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Disorders of Calcium, Parathyroid, Vitamin D and Bone metabolism

Clinical aspects

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ศ.นพ.สุทิน ศรีอัษฎาพร
สาขาวิชาต่อมไร้ท่อและเมตะบอลิสม
ภาควิชาอายุรศาสตร์ ศิริราชพยาบาล

Outline

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- **Calcium homeostasis and bone biology**
- **Calcemic disorders**
  - Hypercalcemia
  - Hypocalcemia
- **Metabolic bone diseases**
  - Osteoporosis
  - Rickets and osteomalacia
  - Renal osteodystrophy

Distribution of total body calcium

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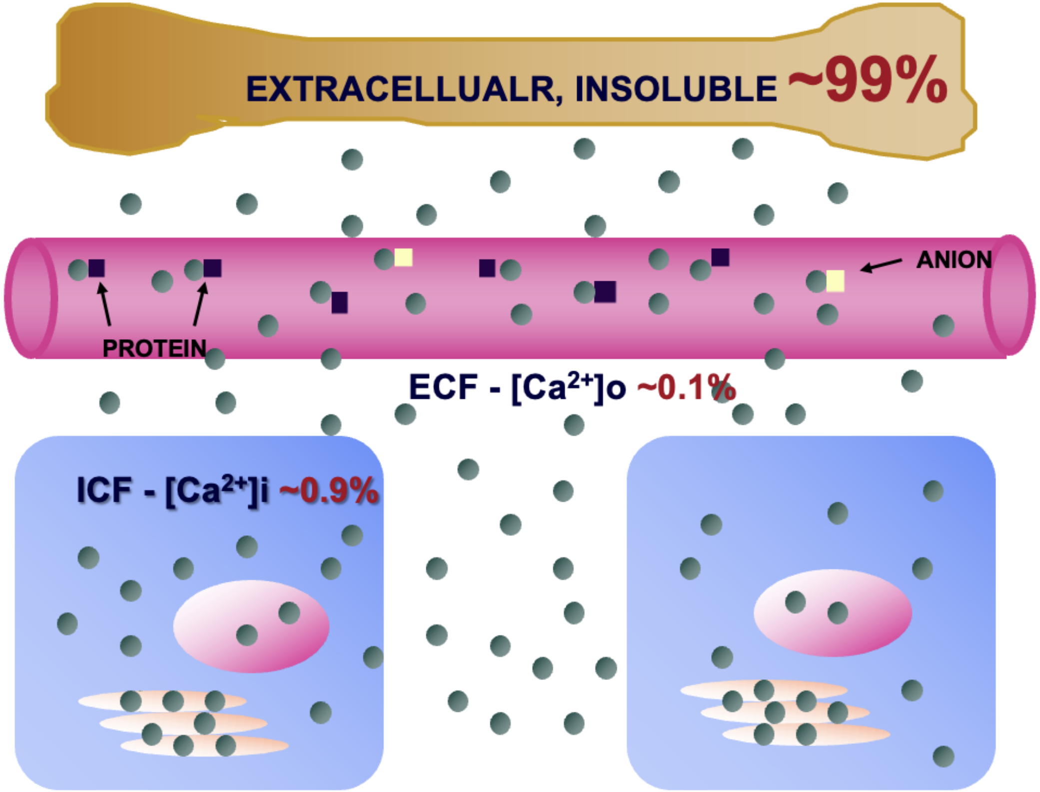

Hydroxyapatite crystals

Forms of calcium in the blood

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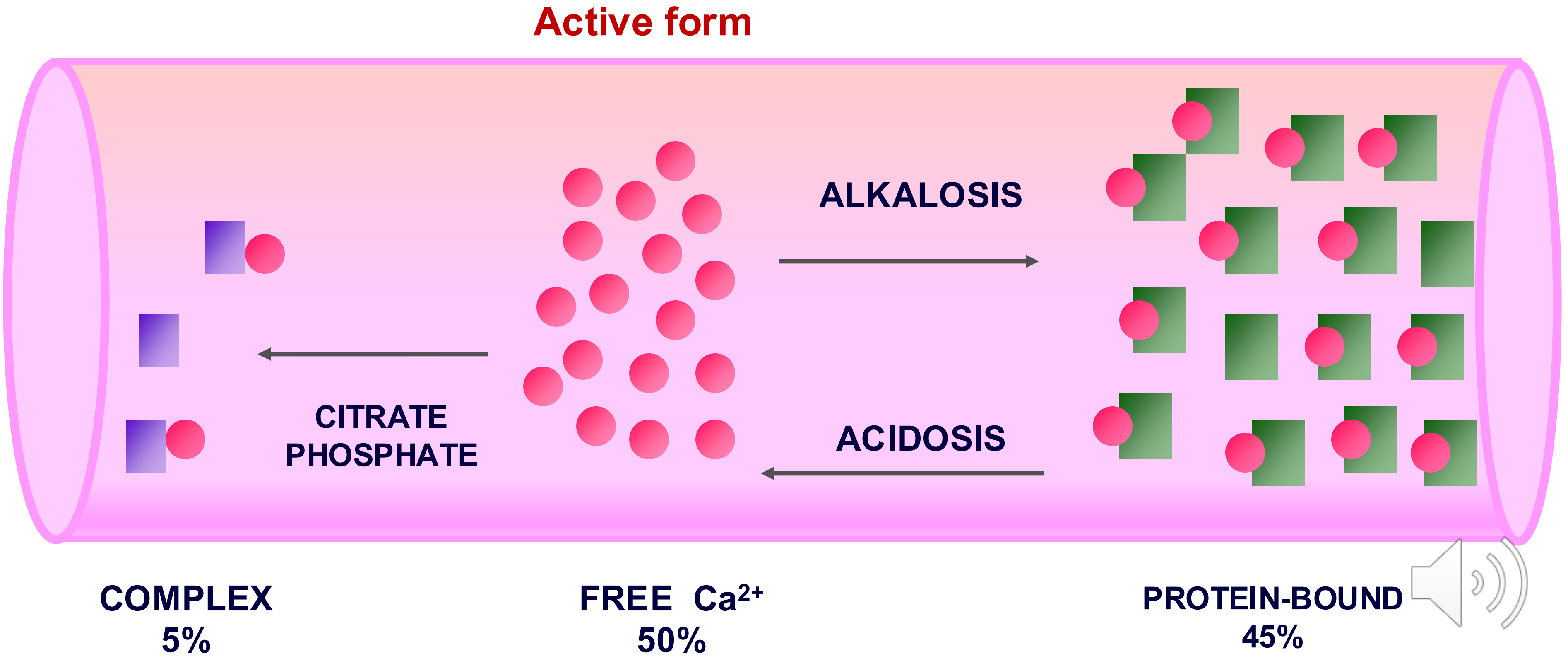

Effects of serum proteins on measured total serum calcium

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- ✓ Every 1 g/dL decrease in serum albumin (from 4 g/dL), the measured total serum calcium decreases 0.8-1.0 mg/dL
- ✓ Every 1 g/dL increase in serum albumin (from 4 g/dL), the measured total serum calcium increases 0.8-1.0 mg/dL

Formula
Corrected serum total calcium = [(4- measured serum albumin) x 0.8] + measured total serum calcium

Serum calcium measurement

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Indication

- Hypocalcemic/hypercalcemic symptoms
- Pathological fractures
- Evaluation of osteoporosis
- Evaluation of metabolic bone disorders
- Renal stones
- Cancers (hematologic, solid)
- Critical illness, burn
- Acute pancreatitis
- Check-up

Consider ionized calcium level

- Critically-ill settings
- Receiving transfusion with citrate blood
- Respiratory alkalosis
- 2^{nd}-3^{rd} trimester of pregnancy

Calcium Homeostasis

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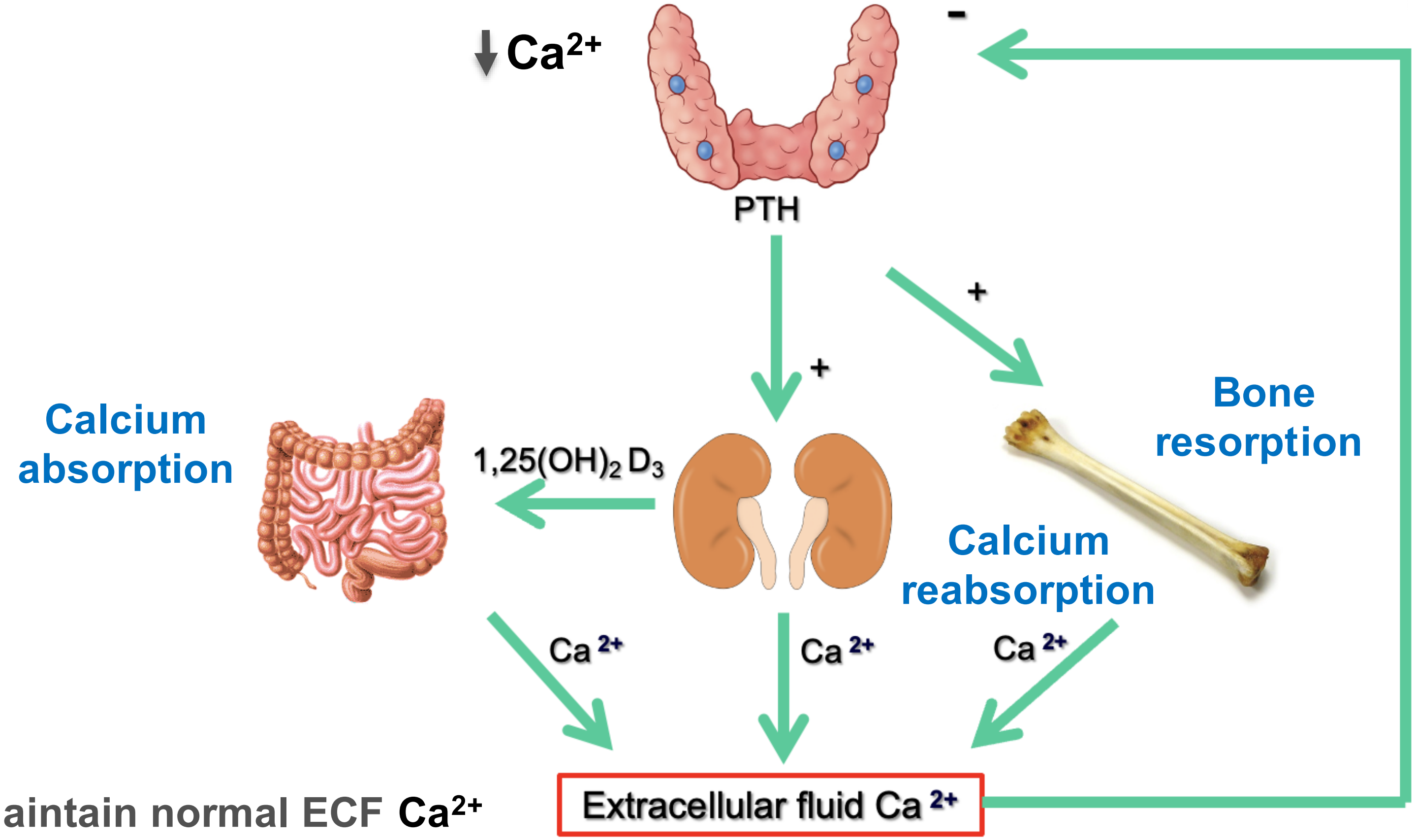

Maintain normal ECF Ca^{2+}

Biological action of parathyroid hormone

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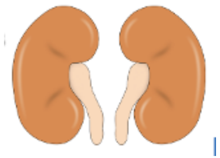
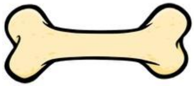
KIDNEY



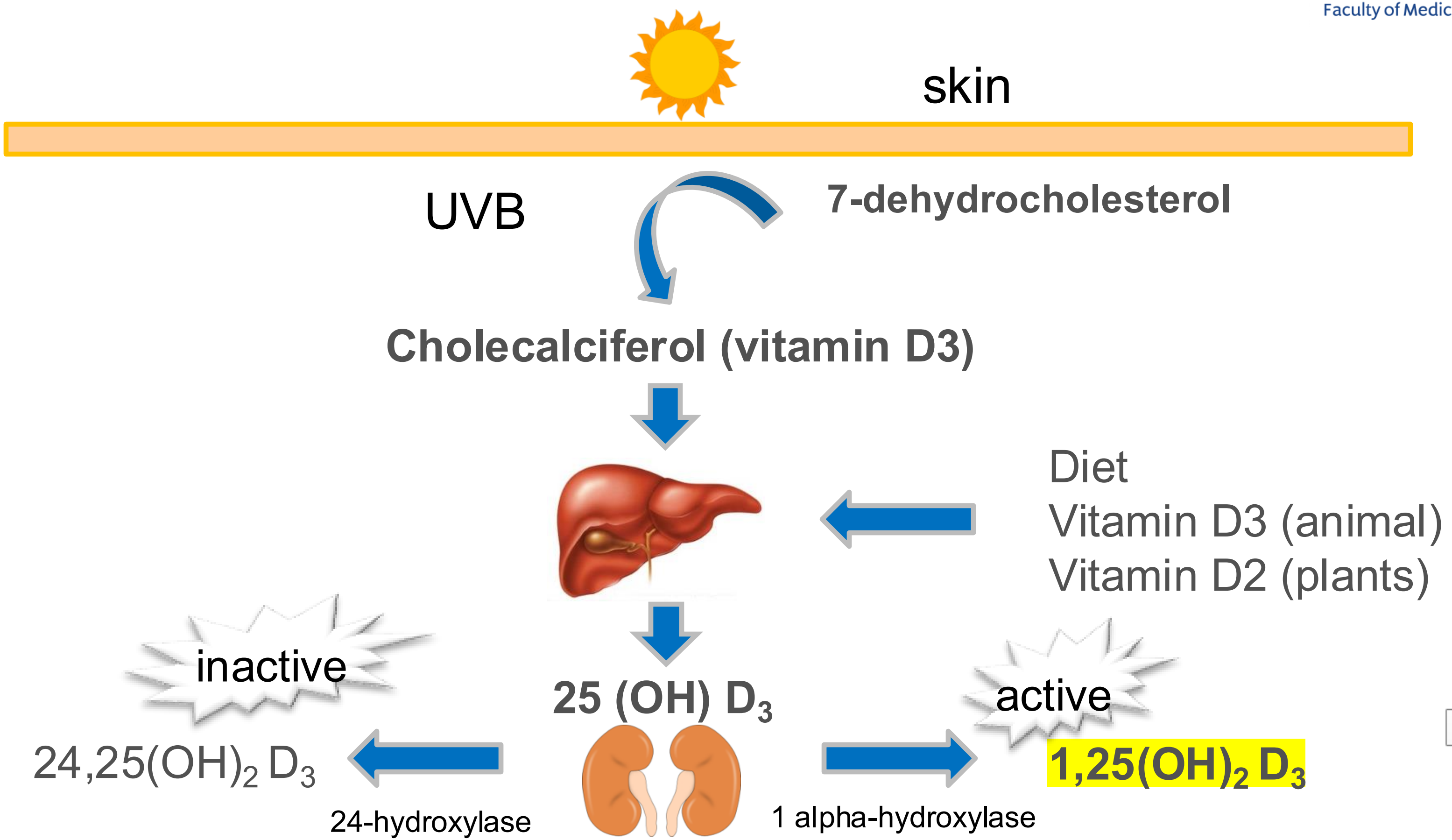
- Stimulates distal tubular calcium reabsorption
- Inhibits proximal and distal tubular phosphorus reabsorption
- Stimulates 1-OHase activity

BONE

- Stimulates osteoblastic bone formation
- Stimulates osteoclastic bone resorption



Vitamin D metabolism



Biological action of 1,25(OH)$_2$ D

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INTESTINE

- Stimulates calcium and phosphorus absorption

KIDNEY

- Inhibits 1α-hydroxylase activity
- Stimulates 24-hydroxylase activity

BONE

- Stimulates osteoblastic bone formation
- Stimulates osteoclastic bone resorption

PARATHYROID GLAND

- Inhibits PTH gene expression

Effects on parathyroid hormone

Control of secretion and synthesis

	PTH ↑	PTH ↓
Serum calcium	low	high
Serum phosphorus	high	low
Serum magnesium (<1 mg/dl)		low
Serum $1,25(OH)_2D$	low	high

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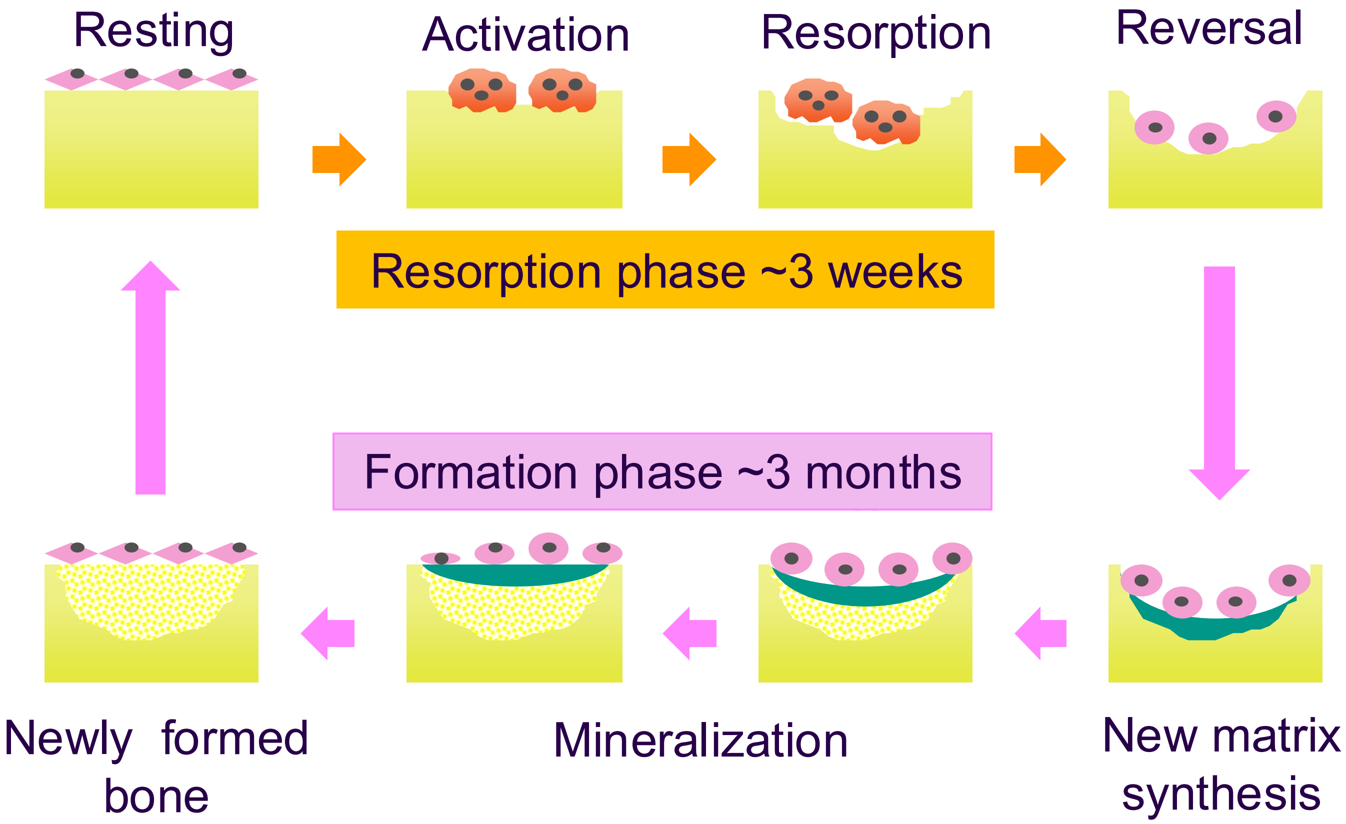
Bone remodeling process at trabecular bone



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Bone structure and histology

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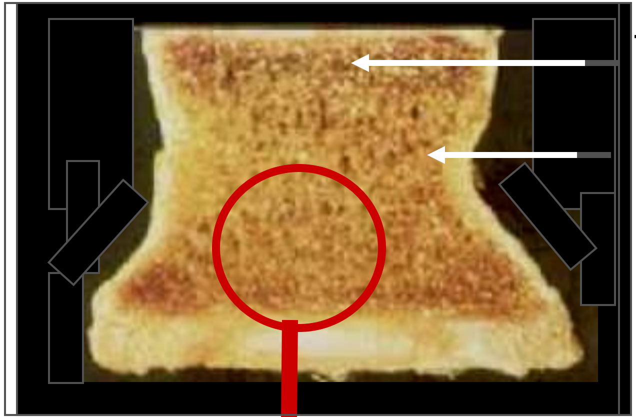
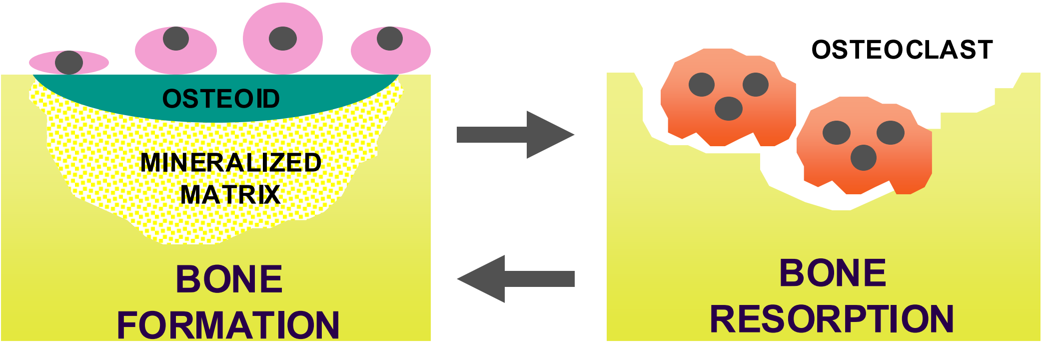
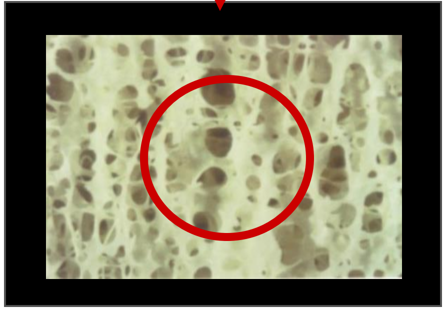
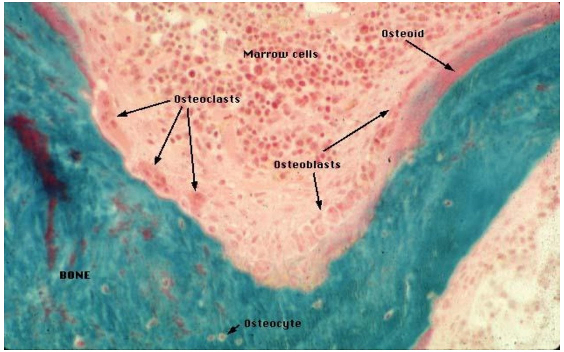
Basic multicellular units









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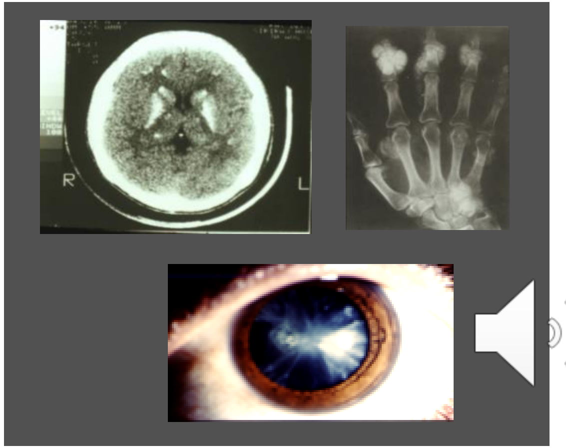
Solubility product

Total serum Ca (mg/dl) x P (mg/dl)

<30	40	>60
OSTEOMALACIA	NORMAL	SOFT TISSUE CALCIFICATION



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Disorders of calcium and bone metabolism

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Clinical manifestations

- Symptoms related to abnormal calcium and phosphate metabolism
  - Hypocalcemia / Hypercalcemia
  - Chronic hypophosphatemia
- Decreased bone strength
  - Fractures (low trauma or pathological fractures)
  - Deformities
- Bone pain
- Growth failure (in children)

Calcemic disorders

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Hypocalcemia	Hypercalcemia

- Depend upon the laboratory reference
- Excluding falsely low calcium level

- ✓ Severity
- ✓ Symptoms
- ✓ Onset
- ✓ Etiology
- ✓ Treatment

Severity of hypercalcemia

mild → moderate → severe

Upper normal limit	mild	moderate	severe
	<12 mg/dL	12-14 mg/dL	> 14 mg/dL

Symptoms of hypercalcemia

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Renal (Stones)

- Polyuria, polydipsia (nephrogenic DI)
- Nephrolithiasis, nephrocalcinosis
- Distal RTA
- Acute and chronic renal insufficiency

GI (Abdominal groans)

- Anorexia, nausea, vomiting
- Constipation
- Pancreatitis
- Peptic ulcer disease

Asymptomatic

Musculoskeletal (Bones)

- Muscle weakness
- Bone pain (if fracture)
- Osteopenia/ osteoporosis

Neurological (Psychic moans)

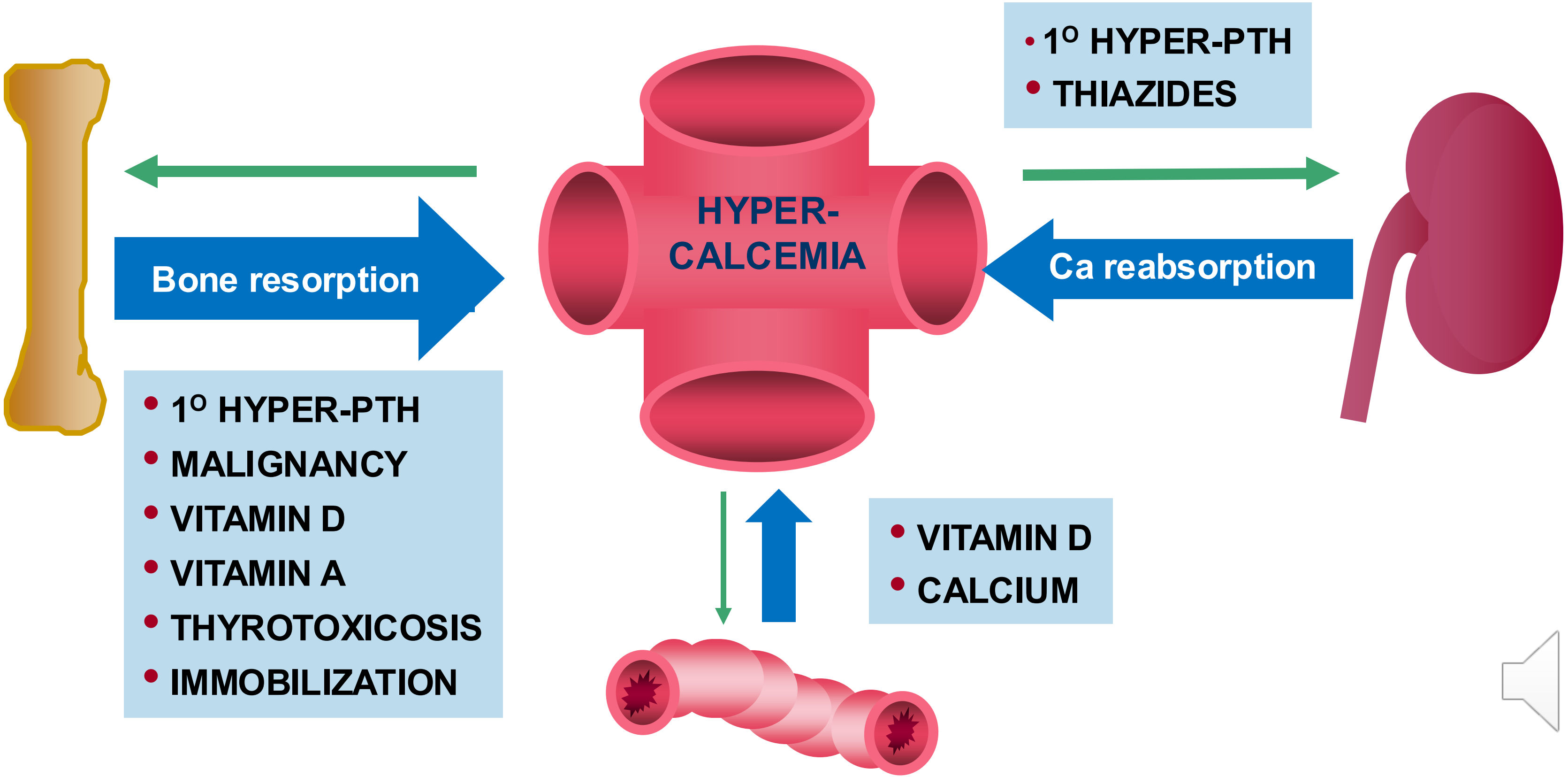
- Inability to concentrate, fatigue
- Confusion
- Coma

Cardiac

- Short QT interval, bradycardia
- Hypertension

Depend on
- ✓ Serum calcium level
- ✓ Onset and duration

Mechanisms of hypercalcemia



Approach

Hypercalcemia

Low P | **Normal P** | **High P**

Suppress PTH

PTH-related

- **Primary hyperparathyroidism**
- Familial hypocalciuric hypercalcemia (FHH)
- Tertiary hyperparathyroidism (in ESRD patients)
- **Drugs**: lithium

Elevated or inappropriately normal PTH

- **Malignancy associated hypercalcemia**
- **Drugs**: HCTZ, vitamin A, Calcium, theophylline toxicity
- **Milk-alkali syndrome**
- **Endocrinopathies**: thyrotoxicosis, PHEO, AI, acromegaly
- **Immobilization**
- **Others**

Vitamin D-related

- Vitamin D intoxication
- Granulomatous diseases
- CYP24A1 loss of function

Depend on multifactorial causes: renal failure, prior treatment

Primary hyperparathyroidism (PHPT)

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Diagnosis of primary hyperparathyroidism

****Biochemical diagnosis****

- **An elevated serum calcium adjusted for albumin** in the presence of an **elevated or inappropriately normal intact parathyroid hormone(PTH)**
- Utilizing either a second or third generation assay on two occasions at least 2 weeks apart

- Most common cause of hypercalcemia in OPD setting
- Incidence: female: male = 3-4:1
- Common age > 50 years (postmenopause)
- **Causes**: parathyroid adenoma (80%), parathyroid hyperplasia (20%)

Pathophysiology of PHPT

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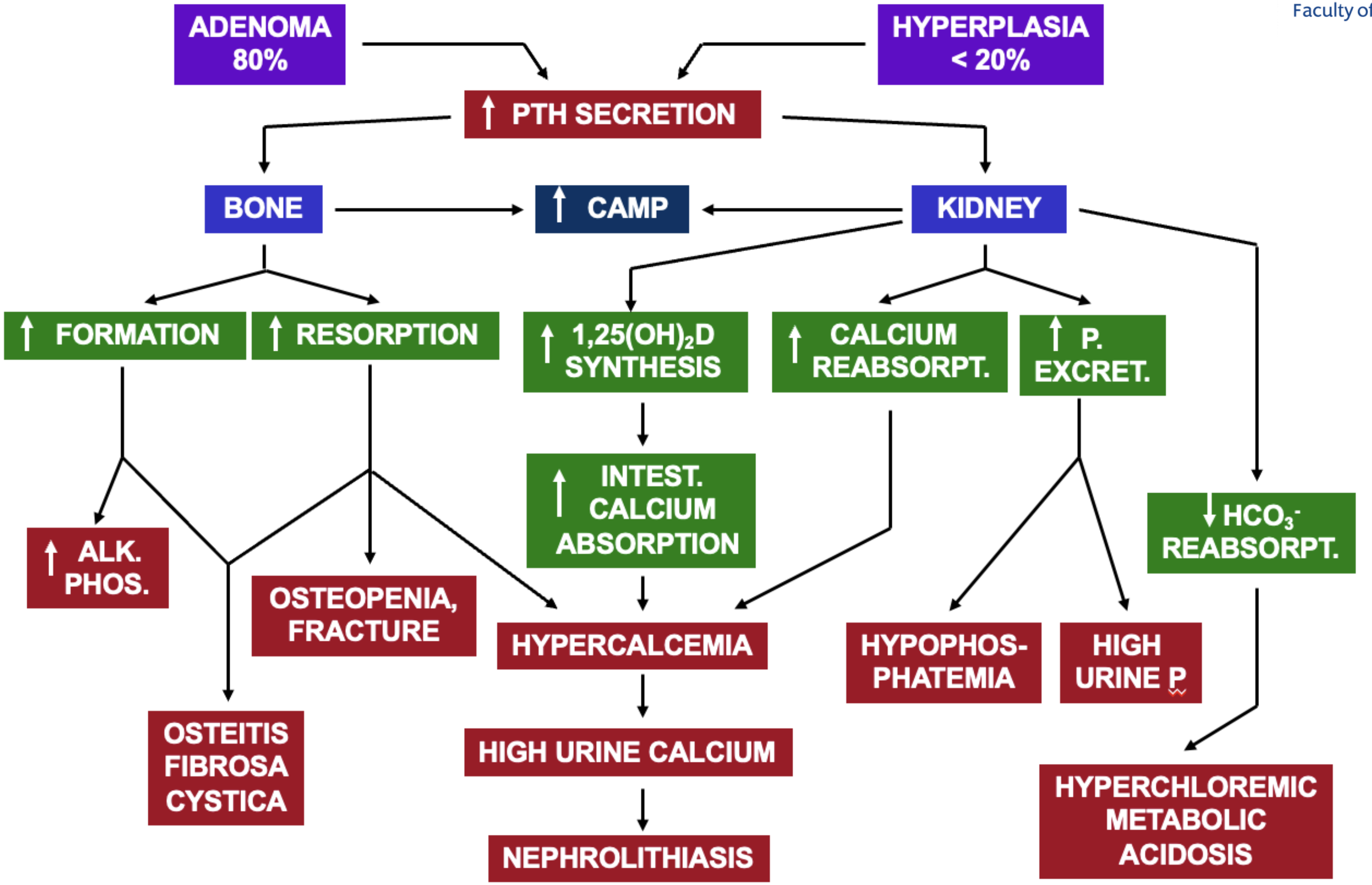

Clinical manifestations of PHPT

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Systems	Symptoms	Investigations
Skeletal	Osteopenia, osteoporosis, subperiosteal bone resorption, pathological fractures	Bone mineral density testing Plain film x-ray
Renal	Nephrolithiasis, polyuria, nephrocalcinosis, hypercalciuria	Plain film KUB, ultrasound KUB 24-hour urine calcium
GI	Constipation, nausea, pancreatitis	
Neuropsychiatric	Fatigue, depression, cognitive dysfunction, psychosis	
CVS	Hypertension, arrhythmias (rare)	EKG 12 leads

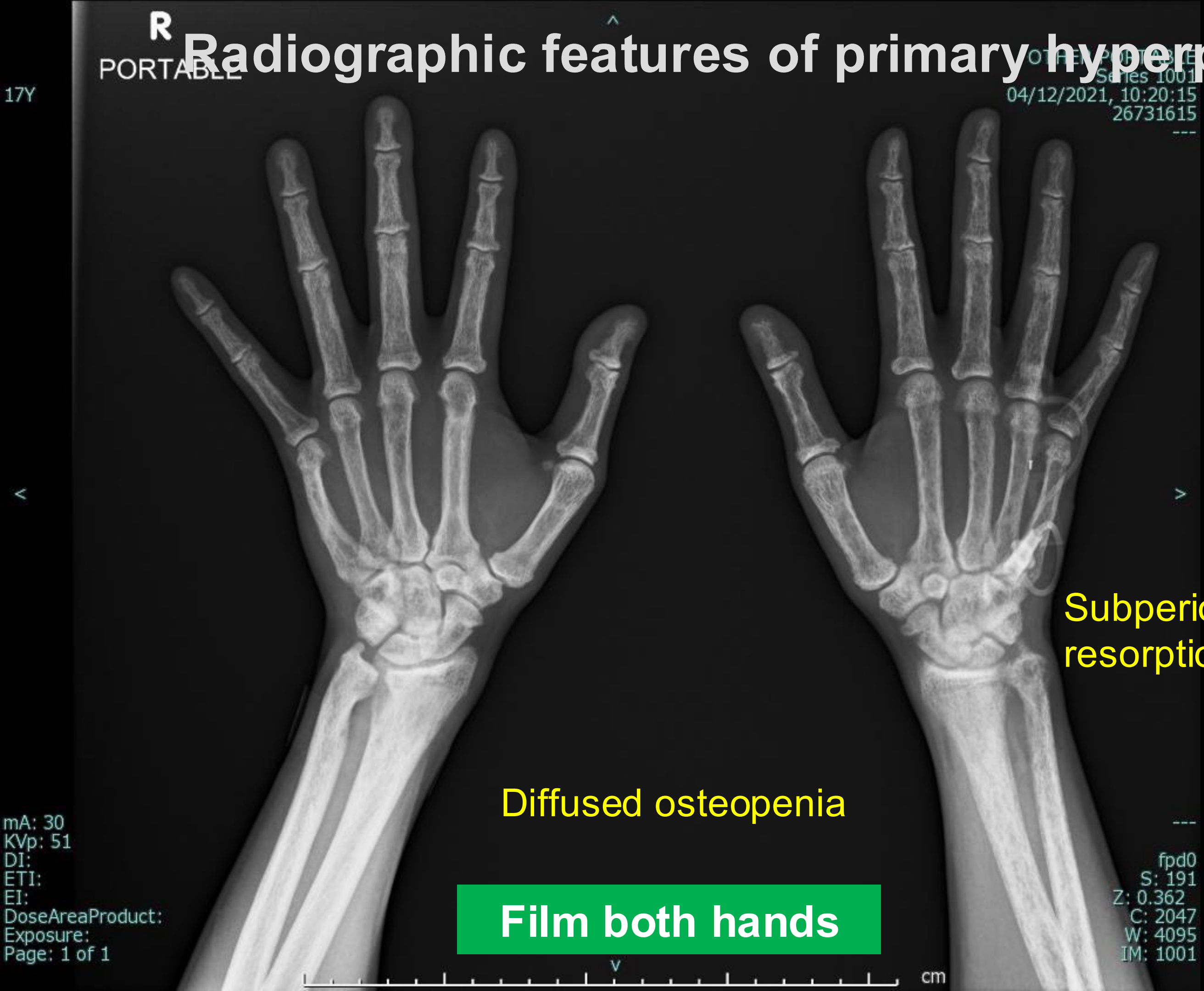
Radiographic features of primary hyperparathyroidism

Film bone survey: skull

Salt and pepper appearance

Diffused osteolytic lesion with osteosclerotic rim

Radiographic features of primary hyperparathyroidism



Acral osteolysis

Subperiosteal resorption

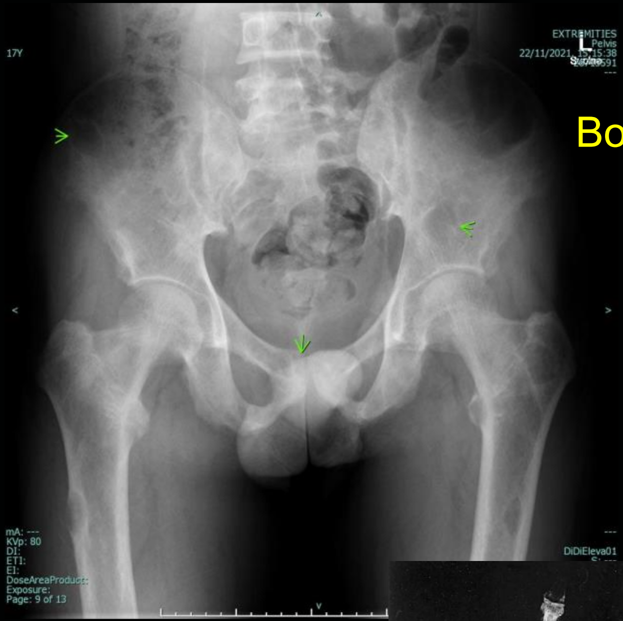
Diffused osteopenia

Film both hands

Radiographic features of primary hyperparathyroidism

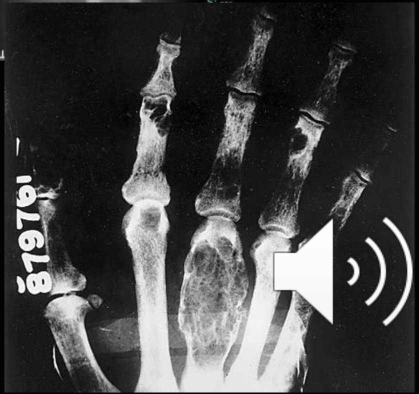
Subperiosteal distal clavicular resorption

Bone cysts



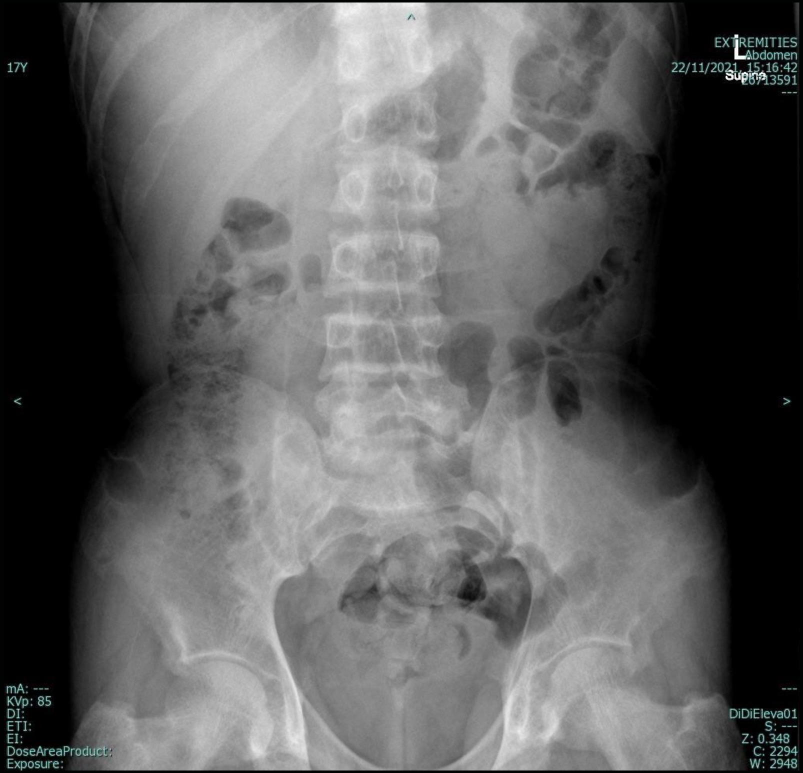
Bone cysts

Brown tumor (osteoclastoma)

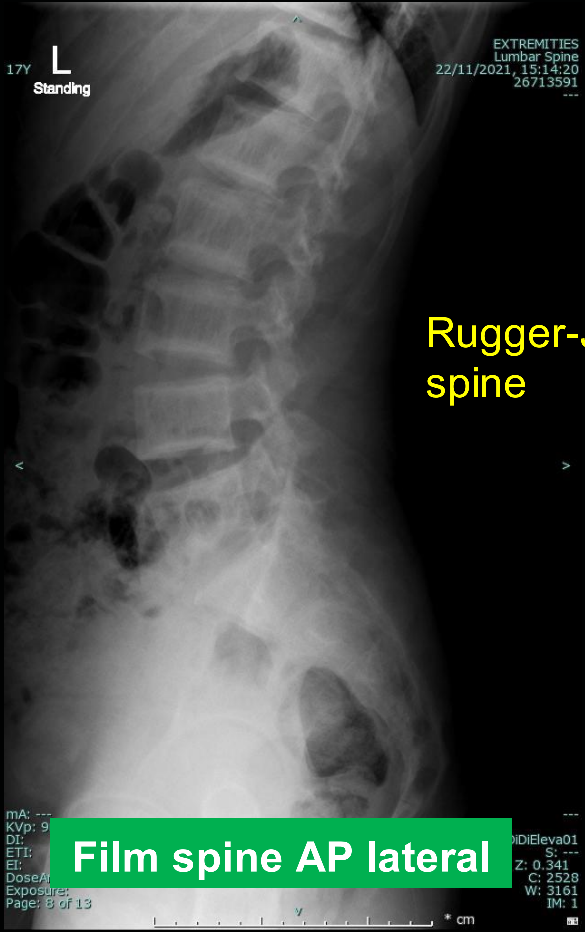


Film bone survey

Radiographic features of primary hyperparathyroidism



Diffuse osteopenia, Sclerotic change at end plate of lumbar



Rugger-Jersey spine

Film spine AP lateral

Radiographic features of primary hyperparathyroidism

Kidney stone & nephrocalcinosis

Management of primary hyperparathyroidism

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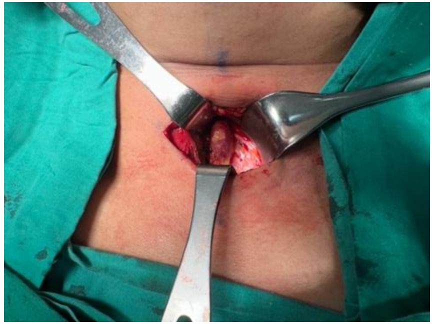
- **Surgical management: parathyroidectomy**
- **Non-surgical treatment:** medications
- **Supportive treatment:** nutritional aspects



- Avoid the use of drugs causing hypercalcemia: thiazides, lithium
- Adequate fluid intake
- Adequate calcium and vitamin D intake**caution in symptomatic patients or moderate to severe hypercalcemia

J Bone Miner Res. 2022 Nov;37(11):2293-2314

Preoperative localization in PHPT

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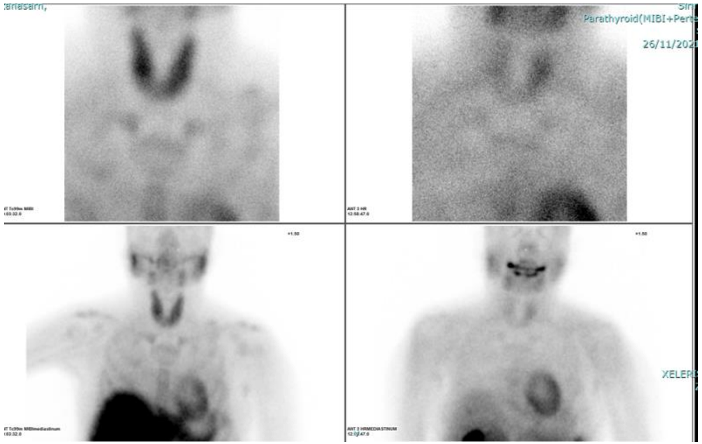
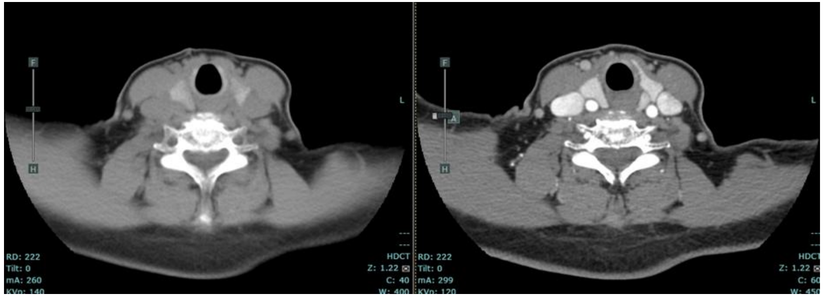
Parathyroid scan



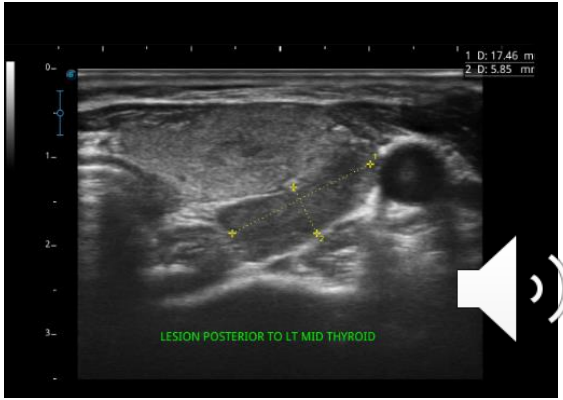
Dual-tracer subtraction of parathyroid imaging

Dual-phase 99mTc sestamibi of parathyroid imaging

4D parathyroid CT scan



US neck



Hypercalcemia of malignancy (HCM)

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- The most common metabolic complication of malignancies
- Affect 2-30% of patients with cancer, depending on cancer type and disease stage
- Associated high morbidity and high mortality
- Most of HCM patients (> 90%) had advanced malignancies at the time of developing hypercalcemia

[1]Fuleihan G et al. *J Clin Endocrinol Metab*. 2023 Feb 15;108(3):507-528.
S Sriussadaporn et al. *J Med Assoc Thai* 2007; 90 (4): 663-71.
Ralston SH et al. *Ann Intern Med.* 1990;112: 499-504.,

Clinical manifestations of HCM

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✓ Symptoms are related to the **severity** of HCM, the **rapidity** of hypercalcemia and/or the presence of bone metastasis

Serum calcium	Severity classification	Symptoms
< 12 mg/dL	Mild	Nonspecific, fatique, anorexia, constipation, mild cognitive dysfunction
12-14 mg/dL	Moderate	Polyuria, polydipsia, confusion, stupor, renal failure, short QT interval on ECG, ST segment abnormalities, ventricular arrhythmia (report in severe cases)
> 14 mg/dL	Severe	

Fuleihan G et al. *J Clin Endocrinol Metab*. 2023 Feb 15;108(3):507-528.

Mechanisms of HCM

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Types	Frequency	Bone metastasis	Causal agents	Typical tumors
Humoral hypercalcemia of malignancy	80%	Minimal, absent	PTH-rP	Squamous cell CA (head and neck, esophagus, lung, cervix), RCC, ovarian, breast
Local osteolytic of hypercalcemia	20%	Common, extensive	Cytokines, chemokines, PTH-rP	Breast cancer, multiple myeloma, lymphoma
Excess $1,25(OH)_2D$ production	<1%	Variable	$1,25(OH)_2D$	Lymphoma (all types)
Excess parathyroid hormone production	<1%	Variable	PTH	Parathyroid cancer, small cell CA of lung, ovarian carcinoma, thymoma, neuroectodermal tumor, PTC

"All mechanisms -> **Increased bone resorption activity"**

Adapt from Stewart A.F. *N Engl J Med* 2005; 352: 373-379.

Primary structures of the amino terminal part of PTH and PTH-rP

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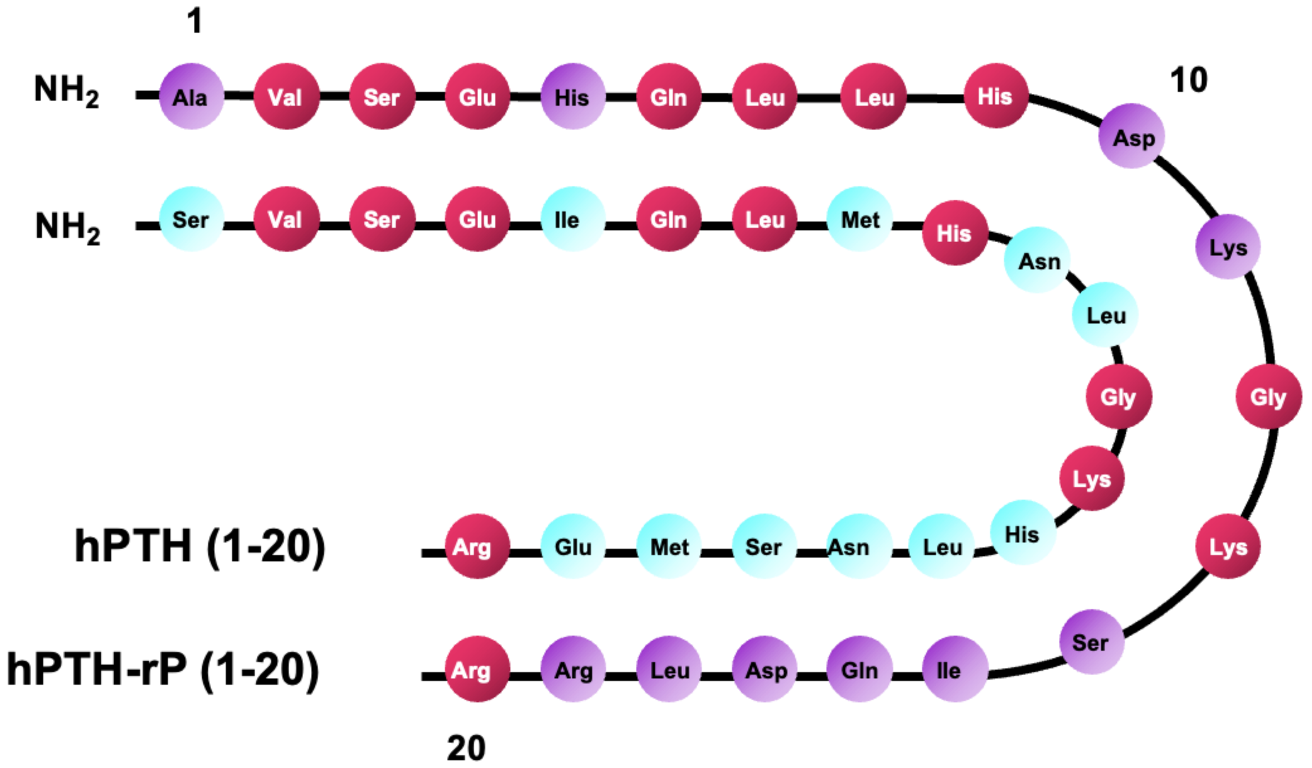

Mechanisms: HHM vs LOH

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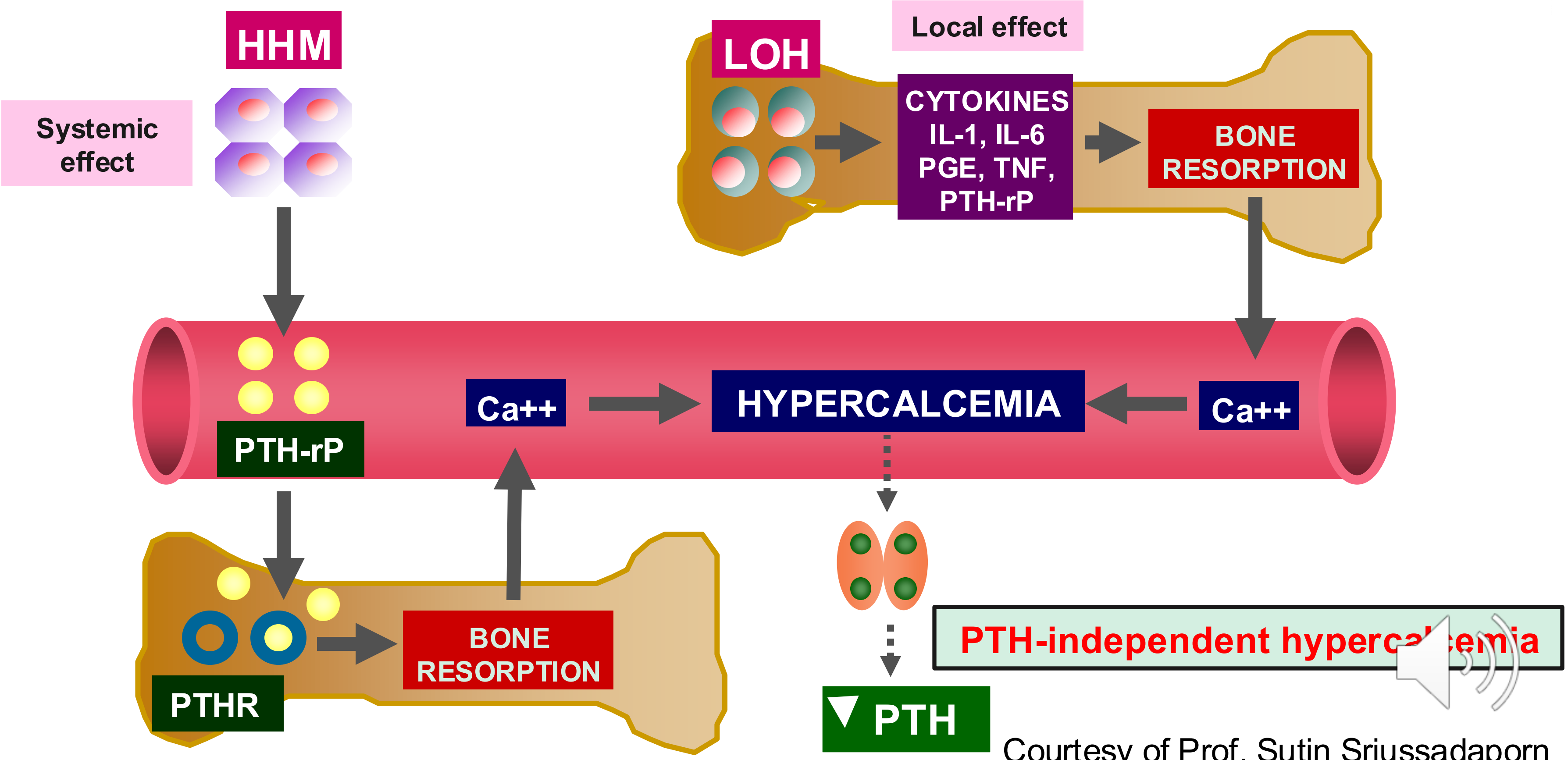

Courtesy of Prof. Sutin Sriussadaporn

Mechanisms: HHM vs PHPT

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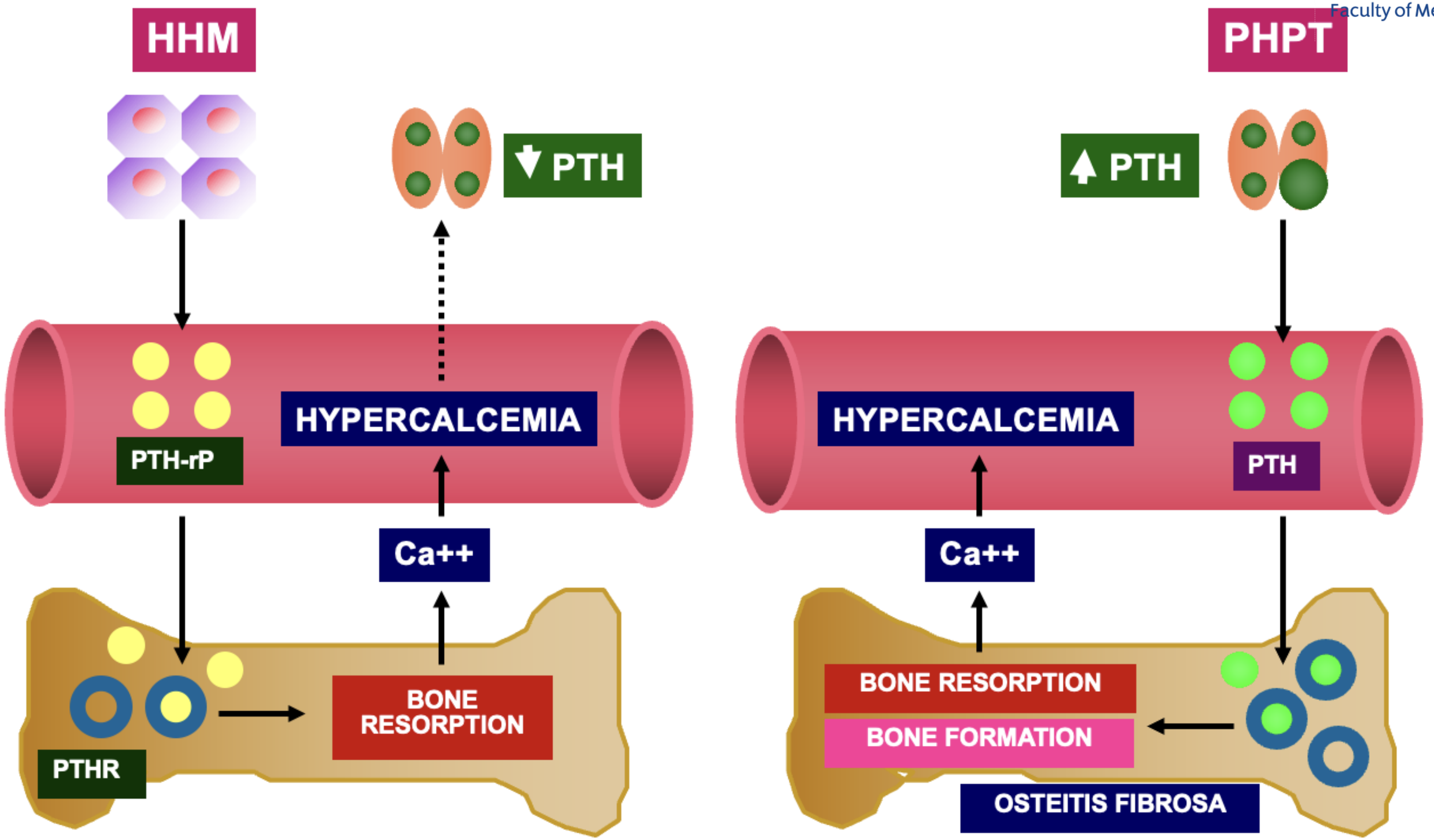

Hypercalcemia: Principles of therapy

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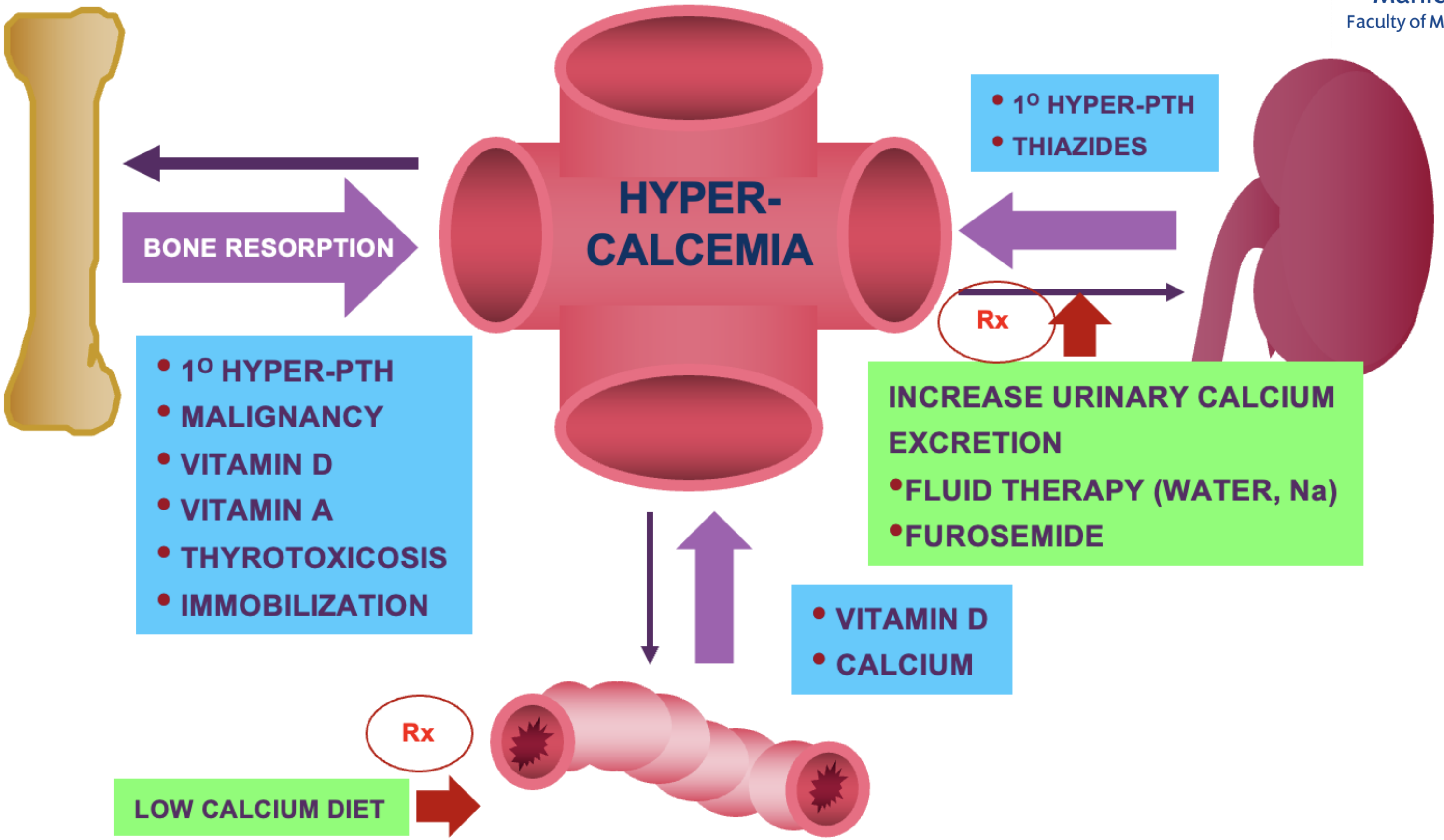
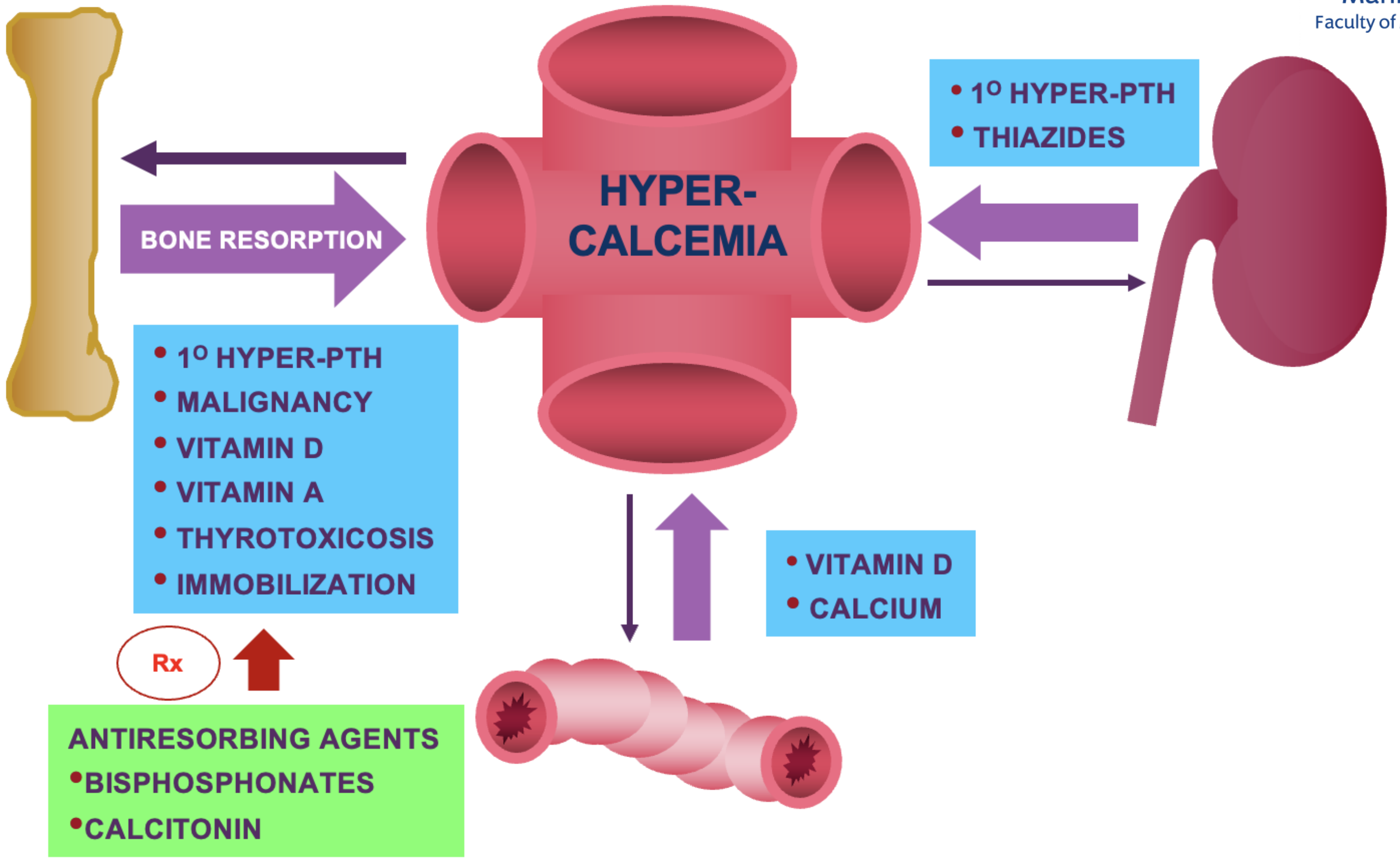


Hypercalcemia: Principles of therapy



Anti-resorptive agents for HCM

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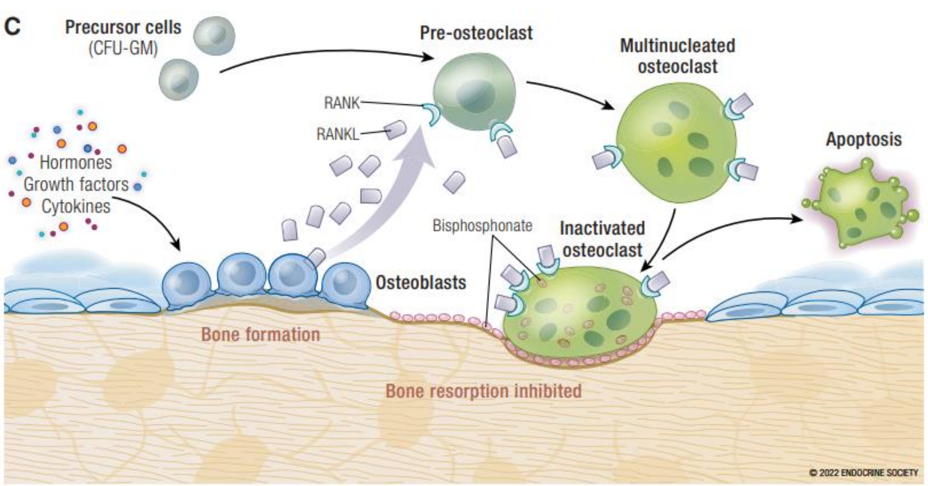
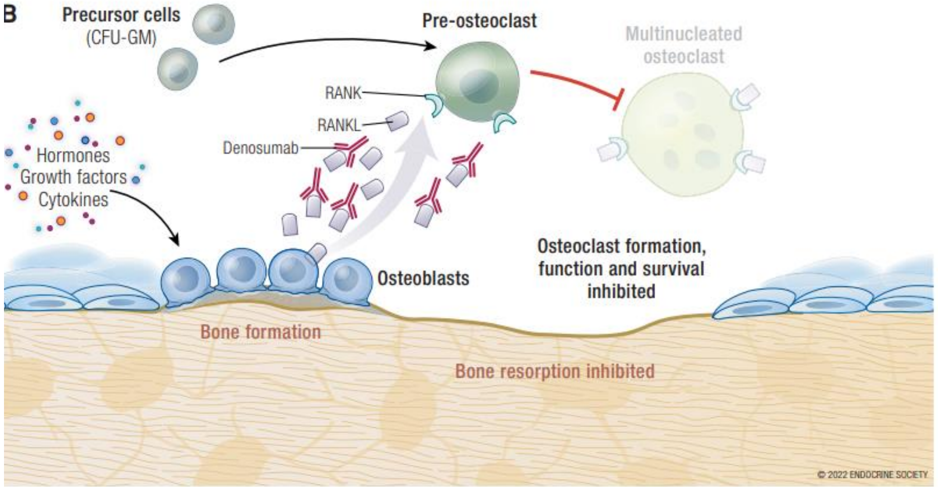
Mature osteoclasts endocytose bisphosphonates, resulting in osteoclast inactivation and apoptosis

Denosumab is a humanized monoclonal antibody that binds to RANKL to block RANK:RANKL binding, resulting in inhibition of osteoclast formation, function, and survival



Bisphosphonates



Denosumab/Dmab

J Clin Endocrinol Metab. 2023 Feb 15;108(3):507-528

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Severity of hypocalcemia

severe ← moderate ← mild

severe	moderate	mild
<7.5 mg/dl	7.5-8.4 mg/dl	> 8.4 mg/dl

Symptoms of hypocalcemia

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Acute hypocalcemia

Neuromuscular manifestations

- Paresthesia, tingling
- Muscle twitching and cramping
- Carpopedal spasm
- Tetany
- Trousseau sign
- Chvostek sign
- Grand mal seizure
- Laryngospasm, bronchospasm
- Psychiatric manifestations (emotional instability, anxiety, depression, confusion, hallucination, psychosis)

Cardiovascular abnormalities

Chronic hypocalcemia

Neuromuscular manifestations

- Extrapyramidal sign, parkinsonism
- Basal ganglia and brain calcification
- Dementia
- Depression

Ectodermal manifestations

- Dry, puffy, coarse skins
- Coarse, brittle, sparse hair with patchy alopecia

Ocular disease

- Cataract

Depend on

- ✓ Serum calcium level
- ✓ Onset and duration

Ca x P

Long standing hypoparathyroidism -> high solubility products

Latent tetany: **TROUSSEAU'S TEST**

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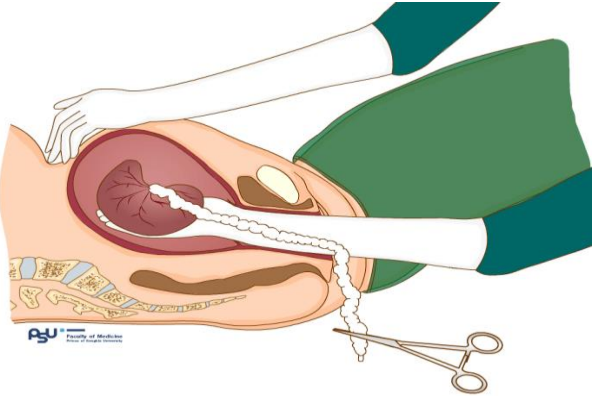
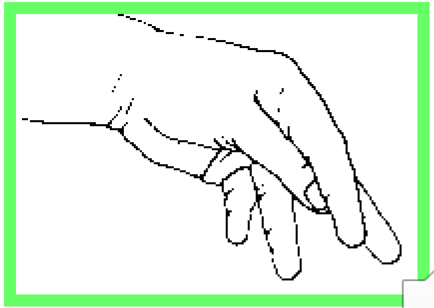
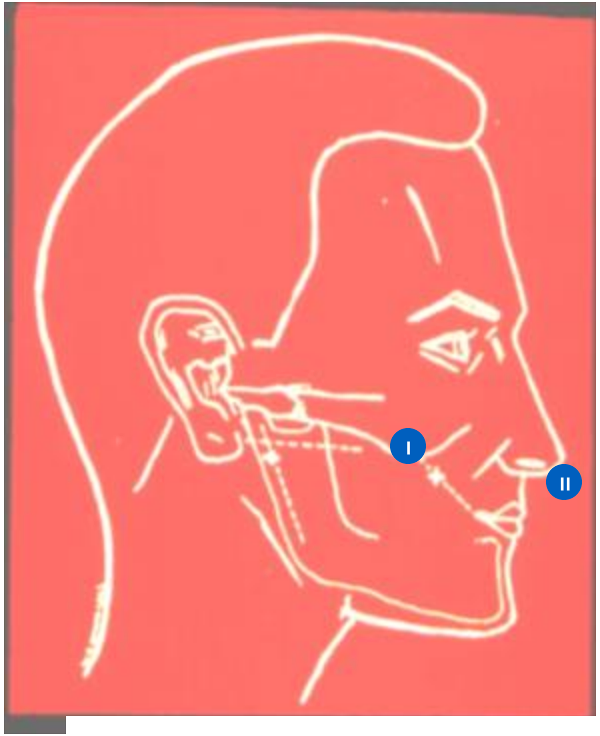
- Apply arm-cuff BP at ~10-20 mm.Hg. above systolic BP for up-to 5 minutes
- Look for carpal spasm





THE ACCOUCHER'S HAND

Latent tetany: CHVOSTEK'S TEST



- Direct stimulation (Chvostek I)
- Reflex stimulation (Chvostek II)

Symptoms of hypocalcemia

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Acute hypocalcemia

Cardiovascular abnormalities
- Prolonged QT interval
- Hypotension
- Myocardial dysfunction, heart failure
- Ventricular arrhythmia, heart block

Gastrointestinal manifestations
- Abdominal cramp

Others: papilledema, pseudotumor cerebri

Chronic hypocalcemia

Dental abnormalities
- Dental hypoplasia
- Defective enamel and root formation

Skeletal manifestations
- Low bone turnover
- Short stature
- Bone pain or deformities

Renal abnormalities
- Hypercalciuria
- Renal calculi

Long standing hypoparathyroidism -> high solubility products

Skeletal manifestations: low solubility product

Rickets

Pseudo fracture line

Osteomalacia

Etiologies of hypocalcemia

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- **Hypoparathyroidism**
- Vitamin D deficiency
  - ✓ Inadequate sunlight exposure
  - ✓ Inadequate vitamin D intake
  - ✓ Malabsorption
  - ✓ Increased vitamin D metabolism: phenytoin
- Hypomagnesemia
- Chronic kidney disease
- Phosphorus loading: Tumor lysis syndrome
- Acute pancreatitis
- Massive blood transfusion

Approach

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Hypocalcemia

Creatinine level

- **Normal** → **PTH**
  - **Low** →
    - **Hypoparathyroidism**
      - Acquired:
        - **Postsurgical**
        - Postradiation/postablation
        - Hypomagnesemia
        - Infiltrative/autoimmune diseases of parathyroid gland
      - Genetic hypoparathyroidism
  - **High** → **25(OH)D level**
    - **Low** →
      - **Vitamin D deficiency**
        - Inadequate intake
        - Low sun exposure
        - Malabsorption
        - Malnutrition
        - Nephrotic syndrome
        - Hepatobiliary diseases
        - Medications
    - **Normal/High** → **$1,25(OH)_2D$ level**
      - **Normal** →
        - **Pseudohypoparathyroidism:** type Ia/Ib, type II **PTH resistance**
        - **Vitamin D-dependent rickets**
      - **High** →
        - **Vitamin D-resis ant rickets (VDDR**
- **High** →
  - **Renal failure**
  - Secondary hyperparathyroidism

from Brenner textbook of Nephrology

Causes of hypoparathyroidism

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Decreased PTH secretion	Resistance to PTH action

• **Post-surgical**: transient, permanent
• **Idiopathic**: autoimmune, genetic, sporadic
• **Developmental disorders of parathyroid gland**
• **Infiltration**: hemochromatosis, Wilson disease, metastasis
• **Post-irradiation**
	• **Pseudohypoparathyroidism**
	    • Type Ia, Ib, Ic
	    • Type II
	• Hypomagnesemia

Investigations for hypoparathyroidism

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	Decreased PTH secretion	Resistance to PTH action
Serum calcium	low	low
Serum phosphorus	high	high
Parathyroid hormone	low or normal	high
Serum $1,25(OH)_2D$	low	low

Abnormal calcification: **high solubility product**

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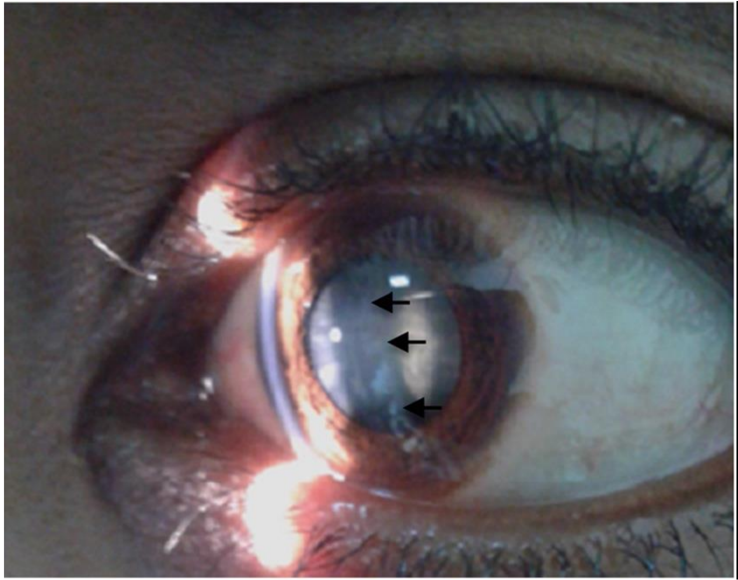
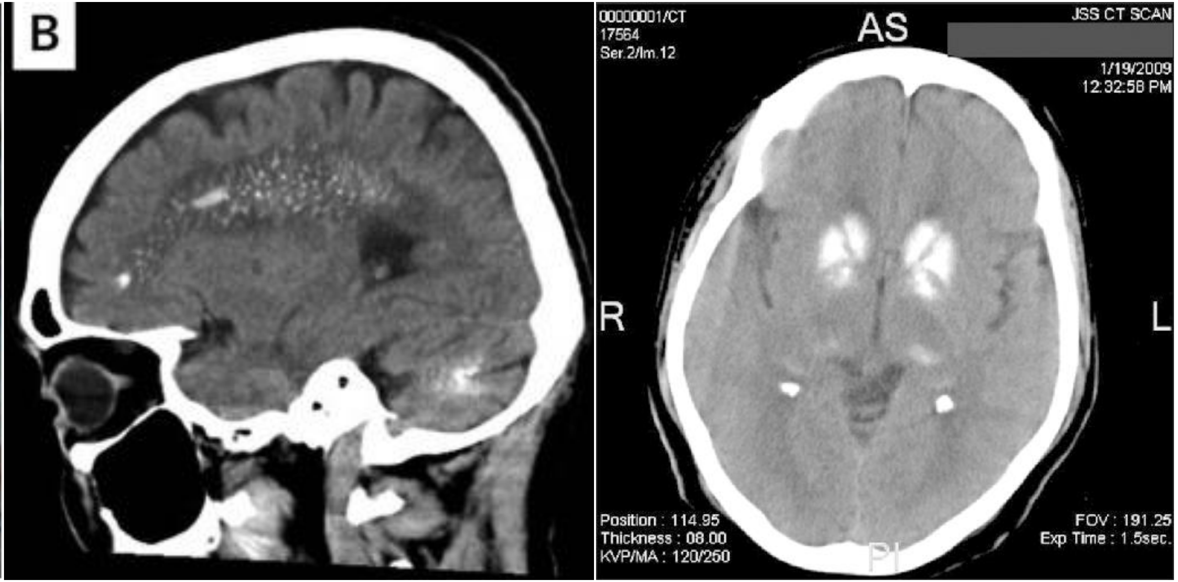


Subcapsular cataract



Cerebral and basal ganglia calcification

Long standing hypoparathyroidism

Pseudohypoparathyroidism

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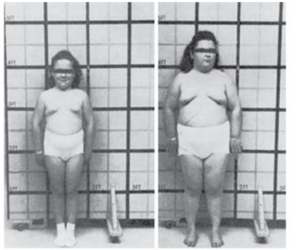
- **Clinical features**
  - Albright hereditary osteodystrophy (AHO) phenotype
    - Brachydactyly (asymmetric short 4th or 5th MCP/MTS bone)
    - Subcutaneous ossification
    - Early onset obesity with short stature (decreased growth velocity)
    - Mental retardation (variable)
  - Ectopic calcification
  - Hormonal resistance: PTH, TSH, GnRH, GhRH



• **Fig. 29.31** Daughter *(left)* and mother *(right)* with pseudohypoparathyroidism and Albright her osteodystrophy.

Outline

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- **Calcium homeostasis and bone biology**
- **Calcemic disorders**
    - Hypercalcemia
    - Hypocalcemia
- **Metabolic bone diseases**
    - Osteoporosis
    - Rickets and osteomalacia
    - Renal osteodystrophy

Osteoporosis

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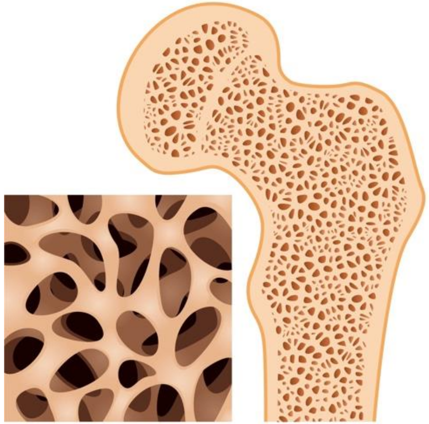
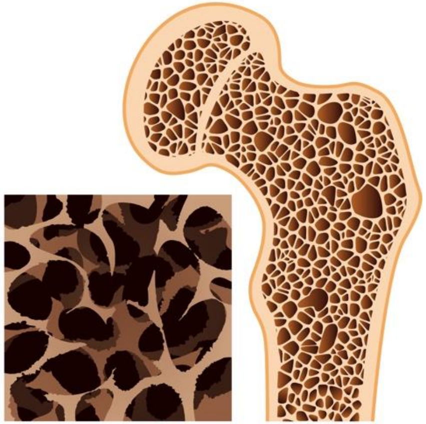
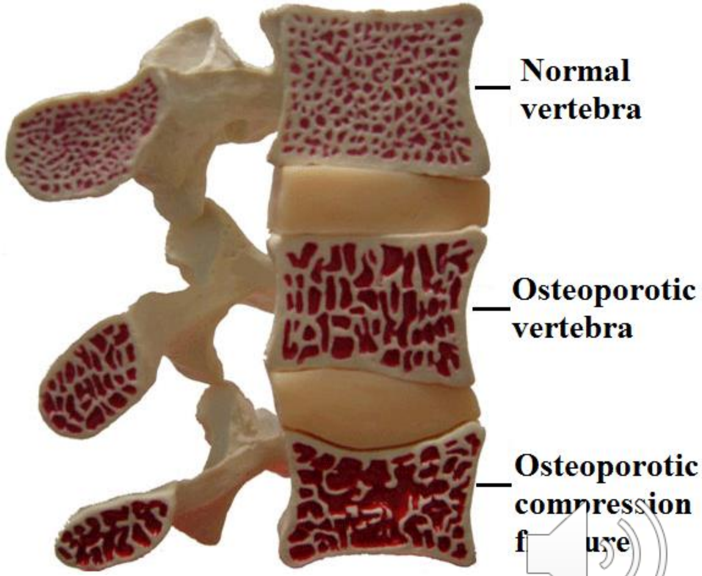
- A disease characterized by **low bone mass** and **microarchitectural deterioration**, leading to enhanced **bone fragility** and consequent **increase in fracture risk**.
- Asymptomatic, fracture occurs-> deformities, pain



Healthy bone



Osteoporosis



Consensus development conference. *Am J Med.* 1993;94(6):646-50.

Normal bone: Bone resorption = formation

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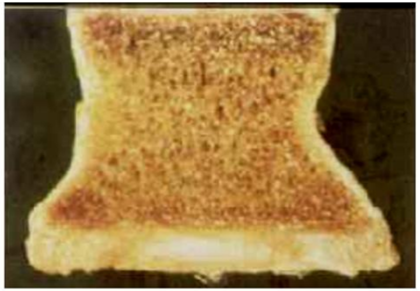
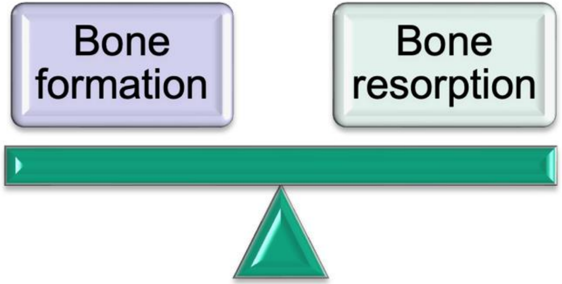
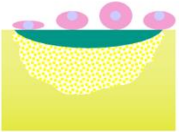


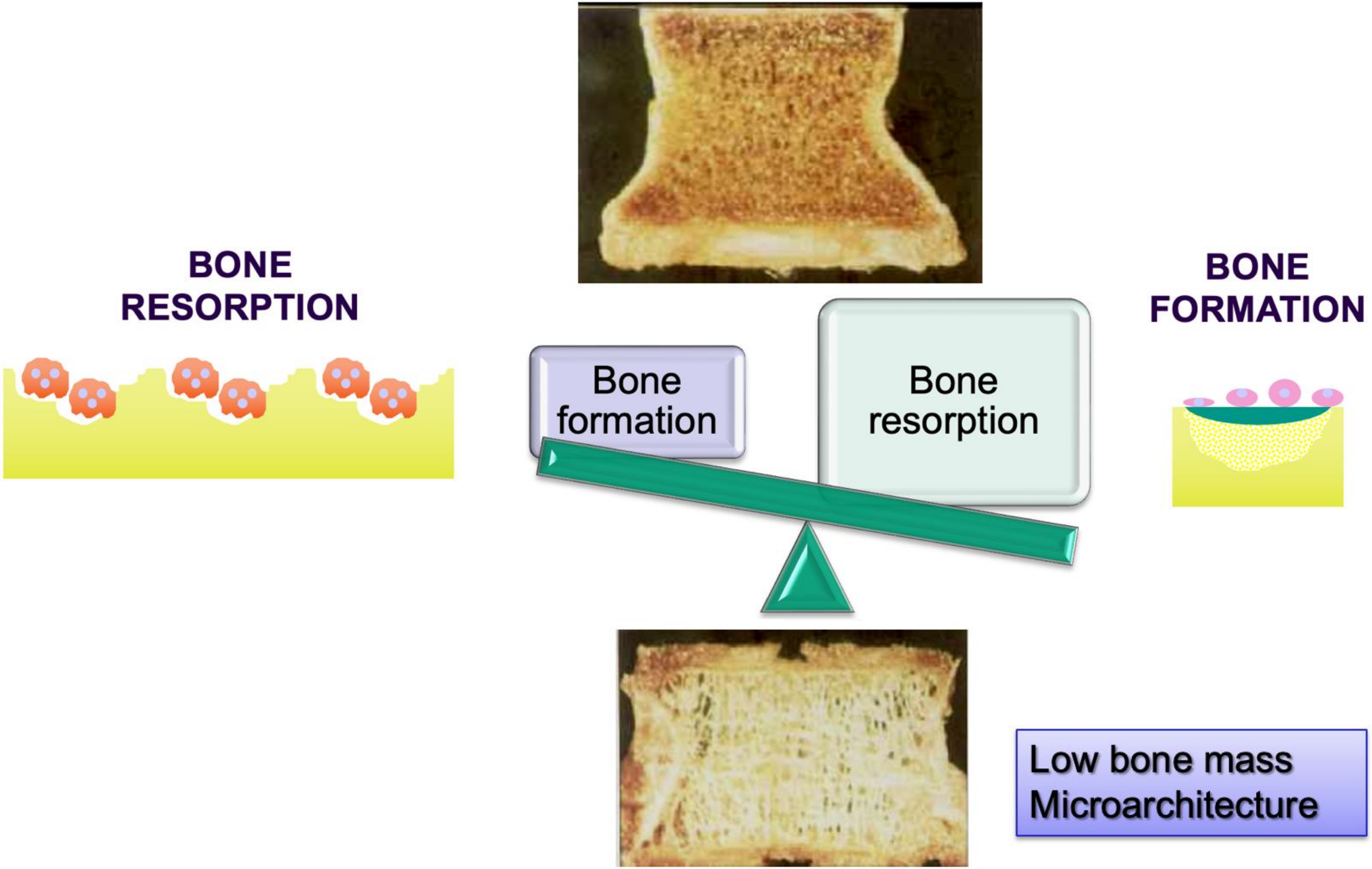
BONE RESORPTION



BONE FORMATION



Osteoporotic bone: Bone resorption > formation



Etiology of Osteoporosis

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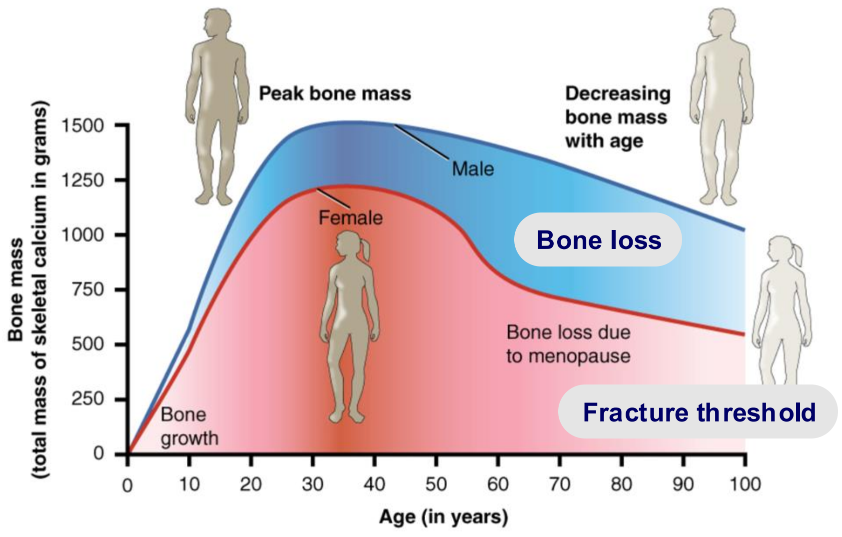
- **Primary osteoporosis (common)**
  - Postmenopausal osteoporosis
  - Age-related osteoporosis
  - Juvenile osteoporosis
- *****Secondary osteoporosis**

Factors affecting peak bone mass and early bone loss



Peak bone mass:
15-20 years after menarche

Causes of secondary osteoporosis

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Endocrine disorders

- Acromegaly
- Diabetic mellitus
- Growth hormone deficiency
- Hypercortisolism
- Hyperparathyroidism
- Hyperthyroidism
- Hypogonadism

Gastrointestinal diseases

- Inflammatory bowel disease
- Malabsorption syndrome
- Post gastric bypass surgery
- Chronic liver disease

Rheumatic diseases

- Rheumatoid arthritis
- Ankylosing spondylitis
- SLE

Hematologic disorders

- Multiple myeloma
- Monoclonal gammopathy
- Beta-thalassemia major

Neurological diseases

- Epilepsy
- Stroke
- Parkinsonism

Renal diseases

- Idiopathic hypercalciuria
- Chronic kidney disease
- Renal tubular acidosis

Genetic diseases

- Osteogenesis imperfecta
- Marfan syndrome
- Ehlers-Danlos syndrome

Look for secondary cause and treat!

Adapt from TOPF Clinical Practice Guideline 2021

Causes of secondary osteoporosis

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Drugs

- **Anti-epileptic drugs**: phenytoin, carbamazepine, phenobarbital
- **Aromatase inhibitors**
- Anti-coagulants
- Immunosuppressive drugs: cyclosporin, tacrolimus
- **Glucocorticoids**
- Thyroid hormone (overreplacement)
- GnRH agonists
- Medroxyprogesterone acetate
- Pioglitazone
- Proton pump inhibitors
- Selective serotonin reuptake inhibitors

Other medical conditions

- Acquired immunodeficiency syndrome
- Chronic obstructive pulmonary disease
- Post-transplantation
- Malnutrition
- Eating disorders
- Nutritional deficiencies: calcium, vitamin D, magnesium

Look for secondary cause and treat!

Adapt from TOPF Clinical Practice Guideline 2021

Clinical manifestations of osteoporosis

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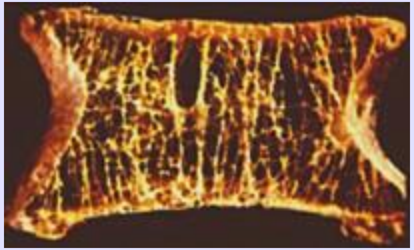
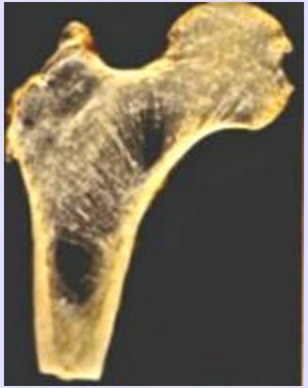
- **Fragility fractures**
  - Fall from standing height
  - Fracture without external trauma
- Chronic back pain
- Spine deformities
- Height loss
- Asymptomatic



SPINE



HIP: NECK, INTER-TROCHANTERIC REGION

FOREARM, RAD

Types of fall and common fracture sites

HIP FRACTURE

Fragility fracture

VERTEBRAL COMPRESSION FRACTURE

FOREARM (COLLES') FRACTURE

Mechanisms of osteoporotic fractures and common fracture sites

Fracture without external trauma

Incorrect body alignment and posture

Osteoporosis: Diagnosis

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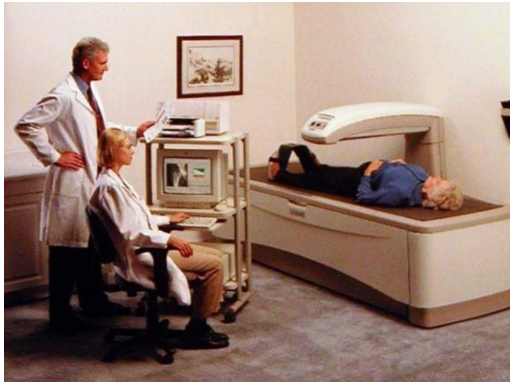
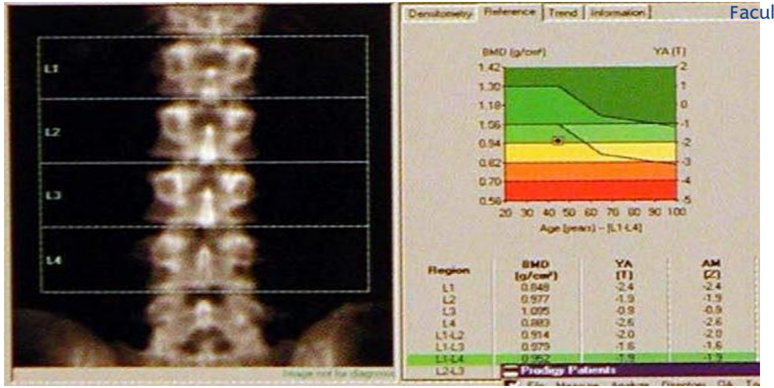
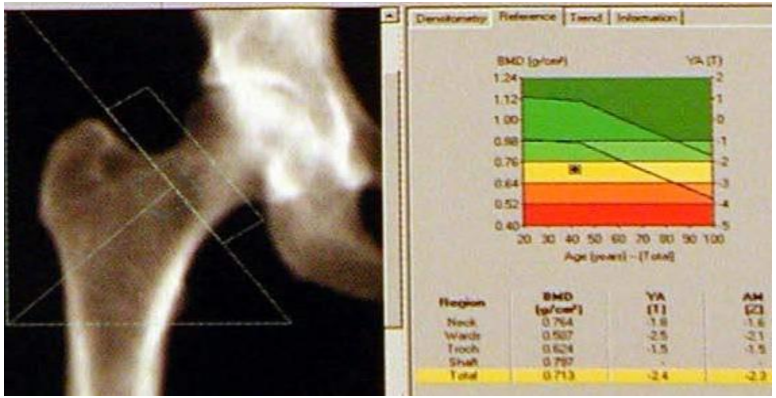
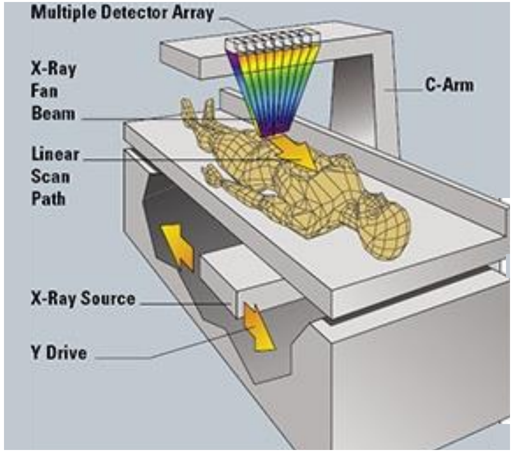
- Bone radiograph
- **Bone densitometry (DXA)** **Primary diagnostic tool**
  - Axial: spine, hip
  - Peripheral: forearm, calcaneus
- Bone ultrasonography
- Quantitative CT scan
- Bone biopsy – limited and typically for complex cases

Dual Energy X-Ray Absorptiometry (DXA)









THE ASSESSMENT OF BONE MASS (BONE MINERAL DENSITY)

WHO Classification of Osteoporosis

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Diagnosis	T-score
Normal	≥ -1.0
Low bone mass (osteopenia)	Between -1.0 and -2.5
Osteoporosis	≤ -2.5
Severe osteoporosis	≤ -2.5 + fragility fractures

- ✓ **Use the lowest T-score at any sites**
- ✓ Applicable only to **postmenopausal women and men ≥ 50 years**

Premenopausal women and men < 50 years

Z-score	Interpretation
>-2.0	Within the expected range for age
≤ -2.0	Below the expected range for age O low BMD for chronological age

WHO Collaborating Centre for Metabolic Bone Diseases, University of Sheffield; UK: 2007

Osteoporosis: Management

- General interventions for all
- Pharmacologic interventions
  - Antiresorptive agents
  - Bone formation stimulating agents
- Prevention of falls and other forces or impacts on bone
- Rehabilitation
- Surgical management

Osteoporosis: General interventions

- Adequate calcium intake
- Adequate vitamin D intake
- Adequate protein intake (1-1.2 g/kg/day), restrict high sodium diet
- Appropriate weight bearing, resistance, and balanced exercise
- Avoid agents known to toxic bone
  - Cigarette, alcohol, coffee, carbonated drinks
  - Drugs: glucocorticoids, thyroid hormone
- Fall assessment and prevention of fall or impaction force on bone

Daily Requirement of Calcium and Vitamin D

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Age	RDA Elemental Calcium (mg/day)				RDA VITAMIN D (IU/day)
	Male	Female	Pregnancy	Lactation	
0-6 month*	200	200			200
7-12month*	260	260			200
1–3 yr	700	700			600
4–8 yr	1,000	1,000			600
9–13 yr	1,300	1,300			600
14–18 yr	1,300	1,300	1,300	1,300	600
19–50 yr	1,000	1,000	1,000	1,000	600
51–70 yr	**1,000**	**1,200**			**600**
71+ yr	**1,200**	**1,200**			**800**

Monitor 25(OH)D 30-50 ng/mL

Institute of Medicine, National Academy of Science, November 2010

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Outline

- **Calcium homeostasis and bone biology**
- **Calcemic disorders**
  - Hypercalcemia
  - Hypocalcemia
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  - Osteoporosis
  - Rickets and osteomalacia
  - Renal osteodystrophy

Rickets and osteomalacia

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- **Disorders of delayed or abnormal bone mineralization**
- **Rickets**
  - Occurs before closure of epiphyses (glowing children)
  - Associated with skeletal deformities -> enlargement of the growth plate
  - Involved cartilaginous part and bone matrix part in the growth plate
- **Osteomalacia**
  - **Generalized softening of bones regardless of age and causes**
  - Involved bone matrix part in bone cortex and trabeculae
  - Occurs for both children and adults

J Bone Miner Metab. 2015 Sep;33(5):467-73.

Bone remodeling sequence in rickets/osteomalacia

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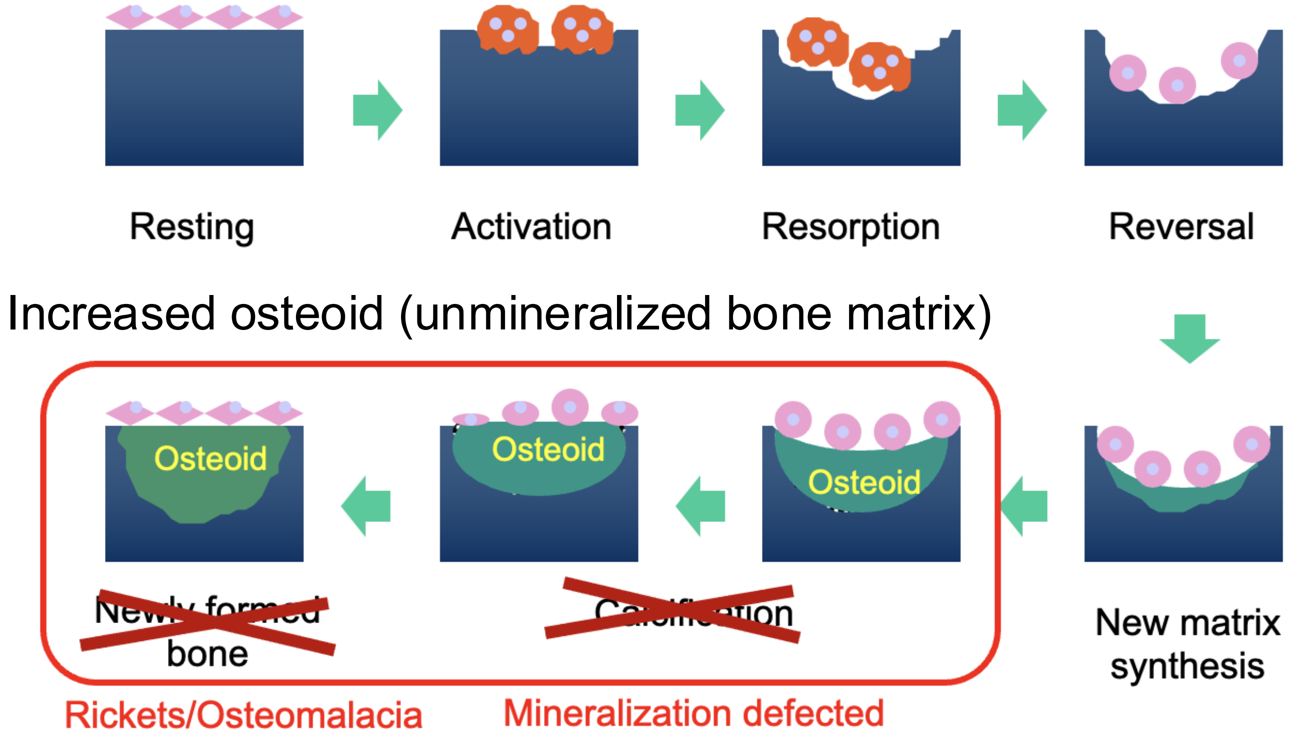

Pathophysiology of Rickets/Osteomalacia

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⇩ Hydroxyapatite crystals -- $Ca_{10}(PO_4)_6(OH)_2$

Vitamin D depletion or deficiency or resistance

Phosphate depletion or deficiency

Calcium deficiency

Matrix abnormalities

Mineralization inhibitors

Impaired mineralization: hereditary hypophosphatasia, medications (1st generation bisphosphonates), and toxicities from **aluminum, fluoride, and iron**

Pathophysiology of Rickets/Osteomalacia

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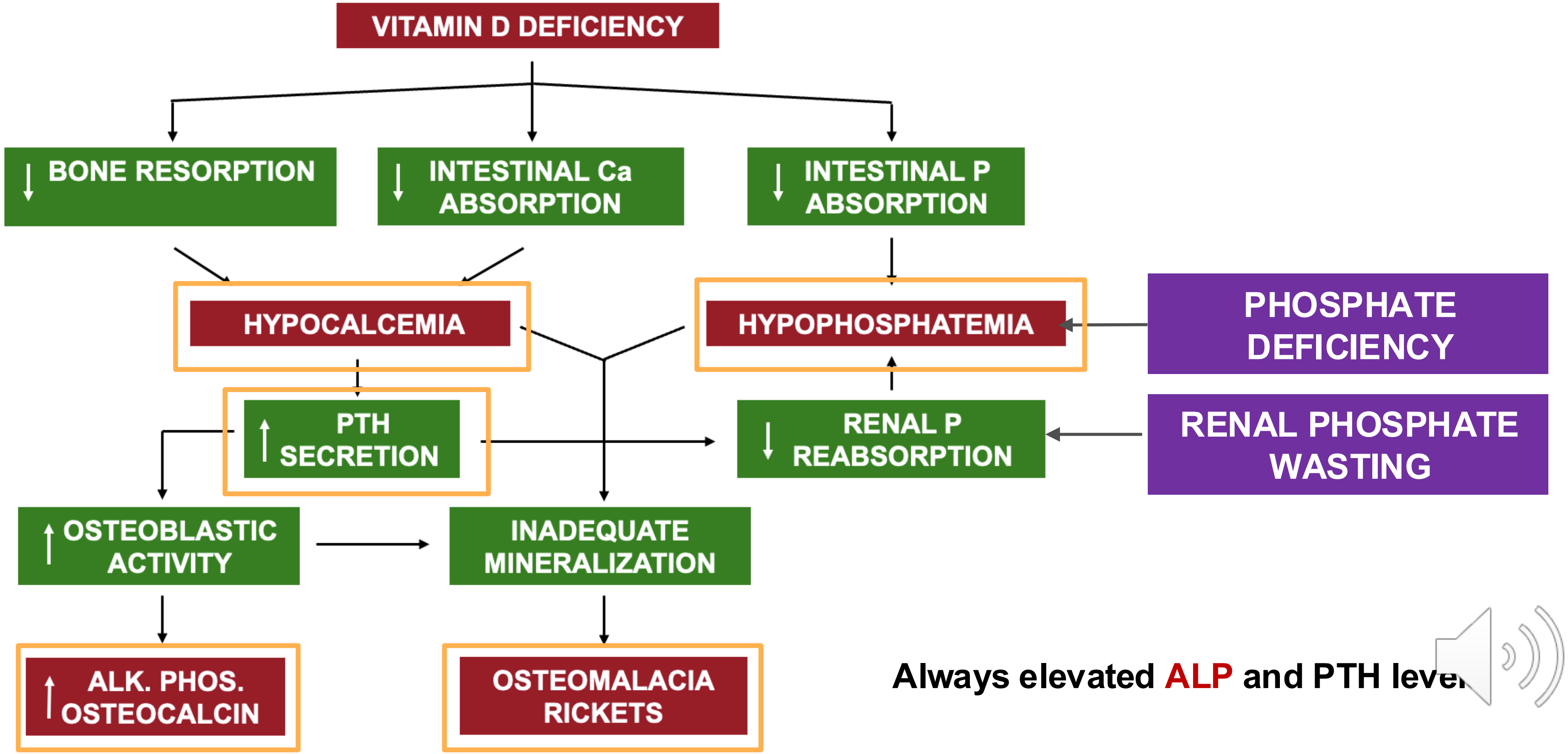

Always elevated ALP and PTH level

Rickets/Osteomalacia: Vitamin D-related

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CONDITION	MECHANISM
Nutritional deficiency	Vit. D deficiency
Malabsorption	Vit. D deficiency
Primary biliary cirrhosis	Vit. D malabsorption
Chronic liver disease	Impaired 25-hydroxylation
Chronic renal disease	Impaired 1-hydroxylation
Vit. D Dependent Rickets Type I	1-Hydroxylase deficiency
Vit. D Dependent Rickets Type II	Abnormal vitamin D receptor
Drugs	
Phenytoin	Increased Vit. D catabolism
Barbiturates	Increased Vit. D catabolism
Cholestyramine	Increased Vit. D excretion

Rickets/Osteomalacia: Hypophosphatemia-related

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CONDITION	MECHANISM
Diminished phosphate intake	Phosphate deficiency
Excess $Al(OH)_3$ intake	Increased binding of intestinal phosphate
X-linked hypophosphatemic rickets	Renal phosphate transport defect
Tumor-induced osteomalacia	Renal phosphate transport defect
Miscellaneous renal tubular defects Renal tubular acidosis Fanconi syndrome (i.e. anti-retroviral drugs)	Renal phosphate transport defect

Clinical Manifestations of Rickets/Osteomalacia

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- Skeletal deformities – specific signs
- Growth failure
- Symptoms of hypocalcemia: muscle cramps, tetany, seizure
- Bone pain
- Muscle weakness and pain
- Abnormal imaging findings
  - Rickets: Rachitic change
  - Osteomalacia: pseudofracture line (or Looser's zone)

Rachitic Changes in Rickets: Extremities

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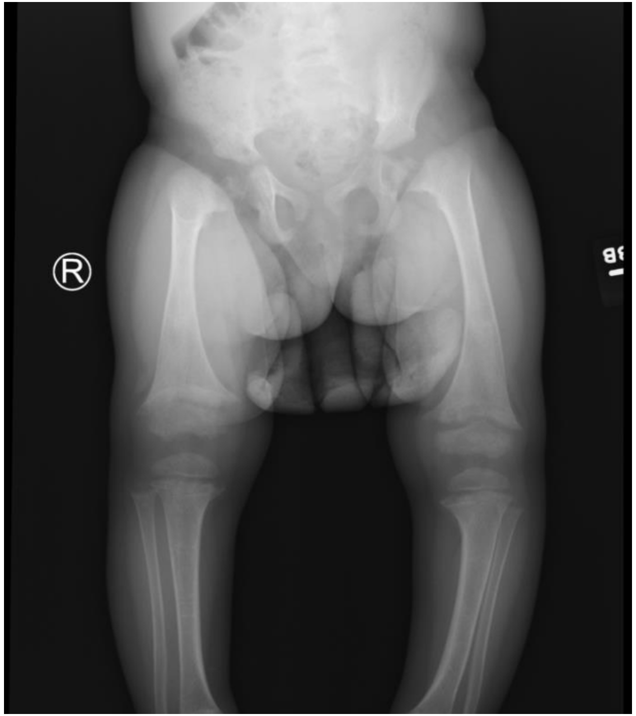
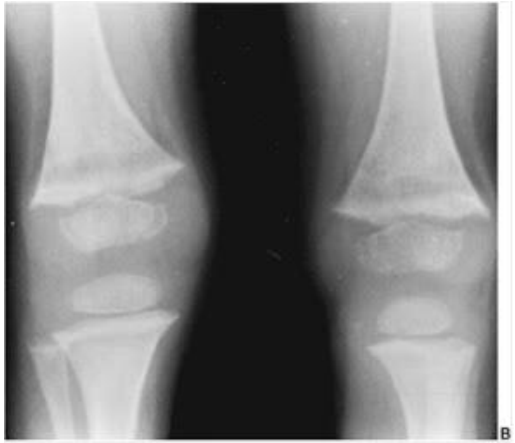


Genu varus (bow legs)

Widening of epiphyseal plate



Fraying and flaring of metaphysis

Rachitic changes in Rickets: Ribs

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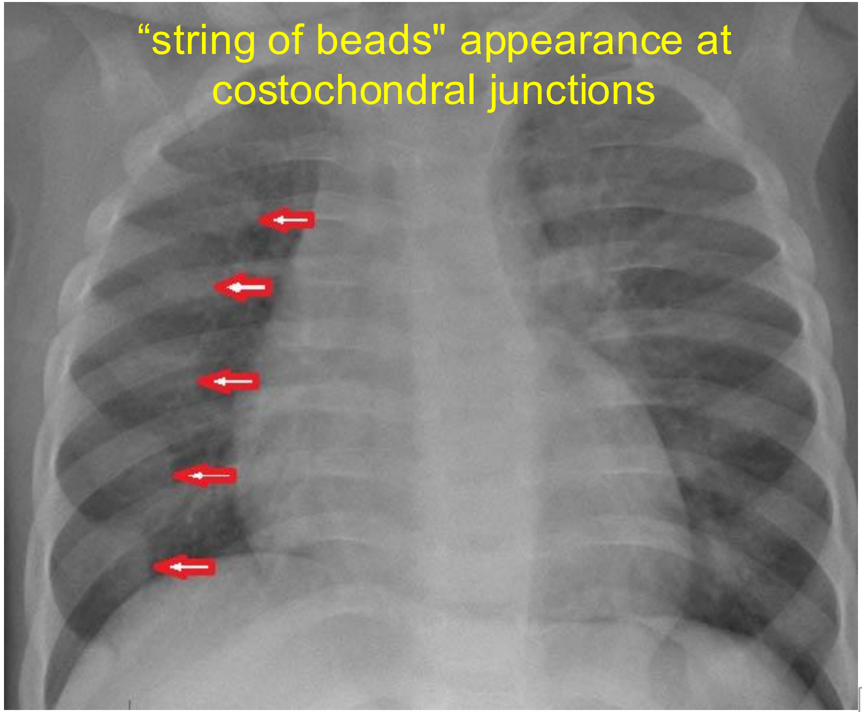
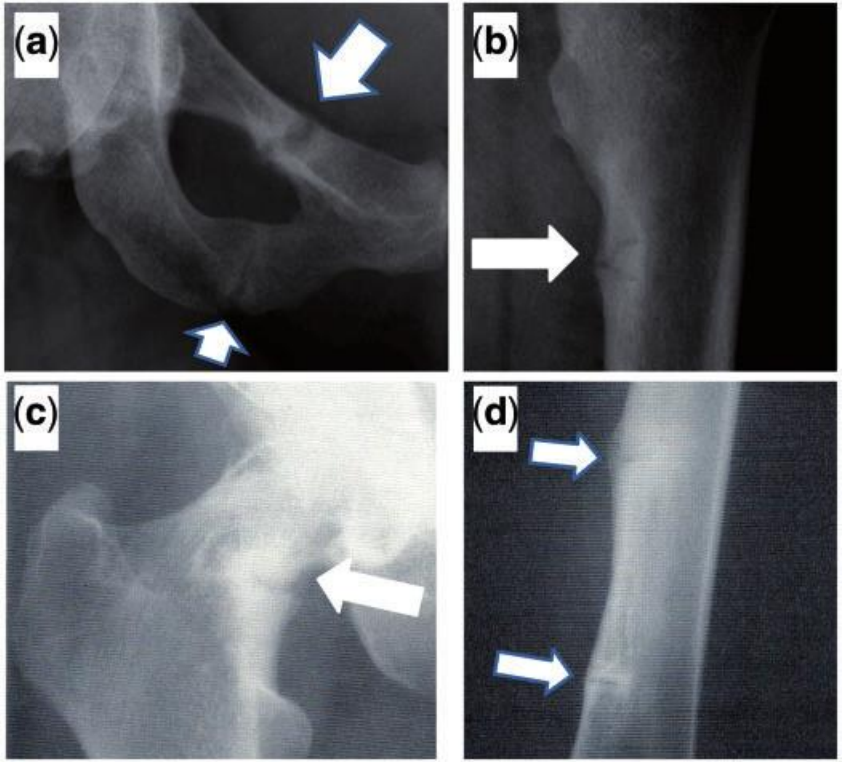


Rachitic rosary

Classic Skeletal Findings in Osteomalacia



Pseudofracture line (Looser's zone)

Biconcave vertebrae
(Codfish vertebrae)

McKenna MJ et al. QJM. 2014 Feb;107(2):99-105.

Outline

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Renal osteodystrophy

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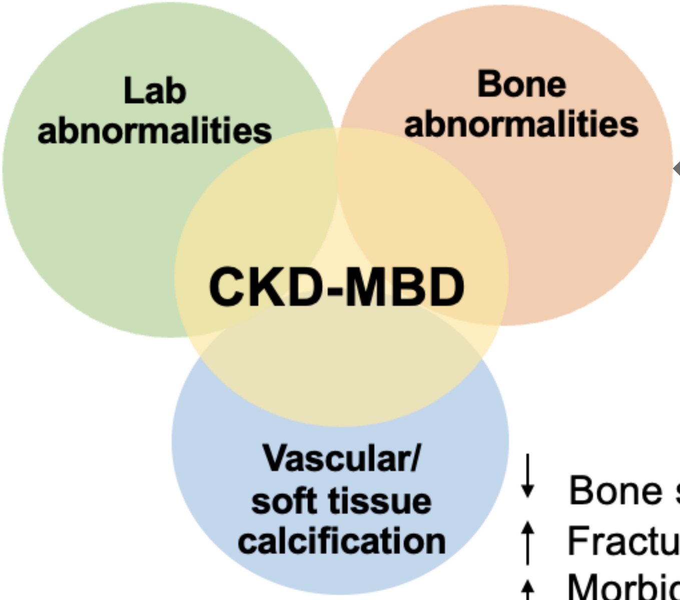
- **An alteration of bone morphology** in patients with chronic kidney disease
- A key component of Chronic kidney disease-Mineral and Bone Disorder (CKD-MBD)



Renal osteodystrophy

↓ Bone strength
↑ Fracture rate
↑ Morbidity and mortality

Bone histomorphometry in CKD-MBD

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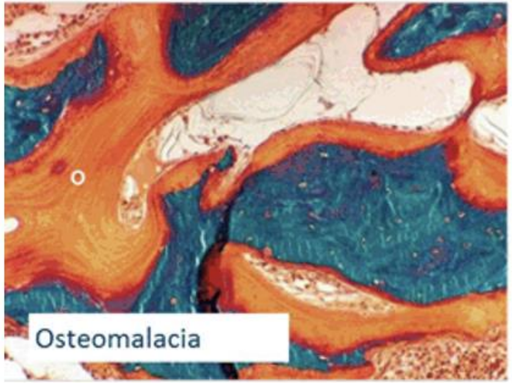
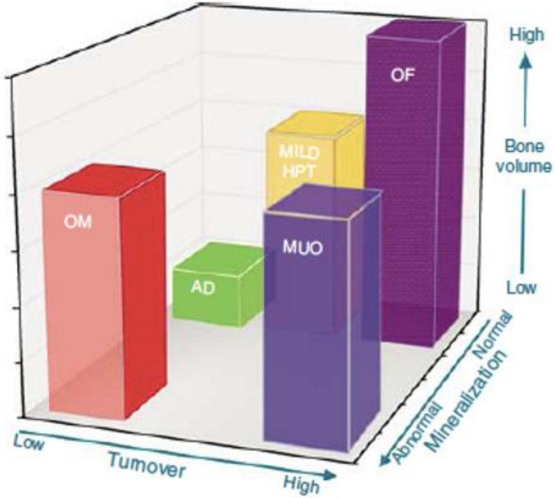
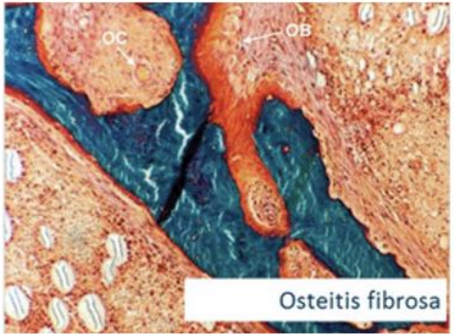
Low bone turnover

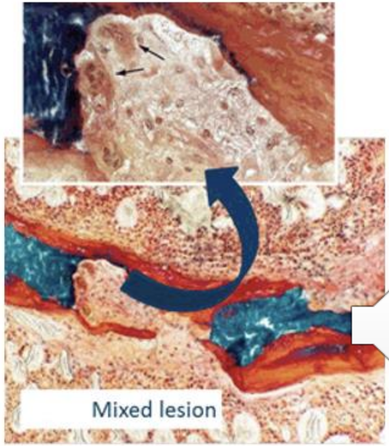




Low areal DXA-BMD (g/cm²)

High bone turnover





Radiologic Findings in Renal Osteodystrophy:
Severe Secondary Hyperparathyroidism

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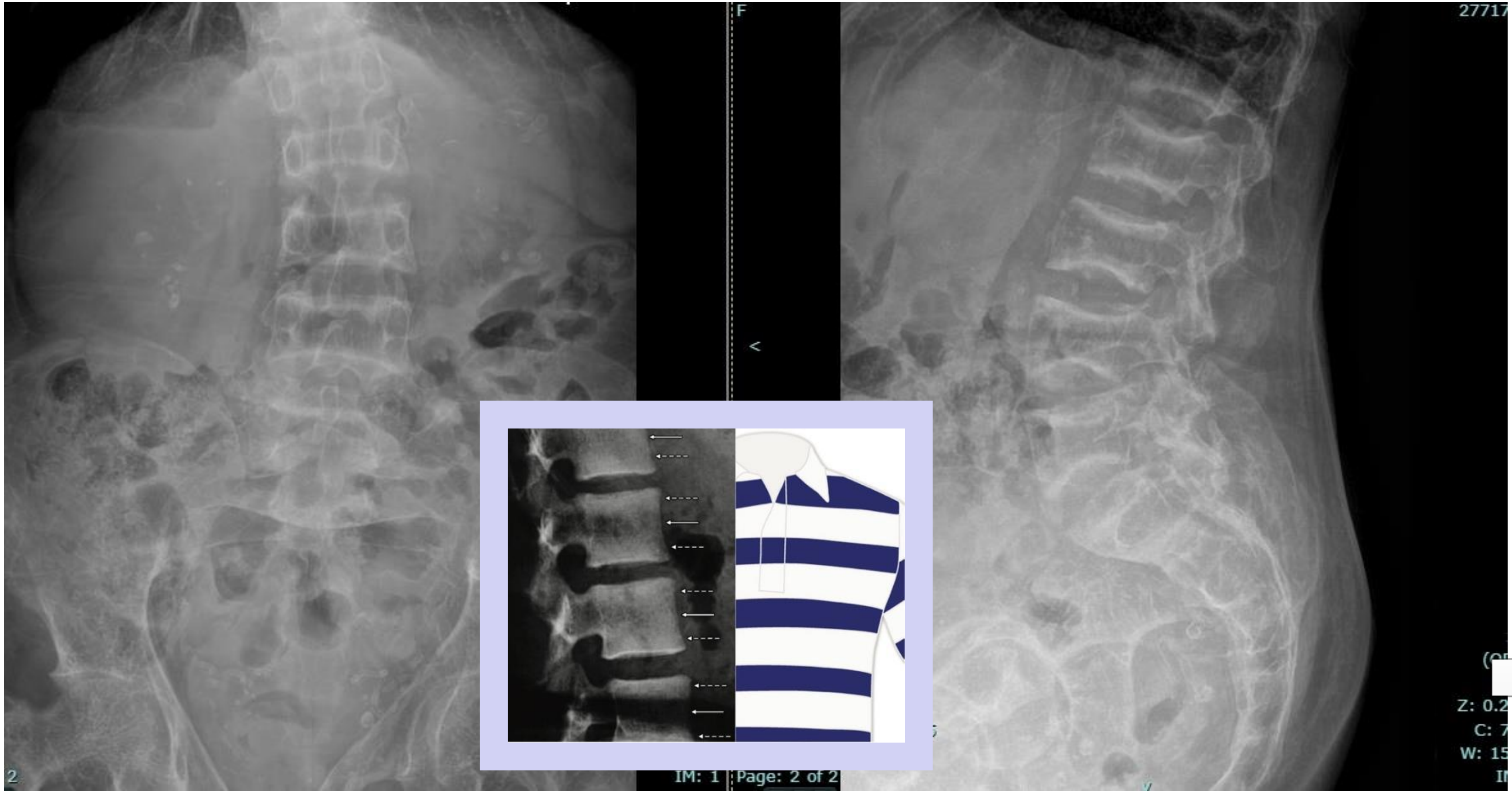

Radiologic Findings in Renal Osteodystrophy: Severe Secondary Hyperparathyroidism

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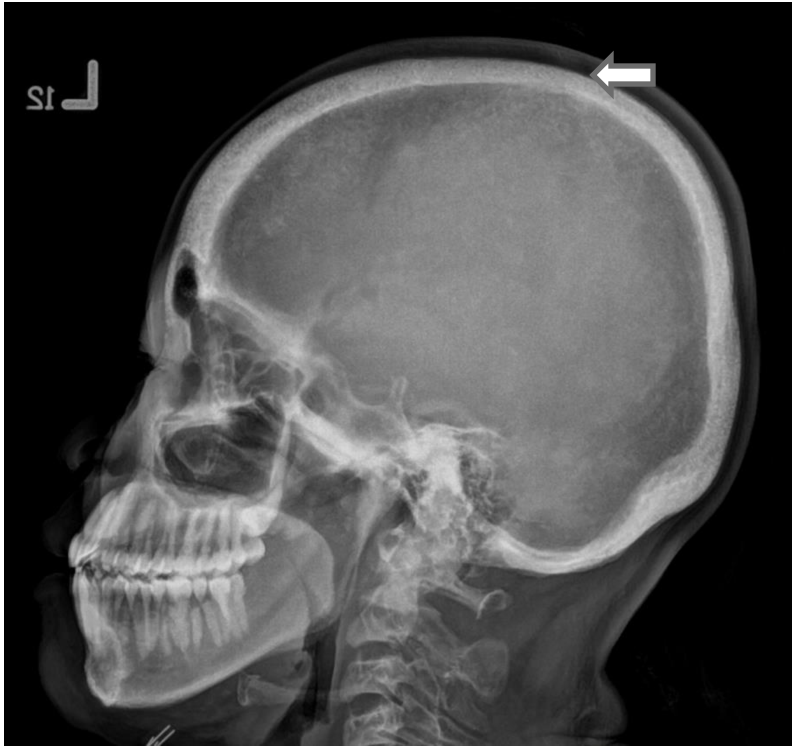

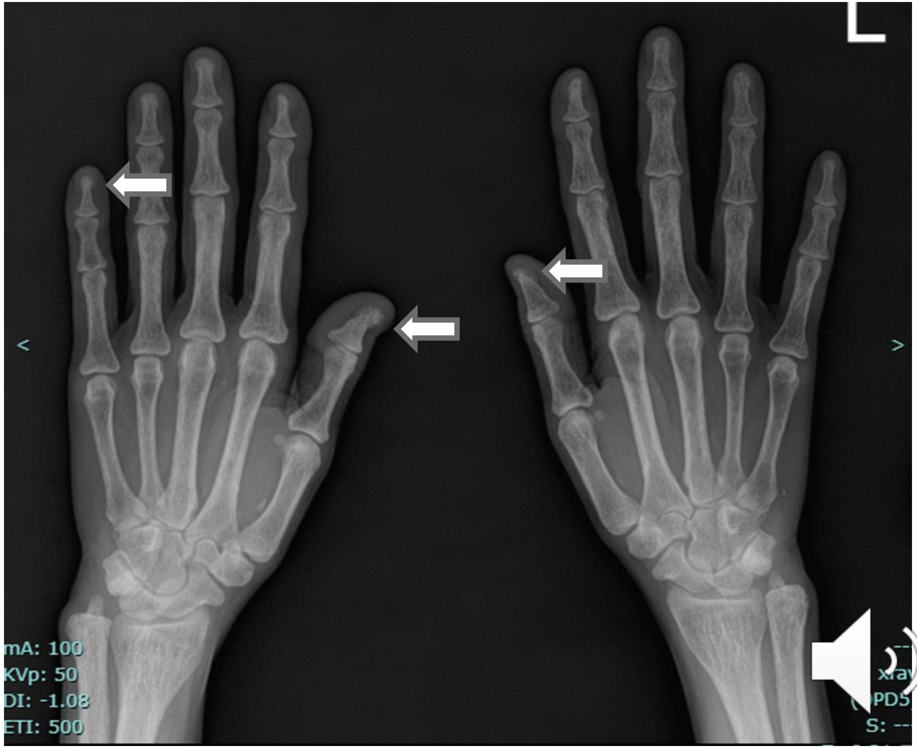

Radiologic Findings in Renal Osteodystrophy:
Severe Secondary Hyperparathyroidism

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Soft tissue calcification

Approach to metabolic bone diseases

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Diseases	Bone pain	Serum Ca	Serum PO4	Alkaline phosphatase	PTH
Osteomalacia/rickets	Without fracture	↓, ←	↓	↑	↑
Osteoporosis	With fracture	←	←	←, ↑	←, ↑
Primary hyperparathyroidism	With fracture	↑	↓	←, ↑	↑, ←
Secondary hyperparathyroidism	With fracture	↓	↑↑	↑	↑↑
Tertiary hyperparathyroidism	Without fracture	↑	↑↑	↑↑	↑↑↑

Conclusion: Diagnosis of Calcemic Disorders, Parathyroid and Metabolic Bone Diseases

- **Bone biopsy and histomorphometry are not generally available**
- **Calcium**: always interprets with serum albumin
- **Phosphorus**: relationship between Ca and P is useful
- **PTH**: always interprets with serum calcium levels (Main investigations for diagnosing parathyroid disorders)
- **Alkaline phosphatase**: Bone vs. liver sources (AST, ALT, GGT)
- **Vitamin D**: 25(OH)D reflect vitamin D status
- **BMD**: low BMD does not always reflect osteoporosis, also presents in other metabolic bone diseases (osteomalacia and renal osteodystrophy)

Conclusion: Osteoporosis

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Clinical clues of secondary osteoporosis

1) Younger age
2) Abnormal serum calcium, phosphorus, PTH and alkaline phosphatase levels (if no recent fractures)
3) Diseases or drugs-related with secondary osteoporosis
4) Specific patterns of bone radiographs
5) Low BMD: low Z-score (comparing to BMD of the same age group)

Thank you for your attention