

IN THE NAME OF GOD

A 29 years-old woman presented with asymptomatic hypercalcemia. Serum calcium was 11.6 mg/dL and phosphorus reported to be 2.8 mg/dL.

1. What points should be considered in her medical and family history?
2. What is the next step in the evaluation of this patient?

Her mother and a sister also have hypercalcemia and have failed neck explorations for parathyroid tumor

3. Has +ve family history of hypercalcemia any implication in the etiologic diagnosis of hypercalcemia?

Her serum intact PTH level was reported to be 64 pg/mL (N: 10 – 65) and creatinine was 0.8 mg/dL

4. What is the most probable diagnosis?
5. What are the differential diagnoses of hypercalcemia?
6. What is the next step in the evaluation of hypercalcemia in this patient?

24 h. urinary calcium reported to be 21 mg and creatinine 1.2 g

7. What is the calcium to creatinine clearance ratio and its role in the diagnosis of hypercalcemia?

Table 1 | Clinical presentation of hypercalcaemia

System	Acute hypercalcaemia	Chronic hypercalcaemia
General	Flushing, fatigue, weight loss	Fatigue
Cardiovascular	Prolonged PR interval, widened QRS complex, shortened QT interval, bundle branch block, bradycardia, arrhythmias, syncope, cardiac arrest	Prolonged PR interval, widened QRS complex, shortened QT interval, bundle branch block, bradycardia, arrhythmias, hypertension, valvular heart disease, vascular calcification
Renal	Thirst, polydipsia; dehydration; polyuria; nocturia; frequent urination; renal failure from obstructive uropathy, nephrolithiasis, nephrocalcinosis, or pre-renal causes	Nephrocalcinosis, nephrolithiasis, chronic renal failure, renal osteodystrophy
Neurological	Tiredness, obtundation, lethargy, confusion, delirium, somnolence, stupor, coma, hypotonia, hyporeflexia, paresis	Dementia, memory loss, sleep disturbance, decreased concentration
Psychiatric	Irritability, depression, anxiety, hallucination, psychosis	Irritability, depression, anxiety
Gastrointestinal	Anorexia, nausea, vomiting, abdominal pain, dyspepsia, constipation, pancreatitis, peptic ulcer	Anorexia, dyspepsia, constipation, pancreatitis, peptic ulcer
Skeletal and muscle	Bone pain, muscle weakness	Bone pain, muscle weakness, myalgias, osteoporosis, osteopenia, fragility fractures, osteitis fibrosa cystica, bone cysts, brown tumours of long bones, chondrocalcinosis, joint calcification
Haematological	Anaemia	Anaemia
Ocular	—	Band keratopathy (cornea)

Hypercalcaemia

Evaluate: timing, symptoms and signs, family and medical history, drug use, physical examination

Repeat measurement of serum calcium while not taking drugs (that is, thiazides or lithium) or vitamin D preparations; correct for serum albumin or measure serum Ca²⁺, or both

Confirmed*

Measure serum parathyroid hormone

High or normal result†

Measure CaCrCl, GFR, serum calcidiol level

Supplementation

Calcidiol <50 nmol/L

Calcidiol >50 nmol/L and GFR >60 mL/min

GFR <60 mL/min

Consider impaired renal function as possible cause of low urinary calcium excretion

CaCrCl <0.01

Familial hypocalciuria hypercalcaemia

Consider genetic testing and screen family members

CaCrCl between 0.01 and 0.02

Differential diagnosis between primary hyperparathyroidism and familial hypocalciuria hypercalcaemia not possible

Genetic testing

CaCrCl >0.02

Primary hyperparathyroidism

Suppressed‡

Consider:
Serum and urine protein electrophoresis (and parathyroid hormone related protein)
Skeletal survey
Chest, abdomen, and pelvis imaging

Skeletal involvement and/or positive imaging (with or without increases in parathyroid hormone related protein)

Malignancy

Monoclonal component

Consider multiple myeloma

Negative results

Measure calcitriol level

Consider lymphoproliferative or granulomatous disorders§

* Corrected serum calcium concentration (see legend) above the mean +2 standard deviations, in at least two samples at least one week apart over a period of three months. Calcium to creatinine clearance ratio (CaCrCl): urinary calcium × serum creatinine / serum calcium × urinary creatinine to be evaluated using blood samples and 24 hour urine collection; values in mg/dL

† Normal means in mid or upper normal range

‡ Consider specific measurements according to clinical presentation (that is, thyroid stimulating hormone, in case of hyperthyroidism; see text for details)

§ Eventually consider measuring serum angiotensin converting enzyme

Classification of Causes of Hypercalcemia (1)

Parathyroid-related:

- 1. Primary hyperparathyroidism**
 - a. Solitary adenomas
 - b. Multiple endocrine neoplasia
- 2. Lithium therapy**
- 3. Familial hypocalciuric hypercalcemia**

Malignancy-related

- 1. Solid tumor with metastases (breast)**
- 2. Solid tumor with humoral mediation of hypercalcemia (lung, kidney)**
- 3. Hematologic malignancies (multiple myeloma, lymphoma, leukemia)**

Classification of Causes of Hypercalcemia (2)

Vitamin D-related

1. Vitamin D intoxication
2. ↑ 1,25(OH)₂D; sarcoidosis and other granulomatous diseases
3. Idiopathic hypercalcemia of infancy

Associated with high bone turnover:

1. Hyperthyroidism
2. Immobilization
3. Thiazides
4. Vitamin A intoxication

Associated with renal failure:

1. Severe secondary hyperparathyroidism
2. Aluminum intoxication
3. Milk-alkali syndrome

Differential Diagnosis of Hypercalcemia (1)

CAUSES

COMMENT

Primary hyperparathyroidism

Most common cause in ambulatory patients

Malignancy, with or without bone metastasis

Most common cause in hospitalized patients

Thiazide / chlorthalidone therapy

Hypercalcemia usually mild; accentuates hypercalcemia of primary HPT

Vitamin D intoxication

Measure 25-(OH)D₂; long persistence because of storage in fat

Sarcoidosis

Vitamin D hypersensitivity; steroid responsive

Familial benign (hypocalciuric) hypercalcemia

Suspect in families of patient with unsuccessful parathyroidectomy

Milk – alkali syndrome

Less common with current decreased use of absorbable antacids

Differential Diagnosis of Hypercalcemia(2)

CAUSES

COMMENT

Immobilization

Increased bone resorption; seen particularly in patients with high bone turnover rate (for example, Paget's disease) or immobilized

Dehydration

Mild hypercalcemia may be seen with 24-hour fasting if water is restricted

Thyroid disease

Cause unknown; more common in hyperthyroidism but occurs with hypothyroidism

Lithium therapy

Change in parathyroid feedback threshold or stimulation of parathyroid cells

Etiologies of Hypercalcemia (1)

Hyperparathyroidism

Primary (common)

Multiple endocrine neoplasia

Parathyroid carcinoma

Secondary (Hypercalcemic)

Familial hypocalciuric hypercalcemia

Malignant tumors (common)

With skeletal involvement

Without detectable skeletal involvement (humoral hypercalcemia of malignancy)

Etiologies of Hypercalcemia (2)

Drugs

- Vitamin D / Vitamin A
- Calcium (massive doses)
- Thiazide diuretics
- Lithium

Granulomatous diseases

- Sarcoidosis, Tuberculosis and others

Endocrinopathies

- Thyrotoxicosis
- Pheochromocytoma
- Addison's disease
- Others

Miscellaneous

- Immobilization
- Acute renal failure (recovery phase)
- Infantile (e, g., William's syndrome)

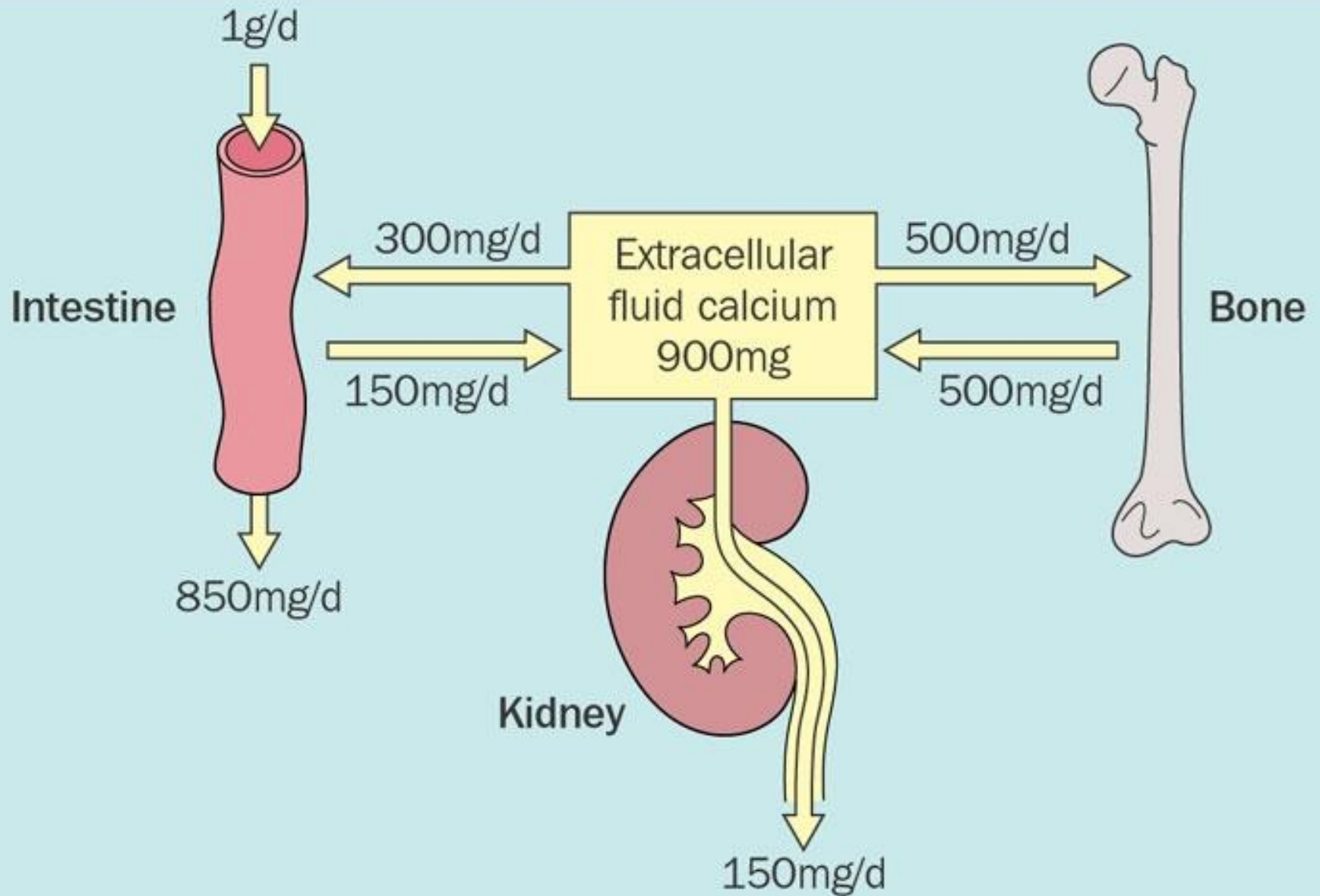
Biochemical and Radiologic Findings in Hypercalcemia

Diagnosis	sCa	sPO ₄	uCa	25(OH)D	1.25(OH) ₂ D	Alkaline Phosphatase	Urinary Cyclic AMP	iPTH	Bone Survey
Primary hyperparathyroidism	↑	↓	n/↑	n	↑	↑	↑↑	↑↑	Osteitis fibrosa cystica
Osteolytic malignancy	↑	↑	↑↑	n	↓	↑↑	↓	↓	Lytic lesions
Humoral hypercalcemia of malignancy	↑	↓	↑↑	n	↓	n	↑↑	↓	n
Sarcoidosis	↑	↑	↑↑	n	↑↑	↑	↓	↓	Punched-out lesions or cortical thinning
Vitamin D intoxication	↑	↑	↑↑	↑↑	n	n	↓	↓	n
Familial hypocalciuric hypercalcemia	↑	↓	↓	n	n	n	↑	↑	n

The bottom line

- **Primary hyperparathyroidism and malignancy are the two most common causes of increased serum calcium levels**
- **The diagnosis of hypercalcaemia is made when the corrected serum calcium concentration is 2 standard deviations above the mean of values found in people with normal calcium levels, in at least two samples at least one week apart over a period of three months**
- **The presence of high or not adequately suppressed serum parathyroid hormone levels should point the diagnosis towards hypercalcaemia of parathyroid origins**
- **Mild hypercalcaemia is usually caused by primary hyperparathyroidism, the treatment for which is typically surgery; those aged 50 or more with serum calcium levels <0.25 mmol/L above the upper limit of normal and without end organ damage may be followed up conservatively. Treatment with a calcimimetic agent, cinacalcet, is an option in selected cases**
- **Severe hypercalcaemia requires admission to hospital and treatment with aggressive intravenous hydration and bisphosphonates along with treatment of the underlying disease**

Calcium fluxes in a normal adult

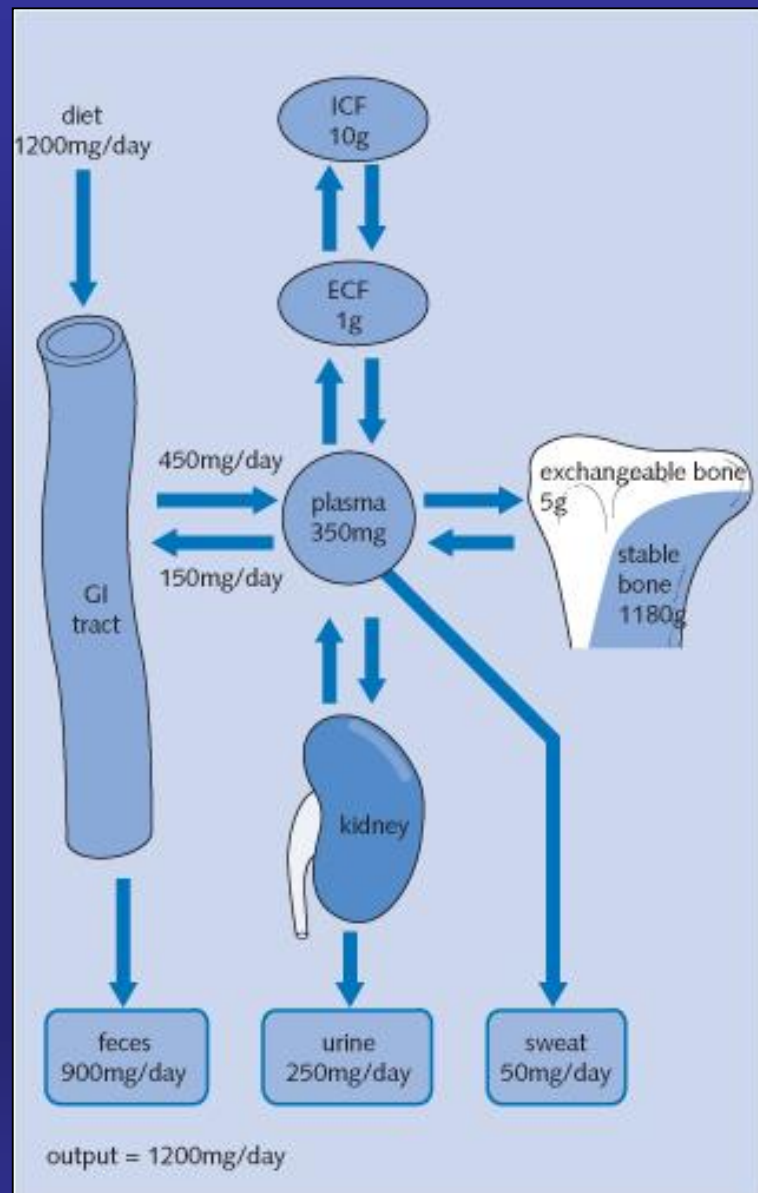


Distribution of Ca, P and Mg in the skeleton and soft tissues in the average 70 kg adult man

	Ca	P	Mg
Total body content	1300 g	700 g	27 g
Percentage in the skeleton	99%	85%	57%
Percentage in the soft tissue	0.6%	14%	40%

States of calcium, magnesium, and phosphate in human plasma

	Calcium (mEq)	Magnesium (mEq)	Phosphate (mM)
Protein – bound	2.30 (45%)	0.55 (31%)	0.15 (13%)
Filterable or free complexed	0.50 (10%)	0.15 (9%)	0.40 (35%)
Ionized	2.15 (44%)	1.05 (60%)	0.60 (5%)



Normal distribution and movements of calcium in the body. (ICF, intracellular fluid; ECF, extracellular fluid.)

Actions of the hormones involved in calcium homeostasis

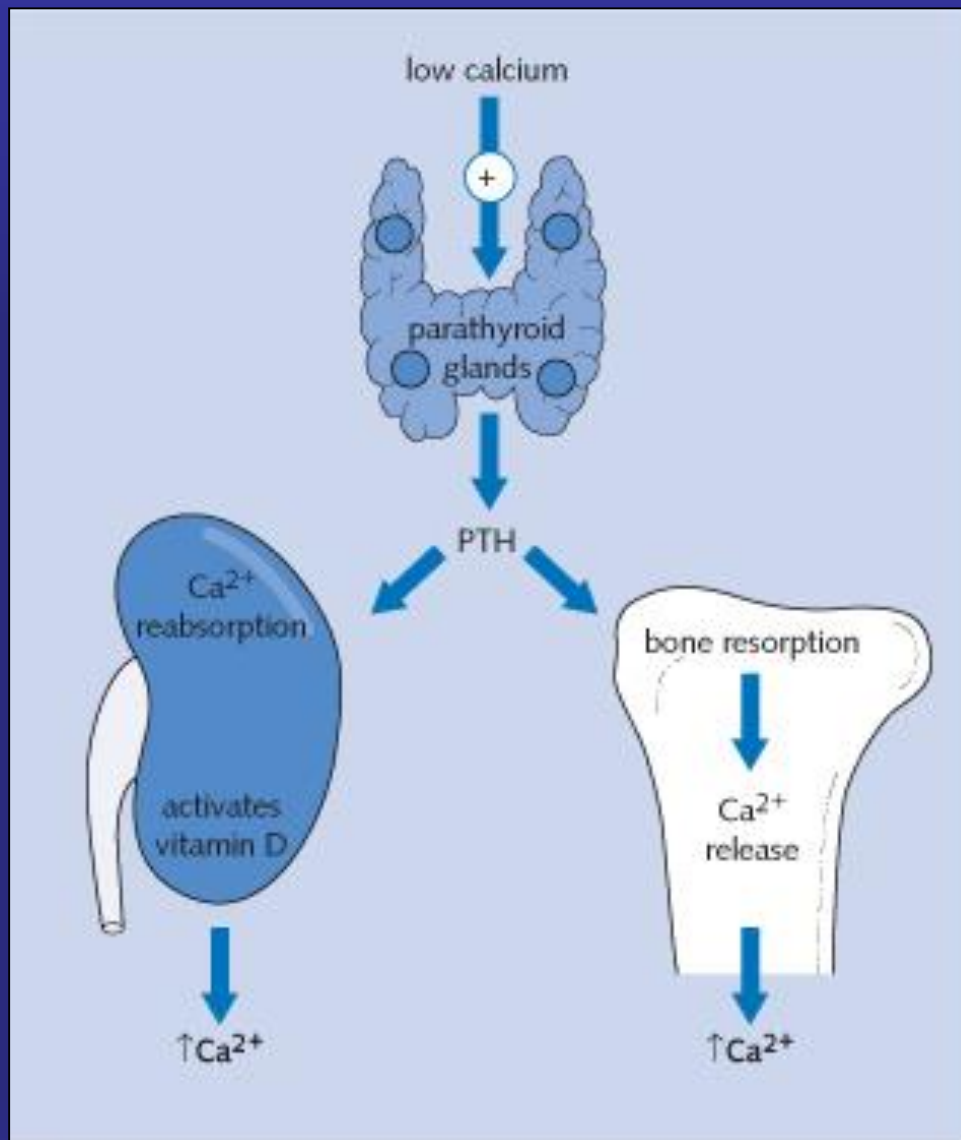
	PTH	Vitamin D	Calcitonin
Secreted/activated in response to:	Low blood calcium	PTH	High blood calcium
Kidneys	Calcium reabsorbed; vitamin D activated	Calcium reabsorbed	Calcium excreted
Bones	Calcium released	Calcium trapped	Calcium trapped
Intestines	Negligible	Calcium absorbed	Negligible

Normal distribution and movements of calcium in the body. (ICF, intracellular fluid; ECF, extracellular fluid.)

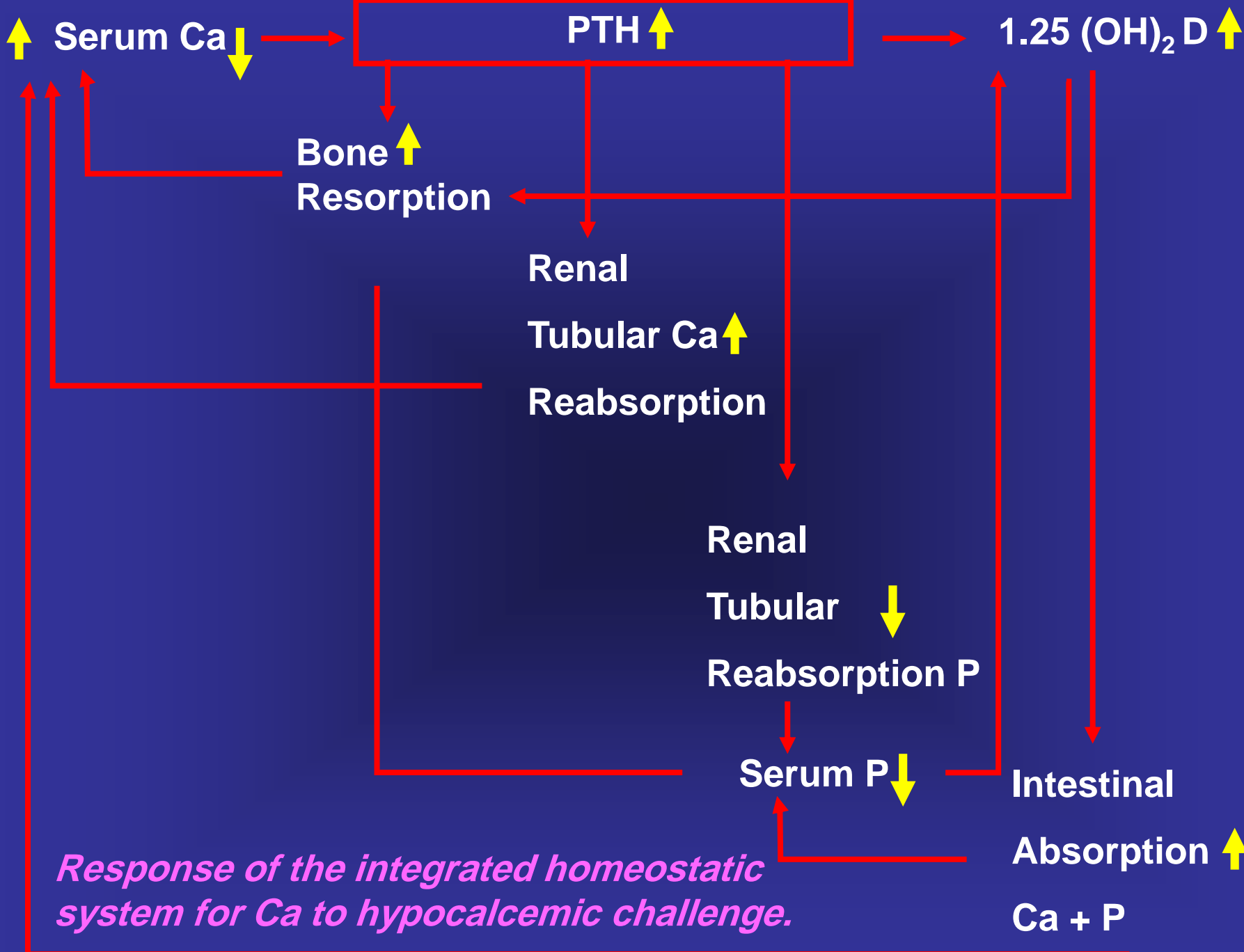
REGULATION OF SERUM CALCIUM LEVELS

Comparative effects of calcium-regulating agents

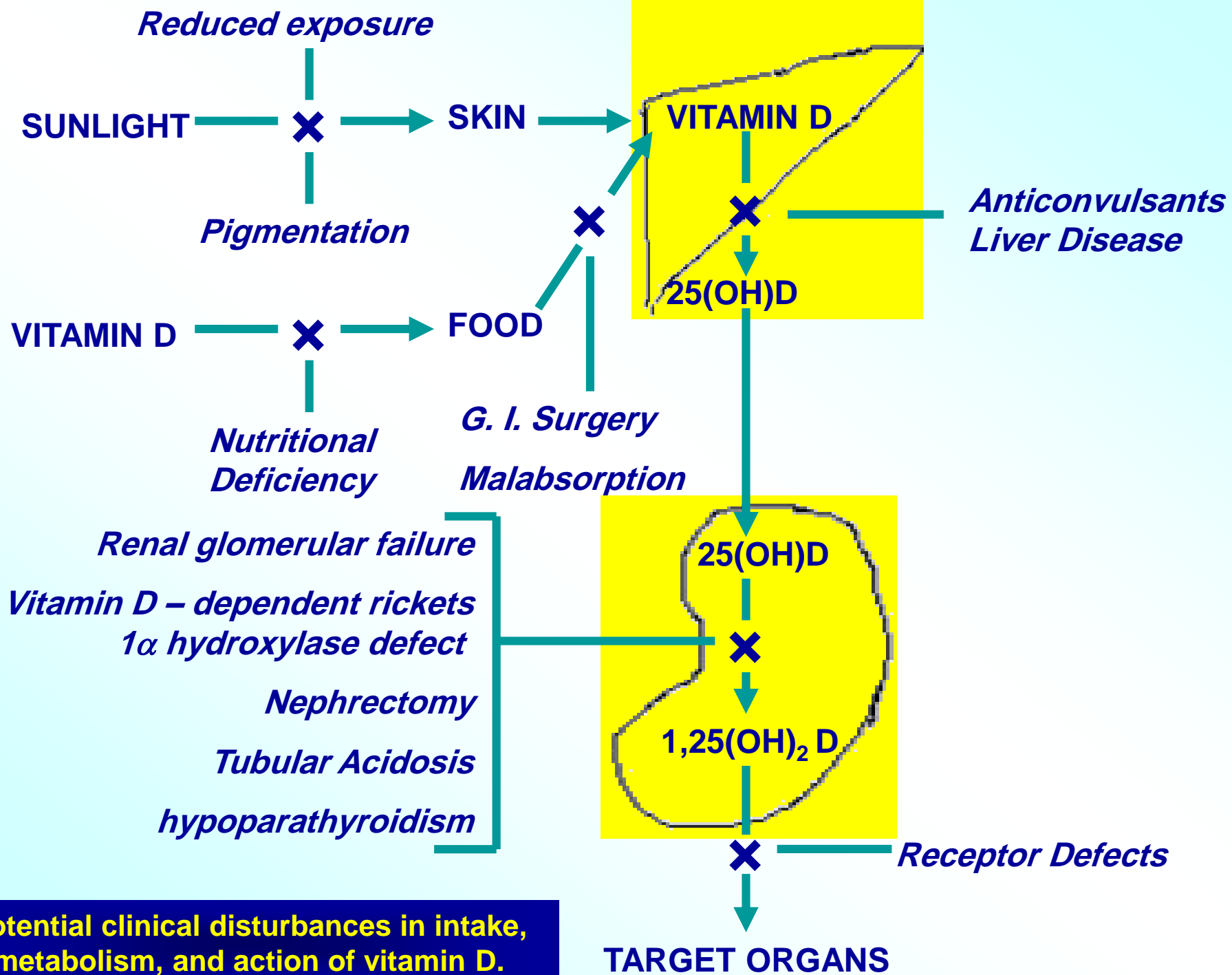
	GI tract	Kidneys	Bones
Parathormone	↑ Calcium absorption (indirect action, via vitamin D)	↑ Calcium reabsorption ↓ Phosphate reabsorption	↑ Calcium and Phosphate reabsorption
Vitamin D	↑ Calcium absorption (direct action)	↑ Calcium reabsorption	↑ Calcium reabsorption
Calcitonin		↓ Calcium reabsorption ↑ Phosphate reabsorption	↓ Calcium reabsorption

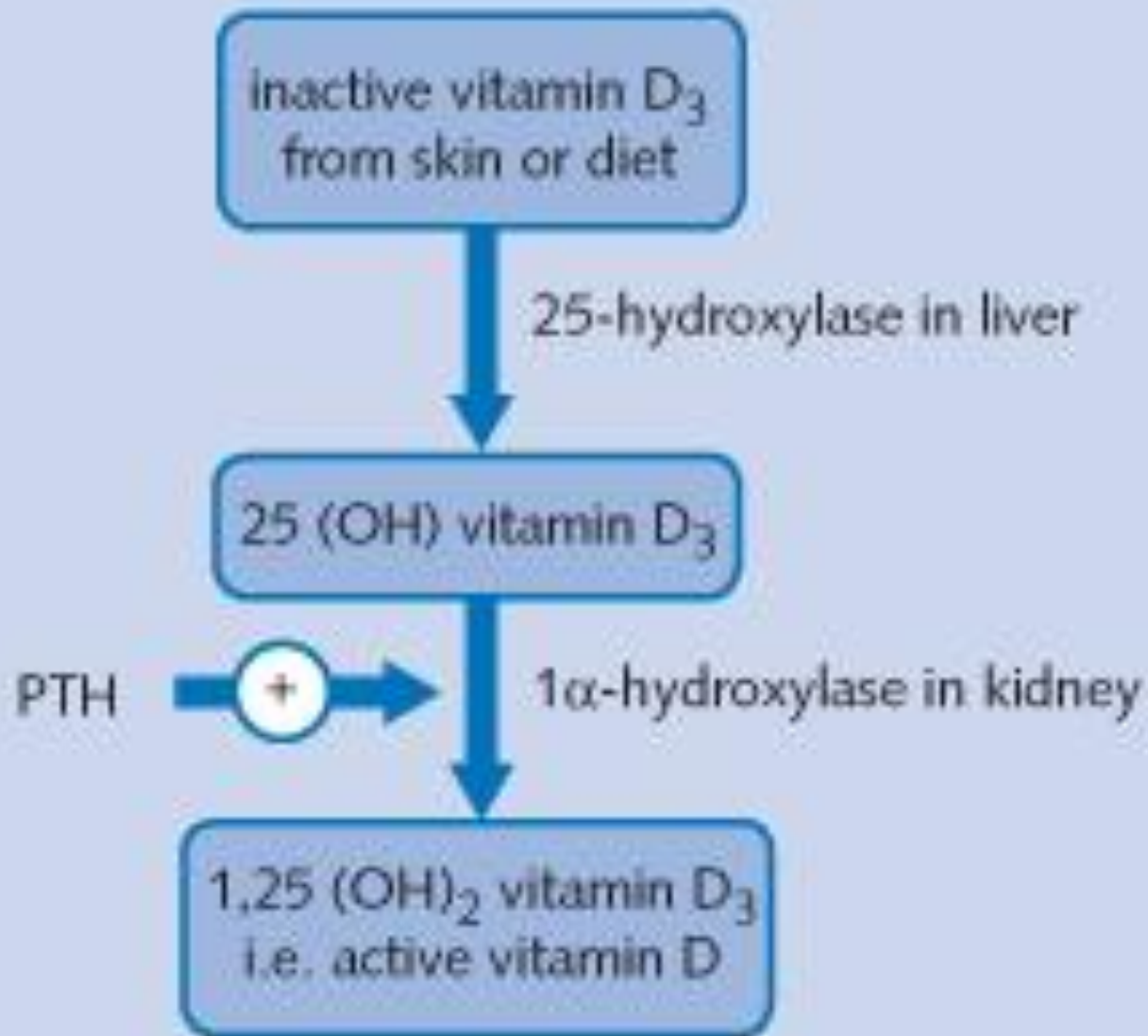


Actions of parathyroid hormone (PTH) on the kidney and bone.



Response of the integrated homeostatic system for Ca to hypocalcemic challenge.





Activation of vitamin D. (25 (OH) vitamin D₃, 25-hydroxyvitamin D₃; 1,25 (OH)₂ vitamin D₃, 1,25-dihydroxyvitamin D₃.)

Pathogenesis of hypercalcemic disorders (1)

1. *Excessive parathyroid hormone*

a. primary hyperparathyroidism

b. secondary hyperparathyroidism (hypercalcemic)

c. lithium therapy

d. familial hypocalciuric hypercalcemia

2. *Excess vitamin D*

a. hypervitaminosis D

b. Sarcoidosis (increased formation of $1,25(\text{OH})_2\text{D}_3$)

c. Idiopathic hypercalcemia of childhood (increased sensitivity to vitamin D?)

Pathogenesis of hypercalcemic disorders (2)

3. *Malignancy associated hypercalcemia (hormonal hypercalcemia of malignancy)*
 - a. *Nonparathyroid tumor producing PTH-like peptide (lung, kidney, other), or nonPTH calcium mobilizing substance (prostaglandin E₂; OAF)*
4. *Disruption of normal bone-extracellular fluid equilibrium*
 - a. *Metastatic tumor*
 - b. *Multiple myeloma (OAF)*
 - c. *Lymphoma, occasionally acute leukemia in blastic phase*
 - d. *hyperthyroidism*
 - e. *Immobilization in young individuals or those with underlying disease (Paget's, etc.)*

Pathogenesis of hypercalcemic disorders (3)

5. *Other*

a. Adrenal insufficiency

b. Thiazide administration (usually in hyperparathyroid patients).

c. Milk-alkali syndrome

d. Hypervitaminosis A

Frequency of diagnosis of hypercalcemia in hospitalized patients

Diagnosis	No, of cases
Malignant disease	89
Primary hyperparathyroidism	51
Overdosage of vitamin D	1
Thyrotoxicosis	2
Associated with artificial-kidney unit	6
Lithium-induced hypercalcemia	1
Thyrotoxicosis plus primary hyperparathyroidism	1
Sarcoidosis plus primary hyperparathyroidism	1
Steroid-responsive hypercalcemia	1
Unavailable for investigation	13
Total	166

SERUM CALCIUM ELEVATED
(Confirm with 3 additional measurements.)

SERUM PTH

High or inappropriately high for serum calcium

**PRIMARY
HYPERPARATHYROIDISM**

Creatinine clearance

24-hour urine calcium

Intravenous urograms and nephrotomograms

Hand x-rays (fine-grain film)

Lateral spine x-rays

Vertebral density measurement

Imaging studies for localization

