Parathyroid glands disorders

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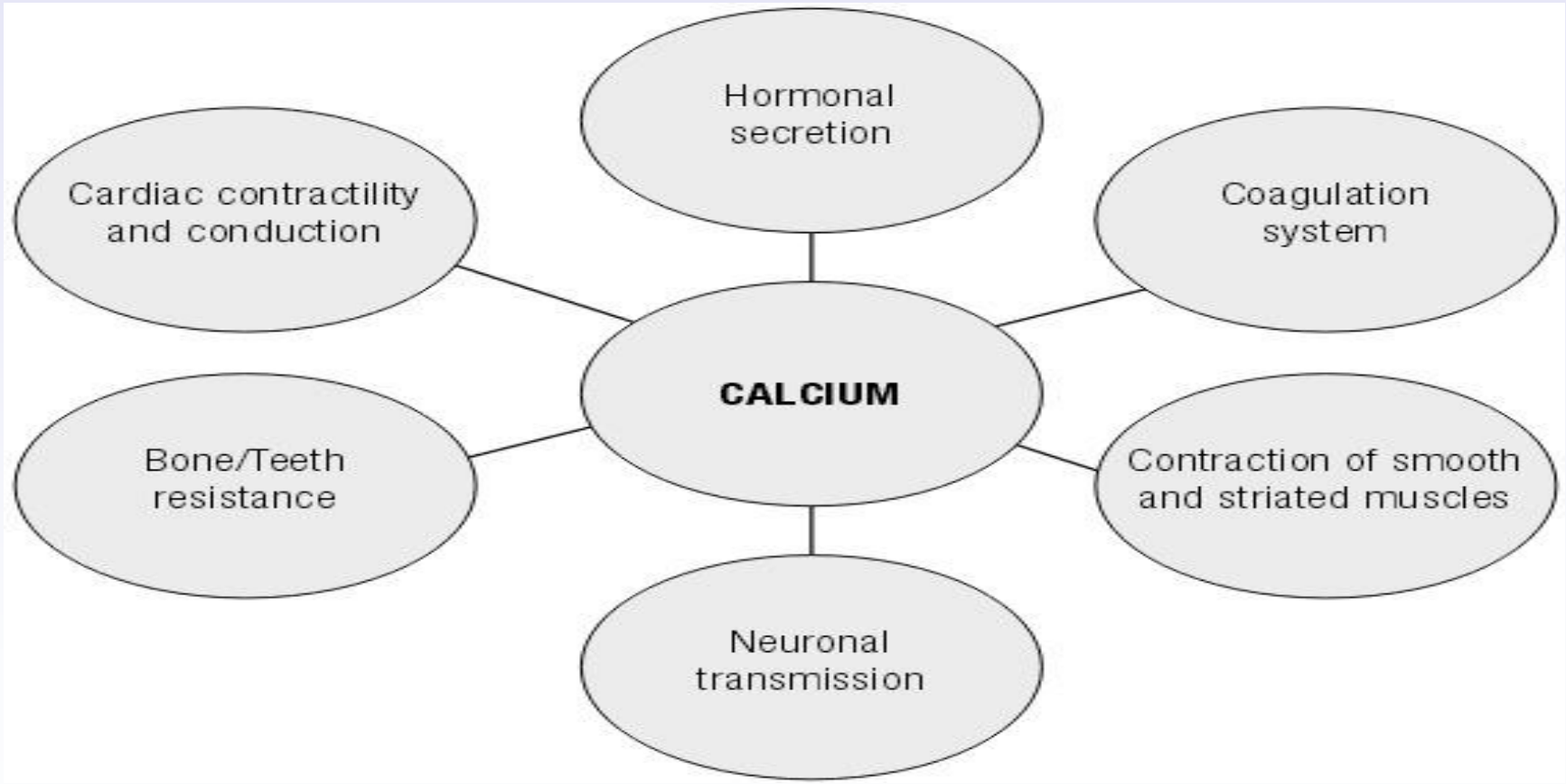
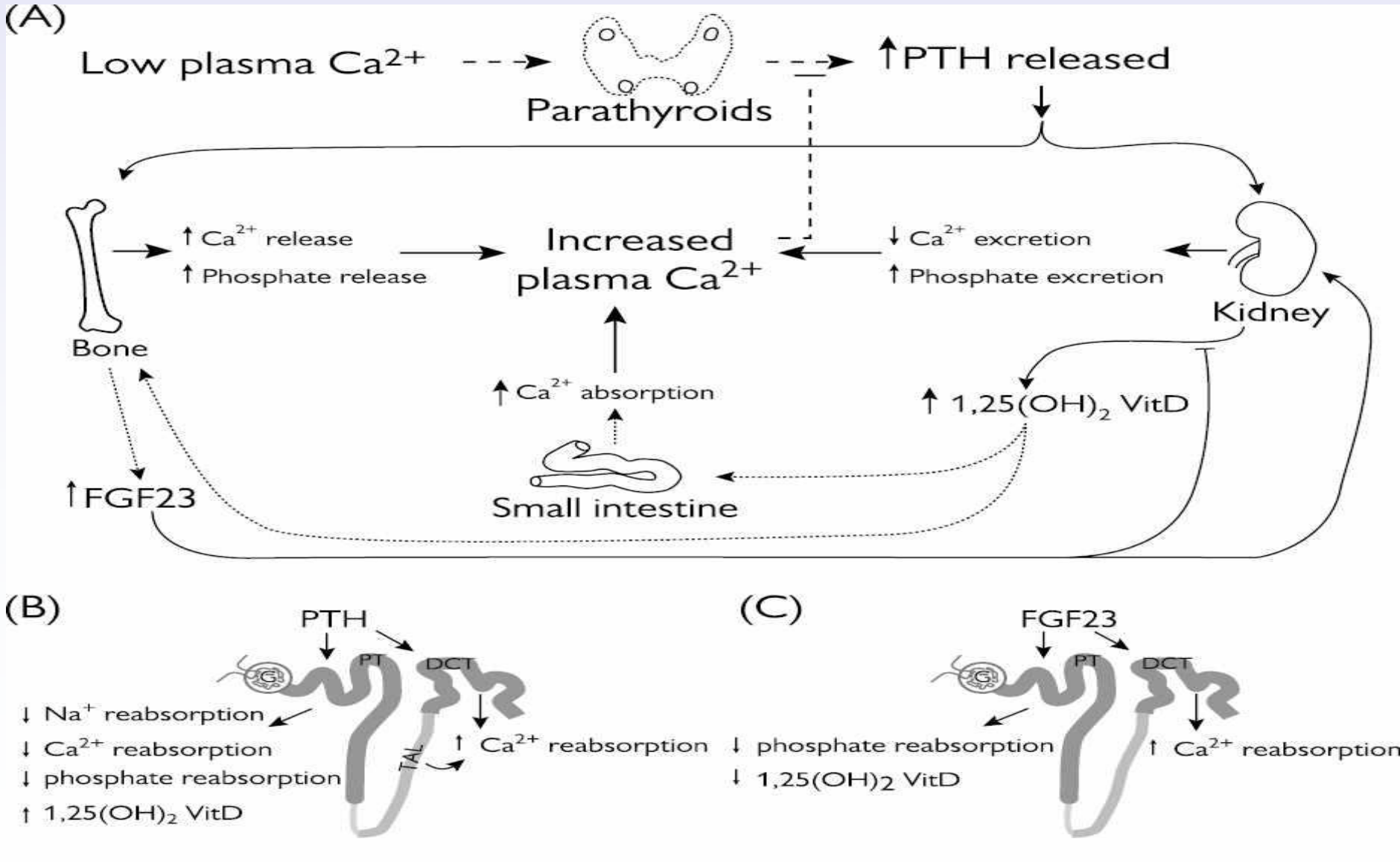
اللهم اغث إخواننا في غزة
وكن لهم ناصراً
ومعيناً وحافظاً وظهيرا
غزة

Calcium



Ca concentration is tightly regulated


(A)
Low plasma Ca2+
Parathyroids
↑PTH released
↑ Ca2+ release
↑ Phosphate release
Increased plasma Ca2+
↓ Ca2+ excretion
↑ Phosphate excretion
Bone
Kidney
↑ Ca2+ absorption
↑ 1,25(OH)2 VitD
↑FGF23
Small intestine
(B)
PTH
PT
DCT
TAL
↓ Na+ reabsorption
↓ Ca2+ reabsorption
↓ phosphate reabsorption
↑ 1,25(OH)2 VitD
↑ Ca2+ reabsorption
(C)
FGF23
PT
DCT
↓ phosphate reabsorption
↓ 1,25(OH)2 VitD
↑ Ca2+ reabsorption

Different forms of calcium

%99

Most of the calcium in the body is stored in the bones as hydroxyapatite

Calcium in the serum:

- %45free ionised form ←physiologically active
(snimubla yltnanimoderp) snietorp ot dnuob -45%
,etaflus ,etartic .g.e) snoina htiw dexelpmoc -10%
phosphate(

Typically measured in routine blood tests

The total serum calcium concentration is adjusted to reflect any abnormality in albumin, the major calcium binding protein. The formula to use is:

corrected calcium = measured total serum calcium in mg/dL + 0.8 x (4.0 - patient's serum albumin concentration in g/dl).

Normal laboratory values

Test	Specimen	Conventional Units	SI Units
Calcium	serum	8.5-10.3 mg/dL	2.12-2.57 mmol/L
Ionised calcium	plasma	4-5.2 mg/dL	1.0-1.3 mmol/L
Calcium	urine	M < 300 mg/d F < 250 mg/d	M < 7.5 mmol/d F < 6.2 mmol/d
Phosphorus	serum	2.5-4.5 mg/dL	0.81-1.45 mmol/L
PTH (intact)	serum	11-67 pg/mL	

M-male, F-female

Causes of hypercalcemia

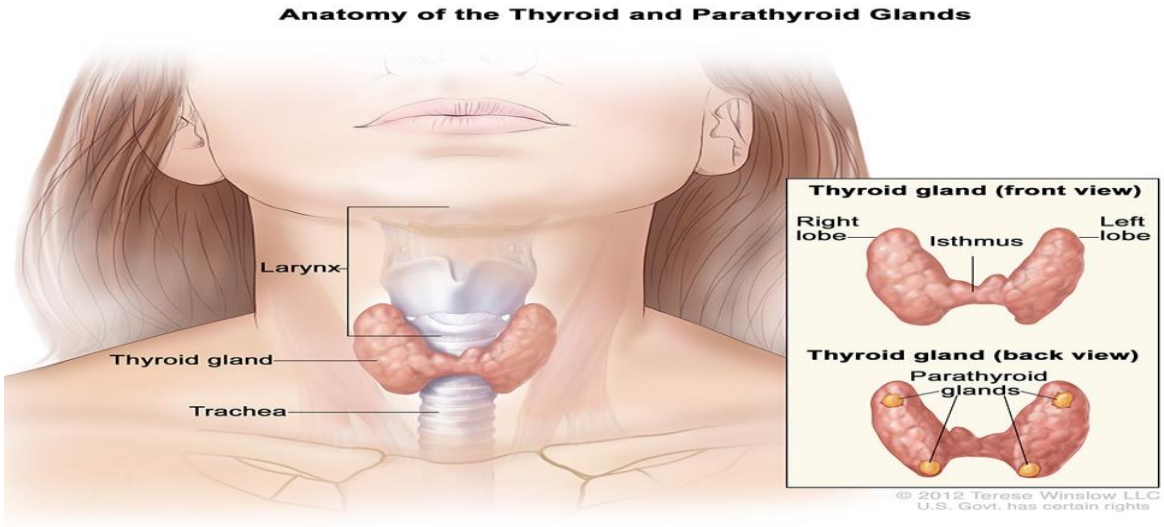
Parathyroid mediated
Primary hyperparathyroidism (sporadic)
Inherited variants
Multiple endocrine neoplasia (MEN) syndromes
Familial isolated hyperparathyroidism
Hyperparathyroidism-jaw tumor syndrome
Familial hypocalciuric hypercalcemia
Tertiary hyperparathyroidism (renal failure)

Non-parathyroid mediated
Hypercalcemia of malignancy
PTHrp
Increased calcitriol (activation of extrarenal 1 alpha-hydroxylase)
Osteolytic bone metastases and local cytokines
Vitamin D intoxication
Chronic granulomatous disorders
Increased calcitriol (activation of extrarenal 1-alpha-hydroxylase)

Medications
Thiazide diuretics
Lithium
Teriparatide
Abaloparatide
Excessive vitamin A
Theophylline toxicity

Miscellaneous
Hyperthyroidism
Acromegaly
Pheochromocytoma
Adrenal insufficiency
Immobilization
Parenteral nutrition
Milk-alkali syndrome

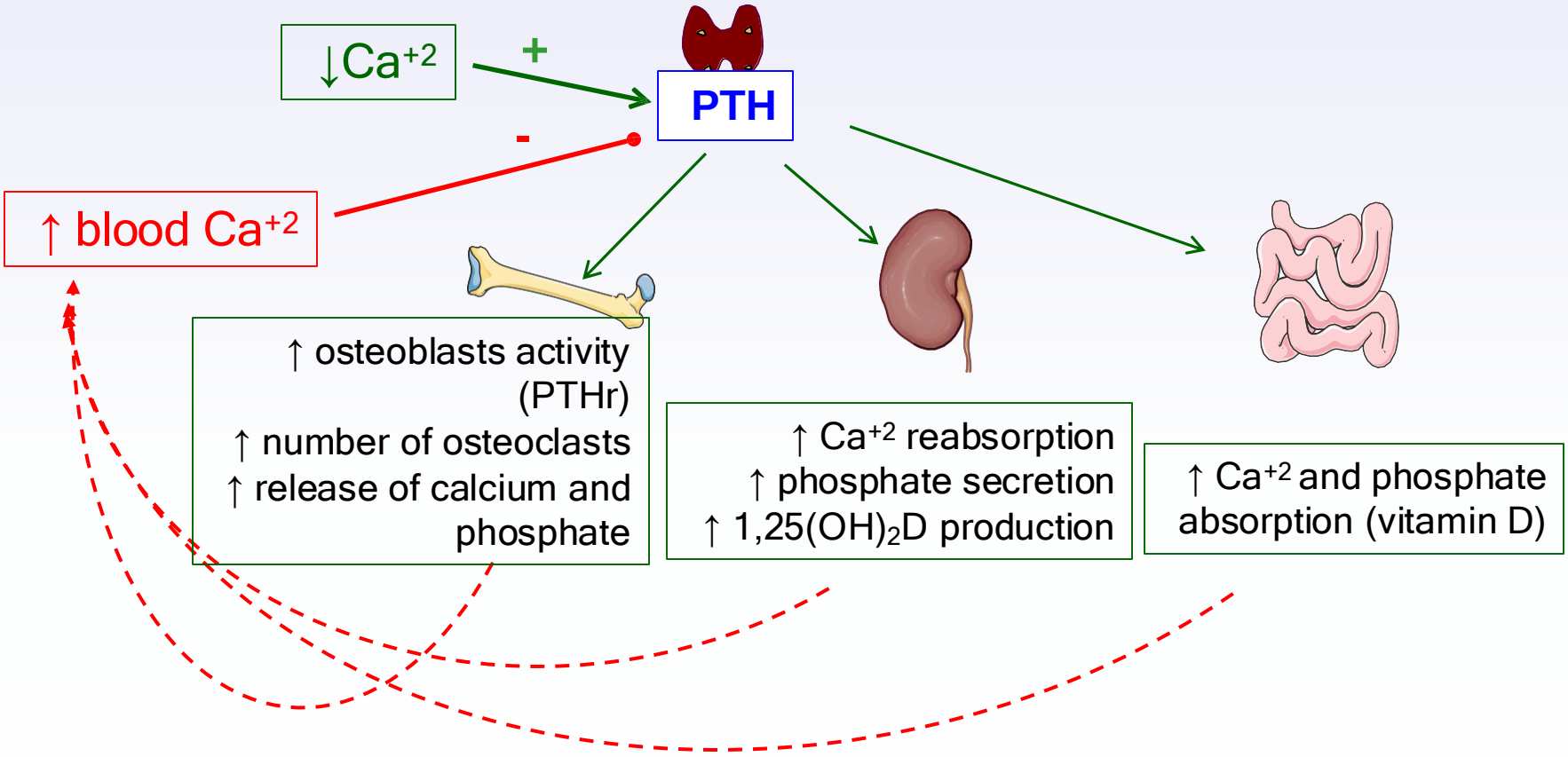
The parathyroid glands are two pairs of glands usually positioned behind the left and right lobes of the thyroid. Each gland is a yellowish-brown flat ovoid that , usually about 6 mm long and 3 to 4 mm wide, and 1 to 2 mm anteroposteriorly. There are typically four parathyroid glands



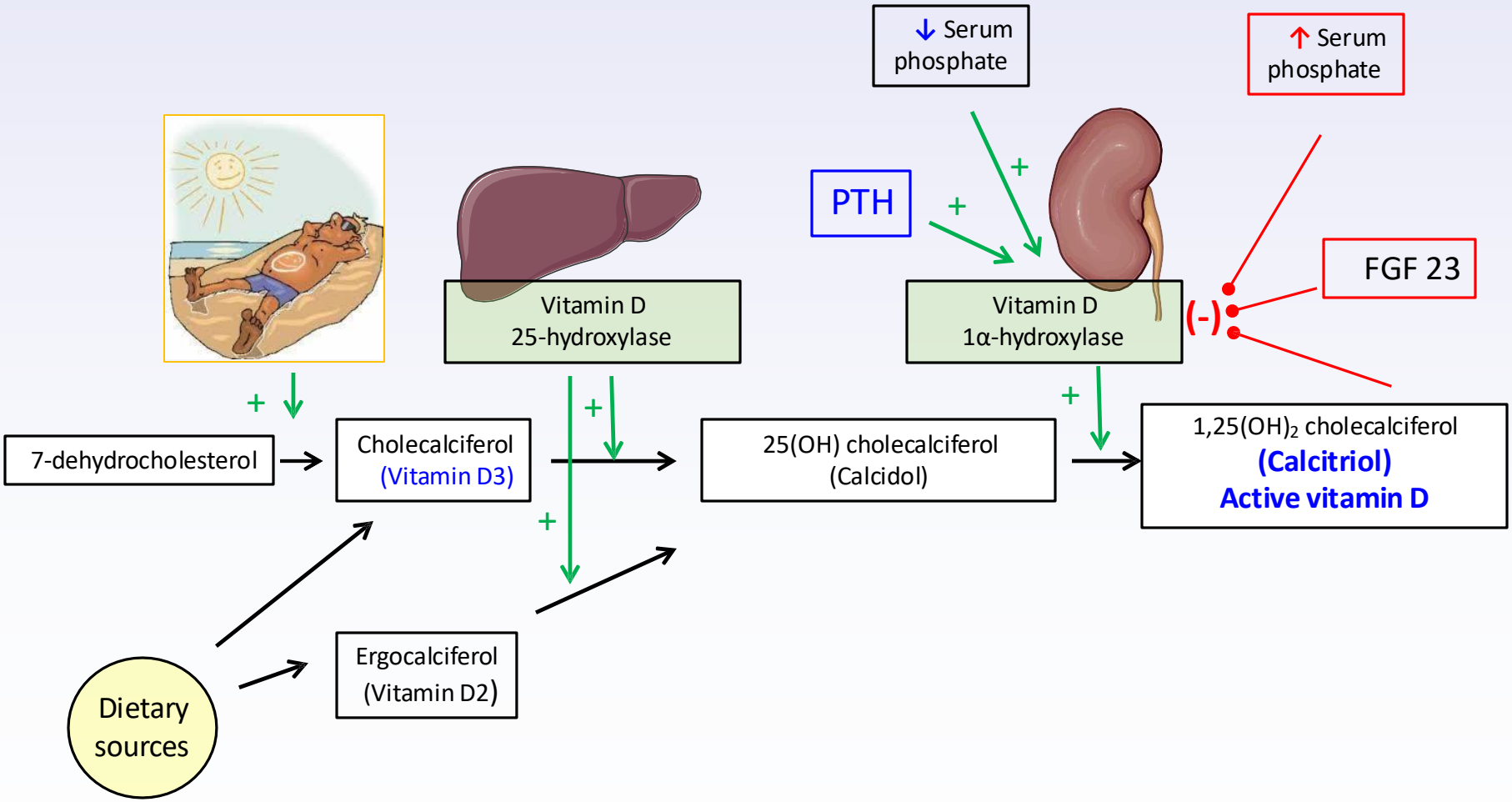
Major mediators of calcium and phosphate balance

Serum		
Ca_s	P_s	
		Parathormone (PTH)
↑	↓	• increases the release of calcium and phosphate from bones • stimulates the formation of active vitamin D in the kidneys (activation of 1 α hydroxylase) • reduces calciuria and increases phosphaturia
		Vitamin D
↑	↑	• increases the uptake of Ca and P in the gastrointestinal tract
		Calcitonin (low physiological importance)
↓		• decreases the uptake of Ca in the gastrointestinal tract • increases calciuria • reduces bone resorption
		FGF 23 (Fibroblast Growth Factor 23)
	↓	• increases phosphaturia

The effect of parathyroid hormone



Synthesis and regulation of active vitamin D (calcitriol)



Hyperparathyroidism

Primary - PTH secretion is disproportionately high in relation to the serum calcium concentration.

Secondary to kidney failure, severe vitamin D and calcium deficiency. Reversible, after removing the cause of the disorder.

Tertiary - is excessive autonomous secretion of parathyroid hormone after a long period of secondary hyperparathyroidism.

TABLE 3

Lab Comparison

Hyperparathyroidism	Calcium	PTH	Vitamin D	Phosphate
Primary	↑	↑→	↑	↓
Secondary	↓→	↑	↓	↑ or ↓
Tertiary	↑	↑↑	↓	↑

Key: ↑Elevated, ↓decreased, →normal.

Source: Brashers. *Pathophysiology.* 2015.[6]

Primary hyperparathyroidism)PHPT)

Primary hyperparathyroidism is characterised by secretion of PTH that is excessively disproportionate to serum calcium levels, resulting from a primary defect of parathyroid cells.

PHPT results from:

- one or more adenomas 80-85%
- hyperplasia of all parathyroid glands 10-15%
- parathyroid carcinoma fewer than 1%

PHPT - familial hereditary syndromes

Hereditary forms of PHPT account for 5% of cases:

- Multiple endocrine neoplasia (MEN)1,2A
- Familial non-MEN hyperparathyroidism
- Hereditary hyperparathyroidism – jaw tumor syndrome

Primary hyperparathyroidism –clinical forms

- The most common clinical presentation of PHPT is asymptomatic or low symptomatic disease
- Atypical occurences include normocalcemic PHPT and parathyroid crisis.

Classical clinical consequences of PHPT

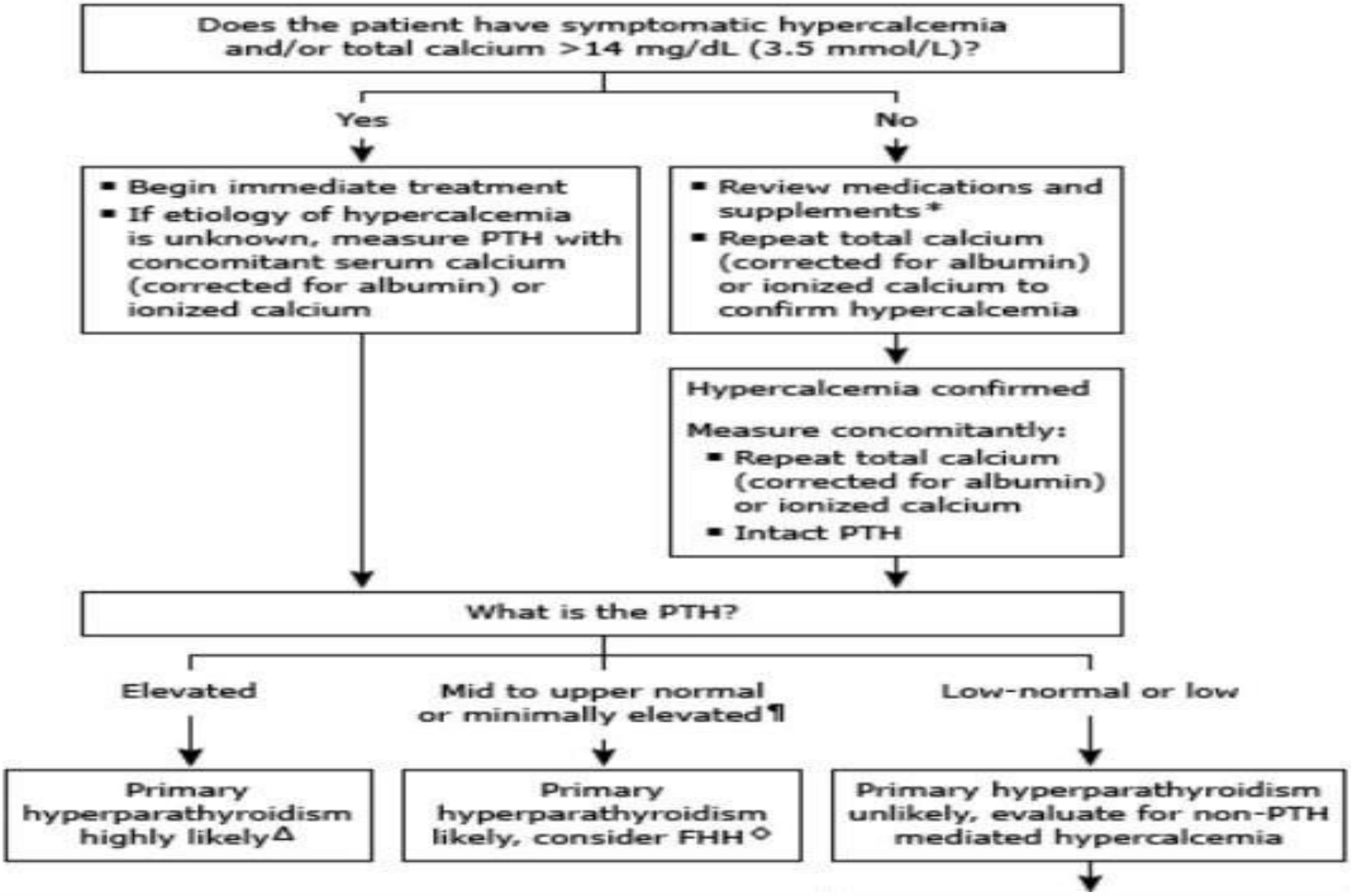
Bone destruction	Hypercalcemia	Hypercalciuria
Osteopenia	Peptic ulcer disease	Urolithiasis
Osteoporosis	Pancreatitis	Nephrocalcinosis
Bone deformities and fractures	Constipation, nausea, vomiting or loss of appetite	Nephrogenic diabetes insipidus
Osteitis fibrosa cystica, brown tumors	Polydipsia and polyuria Bone pain , myalagia	
	Renal failure	
	Cardiovascular features: hypertension, arrhythmia, ventricular hypertrophy, and vascular and valvular calcification	
	Tiring easily or weakness	
	Neuropsychiatric disorders	
	Parathyroid crisis	

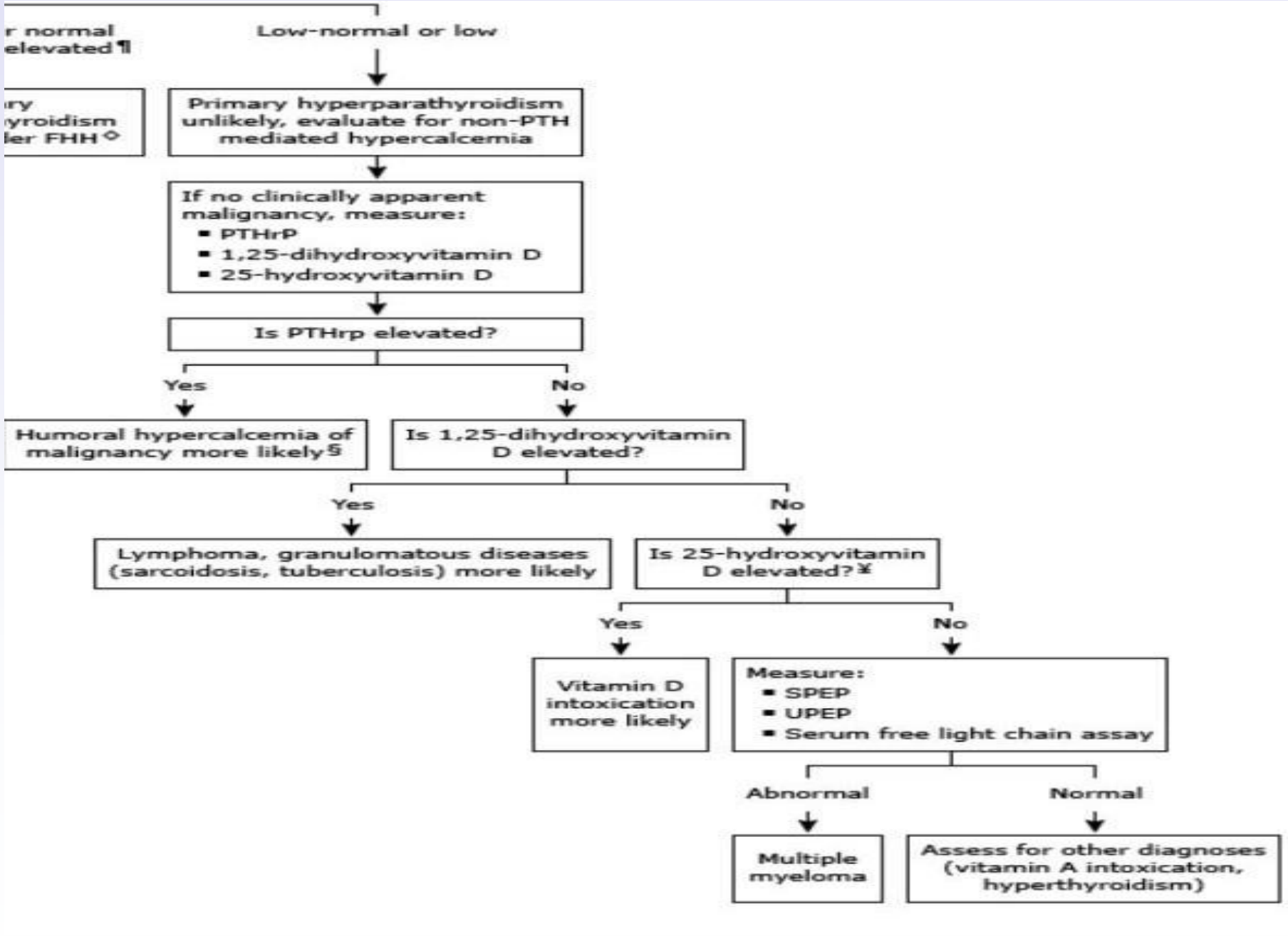
Normocalcemic primary hyperparathyroidism (a variant of PHPT)

- ↑PTH
- Normal serum total and ionized calcium concentration
- The features of PHPT may be present (e.g. low BMD)
- All secondary causes for hyperparathyroidism must be ruled out

Normocalcemic PHPT is considered to be an early form of asymptomatic PHPT or represent a unique phenotype of the disease.

Diagnostic approach to hypercalcemia in adults



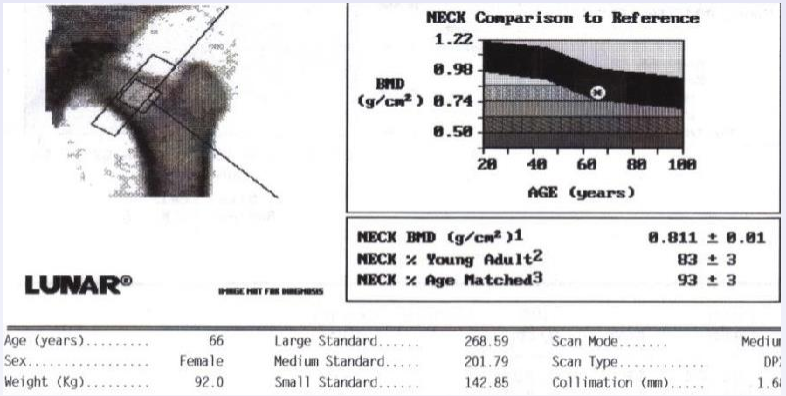

r normal
elevated ¶
Low-normal or low
ry
yroidism
ler FHH ◇
Primary hyperparathyroidism unlikely, evaluate for non-PTH mediated hypercalcemia
If no clinically apparent malignancy, measure:
PTHrP
1,25-dihydroxyvitamin D
25-hydroxyvitamin D
Is PTHrp elevated?
Yes
No
Humoral hypercalcemia of malignancy more likely §
Is 1,25-dihydroxyvitamin D elevated?
Yes
No
Lymphoma, granulomatous diseases (sarcoidosis, tuberculosis) more likely
Is 25-hydroxyvitamin D elevated? ¥
Yes
No
Vitamin D intoxication more likely
Measure:
SPEP
UPEP
Serum free light chain assay
Abnormal
Normal
Multiple myeloma
Assess for other diagnoses (vitamin A intoxication, hyperthyroidism)

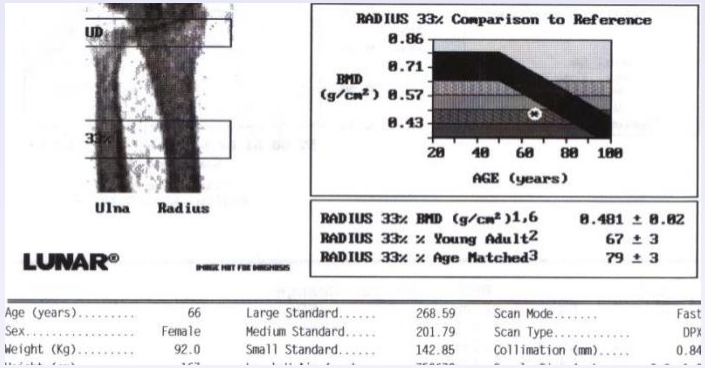
Diagnosis of primary hyperparathyroidism

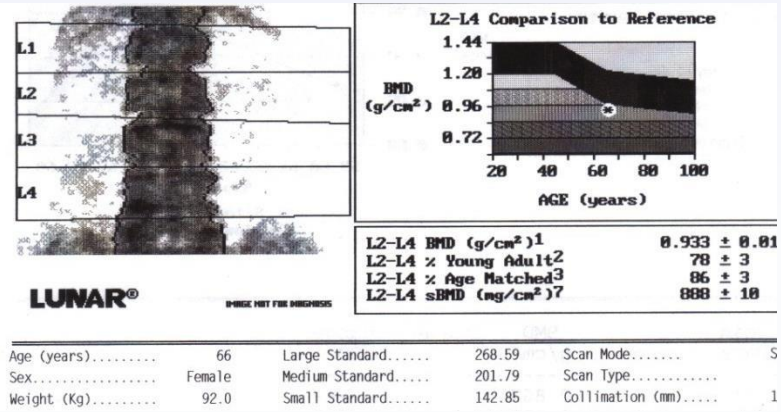
additional evaluation to determine management

Bone densitometry (DXA)	• lumbar spine • Hip total or femoral neck • radius (distal 1/3 site)
Ultrasound abdominal examination	renal imaging

Primary hyperparathyroidism - bone mineral density (DXA)

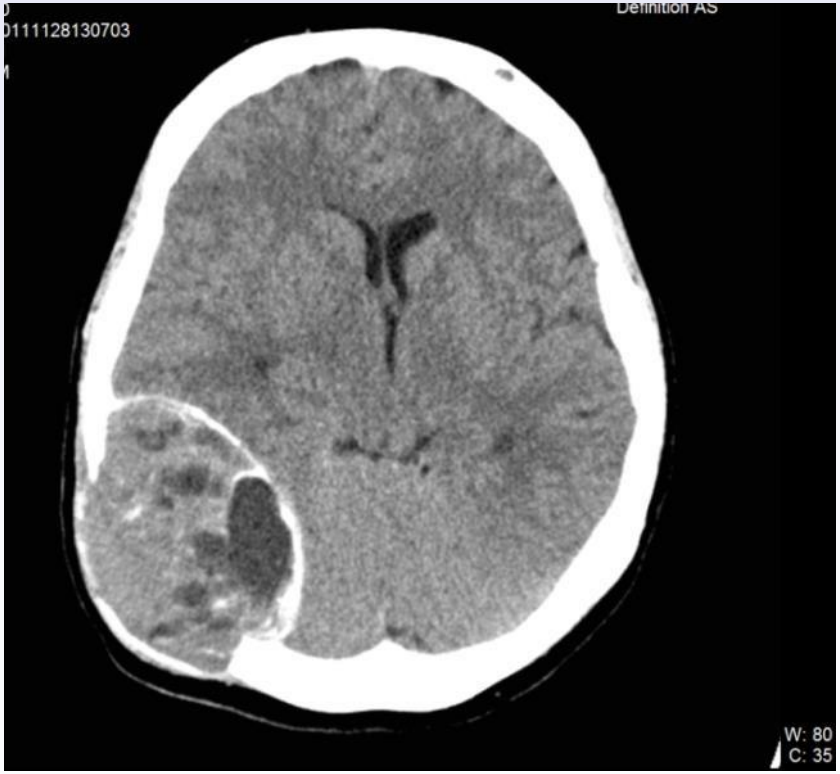






	T- score
Femoral neck	-1.41
Lumbar spine	-2.23
Forearm (1/3 distal)	-3.26

Primary hyperparathyroidism – bone destruction



Brown tumor of the skull of a young woman (CT)

Familial Hypocalciuric Hypercalcemia (FHH)

The reason of FHH is inactivating mutation of the calcium .sensing receptor in parathyroid glands

↑Serum calcium and ↑ N PTH

but

- Urine calcium is low less than 100 mg/24H

.FHH is a rare, lifelong, benign condition

Calculation of calcium/creatinine excretion ratio

CaE = [Urine Ca (mmol)/urine Cr (mmol)]

× [(plasma Cr (micromol)/1000)/plasma Ca (mmol)]

= <0.01 in FHH

= >0.02 in PHPT

These numeric parameters are not fully sensitive or specific and genetic

Common causes of secondary hyperparathyroidism

Disorder	**Comment**
Chronic kidney disease (CKD) GFR below 60 ml/min)	Impaired 1,25$(OH)_2$D production, hyperphosphatemia
Decreased calcium intake	
Calcium malabsorption	Vitamin D deficiency, celiac disease, chronic pancreatitis, post gastrectomy syndrome, bariatric surgery
Renal calcium loos	Renal hypercalciuria
Drugs	Bisphosphonates (inhibiton of bone resorption), anticonvulsants, furosemide, phosphorus

Primary hyperparathyroidism - differential diagnostics

	PHPT (Primary hyperpara-thyroidism)	FHH (Familial Hypocalciuric Hypercalcemia)	Secondary hyperparathyroidism		Malignancy
			Chronic renal failure	Malabsorption, Ca & Vit.D deficiency	
PTH	**N ↑**	**N ↑**	↑ ↑ ↑	↑, N	↓
Ca_s	↑↑	↑	↓, N	↓, N	↑
Ca_{u24h}	↑↑	↓	↓	↓	↑↑
$Phosphate_s$	↓	N	↑	↓, N	↓, N
BMD (DXA)	↓ ↓	N	↓	↓	↓, N

Primary hyperparathyroidism - treatment

1. Selective parathyroidectomy

- The treatment of choice for symptomatic disease is surgical removal of the hyperactive parathyroid glands.
- Surgery may be also recommended in some asymptomatic or low symptomatic patients.
- Parathyroidectomy (PTX) should only be performed by highly experienced surgeons.

2 . Pharmacotheraphy

In many people, the disease may remain mild or asymptomatic for a long period. In these patients, as well as in those after an unsuccessful PTX, who are unwilling to undergo or considered unsuitable for surgery it attempts to apply a symptomatic pharmacotherapy.

So far treatment with calcimimetics or bisphosphonates seems to be the most promising.

Primary hyperparathyroidism - indications for surgery in asymptomatic PHPT

Measurement	Surgery Recommended [a]
Serum Calcium	**> 1.0 mg/dl (0.25 mmol/L) above normal**
Skeletal	**A. Bone Mineral Density** by DXA **T score < -2.5** SD at lumbar spine, hip (total or femoral neck) or radius (distal 1/3 site)[b] or presence of **fragility fracture** **B. Vertebral fracture** by X-ray, CT, MRI or VFA
Renal	A. Creatinine clearance < 60 ml/min B.24h urine for calcium > 400 mg/d (>10 mmol/d) and increased stone risk by biochemical stone risk analysis **C. Presence of nephrolithasis** or nephrocalcinosis by X-ray, US, or CT
Age	< 50 years

[a] Surgery is also indicated in patients for whom medical surveillance is neither desired nor possible.
[b] the use of Z-scores instead of T scores is recommended in evaluating BMD in premenopausal women and men younger than 50 y

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

Localisation studies

Localisation studies should not be used to establish the diagnosis of PHPT or to determine management.

They should be done after a decision for surgery has been made.

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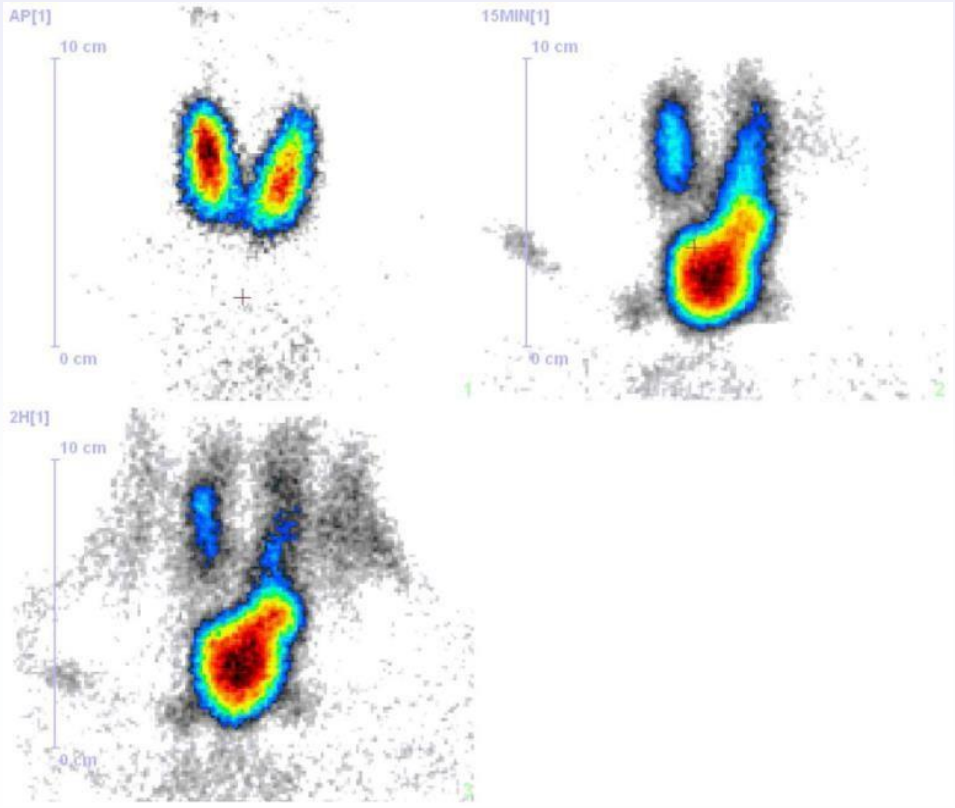
PHPT - localisation tests

The type of imaging	Comments	Sensitivity*
Ultrasonography	Usually a hypoechoic parathyroid adenoma posterior to the thyroid parenchyma with peripheral vascularity seen on colour Doppler. US provides additional anatomic information about the thyroid gland.	up to 80%
Technetium-99m sestamibi scintigraphy	Planar image	60-90%
SPECT – Sestamibi-single photon emission computed tomography	Is a three-dimensional sestamibi scan. The multidimensional images illustrate the depth of the parathyroid gland or glands in relation to the thyroid.	~ 90%
SPECT-CT	SPECT and CT fusion. Adds the ability to discriminate parathyroid adenomas from other anatomic landmarks.	

Parathyroid scintigraphy
(99mTc+MIBI and 99mTc)



"The most important preoperative localisation challenge in PHPT is to locate the parathyroid surgeon!"

John Doppman, 1975

PHPT - postoperative hypocalcemia

Hypocalcemia	**The cause of hypocalcemia**
Transient and mild	suppression of the remaining normal parathyroid tissue
Prolonged and accompanied by hypo- or euphosphatemia and high PTH levels (hungry bone syndrome)	rapid deposition of serum calcium into demineralised bone
Accompanied by hyperphosphatemia and low PTH levels	hypoparathyroidism

Medical Management of Primary Hyperparathyroidism

Pharmacotherapy may be used in mild or asymptomatic an unsuccessful afterPHPT and in in patients parathyroidectomy (PTX), or in those who are unwilling to undergo or considered unsuitable for surgery.

Pharmacological treatment should be reserved for those patients in whom it is desirable to lower the serum calcium or increase BMD.

Medical Management of Primary Hyperparathyroidism

Medicine	Effect
Calcimimetics (cinacalcet)	• Decrease calcemia and calciuria • Reduce, but not normalise PTH • Do not affect BMD
Bisphosphonates (alendronate)	• Improve BMD • Do not alter serum calcium
Denosumab (?)	• RANKL antagonist - decrases bone resorption

Patients with low serum 25-hydroxyvitamin D should be repeatedely administered with doses of vitamin D that bring its serum levels to 20 ng/ml at a minimum (with caution, so as not to aggravate hypercalcemia).

Treatment of severe hypercalcemia)parathyroid crisis)

- Hydration with normal saline
- Bisphosphonates iv. (pamidronate, zoledronic acid)
- Calcitonin sc., im.

Hypoparathyroidism

Hypoparathyroidism is the state of decreased secretion or activity of parathyroid hormone (PTH). This leads to decreased blood levels of calcium (hypocalcemia) and increased levels of blood phosphorus (hyperphosphatemia).

differential diagnosis(Hypocalcemia)etiologies by mechanism

Hypoparathyroidism	Vitamin D deficiency	Low dietary intake of Ca^{+2}	Miscellaneous mechanisms
PTH ↓, N	PTH ↑		
Thyroidectomy or other neck surgery	Low calcitriol: • ↓ intake of dietary Vit. D • Inadequate sunlight exposure • Malabsorption syndrome		Osteoblastic bone metastases
I 131 therapy for G-B disease or thyroid cancer			Pancreatitis
Autoimmune hypoparathyroidism	↓ conversion of 25OHD to $1,25(OH)_2D$ • Renal failure • Hyperphosphatemia • Vitamin D dependent rickets, type 1		Hungry bones syndrome
Infiltration of parathyroids			Hyperphosphatemia
Hypomagnesemia	Calcitriol resistance • Vitamin D resistant rickets		Multiple transfusions
Congenital /genetic			Acute respiratory alkalosis
PTH resistance (pseudo hypoparathyroidism) PTH ↑)	↑ inactivation of vit. D (e.g. carbamazepine, phenytoin)		

Causes of deficient PTH secretion or activity in hypoparathyroid disease states

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

- Surgical removal of the parathyroid glands (usually unintentionally)
- Radiation therapy to the neck, infiltration of parathyroids
- Hypomagnesemia
- Calcimimetics
- Autoimmune:
  - isolated hypoparathyroidism
  -APS 1 (autoimmune polyendocrine syndrome caused by mutations of the autoimmune regulator (AIRE) gene) → antibodies anty CaSR

2. **Resistance to parathyroid hormone** (pseudo-hypoparathyroidism), (extremely rare). Inability of the kidneys and bones to respond to the PTH being produced by normal parathyroids.

Diagnostics of hypoparathyroidism

1. Blood tests:

- ↓ **calcium levels**
- ↑ phosphorus levels
- ↓ **PTH levels** (but normal or elevated in pseudohypoparathyroidism)
- ↔ ALP
- ↔ magnesium
- ↔ creatinine
- ↓ $1,25(OH)_2D$

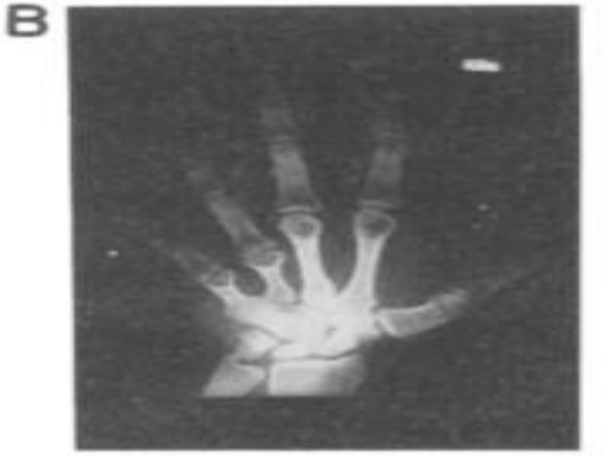
2. 24 urine low calcium excretion

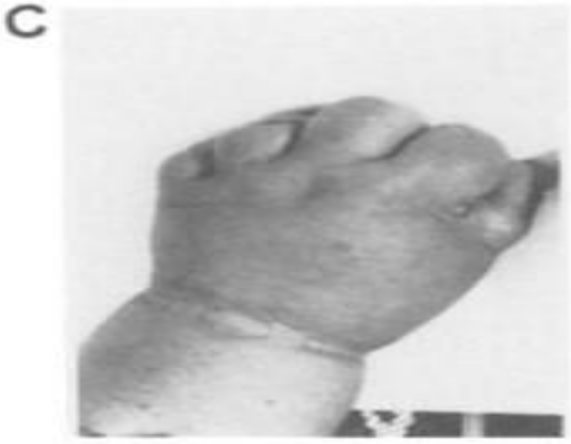
3. ECG: prolonged QT interval

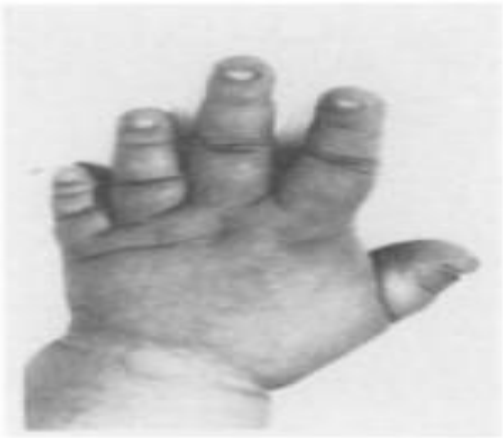
Table 6.6 Investigation of hypocalcaemia

	ALP	PO_4	PTH	Vitamin D	U&E	Mg
Vitamin D deficiency	↑	↓	↑	↓	N	N
Hypoparathyroidism	N	↑	L	N	N	N/↓
Pseudohypoparathyroidism	N	↑	↑↑	N	N	N
PPI-induced hypomagnesaemia/hypocalcaemia	N	N	N	N	N	↓↓

pseudo-hypoparathyroidism







Hypoparathyroidism – symptoms

The major clinical manifestations of hypoparathyroidism are referable to hypocalcemia and are related to the severity and chronicity of the hypocalcemia.

Subjects who develop severe hypoparathyroidism quickly (for example, after neck surgery) can feel tired, irritable, anxious or depressed and demonstrate spontaneous or latent tetany.

Clinical features

↑neuromuscular excitability. In order of ↑ severity, these include:

Tingling—especially of fingers, toes, or lips.

Numbness—especially of fingers, toes, or lips.

Cramps.

Carpopedal spasm.

Stridor due to laryngospasm.

Seizures.

The symptoms of hypocalcaemia tend to reflect the severity and rapidity of onset of the metabolic abnormality.

ECG : LONG QT

Signs

Chvostek's sign is elicited by tapping the facial nerve in front of the ear. A +ve result is indicated by twitching of the corner of the mouth. Slight twitching is seen in up to 15% of normal ♀ , but more major involvement of the facial muscles is indicative of hypocalcaemia or hypomagnesaemia.

Trousseau's sign is produced by occlusion of the blood supply to the arm by inflation of a sphygmomanometer cuff above the arterial pressure for 3min. If +ve, there is carpopedal spasm, which may be accompanied by painful paraesthesiae.

The methods of treatment of hypoparathyroidism:

- Calcium carbonate 1-4 g/d orally, during and between meals
- Activated vitamin D analogues e.g. alfacalcidolum 1-3 µg/d
- Vitamin D supplementation 400–800 IU/d to patients treated with activated vitamin D analogues
- Magnesium supplementation in case of deficiency

- **Treatment of acute severe hypocalcaemia**

Iv calcium

CASE 1

46 yrs old female pt , present to the clinic as she incidently found that she has high serum calcium 11.6 mg/dl (8.5-10.5) she reports no symptoms

What is your approach to this pt ??

CASE 1

Albumin 4.2 g/dl
Pth 55 pg/ml (10-65) , kft nl , vitamin d3 nl
Deffrential ????
Manegemnt ???

CASE 2

A 68-year-old female with a background of stage four chronic kidney disease (CKD) presents with the following blood results to the nephrology clinic. She has had progressive CKD over many years
PTH 19.1 pmol/l (1.05 - 6.83)
Adjusted calcium 2.84 mmol/l (2.1-2.6)
What endocrine abnormality is she most likely to have given her background?
Tertiary hyperparathyroidism
Secondary hyperparathyroidism
Multiple endocrine neoplasia 1 (MEN1)
Pseudohypoparathyroidism
Primary hyperparathyroidism

CASE 3

37 yrs old m pt , known to have crohns dx , he underwent ileo-cecal resection one month ago
He presents to ER complaining of numbness , perioral parasthesia , muscle twitching
Labs show hypocalcemia ca 6.5 pth 20
He was given multiple calcium infusions , which fail to releive sx and to raise calcium to desired level
What is your explanation

Case 4

A 60-year-old man who is known to have lung cancer comes for review. For the past three weeks he has lost his appetite, has been feeling sick and generally feels tired. On examination he appears to be mildly dehydrated. You order some blood tests:

Calcium 11.5 mg/dl
Albumin 40 g/l
Glucose (random) 6.7 mmol/l
Creatinine 115 µmol/l

Which one of his existing medications is most likely to be contributing to his presentation?

Amlodipine
Simvastatin
Bendroflumethiazide
Aspirin
Lisinopril