PARATHYROID DISEASES

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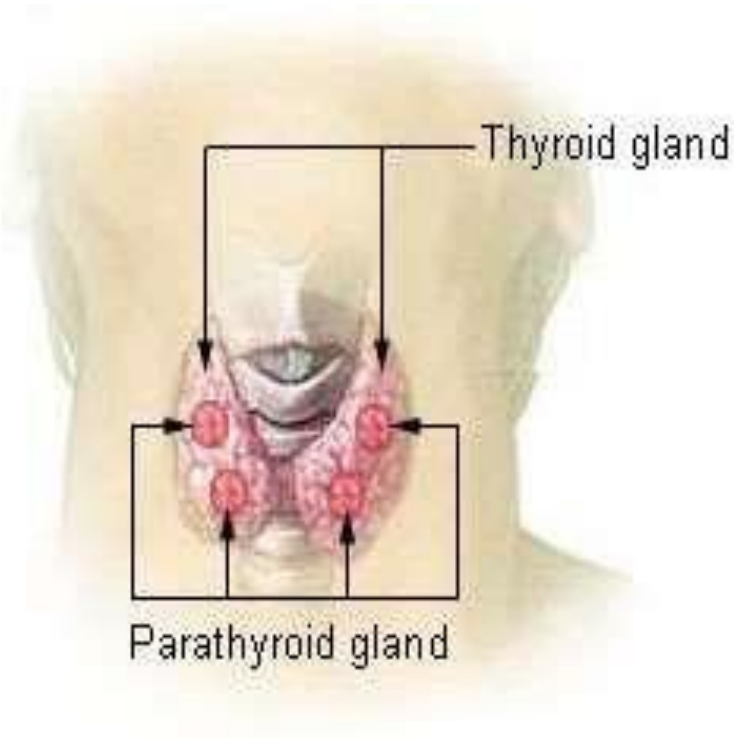
LECTURE PLAN

- Parathyroid hormone secretion regulation
- Hyperparathyroidism
- Hypoparathyroidism

Parathyroid Glands

- Four endocrine glands
- Formed by 3rd/4th pharyngeal pouch
- Located behind thyroid
- Secrete parathyroid hormone (PTH)
- Important for calcium, phosphate homeostasis



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Parathyroid Hormone

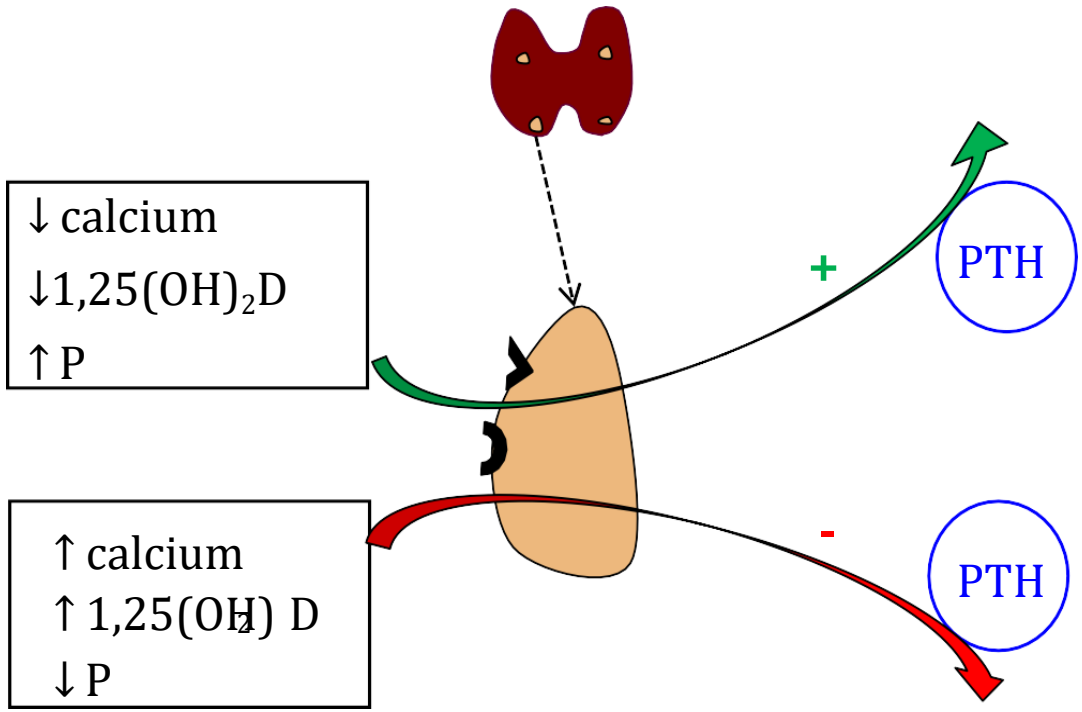
- Protein hormone, water soluble
- Binds to cell **surface receptors** in **bone and kidney**
- Synthesized by **chief cells** of parathyroid gland

Parathyroid Hormone Effects

- Net Effects:
  - **↑[Ca^{2+}] plasma**
  - ↓ [$P04^{3-}$] plasma
  - ↑ [$P04^{3-}$] urine
- Some effects due to direct action PTH
- Some due to activation of vitamin D (indirect)

Parathyroid Hormone

- Secreted in response to:
  - **↓ [Ca^{2+}]** (major stimulus; fastest response)
  - ↑ plasma [$P04^{3-}$]
  - ↓ 1 ,25-$(0H)_2$ vitamin D
- Calcium activates calcium-sensing receptors (CaSRs)
  - ↓ PTH



- Ca SR - calcium-sensing receptor
- VDR - vitamin D receptor

Parathyroid Hormone

MAGNESIUM

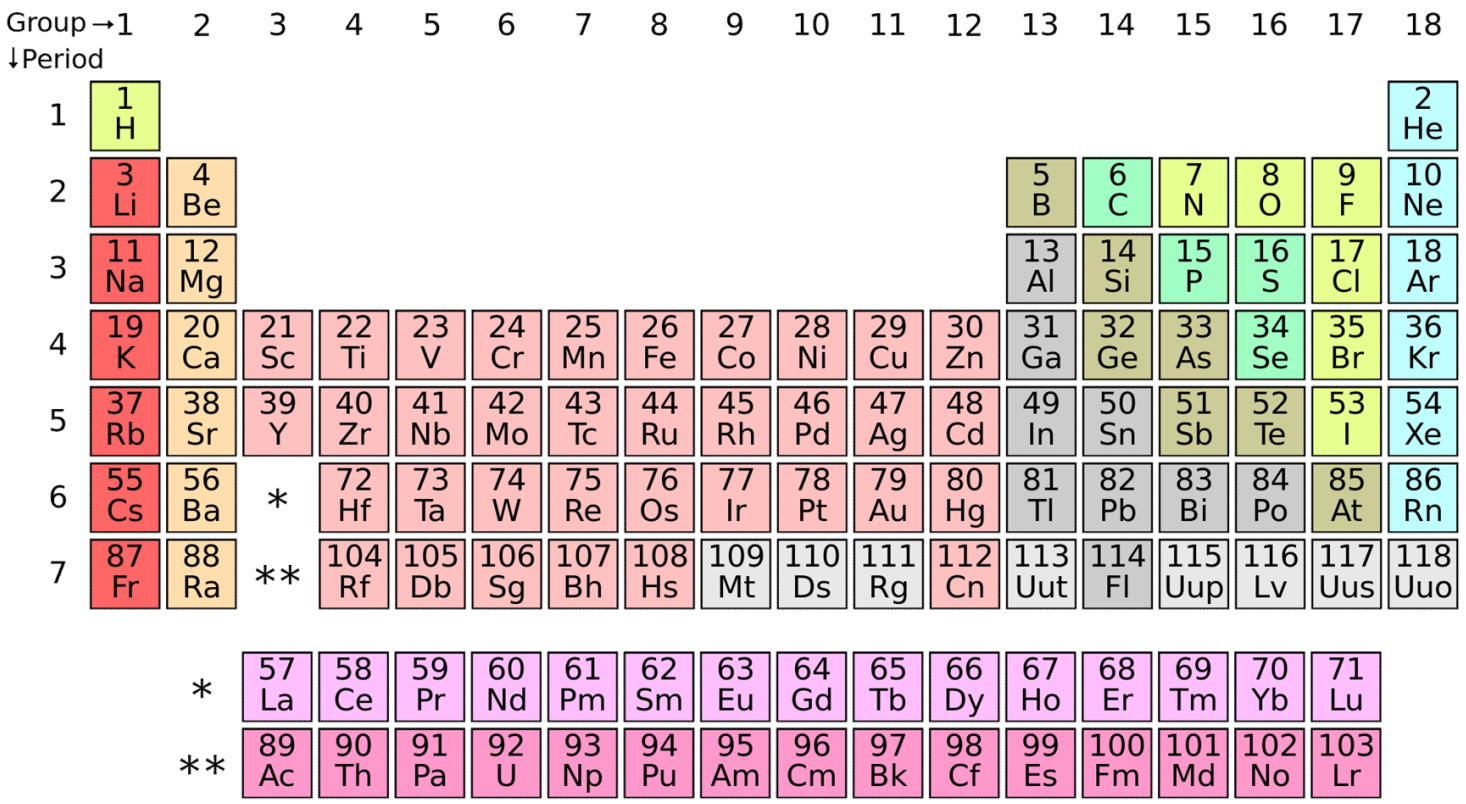
- High magnesium
  - ↓ PTH (same effect as calcium)
  - Magensium can activate CaSRs
- Low Mg
  - ↑ PTH release (same effect as calcium)
  - ↑ GI and renal magensium along with calcium

Parathyroid Hormone

MAGNESIUM

- Very low Mg → inhibits PTH release
  - Some Mg required for normal CaSR function
  - Abnormal function → suppression of PTH release

- **Hypocalcemia often seen in severe hypomagenesemia**



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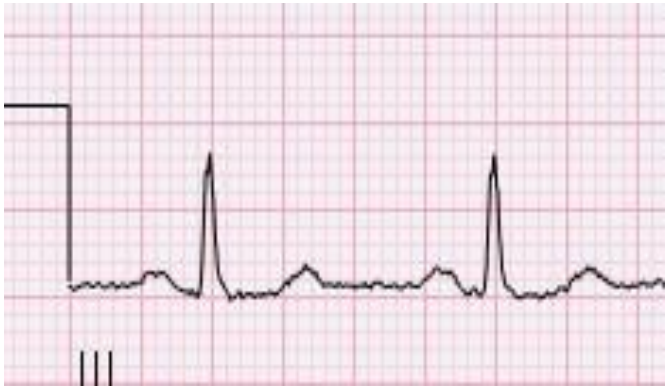
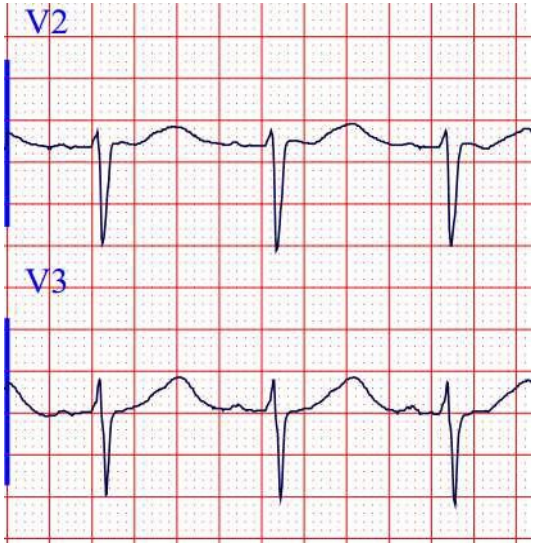
Qt Interval

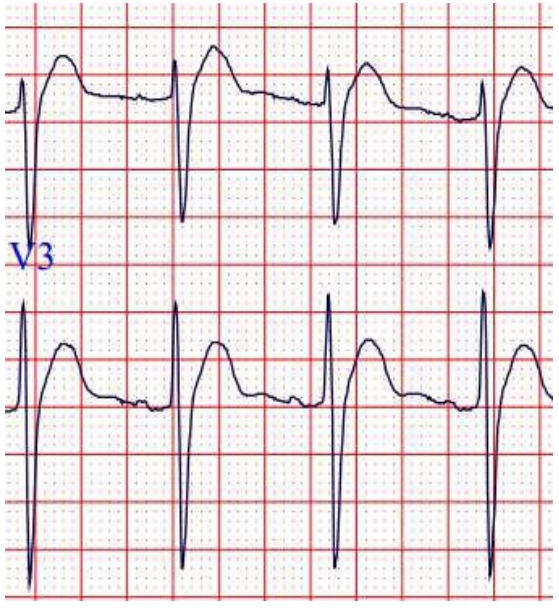
NORMAL QT





Prolonged Qt: ↓Mg, ↓Ca

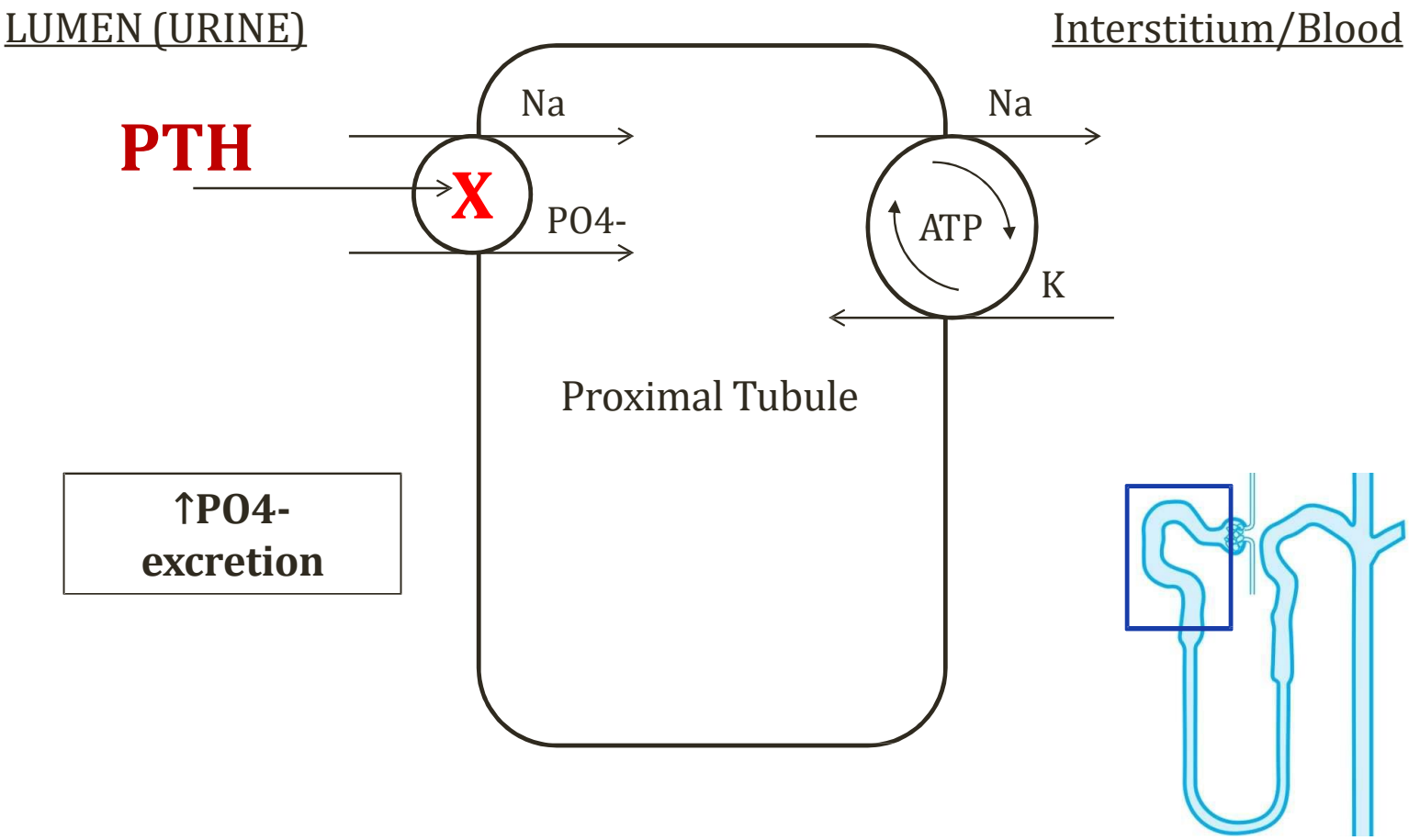
Short Qt: ↑Ca



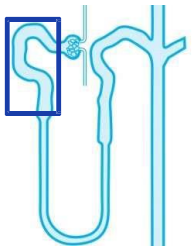
Parathyroid Hormone Effects

- Kidney:
  - ↑ Ca^{2+} resorption (DCT)
  - ↓ $P04^{3-}$ resorption (PCT)
  - ↑ 1 ,25-$(0H)_2$ vitamin D production
- GI:
  - ↑Ca2+ and $P04^{3-}$ absorption (via vitamin D)
- Bone:
  - ↑Ca2+ and $P04^{3-}$ resorption (direct and via vitamin D)

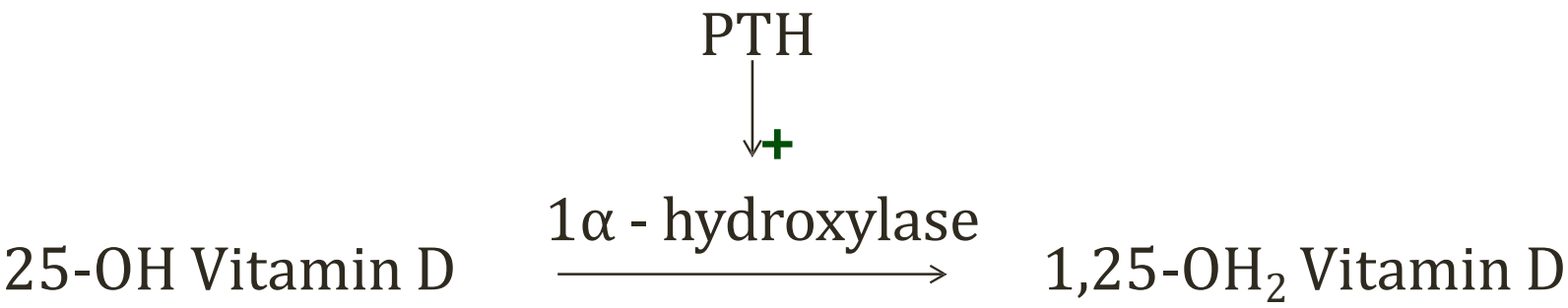
Parathyroid Hormone



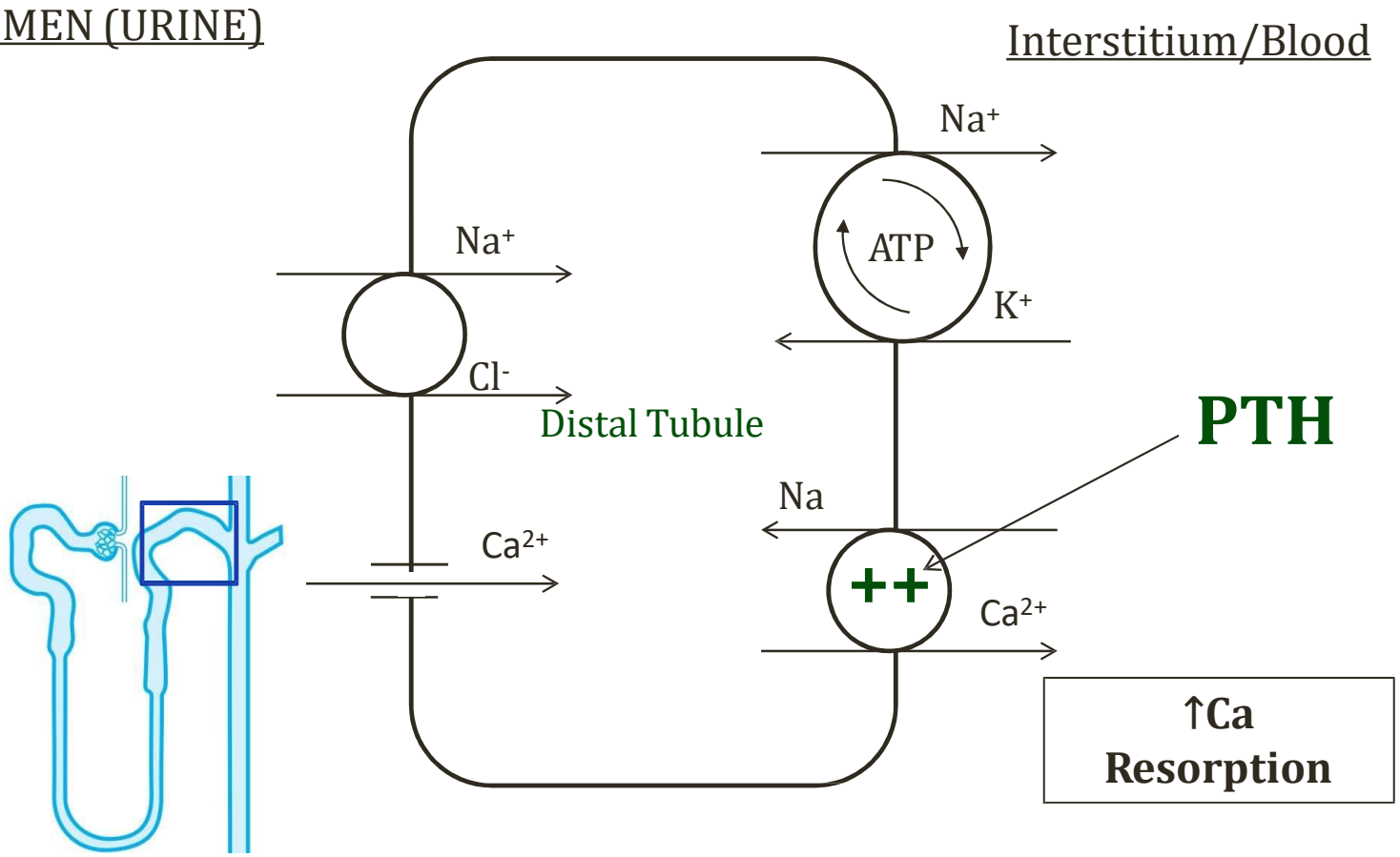
Vitamin D and the Kidney



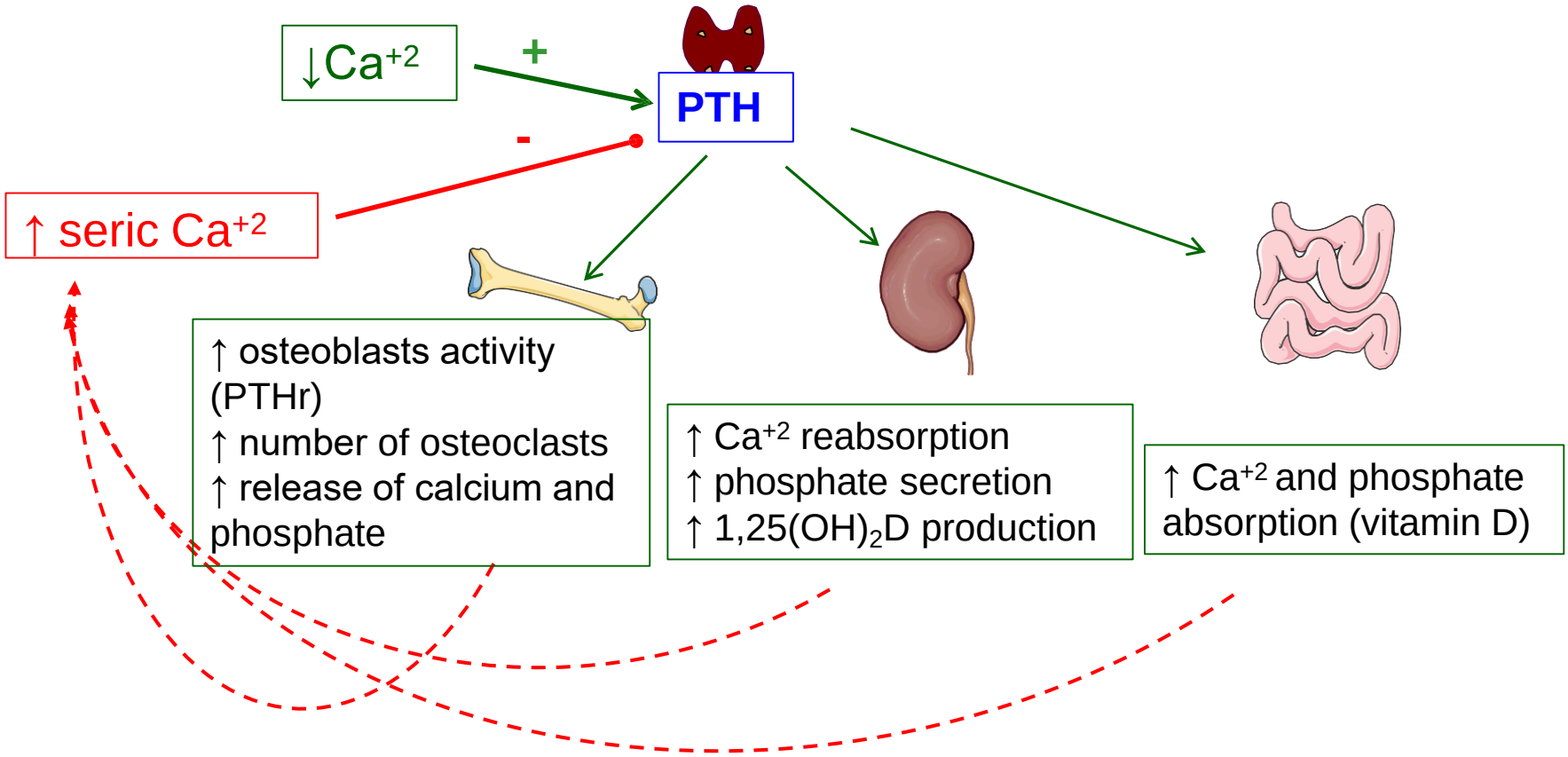
- **Proximal tubule** converts vitamin D to active form
- Can occur independent of kidney in **sarcoidosis**
  - Leads to **hypercalcemia**



Parathyroid Hormone



Parathyroid hormone effects



Parathyroid Hormone

- Multiple effects on bone
- Stimulates bone **resorption and formation**
- Dominant effect varies with dosage/timing of administration of PTH to bone

Parathyroid Hormone

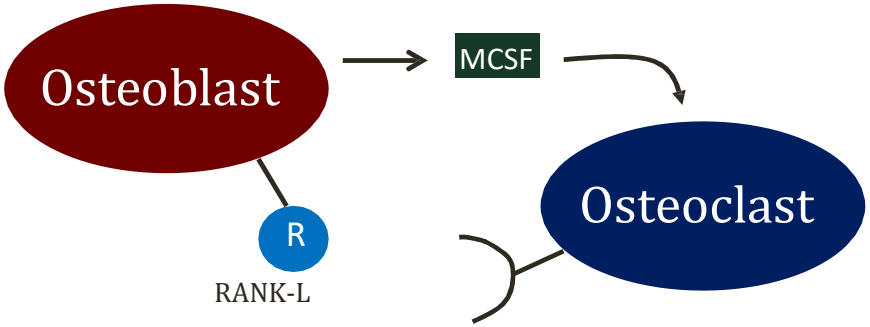
- Continuous administration of PTH
  - Bone resorption →↑ serum calcium
  - Important physiologically
- Low dose once daily bolus administration
  - Increased bone mass (bone formation)
  - **Teriparatide** used to treat osteoporosis

Parathyroid Hormone

- **Osteoblasts**
  - Bone forming cells
  - Contain PTH receptors
  - Can ↑ bone mass in response to PTH
- **Osteoclasts**
  - Bone resorbing cells
  - No PTH receptors
  - Activated indirectly by osteoblasts

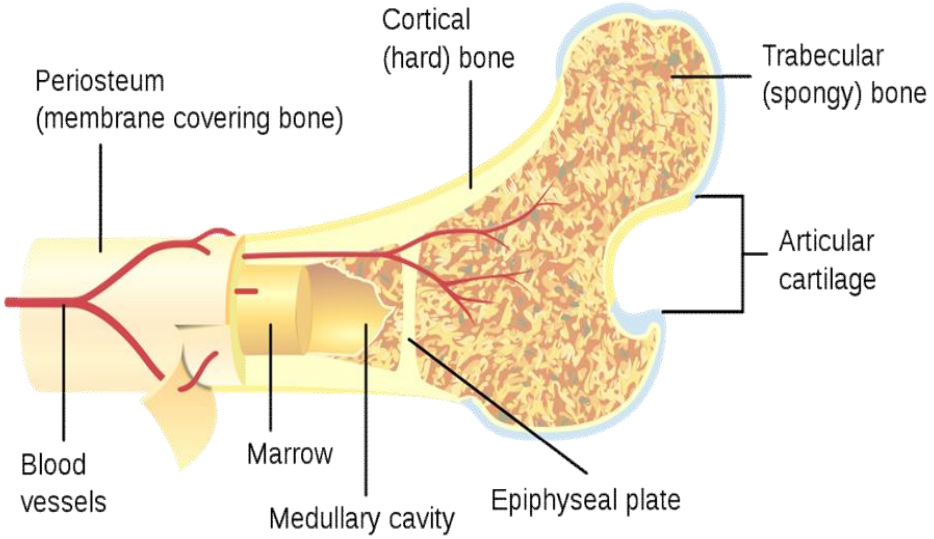
Parathyroid Hormone

- **M-CSF**
  - Macrophage colony stimulating factor
  - Secreted by osteoblasts
- **RANK-L**
  - Receptor activating nuclear factor kβ ligand
  - Expressed on surface of osteoblasts
- Both produced by osteoblasts → activate osteoclasts



Types of Bone

- Cortical bone
  - Hard, outer layer of bone
  - ↓ in response to continuous PTH
- Trabecular bone
  - Spongy, inner layer of bone
  - ↑ in response to intermittent, low dose PTH



PTHrP

PARATHYROID HORMONE-RELATED PROTEIN

- Produced in many tissues
- Numerous normal effects
- Synthesized in large amounts by some **tumors**
  - Renal cell carcinoma
  - Squamous cell lung cancer
- Leads to **hypercalcemia** in malignancy

PARATHYROID DISEASES

HYPERPARATHYROIDISM

Hyperparathyroidism

- Primary (overactive glands)
- Secondary (hypocalcemia)
- Tertiary (seen in renal failure)

Primary Hyperparathyroidism

- Inappropriate secretion of PTH
- Not due to low calcium
- Commonly caused by **parathyroid adenoma**

Primary Hyperparathyroidism

Cauze:

- one or more adenomas (75-80% cases)
- hyperplasia of the parathyroid glands (20%)
- Parathyroid carcinoma (less 1%)

The etiology of hyperplasia of the 4 parathyroid glands is multifactorial. It can be associated with familial hereditary syndromes (5-10%), such as multiple endocrine neoplasia (MEN), type 1 (90%) and 2a (30%) or 2b (4%).

Primary Hyperparathyroidism

- Causes **hypercalcemia**
  - ↑ renal reabsorption of Ca
  - ↑ vitamin D activation
  - ↑ bone resorption (loss of cortical bone)
- Phosphaturia

↑PTH ↑Ca

Primary Hyperparathyroidism

- Urinary calcium usually **high or normal**
- ↑ PTH → ↑ Ca urinary reabsorption → ↑ serum Ca
- ↑ serum Ca → ↑ urinary calcium

Primary Hyperparathyroidism

SYMPTOMS

- "Stones, bones, groans, and psychiatric overtones"
  - Largely historical
  - Modern era, most patients diagnosed early
  - Often asymptomatic; diagnosis by routine blood work
  - **Recurrent kidney stones** is common presentation
  - Other signs/symptoms more often seen **malignancy**

Primary Hyperparathyroidism

SYMPTOMS

- Stones (kidney)
  - High Ca in urine can cause stones
- Dehydration
  - Calcium blunts effects of ADH (nephrogenic DI)
  - Polyuria and polydipsia
  - Can lead to renal failure

Primary Hyperparathyroidism

SYMPTOMS

- Bones (bone pain)
  - Adverse effects on bones of long-standing high PTH
- Groans (abdominal pain)
  - Constipation, anorexia, nausea
  - Increased stomach acid production (unclear mechanism)
  - **Recurrent peptic ulcers**
- Psychiatric overtones
  - Anxiety, altered mental status

CLASIC CLINICAL PESENTATION

Bone involvement	Hipercalcemia	Hipercalciuria
Osteopenia	Peptic ulcers	Urolithiasys
Osteoporosis	Pancreatitis	Nephrocalcinosis
Fractures, bone deformities	Constipations, nausea, vomiting, loss of appetite	Nephrogenic Diabetes insipidus
Osteitis fibrosa cystica, brown tumors	Polydipsia, polyuria	
	Renal failure	
	CV: hypertension, arithmia, ventricular hypertrofia, calcifications (vascular, ventricular)	
	Weakness, fatigue	
	Neuropsychiatric disorders	
	Parathyroid crysis	

Osteitis Fibrosa Cystica

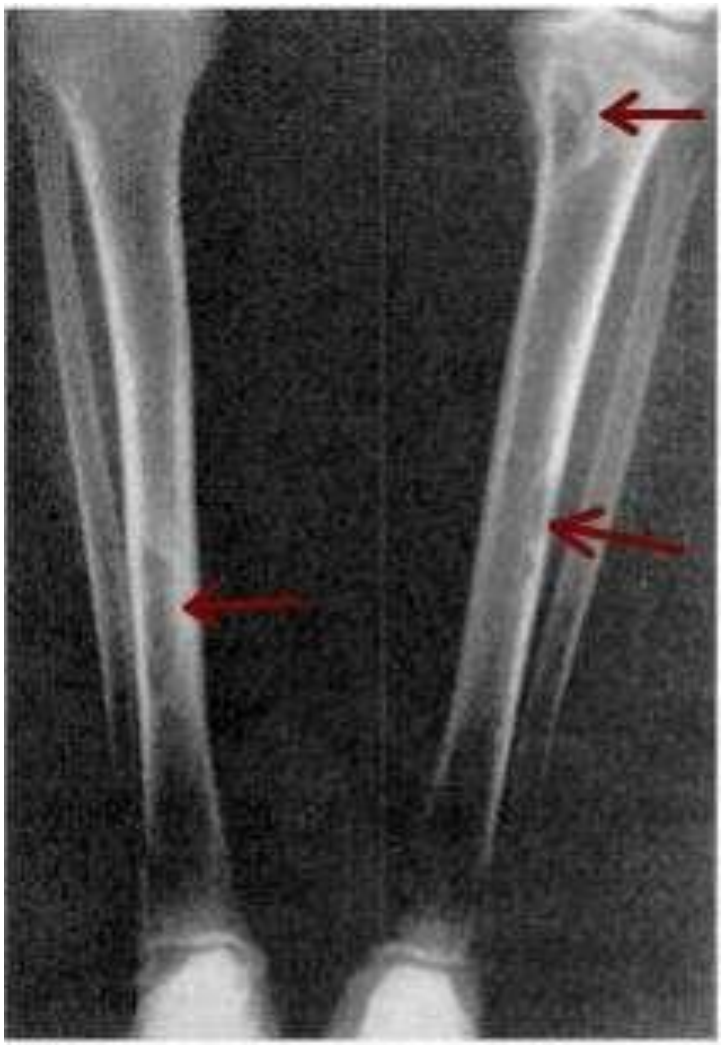
- Classic bone disease of hyperparathyroidism
- Clinical features:
  - Bone pain and fractures

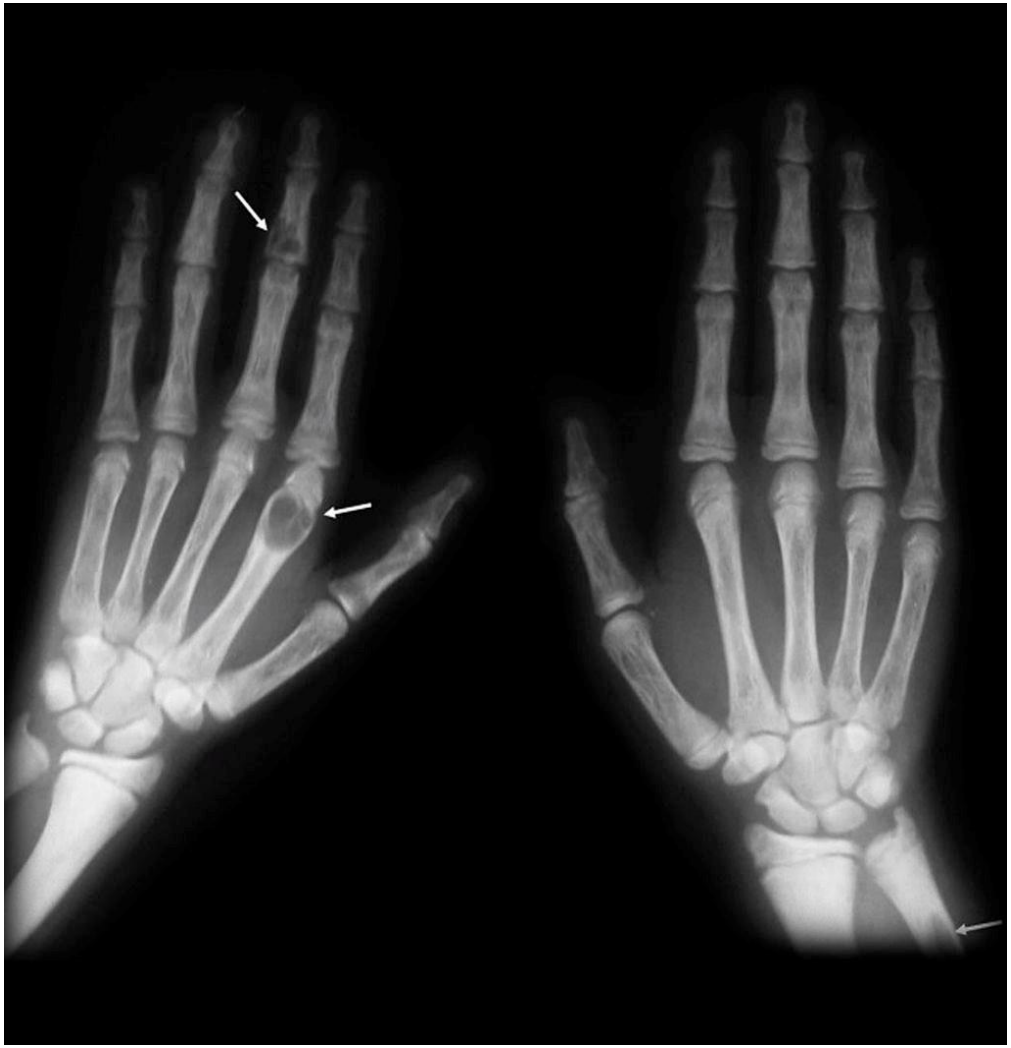
Osteitis Fibrosa Cystica

- **Subperiosteal** bone resorption
  - Commonly seen in bones of fingers
  - Irregular or indented edges to bones

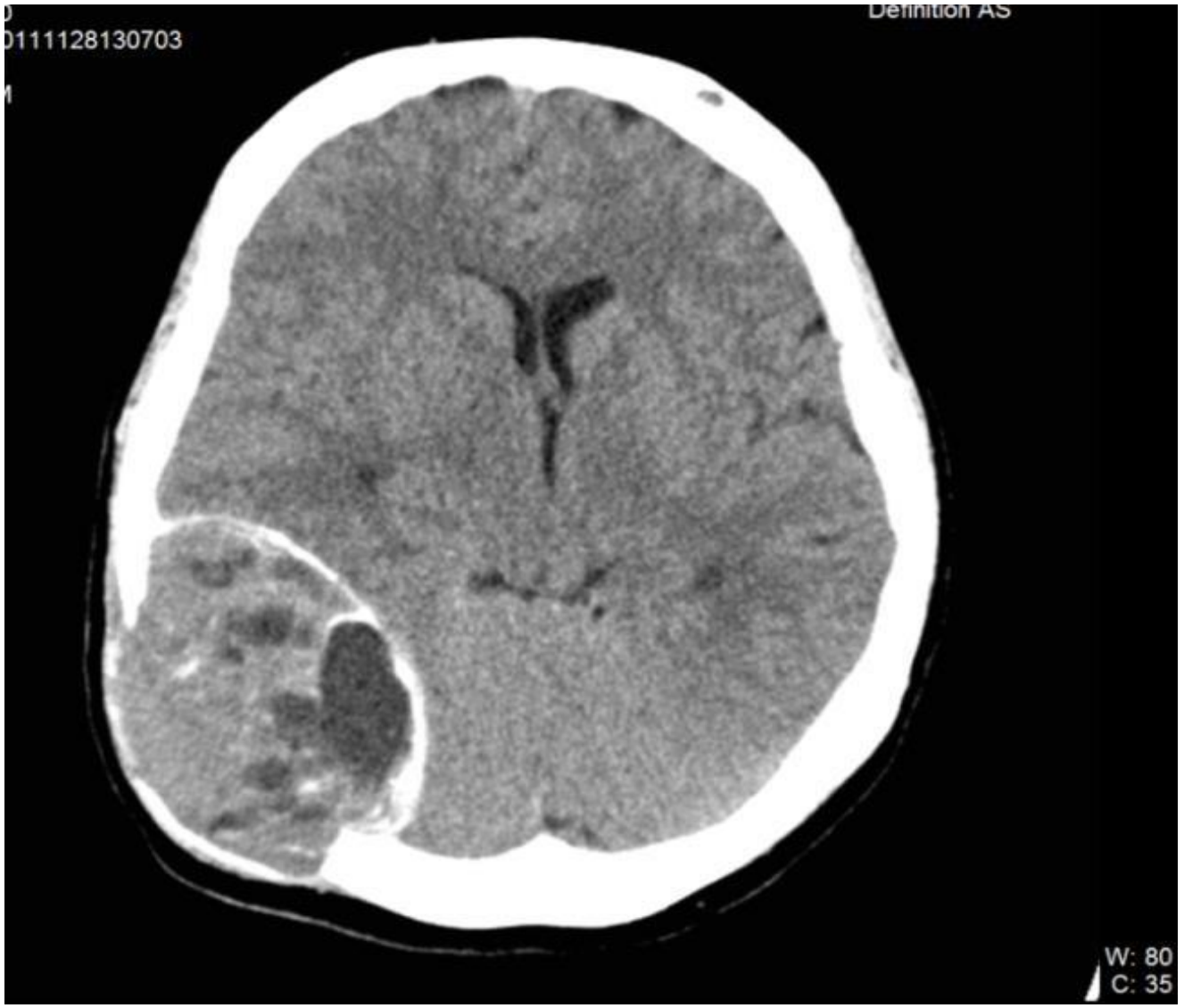
- **Brown tumors** (osteoclastoma)
  - Collections of giant osteoclasts in bone
  - Mixed with stromal cells and matrix proteins
  - Appear as black spaces in bone on x ray

Osteitis Fibrosa Cystica





Primary hyperparathyroidism
Bone destruction



Brown tumor - (CT)

PARATHYROID CRISIS

Rare

Serum Calcium > 15 mg/dl

Marked signs of hypercalcemia:

- dehydration (hypercalciuria)
- CNS disorders (confusion, nausea, vomiting)
- Constipation, paralytic ileus
- bradycardia (ECG - QT shortening)

DIAGNOSIS OF PRIMARY HYPERPARATHYROIDISM

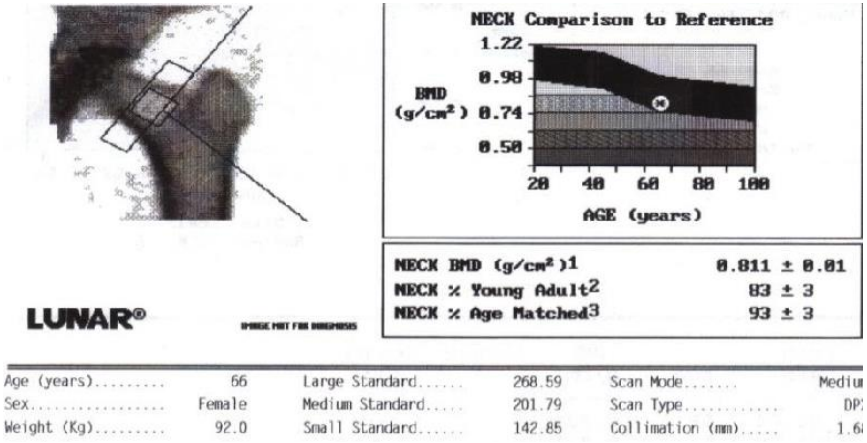
The diagnosis is established by evaluating the parameters:
Ca and PTH.

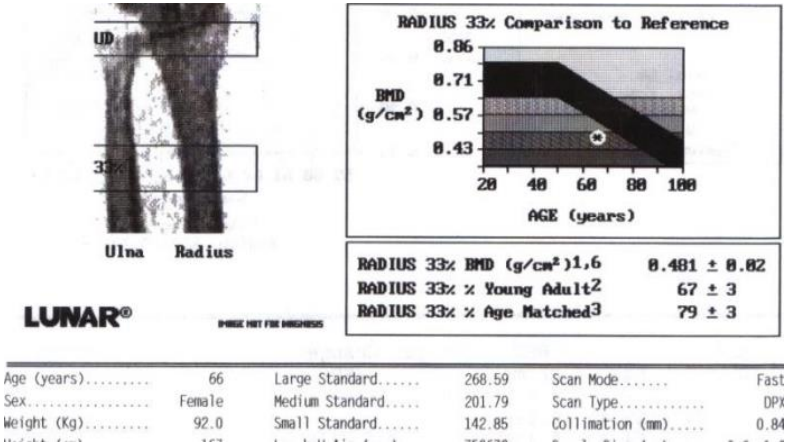
Primary hyperparathyroidism is associated with hypercalcemia and elevated PTH levels

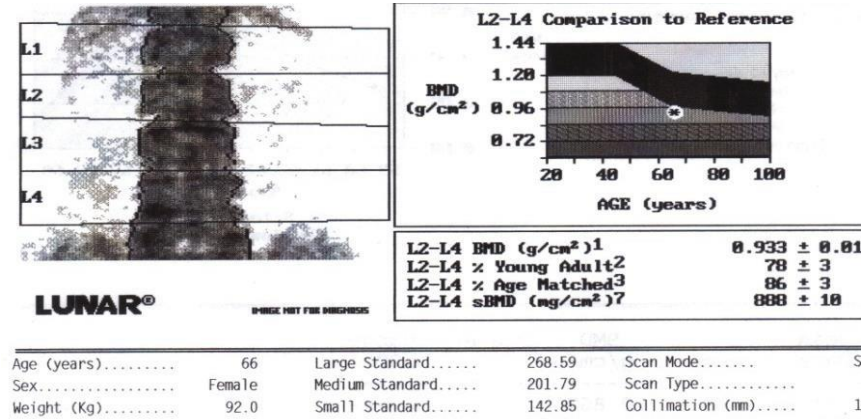
DIAGNOSIS OF HYPERPARATHYROIDISM
ADDITIONAL EVALUATIONS FOR THE TACTICAL DECISION

Bone densitometry (DXA)	• Lombar region • Hip (total or femoral neck) • radius (distal 1/3 site)
USG	renal
Rx deformed or painful parts of the skeleton	
Vertebral **F**racture **A**ssessment (**VFA**) by DXA or x-ray (assessment of risk of vertebral fracture)	Diagnosis of compression vertebral fractures in asymptomatic patients without osteoporosis on DEXA scan
Genetic disorders?	

PRIMARY HYPERPARATHYROIDISM
OSTEDENSITOMETRY







	T- score
Hip	-1.41
Lombar vertebrae	-2.23
Radius(1/3 distal)	-3.26

Patients with asymptomatic HPTP may have low BMD, especially in predominantly cortical areas (radius) compared to trabecular areas (vertebrae).

Primary Hyperparathyroidism

TREATMENT

- Parathyroidectomy
  - Removal of gland with adenoma
  - Pre-op nuclear imaging often done to identify location
- Risks of **recurrent laryngeal nerve** damage
  - May result in hoarseness
- Post-op **hypocalcemia**
  - Remaining parathyroid glands may be suppressed
  - Numbness or tingling in fingertips, toes, hands
  - If severe: twitching or cramping of muscles

PRIMARY HYPERPARATHYROIDISM
INDICATIONS FOR SURGERY

Parameters	Recommended intervention
Serum Calcium	**> 1.0 mg/dl (0.25 mmol/L) above normal**
Skeletal	**A.Bone Mineral Density** on DXA **T score < -2.5** SD in lombar vertebrae, hip or radius (distal 1/3) or the presence of a **fragility fracture** **Vertebral fracture on** X-ray, CT, MRI
Renal	A. Creatinine clearance < 60 ml/min B. urinary calcium 24h > 400 mg/d (>10 mmol/d) and elevated risk of stone formation **C.Presence of nephrolithiasis or nephrocalcinosis** X-ray, USG, CT
Age	< 50 years old

**According to: Guidelines for the Management of Asymptomatic Primary Hyperparathyroidism: Summary Statement from the Fourth International Workshop. Bilezikian et al.,JCEM,2014,99*

Location imaging is not used to diagnose HPTP or to determine treatment tactics

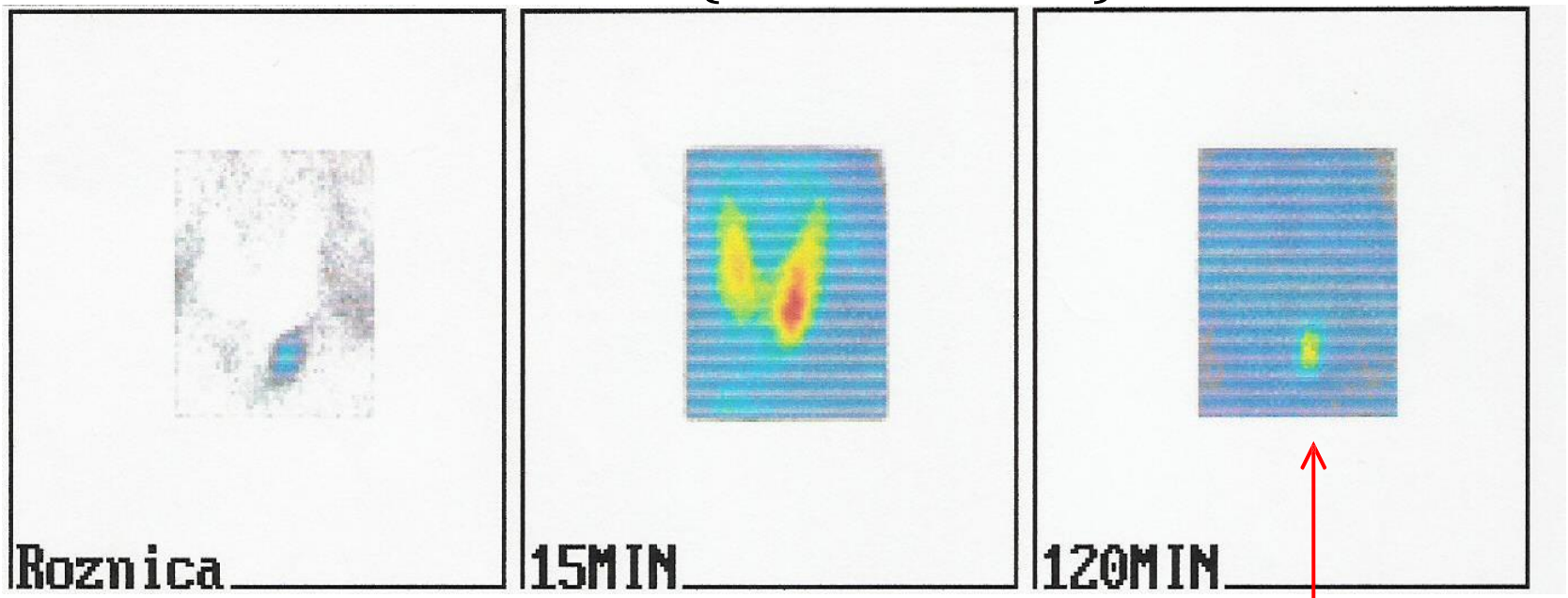
!It is performed after the decision to perform surgery

HPTP LOCATION IMAGING

Tipul	**Comentarii**	**Sensibilitate ***
Ultrasound	Usually - adenoma of the parathyroid with hypoechoic characteristic, posterior to the thyroid tissue with peripheral vascularization. USG provides additional information regarding the thyroid gland	up to 80%
Technetium-99m sestamibi scinti	Uniplane image	60-90%
SPECT — Sestamibi-single photon emission computed tomography	3D Dimensional Image - the presence of multiple dimensions shows the location of the parathyroid glands relative to the thyroid gland	~ 90%
SPECT-CT	SPECT and CT fusion. It offers the possibility to distinguish the parathyroid glands from the adjacent tissues.	
Computed tomography (CT)	Low sensitivity	
Magnetic resonance imaging (MRI)	For reinterventions - helps to locate the parathyroid tissue	40-85%

* Sensivity for detecting solitary adenoma. No imaging technique accurately predicts multiglandular disease

PARATHYROID SCINTI (TC99 + MIBI)

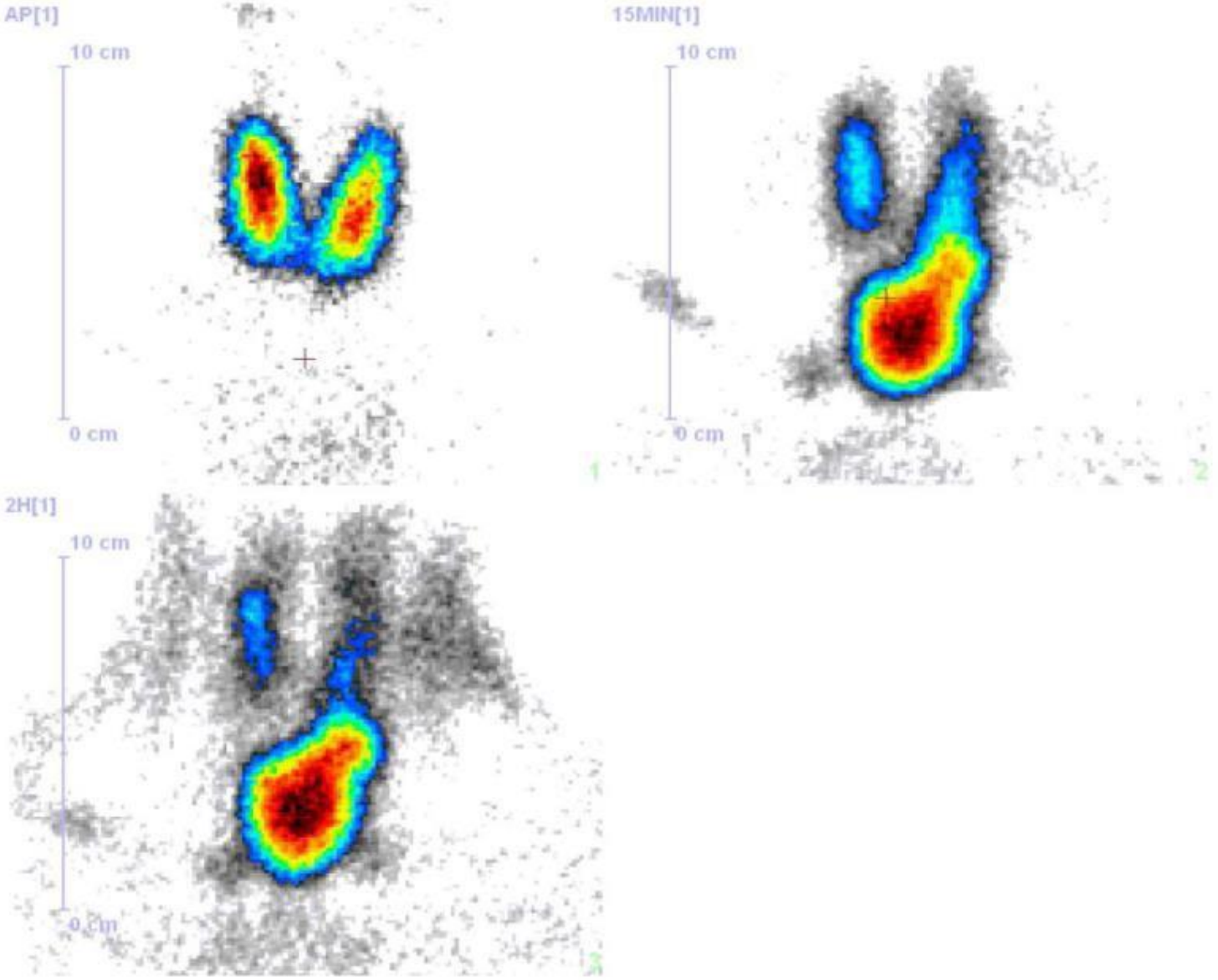


Adenoma paratiroidei pe stânga, inferior

99mTc-sestamibi is taken up by the mitochondria in thyroid and parathyroid tissue; however, the radiotracer is retained by the mitochondria-rich oxyphil cells in parathyroid glands longer than in thyroid tissue. Radionuclid usually washes out of normal thyroid tissue in under an hour. It persists in abnormal parathyroid tissue.

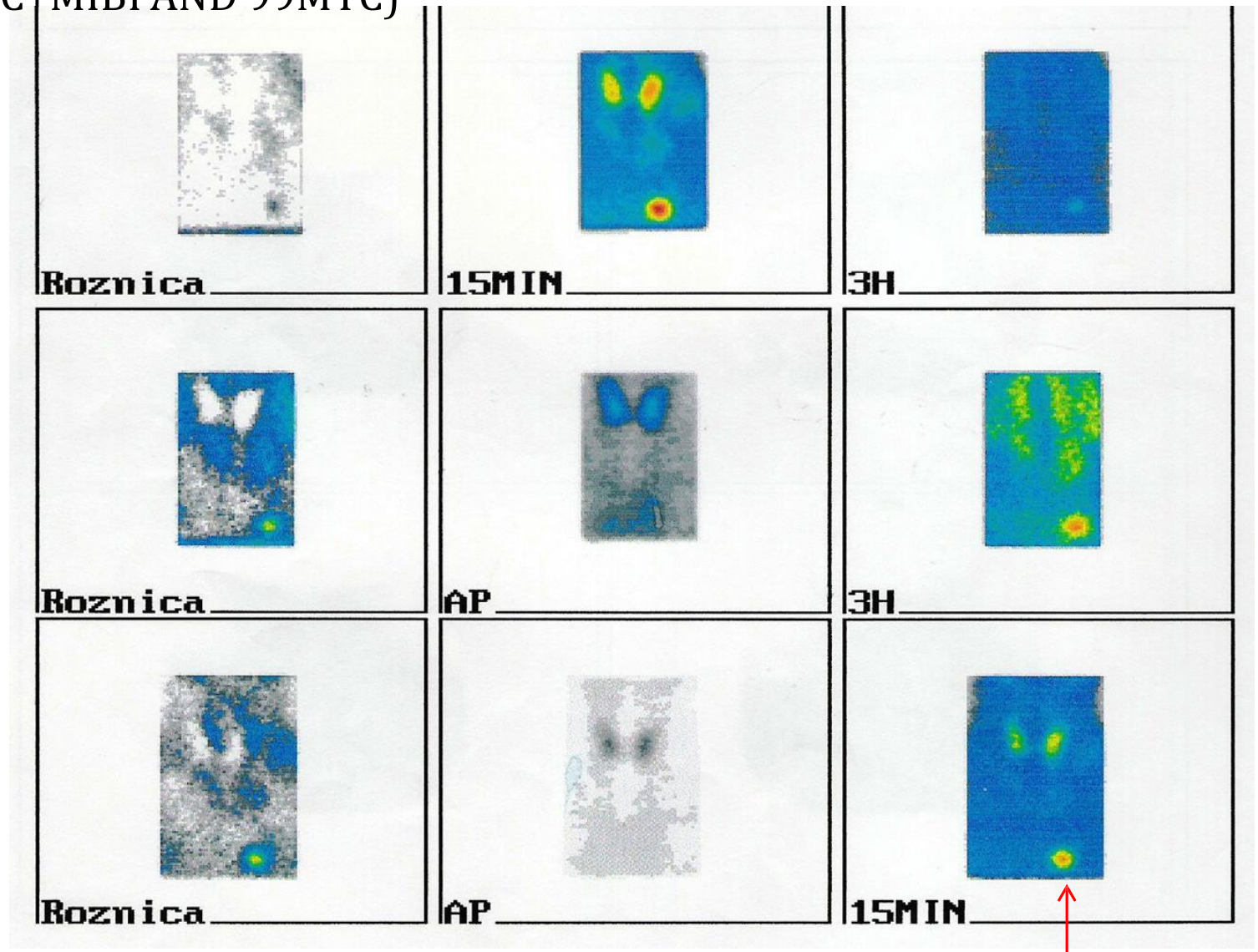
PARATHYROID SCINTISCAN

(99MTC+MIBI AND 99MTC)

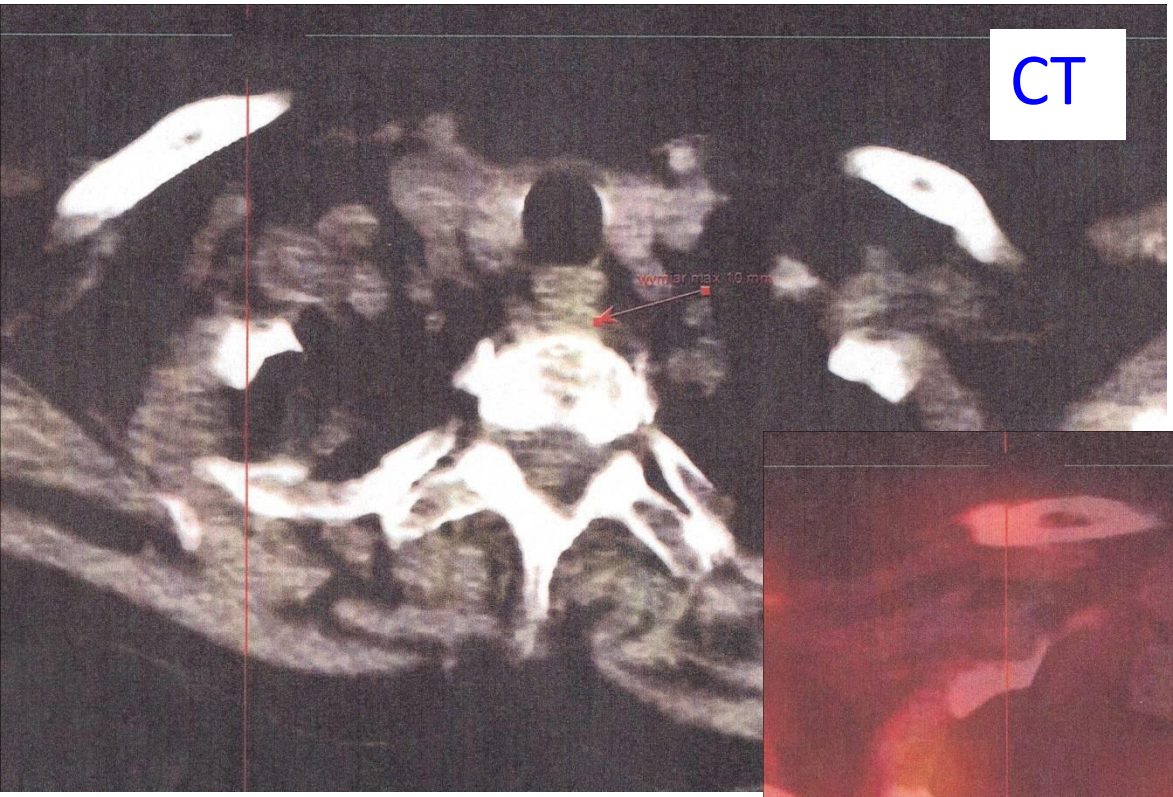


PARATHYROID SCINTISCAN

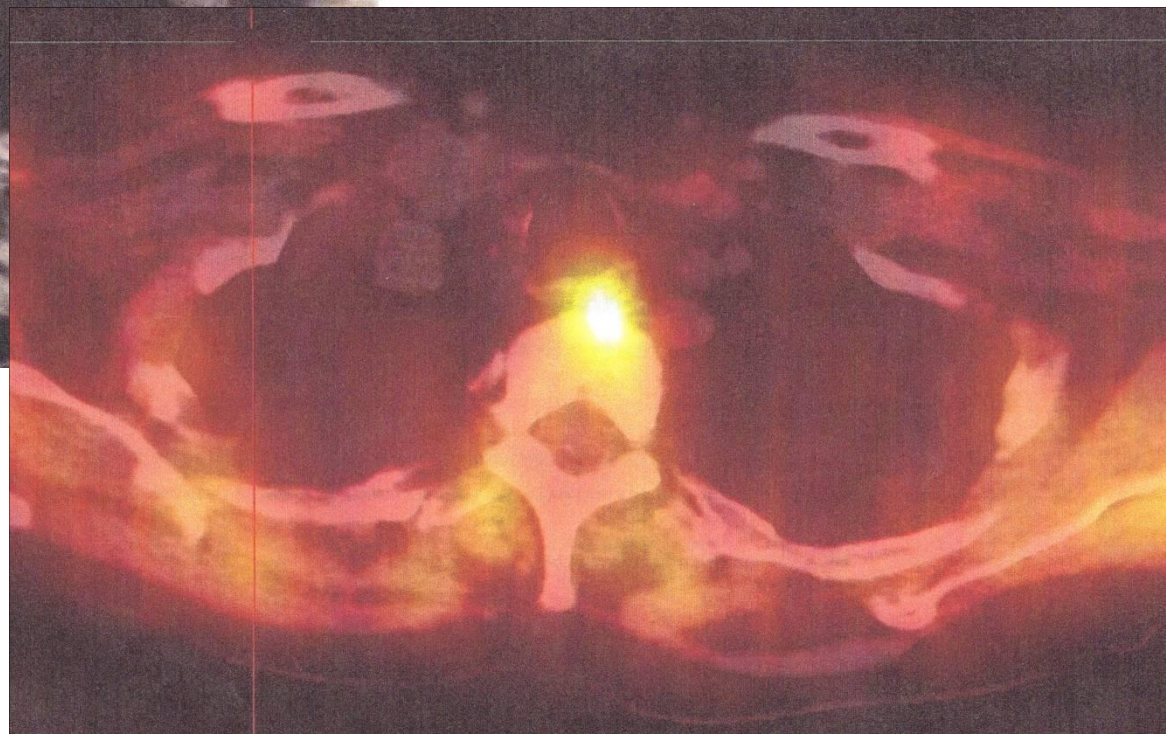
(99MTC+MIBI AND 99MTC)



Ectopic parathyroid in the chest



SPECT/CT



SURGICAL TECHNIQUES

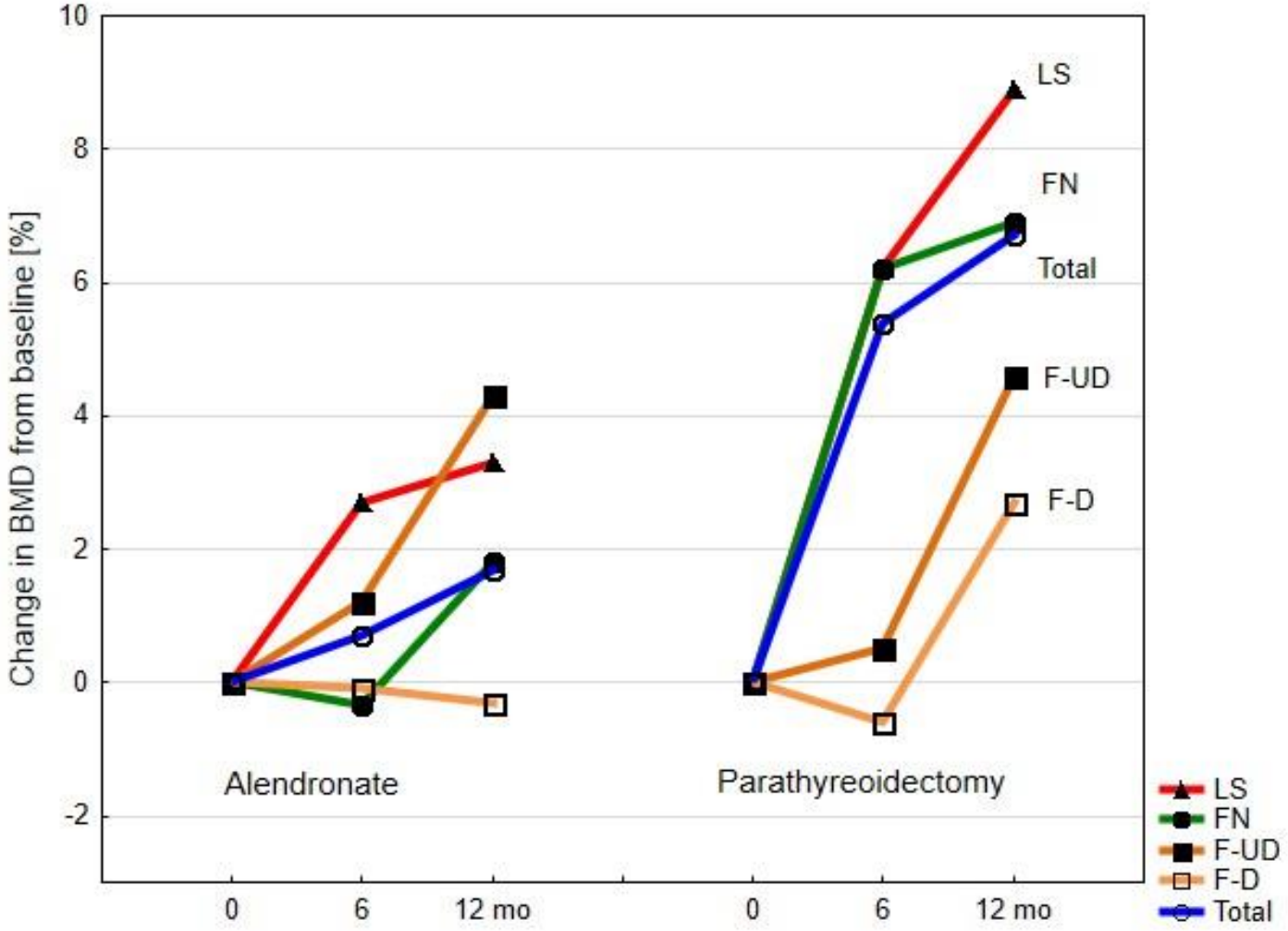
1) Minimal invasive – solitary adenoma

2) Bilateral cervical exploration - is the ideal operation for most patients with multigland disease, including those with genetic disease. In patients with hereditary PHPT all parathyroid cells are mutated. The extent of resection is „not too much and not too little". Recommended operation for MEN 1 patients with is a subtotal PTX removing $3^1/_2$ glands and leaving a viable 30 to 50 mg remnant from the most normal- appearing gland.

SUCCESSFUL PARATHYROIDECOMY

1. Normalization of biochemical parameters
2. Reduction of nephrolithiasis
3. BMD improvement, bone reconstruction

EVOLUTION OF BMD POST-OP AND ON TREATMENT WITH ALENDRONATE

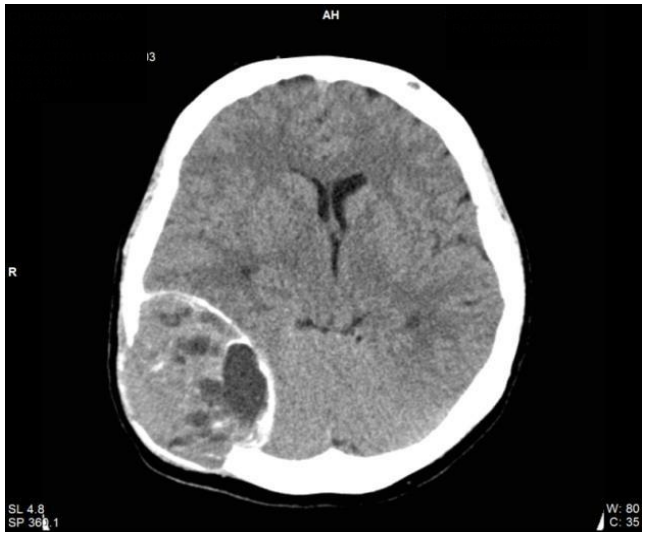


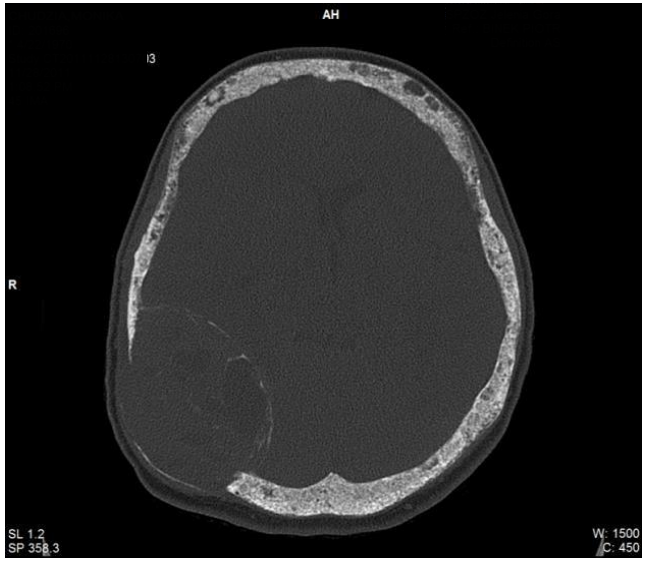
LS-lumbar spine, FN-femoral neck, F-D- forearm 1/3 distal, F-UD-forearm ultradistal, total -total body

According to: Szymczak J, Bohdanowicz-Pawlak A. HMR 2013

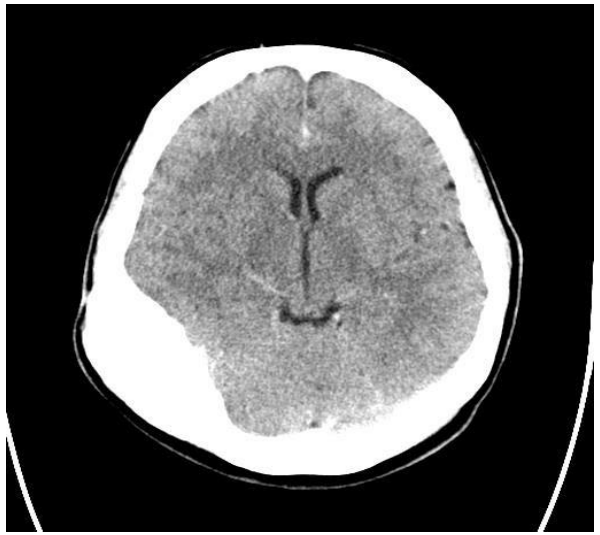
IMAGISTIC FOLLOW-UP

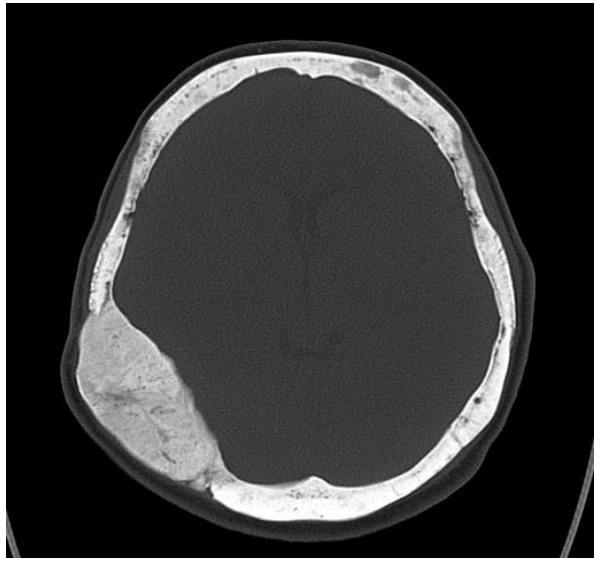
before PTX





6 months after PTX





HPTP DRUG THERAPY

Pharmacotherapy can be used in asymptomatic or mild patients or in patients with failed parathyroidectomy, or who have contraindications for intervention.

MEDICATION

Drug	**Effect**
Calcimimetics (cinacalcet)	• Decreases calcemia and calciuria • Reduce, but do not normalize PTH • It does not affect BMD
Bisphosphonates (alendronate)	• Improves BMD • Does not change serum Ca
Denosumab (?)	• RANKL antagonist – decrease bone resorbtion

TREATMENT OF SEVERE HYPERCALCEMIA (PARATHYROID CRISIS)

- Hydration with saline solution
- Furosemide (after hydration)
- Bisphosphonates iv. (pamidronate, zoledronic acid)
- Glucocorticoids (prednisone 10-40 mg / d)
- Calcitonin sc., im.
- Calcimimetics (cinacalcet) - 10-80 mg / d

PRIMARY HYPERPARATHYROIDISM - DIFFERENTIAL DIAGNOSIS

HYPERCALCEMIA ACCORDING TO ETIOLOGY

Excess PTH	PTH independent bone resorption	Excess of Vit. D	Excess of alimentary Ca
Hiperparathyroidism: • primary • secundary • Tertiary	PTHrP secreting malignancy	↑ intake of Vit. D	Milk alkali syndrome (calcium-alkali syndrome - ↑ intake of $CaCO_3$)
Familial hypocalciuric hypercalcemia (FHH) - (inactivating mutation in the calcium sensing receptor gene)	Osteolytic bone metastases	Ectopic $1,25(OH)_2D$ production (lymphoma, granuloma)	
Lithium (reduces sensitivity of PTH secretion to inhibition by calcium)	Paget's disease		
	Immobilisation		
	Hyperthyroidism		

2º Hyperparathyroidism

- Occurs in renal failure patients
- Chronically low serum calcium → ↑ PTH
- No symptoms of hypercalcemia
- Results in **renal osteodystrophy**
  - Bone pain (predominant symptom)
  - Fractures (weak bones 2° chronic high PTH levels)
  - If severe, untreated can lead to osteitis fibrosa cystica

↑PTH ↓Ca

COMMON CAUSES OF SECONDARY HYPERPARATHYROIDISM

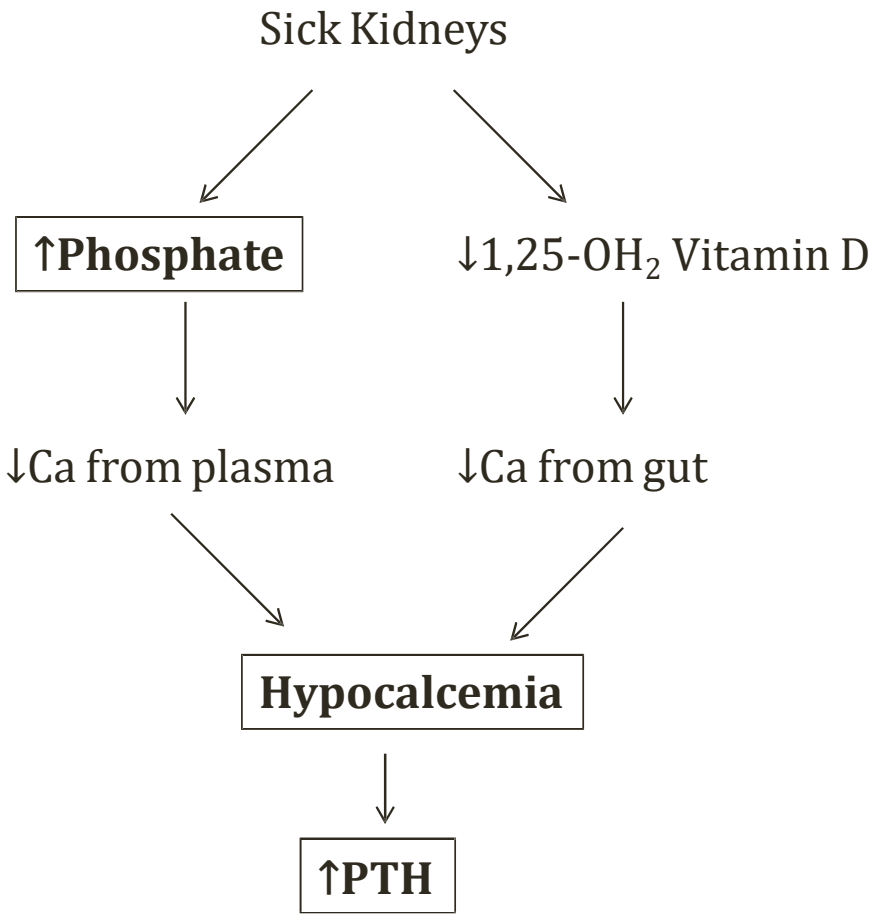
Cause	Comment
CKD (GFR below 60 ml/min)	Impairment of 1,25 (OH) 2D, hyperphosphatemia
Decreased calcium intake	
Calcium malabsorption	Vitamin D Deficiency, celiac disease, chronic pancreatitis, postgastrectomy syndrome, bariatric surgery
Renal calcium loss	Renal hypercalciuria
Drugs	Bisphosphonates, anticonvulsants, furosemide, phosphorus

2o Hyperparathyroidism

Treatment

- Maintaining the serum calcium and phosphorus levels within the normal range along with control of PTH and vitamin D levels is the key in management of secondary hyperparathyroidism.
- Parathyroidectomy is a surgical modality available if medical therapy is unsuccessful or refractory.
- Surgical techniques include subtotal parathyroidectomy and total parathyroidectomy with or without autotransplantation

Calcium-Phosphate in Renal Failure



3º Hyperparathyroidism

- Consequence of chronic renal failure
- Chronically low calcium → chronically ↑ PTH
- Parathyroid becomes autonomous
- VERY high PTH levels
- Calcium may become elevated
- Often requires parathyroidectomy

3º Hyperparathyroidism

Management

- Vitamin D
- P binders
- Calcimimetics

- Surgery - subtotal parathyroidectomy and total parathyroidectomy

HYPOPARATHYROIDISM

Hypoparathyroidism

- Inappropriately low PTH secretion
- Not due to hypercalcemia
- Causes **hypocalcemia**

↓PTH ↓Ca

CAUSES OF INSUFFICIENT PTH SECRETION OR INSUFFICIENT PTH ACTIVITY

1. Acquired deficiency of parathyroid hormone secretion (> 99% of all cases):

Surgical removal of the parathyroid glands (usually unintentional)
Neck radiotherapy, parathyroid infiltration
hypomagnesemia
Calcimimetics
Autoimmune:
isolated hypoparathyroidism
APS 1 (autoimmune polyendocrine syndrome caused by mutations in the autoimmune regulator gene (AIRE)) → anti-CaSR antibodies
Neonatal hypocalcemia

2. Congenital lack of PTH secretion due to absent, hypoplastic or ectopic parathyroid glands (eg DiGeorge's syndrome), (extremely rare)

3. Resistance to parathyroid hormone (pseudohypoparathyroidism), (extremely rare). Inability of the kidneys and bones to respond to PTH caused by normal parathyroid glands.

SYMPTOMS OF HYPOPARATHYROIDISM

1. Hypocalcemia:
   Tetany, paresthesias, neurological disorders, convulsions

2. Calcium phosphate storage in soft tissues
   (basal ganglia, joint capsules, subcutaneous tissue, vitreous humor, muscles, bones).

Hypocalcemia

SIGNS/SYMPTOMS

- Neuromuscular irritability
  - Nerves: **tingling** of fingers, toes, around mouth
  - Muscles: intermittent **spasms** (tetany)
- Tetany
  - Trousseau's sign: Hand spasm with BP cuff inflation
  - Chvostek's sign: Facial contraction with tapping on nerve
- Seizures

https://www.youtube.com/watch?v=kvmwsTU0InQ

https://www.youtube.com/watch?v=S2BS0XqFcY0

TETANY

INCREASED NEUROMUSCULAR EXCITABILITY ASSOCIATED WITH HYPERCALCEMIA

Three subtypes of tetany may occur in isolation, but all three may occur simultaneously on the same subject. These are:

- **Tetanic attack**

Sensory symptoms: paresthesias of the lips, tongue, fingers and toes
Carpopedal spasm
Facial muscle spasm
Generalized muscle pain and spasm

- **Latent tetanus** that requires stimuli (Chvostek and Trousseau signs are easy to make to highlight latent tetany).
- **Tetanic equivalents**

Involvement of the autonomic nervous system may be present as: diplopia, blepharospasm, laryngospasm, bronchial spasm, cardia and sphincter of the bladder. Similarly, blood vessels can be affected by causing migraines, angina pectoris, abdominal angina or Raynaud's syndrome.

SYMPTOMS OF HYPOPARATHYROIDISM

Patients who gradually develop hypoparathyroidism may associate:

- Calcification of the basal ganglia (Fahr's syndrome) with symptoms of impaired motor and speech function, seizures, headache, dementia and visual disturbances
- Cataract (mineral deposits)
- Dry, thick skin, rough, brittle hair, brittle nails
- Defects in tooth enamel

HYPOPARATHYROIDISM DIAGNOSIS

1. Testing:

↓ calcium

↑ P

↓ PTH (normal or elevated in pseudohypoparathyroidism)

↔ magnesium

↔ creatinine

↓ $1,25(OH)_2D$

2. Low urinary calcium excretion in 24 hours

3. Imagistics if necessary:

- X-ray, CT – calcifications in the basal ganglia of the brain and other soft tissues
- USG renal

Ophtalmologist (cataract) and neurologist

4. ECG: QT interval prolonged

HYPOPARATHYROIDISM - DIFFERENTIAL DIAGNOSIS

OTHER SOURCES OF HYPOCALCEMIA

Hypoparathyroidism	Vitamin D deficit	Low intake of Ca^2	Other
PTH ↓, N	PTH ↑		
Thiroidectomy, neck surgery	Low Calcitriol: • ↓ Vitamin D intake. • Inadequate sun exposure • Malabsorption syndrome		Osteoblastic bone metastases
I 131 therapy for DTG or thyroid cancer			Pancreatitis
Autoimmune hyperparathyroidism	↓ conversion 25OHD to $1,25(OH)_2D$ • Renal insufficiency • hyperphosphataemia • Vitamin D rickets, type 1		Hungry Bones Syndrome
Parathyroid infiltration			Hyperphosphatemia
hypomagnesemia	Calcitriol resistance • Vitamin D resistant rahitism		Multiple transfusions
Congenital /genetic			Acute respiratory alkalosis
PTH resistance (pseudo hypoparathyroidism) PTH ↑)	↑ inactivation of vit. D (e.g. carbamazepine, phenytoin)		

PURPOSE OF HYPOPARATHYROIDISM TREATMENT

- Maintaining the Ca level in the lower limit of the norm so that the patient does not show clinical picture
- Reduction of serum phosphorus to the upper limit of the norm to prevent tissue calcification
- Calciuria - within normal limits to prevent nephrocalcinosis

TREATMENT OF HYPOPARATHYROIDISM

- Diet rich in Ca and poor in P
- Calcium per os daily
- Vitamin D

- Supplemented with Magnesium as needed
- Recombinant PTH - an adjunct to Ca and vitamin D – carefully, can cause osteosarcoma

The tetanus crisis will be treated with Calcium i / v Calcium gluconate - 10 ml of 10% solution in 10 min, if necessary continue with 20-30 ml of 10% calcium gluconate in 5% glucose.

Calcium and PTH

- 1st look at calcium: Low/High
- Next, look at PTH: Low/High
- Same direction = parathyroid problem
  - Both ↑: Hyperparathyroidism
  - Both ↓: Hypoparathyroidism
- Opposite direction
  - Normal response to calcium problem
  - Renal failure (low serum calcium – 2o hyperparathyroidism)
  - Renal losses (pseudohypoparathyroidism)