Metabolic and Endocrine Bone Disorder

Dr Rakesh Sehrawat
Assistant Professor
Dept. of Orthopaedics
HIMSR and HAHC Hospital
New Delhi

Calcium Metabolism

- Calcium is the fifth most abundant element in the human body, with 1000 g present in adults.
- It plays a key role in skeletal mineralization, as well as a wide range of biologic functions.
- Calcium is an essential element that is only available to the body through dietary sources.

- Calcium requirement is dependent on the state of calcium metabolism, which is regulated by three main mechanisms:
  1. Intestinal absorption,
  2. Renal reabsorption, and
  3. Bone turnover.

- These in turn are regulated by a set of interacting hormones, including parathyroid hormone (PTH), 1,25-dihydroxyvitamin D [1,25(OH)2D], ionized calcium itself, and their corresponding receptors in the gut, kidney, and bone.

Calcium Distribution

- Majority of total body calcium (**99%**) is present in the **skeleton** as **calcium-phosphate complexes**, primarily as **hydroxyapatite**, which is responsible for much of the material properties of bone.

- In bone, calcium serves two main purposes:
  - It provides skeletal strength and,
  - Concurrently, provides a dynamic store to maintain the intra- and extracellular calcium pools.

- **Nonbone calcium** represents 1% of total body calcium (10 g in an adult):
  - It is in constant and rapid exchange within the various calcium pools, and
  - It is responsible for a wide range of essential functions, including extra- and intracellular signaling, nerve impulse transmission, and muscle contraction.

- **Serum calcium** ranges from 8.8 to 10.4 mg/dl (2.2 to 2.6 mM) in healthy subjects.
  - It comprises free ions (51%), protein-bound complexes (40%), and ionic complexes (9%)

- Non-ionized calcium is bound to a variety of proteins and anions in both the extra- and intracellular pools.
  - The main calcium binding proteins include albumin and globulin in serum and calmodulin and other calcium-binding proteins in the cell.

- The major ionic complexes in serum are calcium phosphate, calcium carbonate, and calcium oxalate.

Calcium Balance

- Calcium balance refers to the state of the body stores of calcium at equilibrium over some extended time period (usually days, weeks, or months).

- It results from the net effects of intestinal absorption and renal, intestinal, and sweat gland excretion on bone calcium, the dominant calcium pool.

- Bone balance changes throughout the normal lifespan, depending on relative rates of bone formation and resorption.

1. Children are in positive bone balance (formation > resorption), which ensures healthy skeletal growth.

2. Healthy young adults are in neutral bone balance (formation = resorption) and have achieved peak bone mass.
3. Elderly individuals are typically in negative bone balance (formation < resorption), which leads to age-related bone loss.

- Factors that promote positive bone balance in adults include exercise, anabolic and antiresorptive drugs.

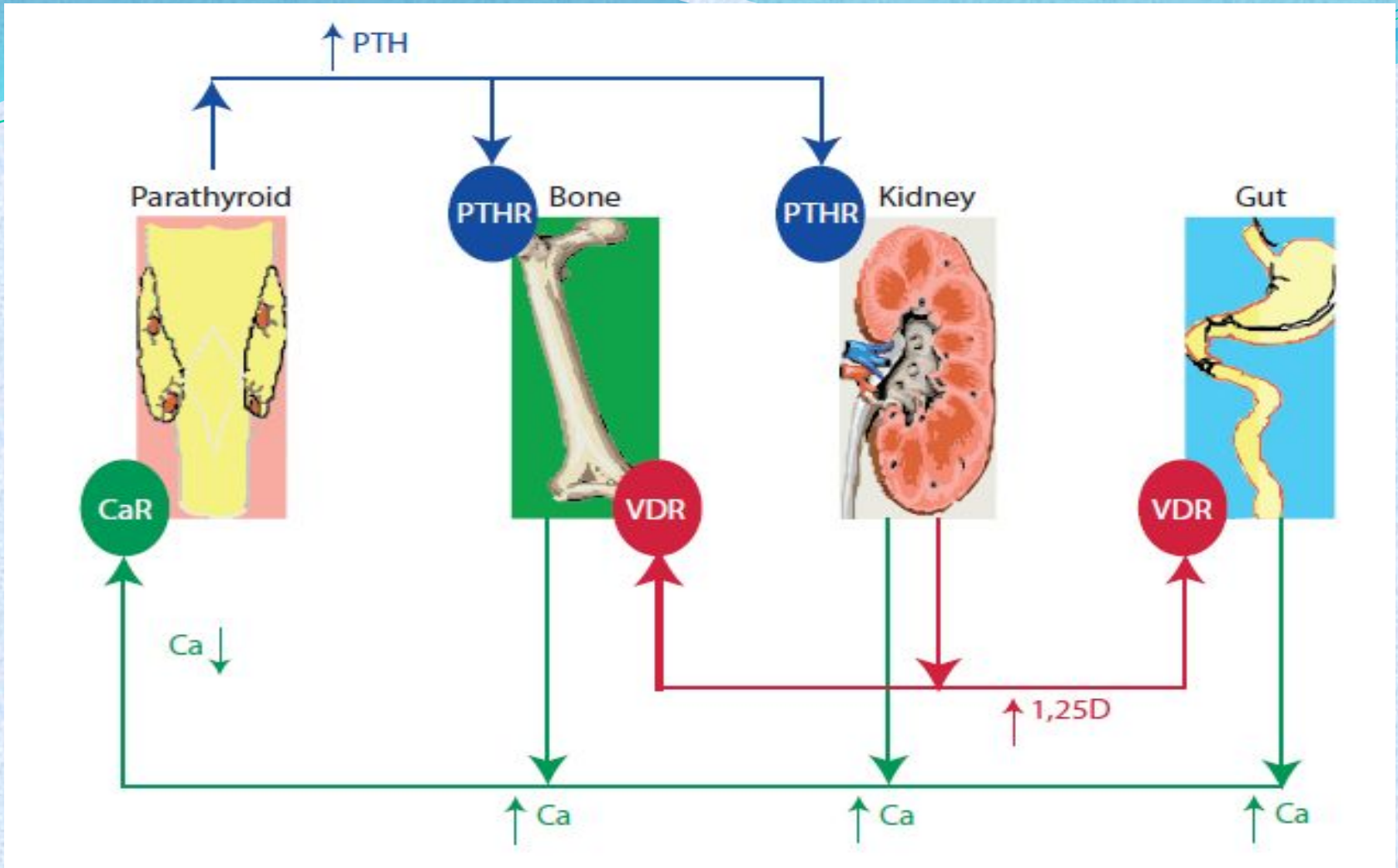
- Conditions that promote bone formation over bone resorption (*e.g.*, "hungry bone" syndrome, osteoblastic prostate cancer) also result in positive bone balance.

- Immobilization, weightlessness, and gonadal steroid deficiency, among others, produce negative bone balance.

Calcium Homeostasis

- Calcium homeostasis is largely regulated through an integrated hormonal system that controls calcium transport in the gut, kidney, and bone. It involves two major calcium-regulating hormones and their receptors—(1) PTH and the PTH receptor (PTHR); (2) 1,25(OH)2D and the vitamin D receptor (VDR), as well as serum ionized calcium and the calcium-sensing receptor (CaR) (Figure 1).

- Serum calcium homeostasis has evolved to simultaneously maintain extracellular ionized calcium levels in the physiologic range while allowing the flow of calcium to and from essential stores.



Regulation of serum calcium homeostasis. Serum calcium homeostasis is regulated by a rapid negative feedback hormonal pathway involving the concentration of ionized calcium in serum (Ca, green arrows) and the secretion of parathyroid hormone (PTH, blue arrows) from the parathyroid. CaR: Calcium Receptor; VDR: Vitamin D Receptor; PTHR: Parathyroid hormone Receptor

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- **A decrease in serum calcium:**

1. Inactivates the CaR in the parathyroid glands to increase PTH secretion, which acts on the PTHR in kidney to increase tubular calcium reabsorption, and in bone to increase net bone resorption.

2. The increased PTH also stimulates the kidney to increase secretion of 1,25(OH)2D, which activates the VDR in gut to increase calcium absorption, in the parathyroid glands to decrease PTH secretion, and in bone to increase resorption.

3. The decrease in serum calcium probably also inactivates the CaR in kidney to increase calcium reabsorption and potentiate the effect of PTH.

This integrated hormonal response restores serum calcium and closes the negative feedback loop.

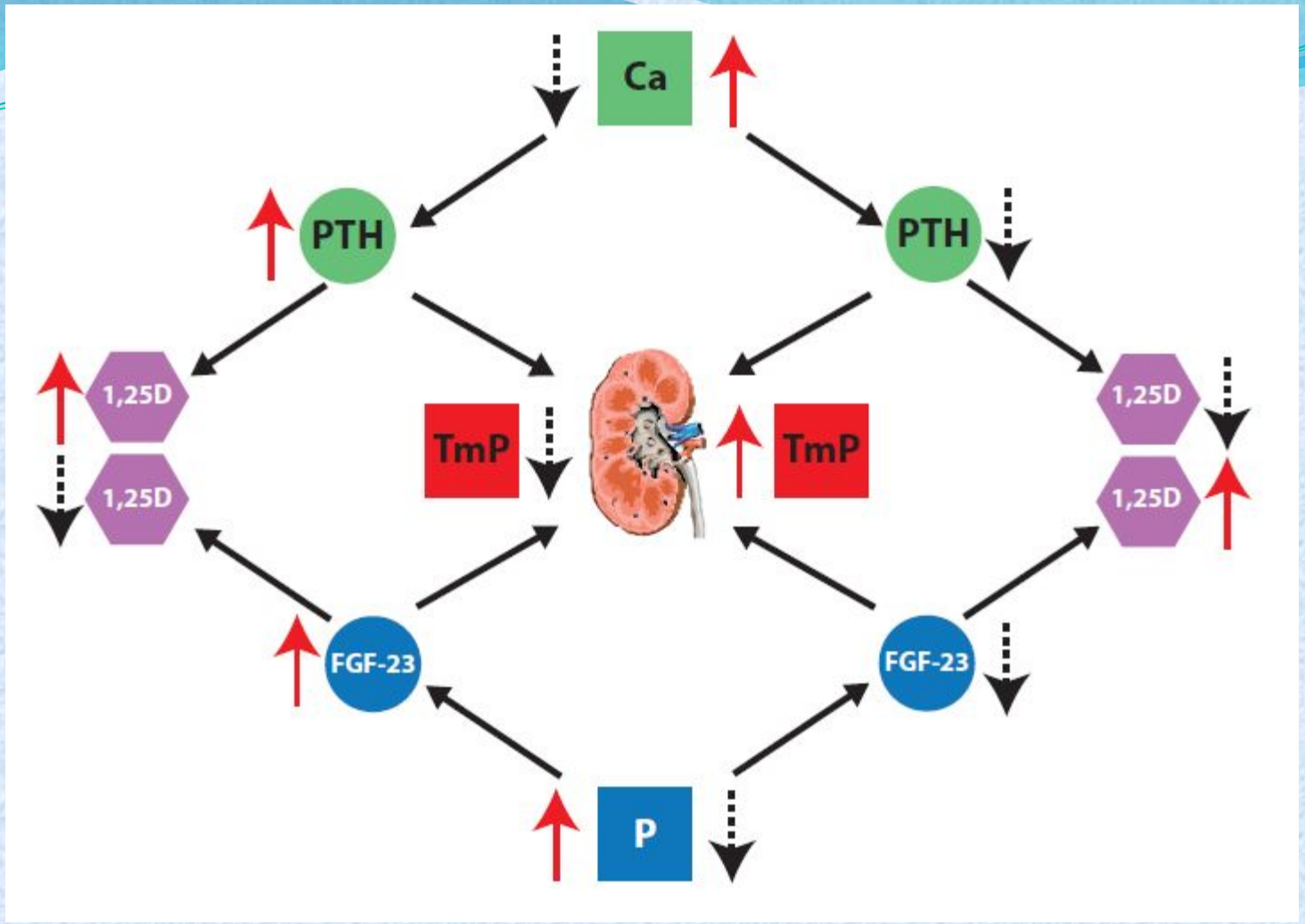
- **Increase in serum calcium:** these actions are reversed, and the integrated hormonal response reduces serum calcium.

- Together, these negative feedback mechanisms help to maintain total serum calcium levels in healthy individuals within a relatively narrow physiologic range of 10%.

Calcium–Phosphate Interactions

- Calcium and phosphate (inorganic phosphorus) interact in several fundamental processes.
- In the skeleton, calcium and phosphate metabolism work in cohort with osteoblasts, osteocytes, and extracellular matrix proteins to mineralize osteoid as it is deposited.
- On the other hand, in non-skeletal tissues, there is a less understood regulatory system that prevents the harmful deposition of calcium-phosphate complexes in soft tissue.

- The hormonal system regulating phosphate homeostasis involves two main hormones:
  1. Fibroblast growth factor 23 (FGF-23) and FGF/Klotho receptor complex , and
  2. PTH and PTH receptor.



Regulation of serum phosphate (P) homeostasis: interface with serum calcium (Ca) homeostasis at the kidney. Serum phosphate homeostasis is regulated by a negative feedback hormonal pathway (black arrows) involving the concentration of phosphate in serum (P, blue square) and the secretion of fibroblast growth factor 23 (FGF-23; blue circles) from bone cells.

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- **A fall in serum P:** decreases secretion of FGF-23 , which restores serum P by acting on the type 2 sodium-phosphate renal tubular transporters (NaPi-II) to increase phosphate reabsorption (TmP; red squares) and by increasing secretion of renal 1,25-dihydroxyvitamin D (1,25D; purple hexagons) to increase phosphate gut absorption.

- **A rise in serum P:** increases FGF-23 secretion, which restores serum P by lowering phosphate reabsorption (TmP; red squares) and by lowering secretion of renal 1,25-dihydroxyvitamin D (1,25D; purple hexagons) to decrease phosphate gut absorption.

- Changes in the Ca–PTH homeostatic system also have major effects on serum P, but not through a negative feedback pathway, because serum P does not directly regulate PTH secretion.

- Ca-induced changes in PTH secretion (green circles) induce changes in serum P by regulating tubular phosphate reabsorption (TmP; red squares) through the activity of the NaPi-ll renal tubular transporters.

- Although both FGF-23 and PTH have the same action on renal tubular reabsorption (TmP; red squares), these hormones have opposing effects on renal 1,25-dihydroxyvitamin D (1,25D; purple hexagons) secretion.

- The P-FGF23 homeostatic system is more slowly acting than the Ca-PTH homeostatic system; and the receptor for serum P remains to be discovered.

RICKETS

- Metabolic **disorder of growing bone** (immature skeleton)
- End result: **defective mineralization of bone**(osteoid).
- **Osteoid formation is normal**
- **Caused by**
  - **Deficiency** of : calcium or phosphate or vitamin D
  - **Vitamin D resistant rickets**
  - **Vitamin D–dependent type I** (inability to hydroxylate)
  - **Vitamin D–dependent type II** (receptor insensitivity)
  - **Renal osteodystrophy**

Calcium deficiency rickets

- **Caused by**:
  - **Deficiency of vitamin D** (mc)
    - Dietary
    - Lack of sunlight exposure
    - Congenital
  - **Malabsorption of vitamin D**
  - **Isolated calcium deficiency**
  - Liver disease
  - Anticonvulsant therapy: **phenytoin**
  - Renal osteodystrophy
  - Vitamin D dependent rickets Type I

Phosphate deficiency rickets

- **Caused by:**
  - **Primary hypophosphatemia**
  - **Fanconi syndrome's:**
    - Cystinosis
    - Tyrosinosis
    - Lowes syndrome
  - Proximal renal tubular acidosis
  - Dietary deficiency
  - Malabsorption of phosphate

Vitamin D resistant rickets

- Caused by:

1. Proximal renal tubular lesions
2. Distal renal tubular acidosis
3. Combined proximal and distal renal tubular lesions

Proximal renal tubular lesions

- Caused by group of disorders known as **Fanconi's syndrome**
- **Reduced reabsorption of phosphate** from glomerular filtrate in PCT: Cause **hypophosphatemic rickets.**

Distal renal tubular acidosis

- **Excessive excretion of calcium** □ hypocalcemia
- **Secondary hyperparathyroidism** causes bone lesion
- **Acidosis** itself can mobilize calcium from bone.

End organ resistant rickets

- End organs are resistant to active form of vitamin D i.e. 1,25(OH)2 D3.
- Also known as **vitamin D dependent rickets type II**.
- **Sex linked dominant**

Renal osteodystrophy

- Skeletal changes produced as a result of chronic glomerular renal disease
- Reduced renal mass

↓

Impaired conversion of 25(OH) vit D to 1, 25 (OH) vit D

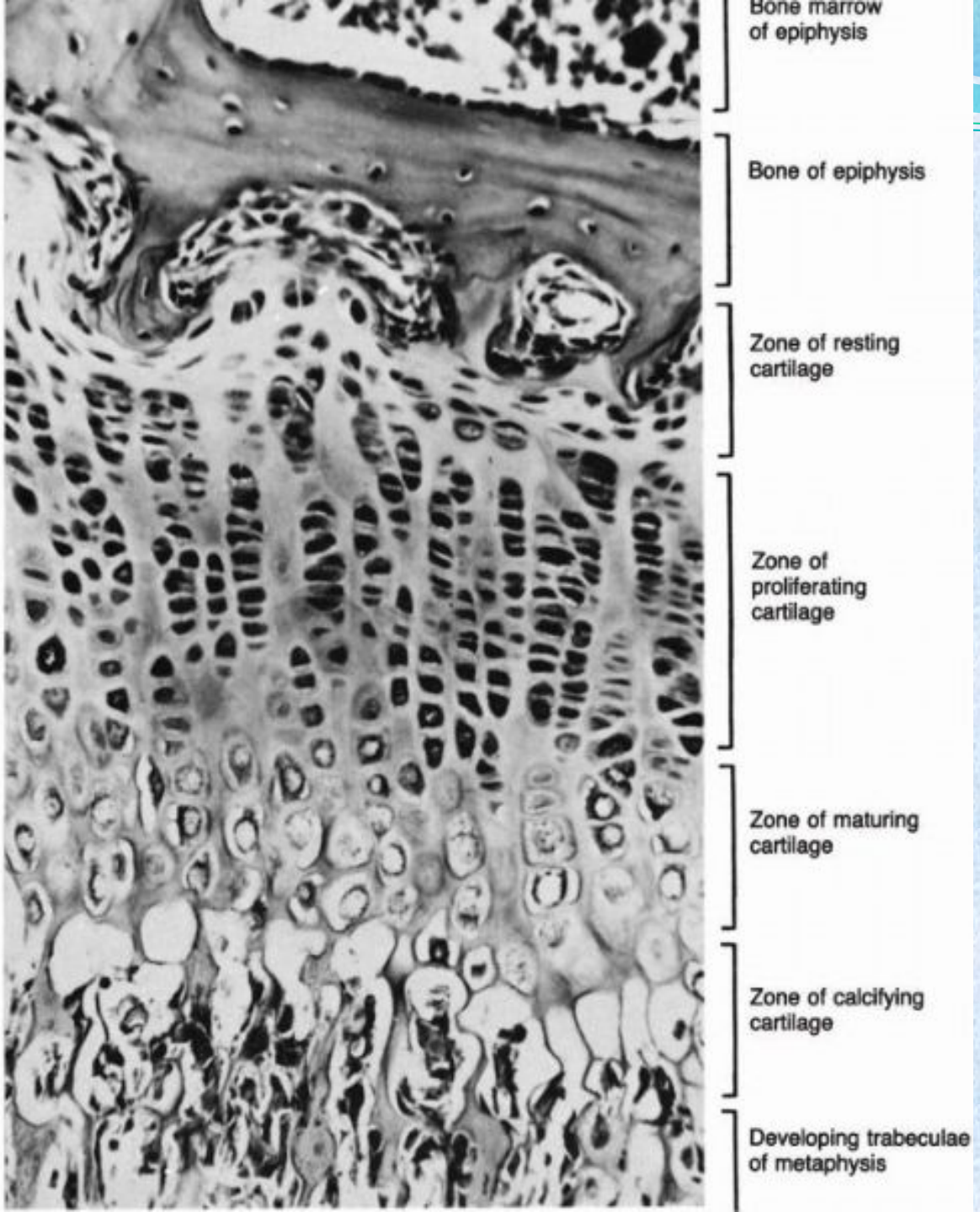
↓

Decreased absorption of calcium → Hypocalcemia

- **Decreased glomerular filtration of phosphate** → increased serum phosphate

- Uremic patient is acidotic and hypoalbuminemic **ionized calcium is high.**
- **Skeletal changes:**
  - Rickets/ osteomalacia
  - Osteitis fibrosa cystica
  - Osteoporosis
  - Osteosclerosis
  - Metastatic calcification

	Biochemical Abnormality					
Type of Rickets	Calcium	Phosphate	ALP	PTH	25 (OH) Vitamin D	1,25 $(OH)_2$ Vitamin D
Calcium deficiency	**N/**↓	↓	↑	↑	↑	↑
Phosphate deficiency	**N**	↓	↑	**N**	**N**	**N**
Vitamin D deficiency	↓	↓	↑	↑	↓	↓
Vitamin D resistant (Fanconi's syn)	**N**	↓	↑	**N**	**N**	**N**
Vitamin D dependent type I (inability to hydroxylate)	↓	↓	↑	↑	↑↑	↓↓
Vitamin D dependent type II (receptor insensitivity)	↓	↓	↑	↑	**N/**↑↑	↑↑↑↑
Renal osteodystrophy	↓	↑	↑	↑↑	**N**	↓↓



Normal Growth Plate

Pathophysiology of rickets

- Changes of growth plate in rickets:

1. **Thickening of growth plate**: defective mineralization of zone of provisional calcification, **cartilage cells continue to proliferate but do not die.**
2. **Widening of growth plate**: proliferating cells in growth plate extends beyond normal width of bone. Present as **palpable enlargement at wrist, ankle, knee, elbow, costochondral junction**.

3. **Cupping or flaring of metaphysis**: there is softening of metaphysis, axial pressure pushes the epiphysis into metaphysis(Piston theory).
4. **Fraying of metaphysis**: irregular calcification causes **loss of sharpness of edges of metaphysis.**
5. **Widening of epiphysis**

- **Softening and deformity of diaphysis**: bowing of long bones.

Clinical features of rickets

- Usually manifested by 6 months, unusual below 3 months
- Regional manifestations:

1. **Skull:**
   a) **Craniotabes (softening of skull bones**): **earliest manifestation**; pressure over skull gives ping pong ball like feeling.
   b) **Frontal bossing**: prominent frontal bones
   c) **Parietal bossing**
   d) **Widened sutures**
   e) **Delayed closure of anterior fontanelle**
   f) **Hot cross bun skull or caput quadratum**: widened sutures and thickening of bone around sutures create a cruciate pattern.

2. **Chest**

a) **Rachitic rosary**: prominent **costochondral junction**

b) **Pectus carinatum(pigeon chest)**

c) **Harrison's groove.**

3. **Spine**

a) Thoracic kyphosis: **Rachitic cat back**

b) Accentuation of lumbar lordosis

c) Scoliosis(uncommon)

4. **Teeth**

a) Delayed eruption

b) Enamel hypoplasia and dental caries

5. **Limbs and joints**

a) **Bone pain and tenderness**: mc manifestation

b) **Widening of wrist, elbow, knee, ankle**

c) **String of pearls deformity**: sausage like enlargement of ends of phalanges and metacarpals.

d) **Bowing of long bones**: genu valgum or varus or windswept deformity

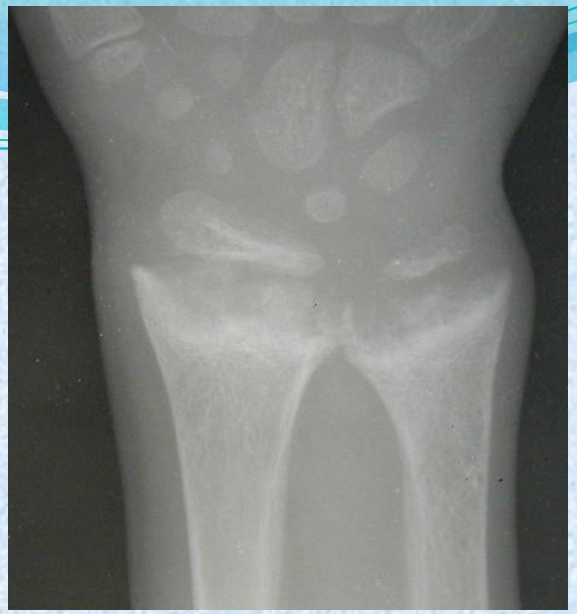
e) **Coxa vara**

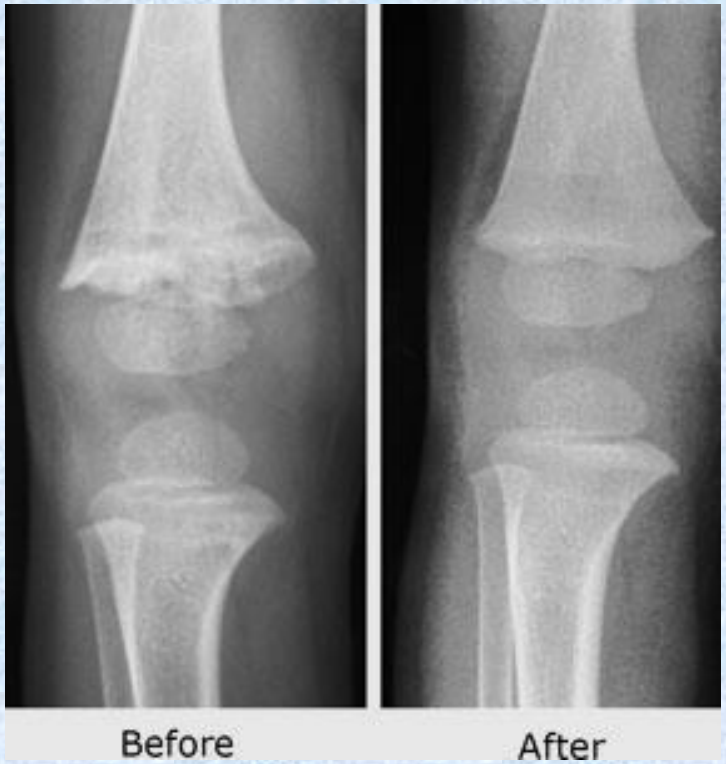
f) **Double malleoli sign**

- **Systemic manifestations:**
  - Abdomen: **rachitic pot belly** due to hypotonia of abdominal muscles
  - **Growth retardation**
  - Apathy, listlessness, irritability
  - Hypotonia and muscle weakness
  - Ligament laxity
  - Tetany, laryngeal stridor and convulsions: **severe hypocalcemia**
  - **Bilateral lamellar cataract**: deficiency of vit D in **early infancy**.

Radiological changes

- **Earliest changes** seen around **wrist**
- Cupping and flaring of metaphysis
- Widening of physis
- Generalized osteopenia
- Cortical thinning
- Coarse and fuzzy trabeculae
- **White line of calcification**: seen after vitamin D administration, **first radiological sign of healing.**





Treatment

- **Nutritional rickets**
  - Daily: 10,000 IU Vit D orally; or

    Weekly: 60,000 IU Vit D orally; or

    Monthly: 6 lac IU Vit D oral or im single dose; with
  - Daily Calcium 500 mg BD
  - For 3 months
  - **Earliest changes on x-ray seen after 3-4 weeks**
  - **Strauss regimen**: monthly high doses of vitamin D for 3 months.

OSTEOMALACIA

- Affects **mature skeleton**
- Mc due to **deficiency of vitamin D**
- **Failure to replace the turnover of calcium and phosphate in the organic matrix of bone**
- Bone is demineralized and replaced by soft osteoid tissue

Causes of osteomalacia

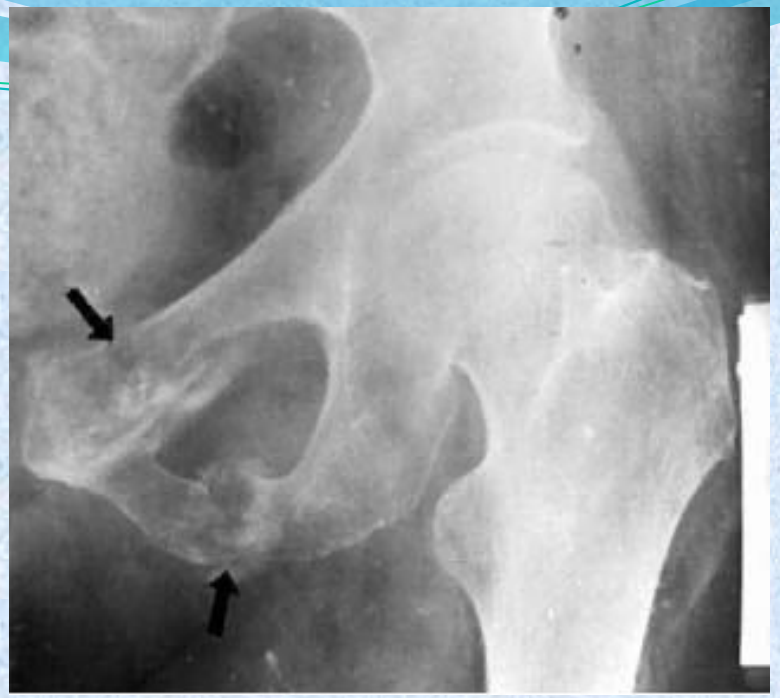
- **Lack of exposure to sunlight**
- **Dietary deficiency of vitamin D**
- Malabsorption syndrome
- Derangement of vitamin D and phosphorus metabolism (hereditary or acquired)
- Partial gastrectomy
- Under nutrition during pregnancy
- Renal osteodystrophy
- Drugs: **phenytoin, steroids**

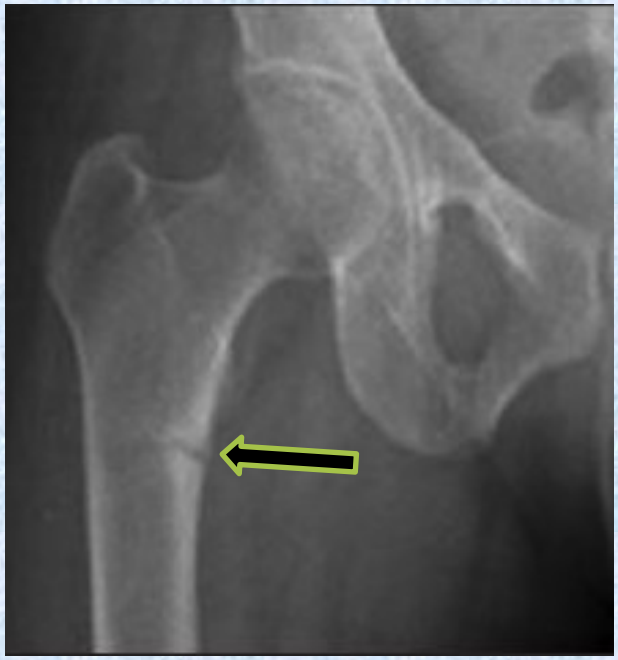
Clinical features

- Diffuse bone pain,
- **Bone tenderness**
- **Muscular weakness**: difficulty in climbing stairs.
- **Tetany**: carpopedal spasm, facial twitching
- **Spontaneous fractures: mc in spine**, cause kyphosis

Radiological features

- Diffuse rarefaction of bones
- **Looser's zone** or **pseudo fractures**: radiolucent zones at sites of stress
- **Tri-radiate pelvis** in females: **champagne glass pelvis**.
- **Protrusio- acetabuli**: acetabulum protruding medially into pelvis





Serum biochemistry

- Serum calcium: mildly decreased or normal
- Serum phosphate: low
- Alkaline phosphatase: raised
- Parathormone level: increased

Milkman's fracture or pseudofracture

- Aka **looser's zone** or **osteoid seams**
- Areas of **demineralized bone** seen at the **sites of mechanical stress (incomplete stress fractures)** or at the **sites of nutrient vessel pulsation**

X-ray:

- **Narrow radiolucent band(2-3mm), perpendicular to cortex**
- Usually **bilateral and symmetrical**
- **Later stages: sclerosis** develops around these lesions, making them more prominent.

Conditions in which milkman fracture are seen:

- Rickets/ osteomalacia
- Renal osteodystrophy
- Paget's disease
- Fibrous dysplasia
- Hereditary hyperphosphatasia

Common locations:

- Medial femoral neck and shaft
- Scapula
- Pubic and ischial rami
- Lesser trochanter
- Ribs and clavicle

Tumor related rickets/ osteomalacia

- Tumors secrete **phosphotomins like fibroblast growth factor 23**, that **disrupt renal tubular reabsorption of phosphate**, result in phosphaturia, which leads to **hypophosphatemia**
- Neurofibromatosis
- Fibrous dysplasia
- Osteoblastoma
- Hemangiopericytoma of bone
- Skin tumors

SCURVY

- **Deficiency of vitamin C**
- Function of vit C and Pathophysiology of scurvy

1. **Collagen synthesis**
   - Vitamin C is required for **hydroxylation of proline and lysine** residues in collagen formation
   - Vitamin C deficiency leads to **deficient collagen synthesis**

   a) **Deranged capillary function tendency to bleed**: subperiosteal bleed, gingival bleed, purpura, ecchymosis, petechiae, perifollicular hemorrhages.

b) **Osteoblast cannot form osteoid defective endochondral ossification**, epiphyseal separation, bones are brittle.

c) Defective dentition

d) Poor wound healing

3. **Neurotransmitter metabolism**

- Vitamin C is required in **conversion of:**

1. **Dopamine to Norepinephrine**
2. **Tryptophan to Serotonin**

- Vit C deficiency leads to irritability and other psychological manifestations

3. **Utilization of folic acid and iron: Anaemia**

4. Reducing agent

- **In scurvy osteoid formation is deficient** while in **rickets, osteoid formation is normal but mineralization of osteoid is defective.**

Clinical manifestation of scurvy

- Usual age of manifestation: **6 to 18 months**

1) **General symptoms**: low grade fever, irritability, tachypnea, digestive disturbances, loss of apetite
2) **Bleeding**: subperiosteal, gingival and conjunctival, purpura and ecchymosis, petechiae, perifollicular hemorrhage, epistaxis.
3) **Defective dentition**: bluish purple spongy swelling of mucous membrane over upper incisors
4) **Generalized tenderness and pseudoparalysis**: generalized pain results in pseudoparalysis with hip and knee in semiflexed position and feet rotated externally.

5) **Scorbutic rosary**: due to **epiphyseal separation**, costochondral junction is disrupted and sternum is displaced backwards with attached costal cartilages. The **ends of ribs become prominent.**

6) **Anaemia**

7) **Bones are brittle and fracture easily**

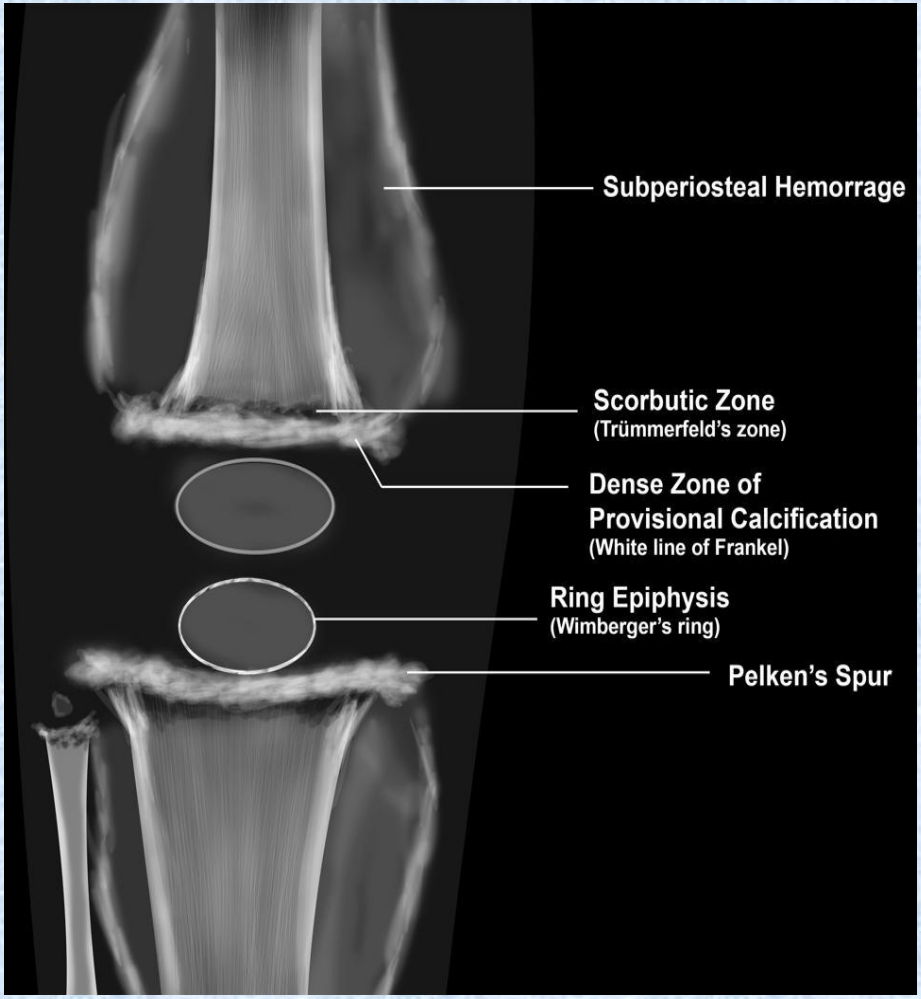
8) **Bone marrow depletion**

9) **Muscle weakness and degeneration of skeletal muscles**.

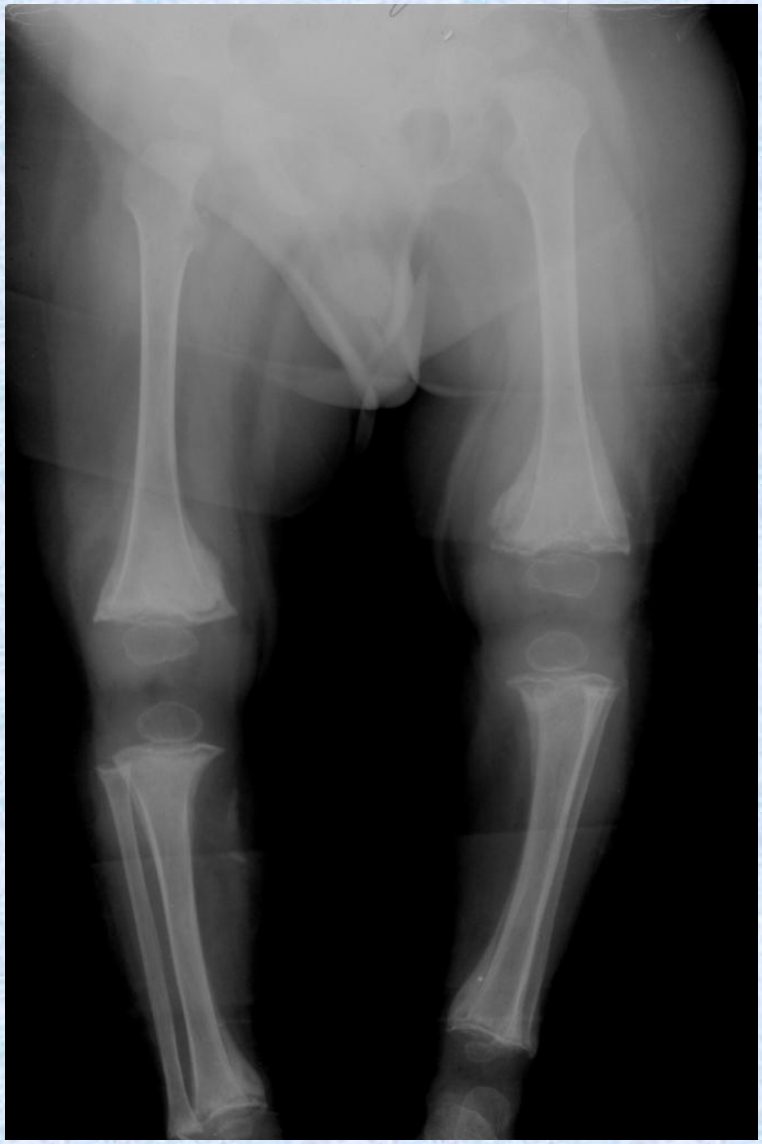
Radiological features

- Occur at **end of long bone** particularly around **knee**.

1. **Ground glass appearance of bone**
2. **Pencil thin cortex**
3. **White line of Frankel**: well calcified cartilage in metaphysis
4. **Wimberger sign or ring sign:** white ring surrounding the epiphyseal centres of ossification.



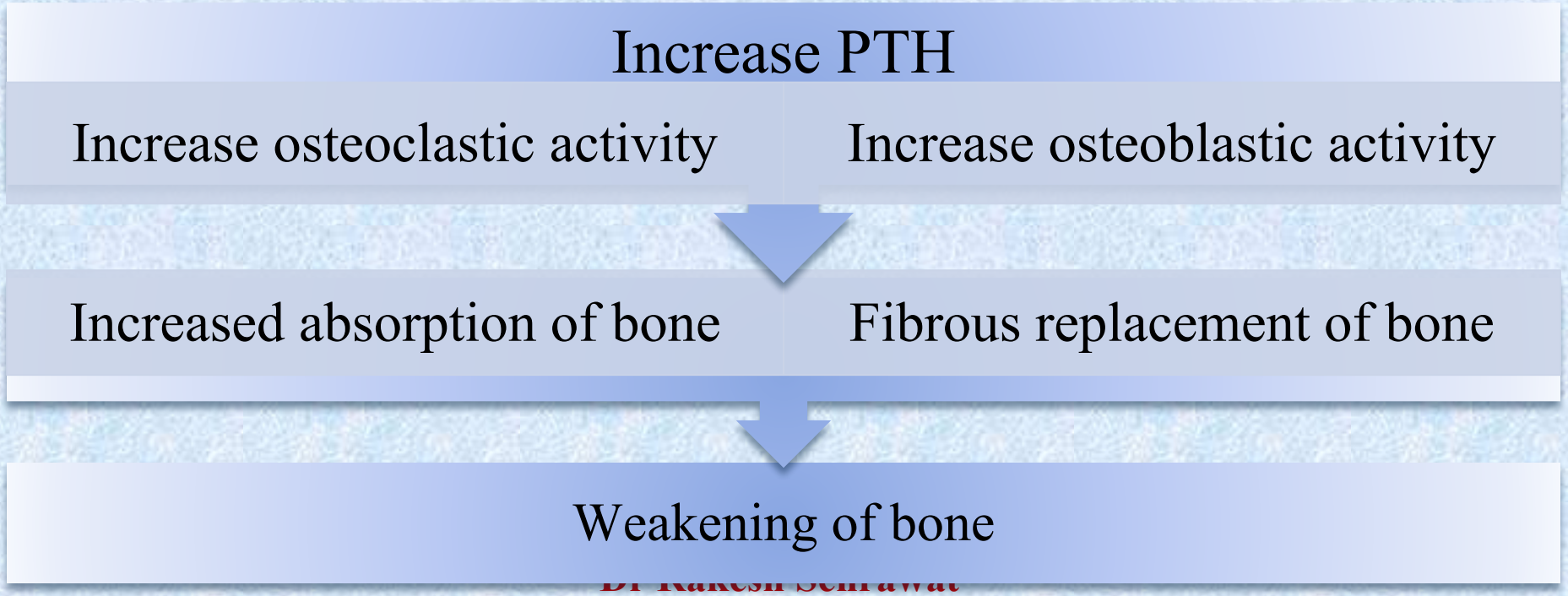
5. **Zone of rarefaction proximal to white line**: epiphyseal separation may occur along this line.
6. Lateral part of this rarefaction is seen as triangular defect.
7. **Palkan spur or lateral spur**: lateral prolongation of white line
8. **Healing phase**: subperiosteal haemorrhages becomes calcified and bone assumes a dumbbell or club shape.



- **White line of frankel** is seen in:
  - Scurvy
  - Healing rickets
  - Plumbism
  - Severe protein energy malnutrition
  - Acute leukaemia
  - Congenital syphilis

Primary hyperparathyroidism (osteitis fibrosa cystica)

- Increased parathormone secretion due to **primary pathology in parathyroid gland.**
- **Primary adenomas are mc cause**



- PTH causes **increased calcium absorption and increased phosphate excretion from kidneys**:
  - Increased serum calcium
  - Decrease serum phosphate
  - Increase ALP
  - Urine : decreased calcium and increased phosphate excretion
- It is more common in **females**
- Most common in **3rd to 5th decade**

Clinical features

- **Bone pains**: mc initial feature
- **Bone tenderness**: mc lower limbs and spine
- General weakness, pallor, hypotonia, anorexia, nausea, vomiting, abdominal cramps.
- **Pathological fractures**: mc at dorsolumbar spine, neck of femur and pubic rami
- Renal colic with hematuria bcz of renal calculi.

Radiological features

- Irregular, diffuse rarefaction of bones
- **Salt pepper appearance: skull bones.**
- **Loss of lamina dura**: lamina dura is thin cortical bone surrounding the teeth and makes up tooth socket.
- **Sub-periosteal resorption of phalanges**.
- **Resorption at lateral end of clavicle**
- Spine: **central collapse of vertebral body and biconvex disc appearance**

- Pelvis and other bones: **coarse striations with multiple cysts**
- **Brown's tumor**: expansile lytic bone lesion.
  - collection of osteoclasts
  - Mc affects maxilla or mandible
- **Extraosseous radiological features: renal calculi**

Pagets disease (osteitis deformans)

- **Increased bone turnover and enlargement and thickening of bone**
- **Internal architecture is abnormal and bones are brittle**
- Primary defect is **increased osteoclastic activity**
- **Secondary increase in osteoblastic activity**
- **Normal serum calcium and phosphate**
- **Increased serum alkaline phosphatase.**
- **Increased 24 hr urinary hydroxyproline and N-telopeptide.**

Clinical features

- More common in **males** and usually presents **after 40 yrs**
- **Pelvis** and **tibia** are commonest sites.
- **Most patients are asymptomatic**,
- Presenting features:
  - **Pain**: dull constant ache
  - **Deformities**: bowing of legs, platybasia (flattening of skull base)
  - **Complications** of the disease

complications

- **Fracture**: in weight bearing bones
- **Cranial nerve compression**: impaired vision, facial palsy, trigeminal neuralgia or deafness
- **Otosclerosis**: causes deafness
- **Spinal canal stenosis and nerve root compression**
- **High output cardiac failure**
- **Osteoarthritis** of Hip and Knee joint
- **Osteosarcoma**: rare

Radiological features

- **Early osteolytic phase:**
  - Radiolucent wedge area in long bones called **candle flame or blade of grass**
  - Flat bones like skull or iliac bone: pure lytic lesions known as **osteoporosis circumscripta.**
- **Late phase of new bone formation**:
  - **Thickening of cortex, coarse trabeculation and expansion of an entire bone or an area of long bone**
  - **Picture frame vertebrae**: thickening of superior and inferior endplate of vertebrae

- **Ivory vertebrae**: diffuse radiodense enlargement of vertebrae
- **Skull**: focal patchy densities **-cotton ball appearance**
- **Pelvis**: disruption of fusion of SI joint and **protrusio acetabuli, Brim sign**(sclerotic ileopectineal line)
- **Long bones**: bowing, thickening and expansion of cortex, areas of lucency and sclerosis.

Treatment

- **Most patients are asymptomatic- no treatment**
- **Indications for treatment**:
  - Persistent bone pain
  - Repeated fractures
  - Neurological complications
  - High output cardiac failure
  - Hypercalcemia due to immobilization

- **Calcitonin**: mc used, reduces bone resorption by decreasing the activity and number of osteoclasts.
- **Bisphosphonates:** Etidronate, Risedronate, Pamidronate, Zolendronate, alendronate.
- **Surgery**: for pathological fractures.

Fluorosis

- **Endemic fluorosis**: content of fuorine in drinking water **3-5 mg/L**
- Toxic manifestations:

A. **Dental fluorosis**

  - **Mottling of teeth enamel**- earliest sign, mc in upper incisors.
  - Mottling confined to permanent teeth.
  - Loss of shine of teeth, chalk white patches, later turn into yellow, brown or black.
  - Severe cases: **loss of enamel- corroded teeth**

B. Skeletal fluorosis

- **Osteosclerosis and calcification of ligaments, joint capsules and tendinous attachments to bone**.
- Bone and joint pain
- **Stiffness in back-** due to calcification of ligaments, earliest in lumbar region,
- **Restriction of spine movements is earliest clinical sign**.
- **Poker back**: entire spine is one continuous column of bone, occurs in late stages

- **Barrel chest**: involvement of rib cage, abdominal respiration
- **Flexion deformities at hip, knee and other joints**.
- **Genu valgum and osteoporosis of lower limbs**:
  - a new form of fluorosis,
  - districts of AP and TN
  - Staple diet: Sorghum(Jowar)

Radiological features of fluorosis

- **Spine:** increased density, calcification of ligaments commonly posterior longitudinal ligament
- **Pelvis:** increased density, calcification of ischio-pubic and sacro-iliac ligaments
- **Forearm and leg: interosseous membrane calcification**.

THANK YOU

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