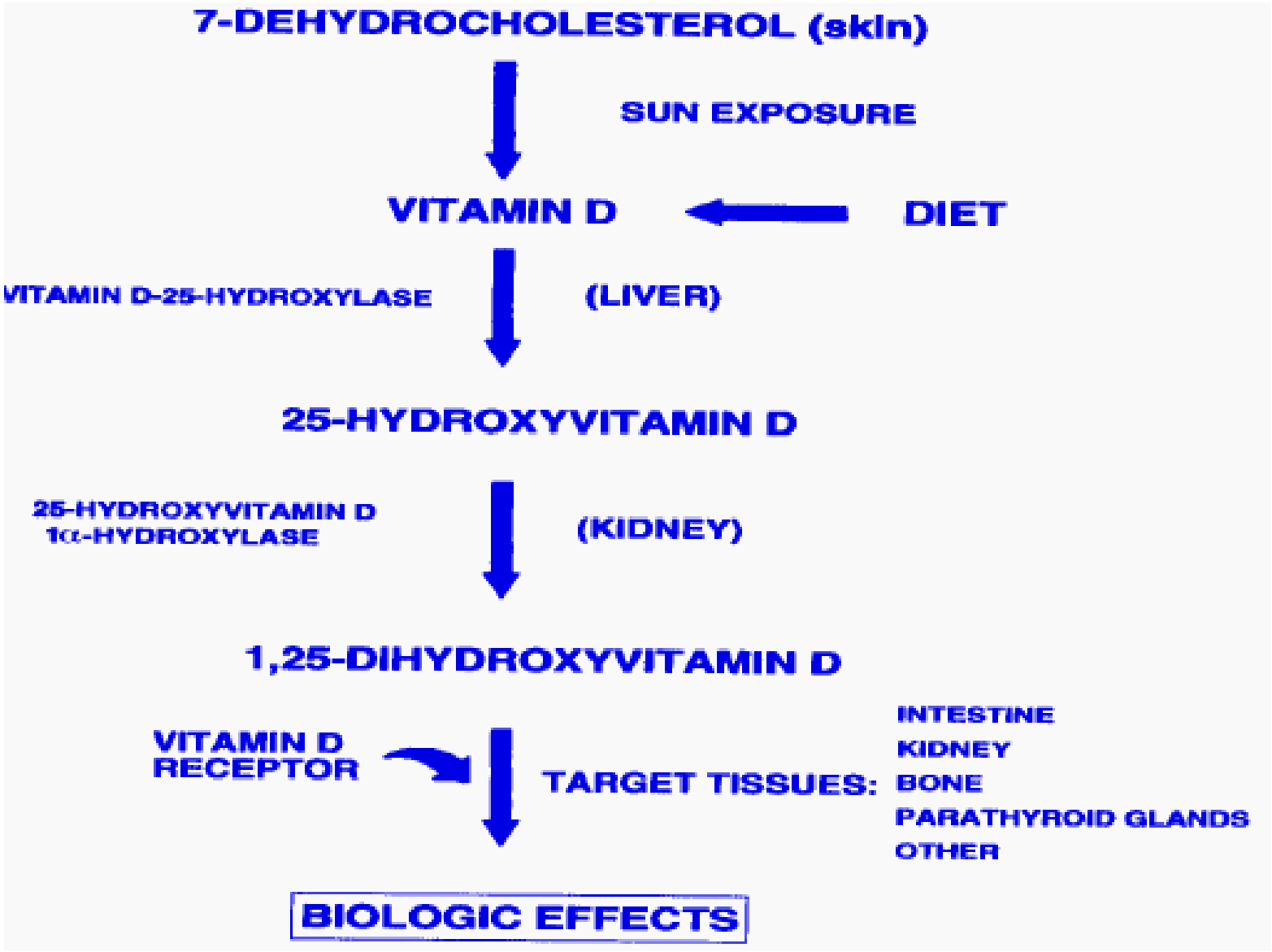
Rickets & Osteomalacia

- Rickets is a disease of the growing bones in which defective mineralization occurs in both bone & cartilage of the epiphyseal growth plates
- It is associated with growth retardation & skeletal deformities
- Osteomalacia is a disorder of the mature bone in which mineralization of new osteoid bone is inadequate or delayed
- Skeletal muscles have a vitamin D receptor and may require vitamin D for maximum function
- Vitamin D deficiency causes muscle weakness
- Brain, parathyroid glands, breast, and colon tissues, others, as well as immune cells have vitamin D receptors and respond to 1, 25-dihydroxyvitamin D

- Recent studies documenting the high prevalence of vitamin D deficiency and the need to increase dietary vitamin D intake
- Epidemiological studies and new information on the role of vitamin D in preventing autoimmune diseases, cardiovascular disease, and cancer
- Prospective and retrospective epidemiologic studies all indicate that levels of 25-hydroxyvitamin D below 20 ng / milliliter are associated with a 30 to 50% increased risk of incident colon, prostate, and breast cancer, along with higher mortality from these cancers.


7-DEHYDROCHOLESTEROL (skin)
SUN EXPOSURE
VITAMIN D
DIET
VITAMIN D-25-HYDROXYLASE
(LIVER)
25-HYDROXYVITAMIN D
25-HYDROXYVITAMIN D
1α-HYDROXYLASE
(KIDNEY)
1,25-DIHYDROXYVITAMIN D
VITAMIN D
RECEPTOR
TARGET TISSUES:
INTESTINE
KIDNEY
BONE
PARATHYROID GLANDS
OTHER
BIOLOGIC EFFECTS

Sources of Vitamin D

- Sun light
  - Synthesis in body from precursor sterol
- All Milk products (fortified)
- Cod liver oil
- Egg yolk

Types

- Hypocalcaemic Rickets (commonest type)
- Hypophosphatemic Rickets (not common)
- Combined Rickets (combination of hypocalcaemia and hypophosphetemia)

Hypocalcaemic rickets (with secondarily elevated parathyroid hormone levels)

- Lack of vitamin D due to:
  - Decreased sun exposure
  - Dietary-deficient intake
  - Malabsorption diseases that affects absorption of vitamin D (e.g. celiac disease, CF, chronic diarrhea…etc)
- Chronic liver diseases (affects conversion of cholecalciferol to calcidiol)
- Anticonvulsant drugs (phenytoin, phenobarbitone due to increased metabolism of vitamin D by inducing cytochrome P450 activity)

- Celiac disease
- Pancreatic insufficiency
  - Cystic fibrosis
- Hepato-biliary disease
  - Biliary Artesia
  - Cirrhosis
  - neonatal hepatitis
- Drugs
  - Anti-convulsants
    - Phenobartbitone
    - Phenytoin
- Diet
  - Excess of phytate in diet with impaired calcium absorption (chapati flour)

Nutritional Rickets

- Globally, nutritional deficiencies are the leading cause of rickets
- Infants fed exclusively with mother's milk can develop nutritional rickets because of the low content of vitamin D in breast milk (30-40 IU/L)
- In premature infants, insufficient amounts of both calcium and phosphorus may cause nutritional rickets
- Infants with low or no sun exposure may develop rickets, particularly if they have dark skin, because of decreased vitamin D production by the skin after exposure to UV light

Nutritional Rickets

Lack of vitamin D

- Commonest cause in Saudi Arabia and in developing countries
- Lack of exposure to U/ V sun light
  - Dark skin
  - Covered body
  - Kept in-door
- Exclusive breast feeding
  - Limited intake of vitamin –D fortified milk and diary products
- During rapid growth
  - Infancy
  - puberty

- Chronic renal failure (Renal Osteodystrophy)
  - progressive renal disease is associated with a decline in serum calcium resulting from several factors
  - RTA (Renal Tubular Acidosis)
- Hereditary Rickets
  - Type 1 vitamin D-dependent rickets occurs because of a defect in one-alpha hydroxylase enzyme which is responsible for the conversion of 25-OH vitamin D into the active metabolite
  - Type 2 vitamin D-dependent rickets occurs because of End-organ resistance to calcitriol is very rare autosomal recessive disorder which is usually caused by mutations in the gene encoding for vitamin D receptors

Chronic liver disease

- Cirrhosis reduces 25-hydroxylation of vitamin D
- Biliary obstruction:
  - Prevents absorption of fat soluble vit D
  - Interrupts its enterohepatic circulation

Renal Osteodystrophy

- As progressive renal disease is associated with a decline in serum calcium resulting from several factors
- Important among these are a rise in serum phosphate as the ability of the kidney to clear absorbed phosphate declines and a fall in serum levels of $1,25(OH)_2$ vitamin D because of diminishing renal production of this metabolite
- The consequent stimulation of parathyroid function can lead to severe secondary and even tertiary hyperparathyroidism and therefore early intervention with phosphate binders and one alpha or calcitriol analogues

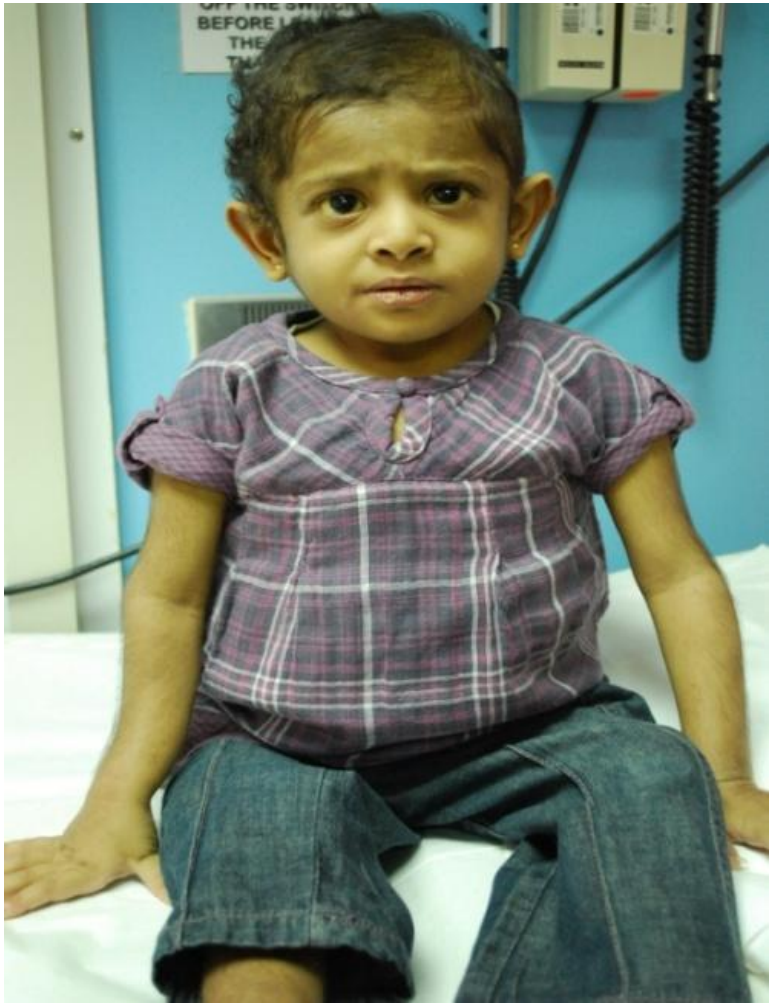
Renal Osteodystrophy (Renal Rickets)

- In end-stage renal disease, renal 1-hydroxylase is diminished or lost, and excretion of phosphate is defective.
- This leads to low levels of 1, 25$(OH)_2$ vitamin D, hypocalcaemia, and failure of osteoid calcification Osteodystrophy (renal rickets) is the only type of rickets with a high serum phosphate level.
- It can be dynamic (a reduction in osteoblastic activity) or hyper dynamic (increased bone turnover)
- Treatment of these patients includes phosphate binders, a low phosphate intake & calcitriol / one Alpha vitamin D

Fanconi's Syndrome

- Is a disease of the proximal renal tubules of the kidney in which glucose, amino acids, uric acid, phosphate and bicarbonate are passed into the urine, instead of being reabsorbed. It may be inherited, or caused by drugs or heavy metals. The loss of bicarbonate results in Type 2 or proximal renal tubular acidosis. The loss of phosphate results in the bone disease rickets (even with adequate vitamin D and calcium). The clinical features of proximal renal tubular acidosis include; polyuria, polydipsia and dehydration, hypophosphatemic rickets , growth failure, acidosis, hypokalemia, hyperchloremia, hypophosphatemia, phosphaturia, glycosuria, Proteinuria/ aminoaciduria and hyperuricosuria

Hepatic Rickets



Hepatic Rickets

- Vitamin D is hydroxylated in the liver to form 25-hydroxyvitamin D
- Patients with severe parenchymal or obstructive hepatic disease may have reduced production of 25-hydroxyvitamin D
- Occurs in cholestatic liver disease because of decreased intestinal absorption of & impaired hepatic hydroxylation of vitamin D

Malabsorption Rickets

- Malabsorption of vitamin D is suggested by a history of liver or intestinal disease
- Undiagnosed liver or intestinal disease should be suspected if the child has gastrointestinal symptoms, although occasionally, rickets may be the presenting complaint
- Fat Malabsorption is often associated with diarrhea or oily stools, and there may be signs or symptoms suggestive of deficiencies of other fat-soluble vitamins (A, D, E, and K)

Congenital Rickets

- Onset of this type happens in the first six months of life
- It is quite rare in industrialized countries; however, it is common in developing countries, including Saudi Arabia
- It occurs when there is maternal vitamin D deficiency during pregnancy
- Maternal risk factors include poor dietary intake of vitamin D, lack of adequate sun exposure, and closely spaced pregnancies

Hereditary Rickets

- Hypophosphatemic rickets (Vit D resistant)
- Vitamin D dependent rickets

Vitamin D dependent rickets

Type 1

- Rare, autosomal recessive
- Lack of 1 α hydroxylase enzyme
- Clinically and Biochemically similar to nutritional rickets except it appears early at 3-4 months

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 treatment

Vitamin D – Dependant Rickets

- Type 1 vitamin D-dependent rickets occurs because of inherited deficiency of one-alpha hydroxylase enzyme which is responsible for the conversion of 25-OH vitamin D into the active metabolite 1,25- dihydroxy vitamin D
- Type 2 vitamin D-dependent rickets occurs due to end-organ resistance to 1,25- dihydroxy vitamin D (calcitriol)
- Both types are autosomal recessive disorders

Vitamin D–Dependent Rickets (type 1)

- This disorder results from a genetic deficiency in one- alpha hydroxylase enzyme that converts calcidiol to calcitriol in the kidney.
- It is inherited as an autosomal recessive, and the gene is located in band 12q13.3.
- Clinical and laboratory examination findings are similar to those associated with nutritional rickets, with low levels of 1, 25$(OH)_2$ vitamin D with normal values of 25- hydroxyl vitamin D3.
- These patients develop rickets despite receiving vitamin D at the recommended preventive doses
- Medical treatment consists of oral calcitriol (0.5-1.5 mcg/day) or one alpha (dose 1 mcg/day)

Vitamin D-Resistant Rickets (Type 2 Vitamin D–Dependent Rickets)

- It is a rare autosomal recessive disorder, most often caused by mutations in the vitamin D receptor gene
- It usually presents with rachitic changes not responsive to vitamin D treatment and the circulating levels of both 25 (OH) vitamin D3 and 1,25 (OH)2 vitamin D3 are normal or elevated, differentiating it from vitamin D dependent rickets type 1
- Alopecia capitis or alopecia totalis is seen in some families with vitamin D-dependent rickets type 2
  - This is usually associated with a more severe phenotype

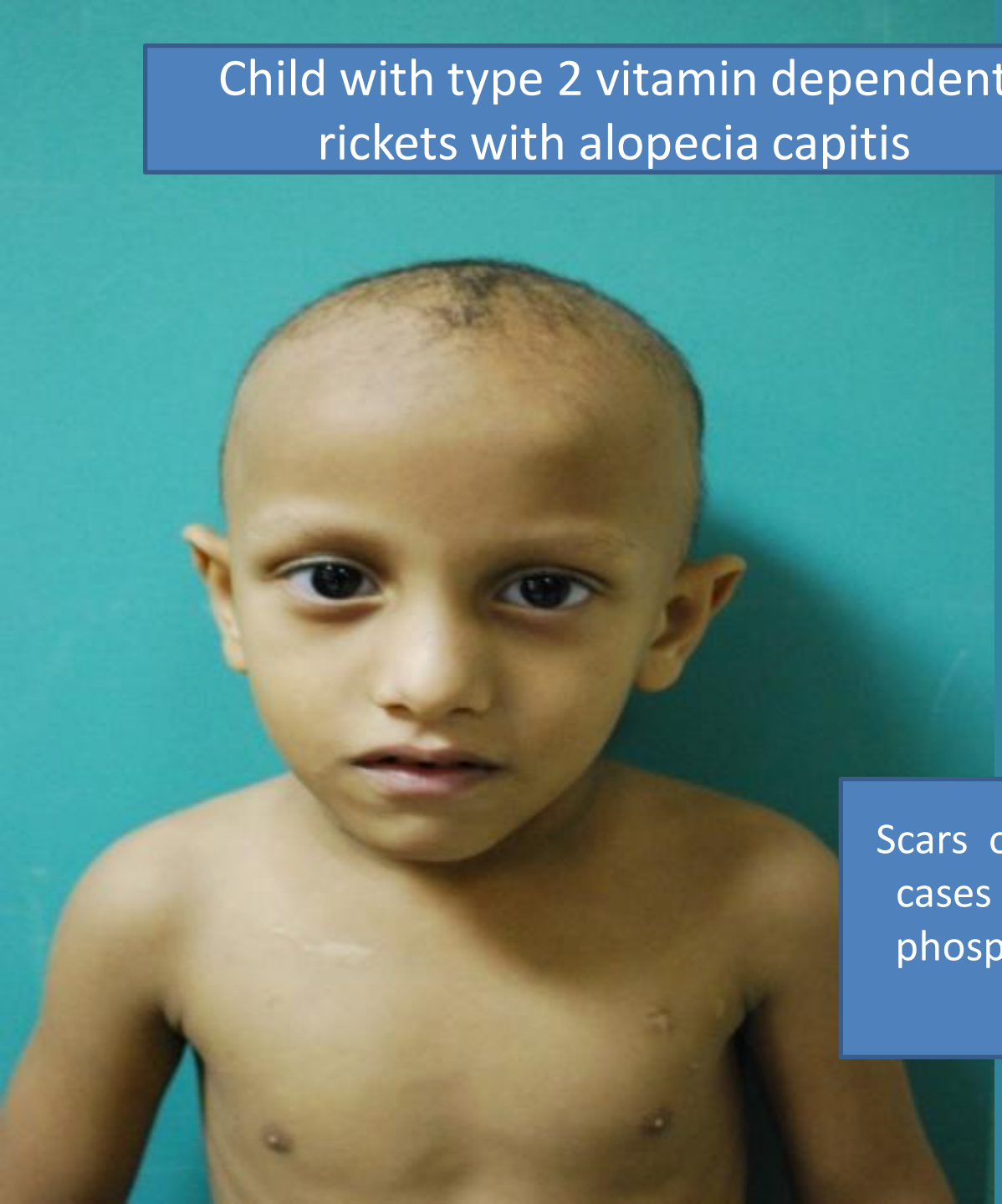
Vitamin D-Resistant Rickets (Type 2 Vitamin D–Dependent Rickets)

- The clinical picture is evident early in life, and consists of rickets with very severe hypocalcaemia, although a variant without alopecia has been reported
- Patients without alopecia appear to respond better to treatment
- Serum levels of 1, 25$(OH)_2$ vitamin D_3 are typically normal or elevated
- It can be lethal in the perinatal period
- Several mutant forms of receptor defect rickets are recognized, with a wide range of severity & response to calcitriol therapy

Vitamin D-Resistant Rickets (Type2 Vitamin D–Dependent Rickets)

- Patients are benefiting from continuous high dose of intravenous calcium and phosphate through central line followed by oral therapy with high doses of calcium & phosphate (with secondary risk of nephrocalcinosis, hypercalciuria, nephrolithiasis, and cardiac arrhythmias)

Child with type 2 vitamin dependent rickets with alopecia capitis



Scars of central line insertion in these cases for large doses of calcium and phosphate as main therapy of these cases

Hypophosphatemic Rickets

- Hypophosphatemic rickets is less common than hypocalcemic rickets
- Pediatrician should be aware of its occurrences
- Characterized by rickets associated with Hypophosphatemia
- Skeletal deformities are present but hypocalcaemia, myopathy, and tetany are absent & serum parathyroid hormone is normal

Hypophosphatemic rickets (without secondarily elevated parathyroid hormone level)

- Nutritional phosphate deficiency
- Prematurity
- Decreased intestinal absorption of phosphate
  - Ingestion of phosphate binders (aluminum hydroxide)
- Renal phosphate wasting
  - RTA (proximal type)
  - Vitamin D resistant rickets
- Tumor induced Osteomalacia (oncogenic osteomalacia)
- Hereditary Hypophosphatemic rickets

Hypophosphatemic Rickets

- Poor dietary intake
- Malabsorption diseases
- Prematurity
- Renal phosphate wasting
- Hereditary hypophosphatemic rickets
- Renal tubular acidosis (type II proximal)
- Oncogenic Hypophosphatemia due to production of PTH-related peptides from solid tumors

McCune-Albright Syndrome

- Patients with this syndrome may have hypophosphatemia secondary to urinary phosphate leak, which may cause osteomalacia
- Fasting phosphate levels should always be monitored in these patients, and phosphate supplements prescribed when indicated.

Hereditary Hypophosphatemic Rickets

- X-linked dominant / Autosomal dominant
- Males affected more than females
- Commonest inherited form of rickets
- Prevalence 1: 25000
- Phosphate wasting by renal tubules leads to:
  - Low serum phosphate
  - Normal calcium
- In-appropriate low or normal 1,25-di hydroxy vitamin D
  - phosphate is the major stimulus for 1α hydroxylase
- Severe rickets and short stature by 1-2 years

Hypophosphatemic Ricket

- Mutations of PHEX (phosphate regulating gene with homologies to endopeptidases on the X chromosome) and DMP1 (dentin matrix protein 1) result in X-linked hypophosphatemic rickets and autosomal recessive hypophosphatemic rickets, respectively.
- Most families of patients with familial hypophosphatemia exhibit an X-linked dominant inheritance.
- FGF-23 (fibroblast growth factor 23) has been implicated in the renal phosphate wasting in tumor-induced Osteomalacia and autosomal dominant hypophosphatemic rickets.
- Because calcium levels remain normal, neither tetany nor secondary hyperparathyroidism are present.

Oncogenic Osteomalacia

- Is a paraneoplastic syndrome with hypophosphatemia secondary to decreased renal phosphate reabsorption, normal or low serum 1, 25-dihydroxyvitamin D concentration and osteomalacia
- Several mesenchymal tumors of bone or connective tissue (e.g. fibroangioma, and giant cell tumors) secrete a phosphaturic substance (parathyroid like protein) that results in rickets.
- The age of onset has been late childhood, adolescence, or young adulthood.

Oncogenic Osteomalacia

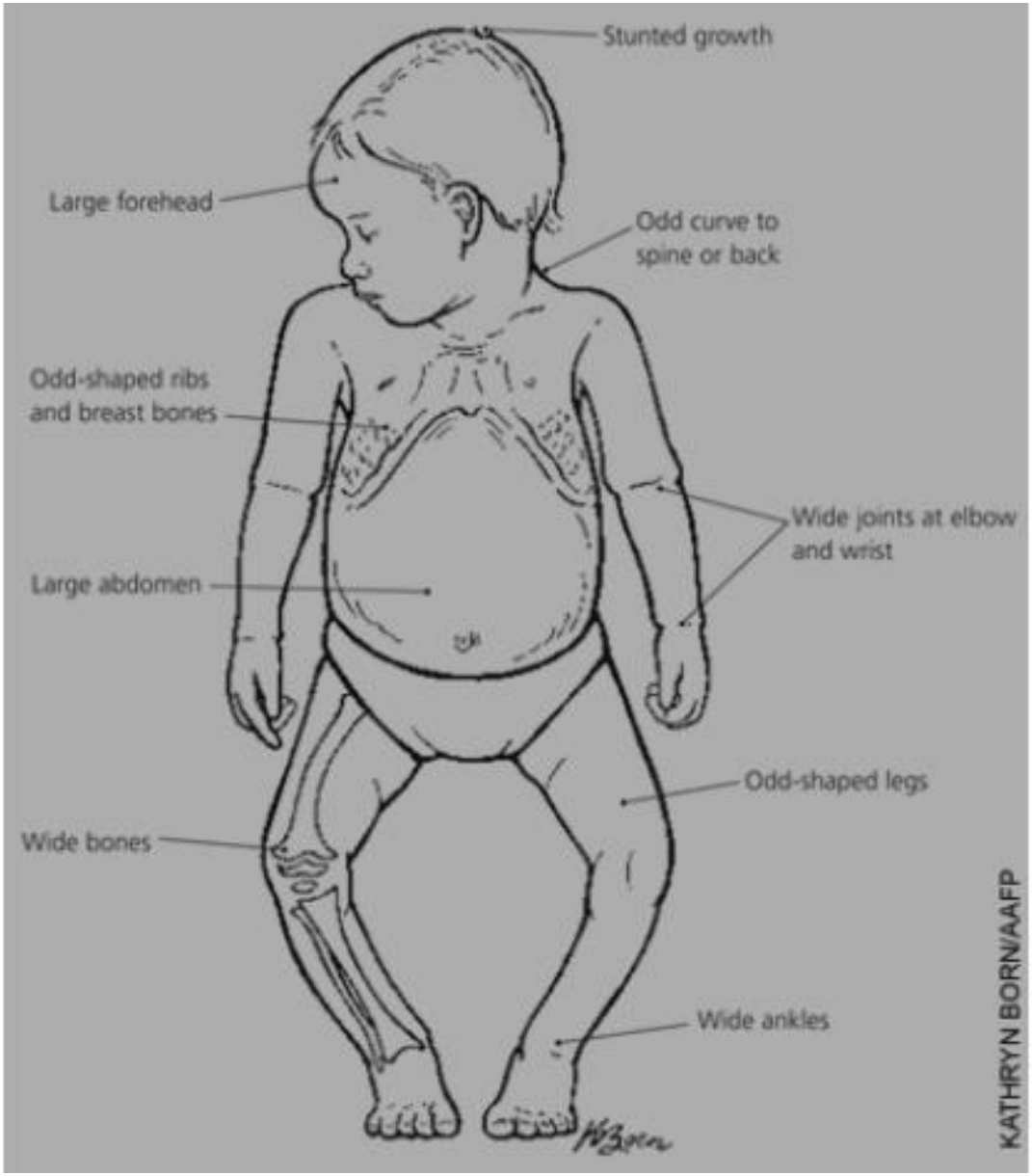
- The clinical characteristics are similar to those associated with familial hypophosphatemia.
- FGF-23 causes renal phosphate wasting in tumor-induced osteomalacia.
- Treatment is surgical removal of the tumor (if it can be located), with excellent results.

Congenital Rickets

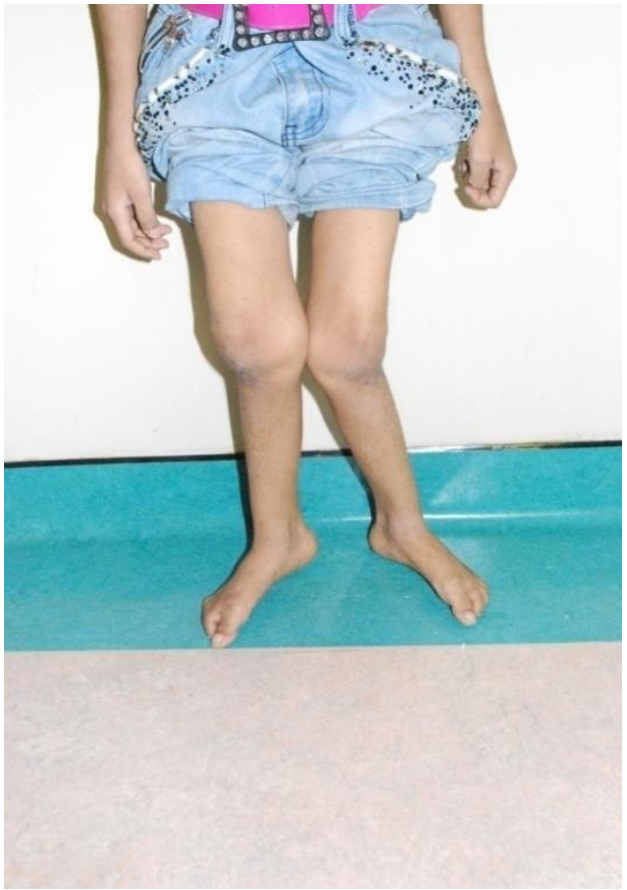
- These newborns may have symptomatic hypocalcaemia, intrauterine growth retardation, and decreased bone ossification, along with classic rachitic changes
- Subtle maternal vitamin D deficiency may have an adverse effect on neonatal bone density and birth weight
- It can also cause a defect in dental enamel, and predispose infants to neonatal hypocalcaemic tetany
- Use of prenatal vitamins containing vitamin D prevents this entity as well prophylactic vitamin D supplementation from birth dose of 500 to 1000 unit/day will prevent this entity

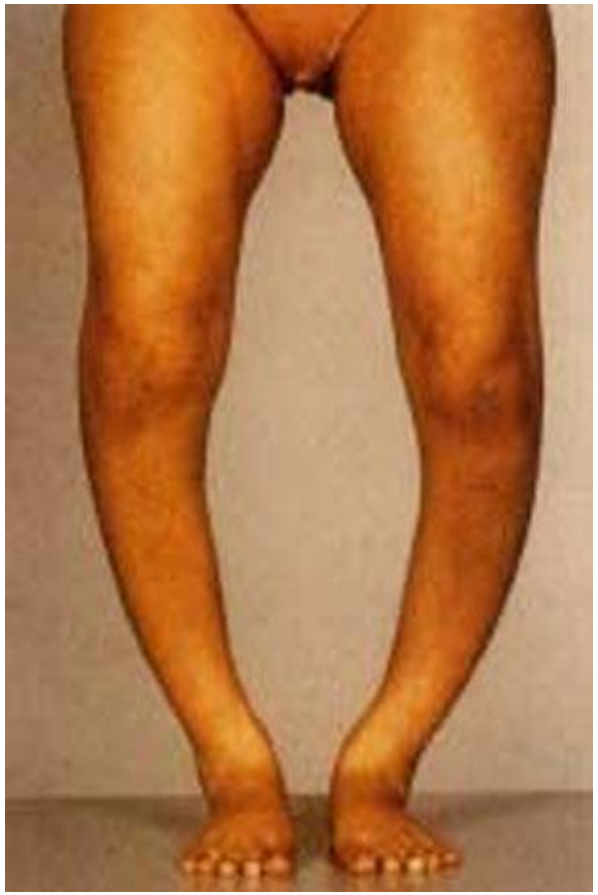
Clinical Features

- In infants, clinical features of hypocalcaemia include
  - seizures, apnea, and tetany.
- In children, clinical features of rickets include
  - delayed motor milestones
  - Hypotonia
  - enlargement of wrists
  - progressive bowing of long bones, rachitic rosary, Harrison sulcus, late closure of anterior fontanel, parietal and frontal bossing, craniotabes
  - delay in teeth eruption, enamel hypoplasia, decreased bone mineral density, myopathy with normal deep tendon reflexes,
  - propensity for infections (as a consequence of impaired phagocytosis and neutrophil motility).


Stunted growth
Large forehead
Odd curve to spine or back
Odd-shaped ribs and breast bones
Wide joints at elbow and wrist
Large abdomen
Odd-shaped legs
Wide bones
Wide ankles
KATHRYN BORN/AAFP

Bowing Vs Knock -knee





Skeletal manifestations

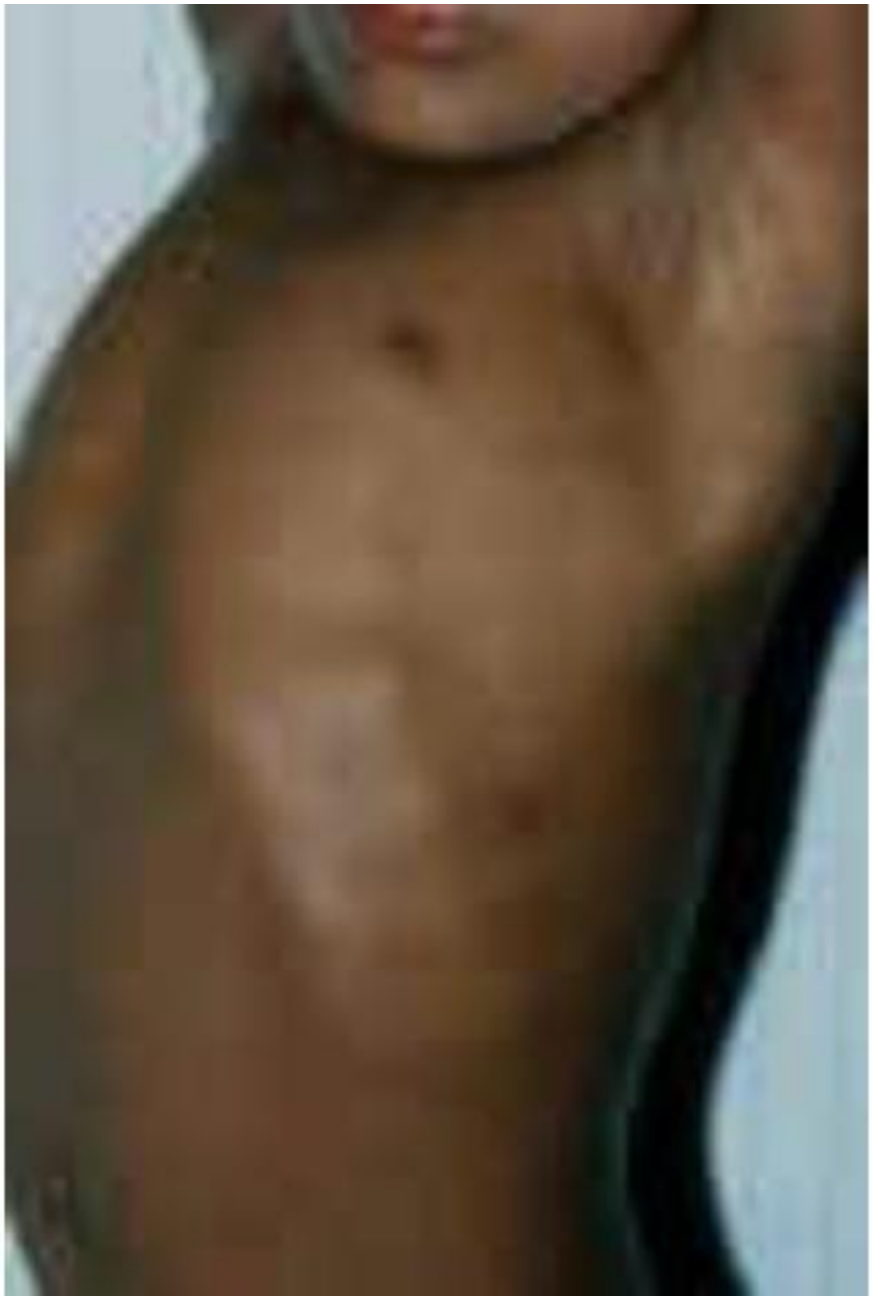
Craniofacial

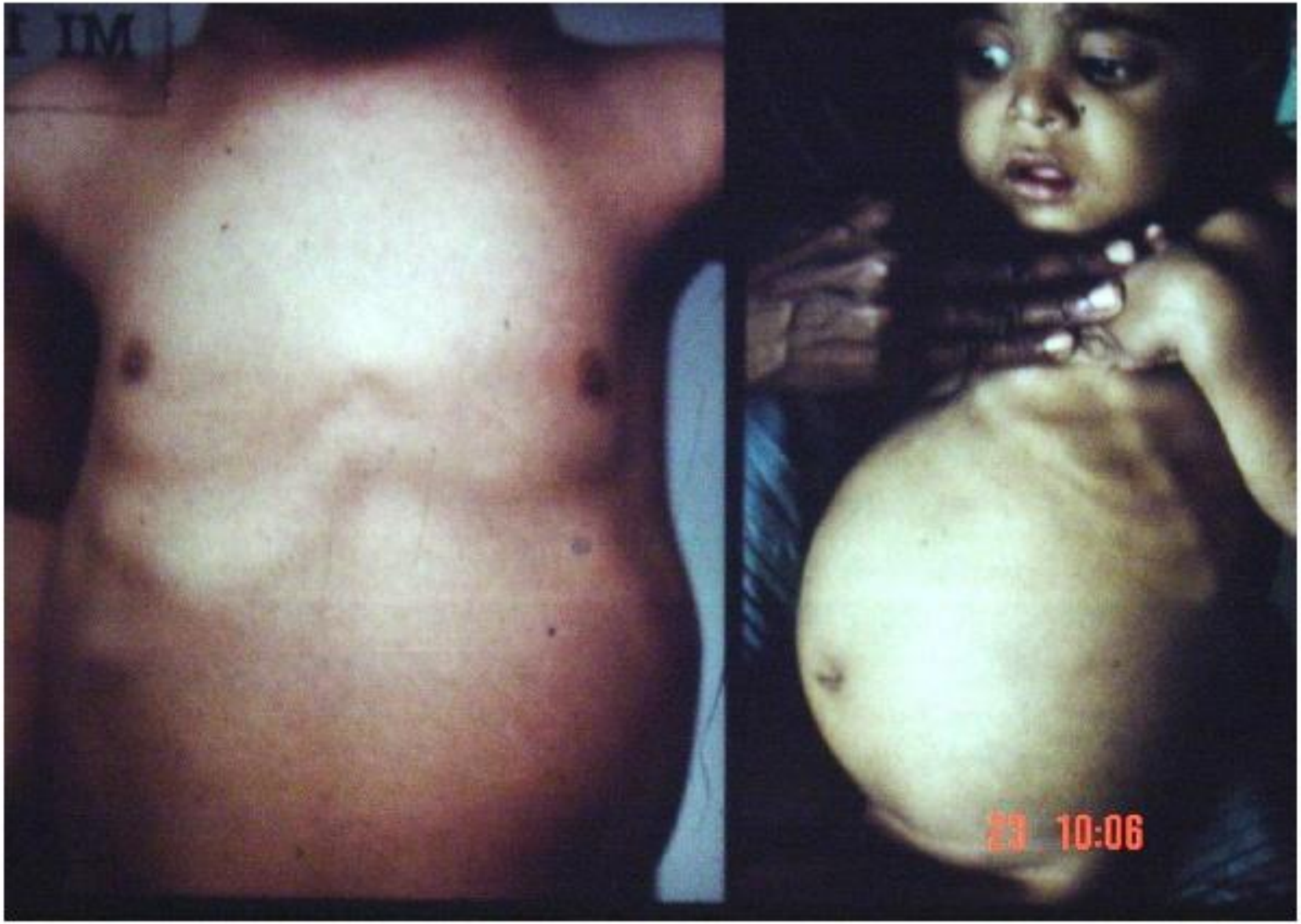
- Craniotabes
- Delayed closure of anterior fontanel
- Frontal and parietal bossing
- Delayed eruption of primary teeth
- Enamel defects and caries teeth

Skeletal manifestations

Extremities

- Enlargement of long bones around wrists and ankles
- Bow legs, knock knees, anterior curving of legs
- Coxa vara and green stick fractures
- Deformities of spine, pelvis and leg – rachitic dwarfism
- Lower extremities deformities are extensively involved in familial hypophosphatemic rickets
- Upper limb more involved than lower limbs in Hypocalcemic rickets

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Biochemical findings of rickets

- Vitamin D deficiency rickets
  - Low- normal serum calcium level
  - Normal – low phosphate level
  - Increased secretion of PTH (secondary hyperparathyroidism) to compensate for low calcium
  - Hyperparathyroidism will increase renal excretion of phosphate, leads to low serum phosphate level
  - Elevated alkaline phosphatase enzyme
  - Reduced urinary calcium level
  - Low level of both 25 hydroxy vitamin D
  - Elevated parathyroid hormone level

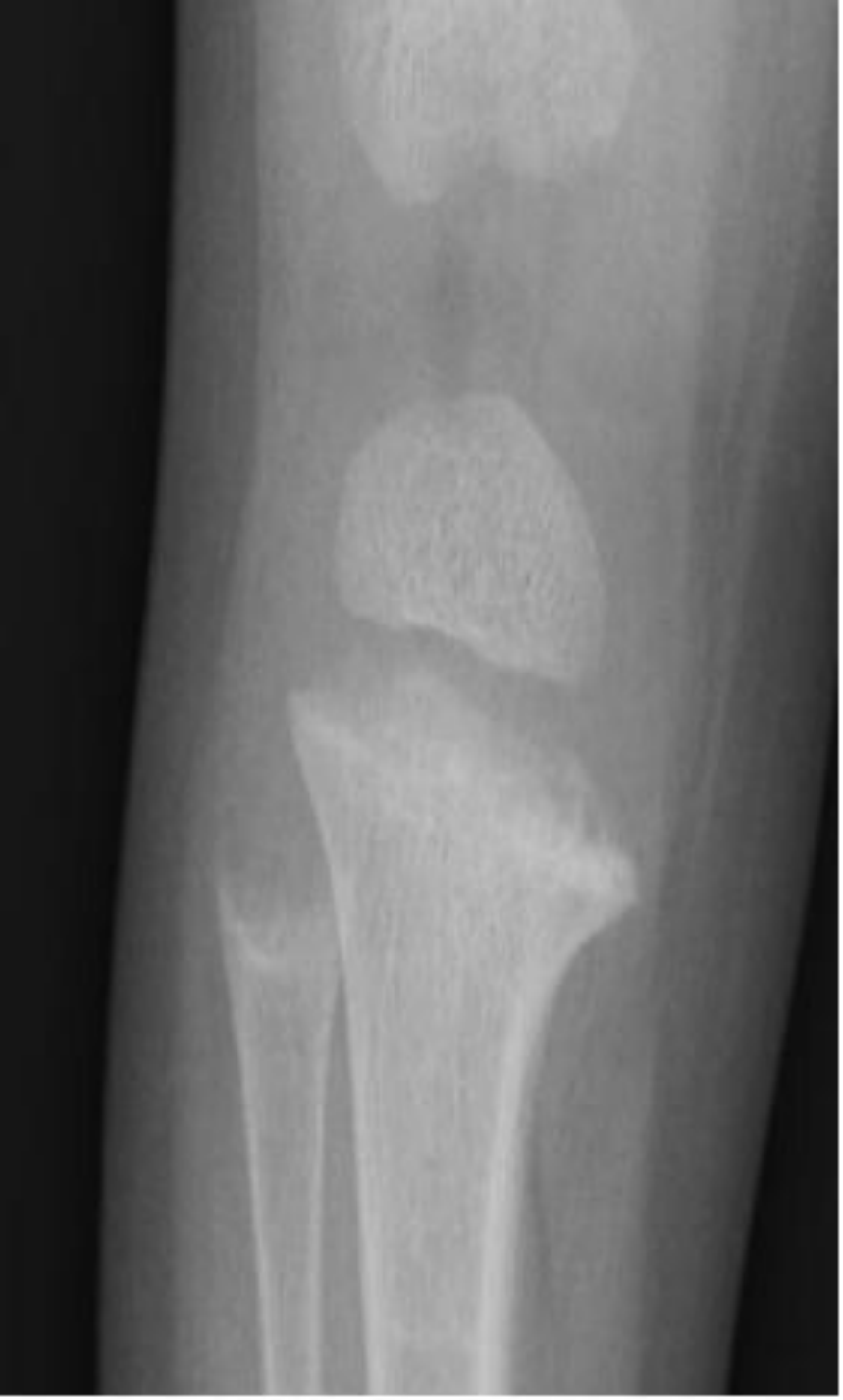
Biochemical findings of rickets

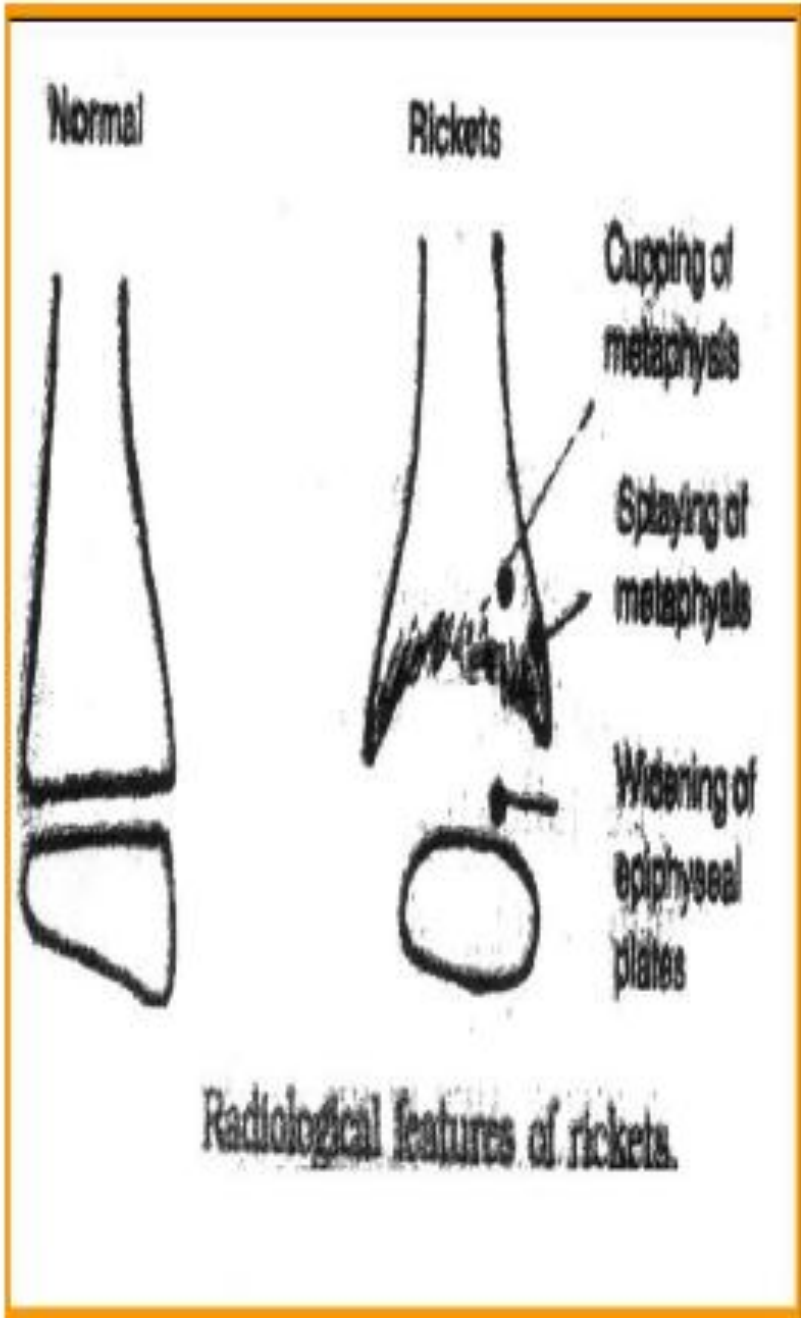
Hypophosphatemic rickets

- Low serum phosphate level
- Normal calcium level
- Normal parathyroid hormone level
- High alkaline phosphatase level
- Low or normal 1,25-di hydroxy vitamin D
  - phosphate is the major stimulus for 1α hydroxylase

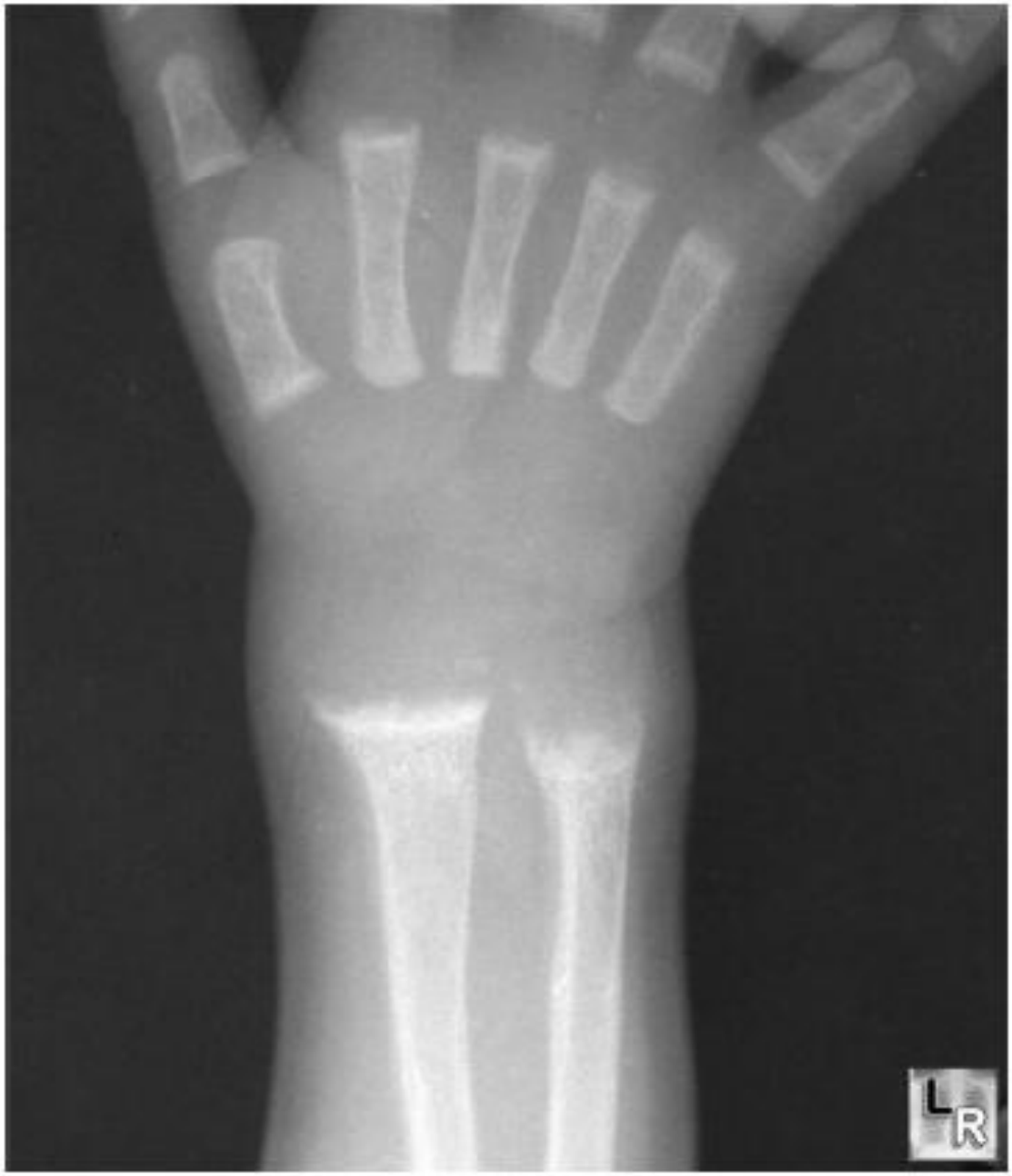
Radiological findings of rickets

- Generalized Osteopenia
- Widening of the unmineralised epiphyseal growth plates
- Fraying of metaphysis of long bones
- Bowing of legs
- Pseudo-fractures (also called loozer zone)
  - Transverse radio lucent band, usually perpendicular to bone surface
- Complete fractures
- Features of long standing secondary hyperparathyroidism (Osteitis fibrosa cystica)
  - Sub-periosteal resorption of phalanges
  - Presence of bony cyst (brown Tumor)





Radiological features of rickets.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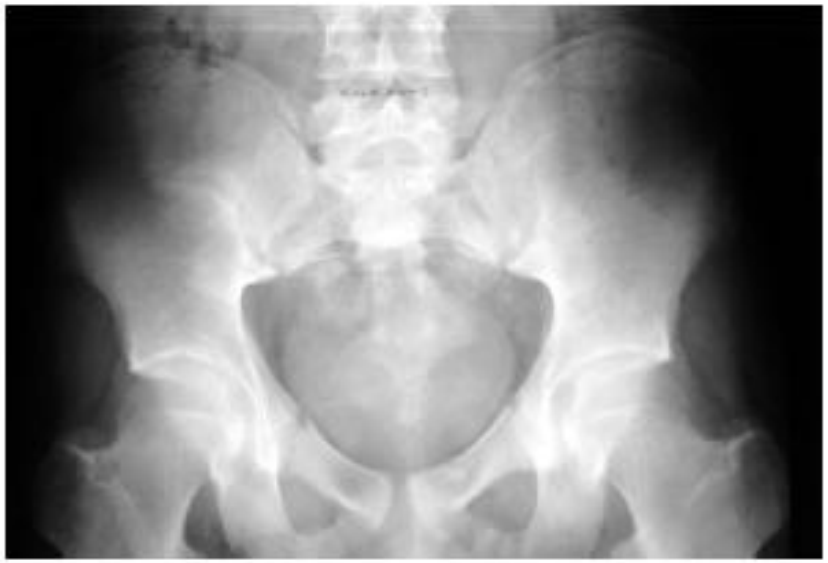

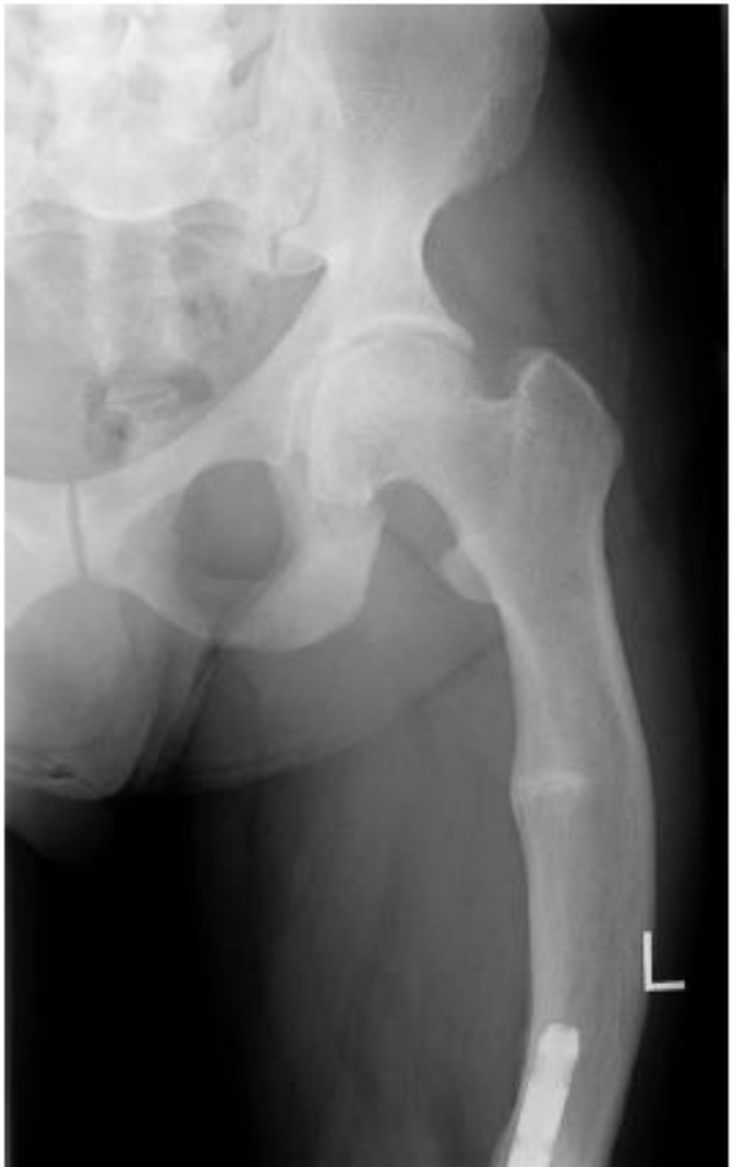
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Prevention

- Pay much attention to the health care of pregnant and lactating women, instruct them to take adequate amount of vitamin D
- Adequate sensible sun exposure is an excellent source of vitamin D and should be recommended to all patients for both the treatment and prevention of vitamin D deficiency
- Usually, exposure of the arms and legs (with sun protection on the face) for about 15 to 30 minutes (depends on degree of skin pigmentation, time of day, season, latitude, dust, and age of patient) between 10 a.m. and 3 pm at least twice a week is sufficient to stimulate cutaneous vitamin D production
- Advocate breast feeding, give supplementary food on time
- Vitamin D supplementation:
  - In premature, twins and weak babies, give Vitamin D 800IU per day
  - For term babies and infants the demand of Vitamin D is 400IU per day
  - For those babies who can't maintain a daily supplementation, inject muscularly Vitamin D3 10000-200000 IU

Therapy

- Administration of vitamin D preparation
  - Vit D2 or vitamin D3 in nutritional rickets
  - 1α hydroxy vitamin D = one alpha in renal rickets, Hypophosphatemic rickets
  - 1, 25 Di hydroxy Vitamin D = Calcitriol in hepatic rickets
- Calcium supplement initially in severe disease
  - To avoid hungry bone hypocalcaemia
- Phosphate supplements in Hypophosphatemic rickets
- Intravenous calcium and phosphate in vitamin D receptor resistance

Therapy of vitamin D dependent rickets type 2

- The use of continuous daily of calcium intravenous infusion / high oral dose of elemental calcium (some reported cases as high as 14 -to-20 gram per day) supplemented with oral phosphate is an effective method of treatment of vitamin D dependent rickets type II.
- The treatment is more effective when is started early in the course of the disease and lead to early healing and better growth with prevention of bone deformities as well early treatment may also lead to improvement in alopecia, the mechanism for which needs to be elucidated.

Treatment of hypophosphatemic rickets

- Optimal therapy consists of oral phosphate in a dose of 40-60 mg/kg/day (1-2 mmol/kg/day) in 5 divided doses plus oral calcitriol (15-25 ng/kg/day).
- Calcitriol (Rocaltrol) prevents increases in parathyroid hormone caused by phosphate therapy.

Hungary bone syndrome

- This is a phenomenon due to vitamin D therapy” which is the worsening of hypocalcaemia after the starting of vitamin D therapy for hypocalcaemia rickets may occur.
- it is important to consider supplementing calcium during the first two weeks of therapy, to prevent the possibility of hypocalcaemia and seizures attributed to hungry bones
- Untreated or neglected rickets can cause permanent bone deformity and lead to stunted growth. Surgical intervention may be necessary to repair severe bony abnormalities




Thanks