APPROACH TO **HYPERCALCEMIA**

Introduction

- Calcium is one of the most abundant mineral in the human body and it has many important biological functions
- 1000-2000 g of Ca is present normally in human body
- 99% - in the skeleton
- Remaining amount -distributed in the ECF and other soft tissues
- Influx and efflux of calcium across the skeletal system occurs daily ,mediated by coupled osteoblastic and osteoclastic activity

Distribution of calcium outside skeletal system

- In Blood , total Ca conc is normally 8.5-10.5 mg/dl, of which approx 50% is ionized

- Remainder is bound ionically to negatively charged proteins- Predominantly albumin and immunoglobulins or lossely complexed with PO_4 , citrate ,SO_4 and other anions

Protein binding of calcium

- Influenced by pH.

- Metabolic acidosis→decrease protein binding → increase ionized calcium.
- Metabolic alkalosis →increase protein binding→ decrease ionized calcium.
- Fall in pH by 0.1 increases serum calcium by 0.1 mmol/L

- As ionized form is the active form of calcium, serum calcium levels should be adjusted for abnormal serum albumin levels.

- **Corrected calcium**

- For every 1-g/dL drop in serum albumin below 4 g/dL, measured serum calcium decreases by 0.8 mg/dL.

- Corrected calcium =

Measured Ca + [0.8 x (4 - measured albumin)]

(Calcium in mg/dl; albumin in g/dl)

FUNCTIONS of Calcium

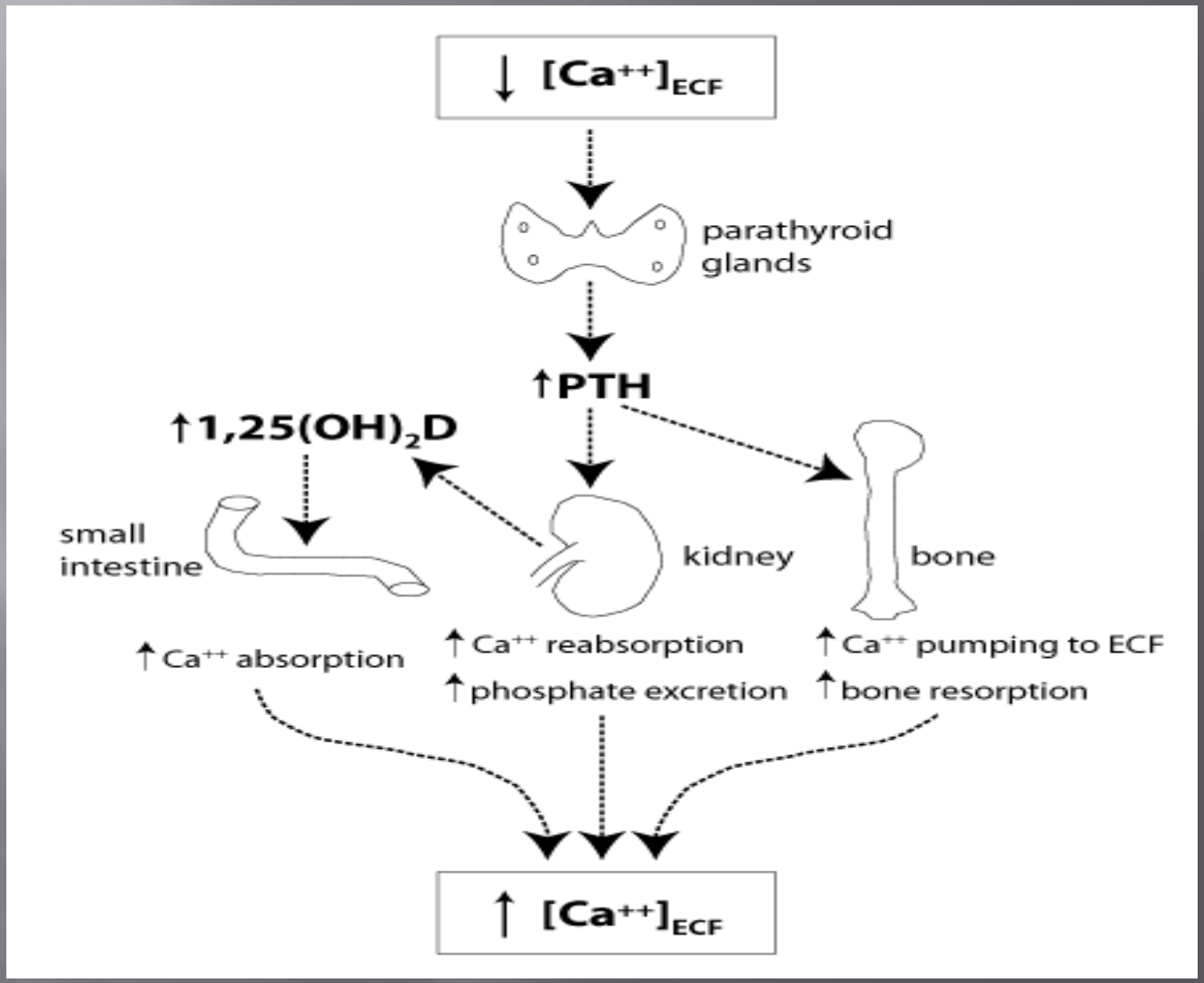
- Muscle contraction
- Neuromuscular / nerve conduction
- Intracellular signalling
- Bone formation
- Coagulation
- Enzyme regulation
- Maintainance of plasma membrane stability

Metabolism

- Dietary intake of Ca 400-1500 mg/day
- Daily intestinal absorption of Ca 200-400 mg/d
- Renal excretion regulated by conc of ionised Ca in blood
- Approx 8-10 g/day of Ca filtered by the glomeruli, of which only 2-3% appears in urine (200mg)
- 65% absorbed in PCT –passively –paracellular route that is coupled to Nacl reabsorption
- cTAL of Henles loop- 20% paracellular mechanism

Requires a protein Paracellin-1 which is inhibited by increased blood conc of Ca and Mg acting via CaSR expressed on BL membrane

Calcium Homeostasis



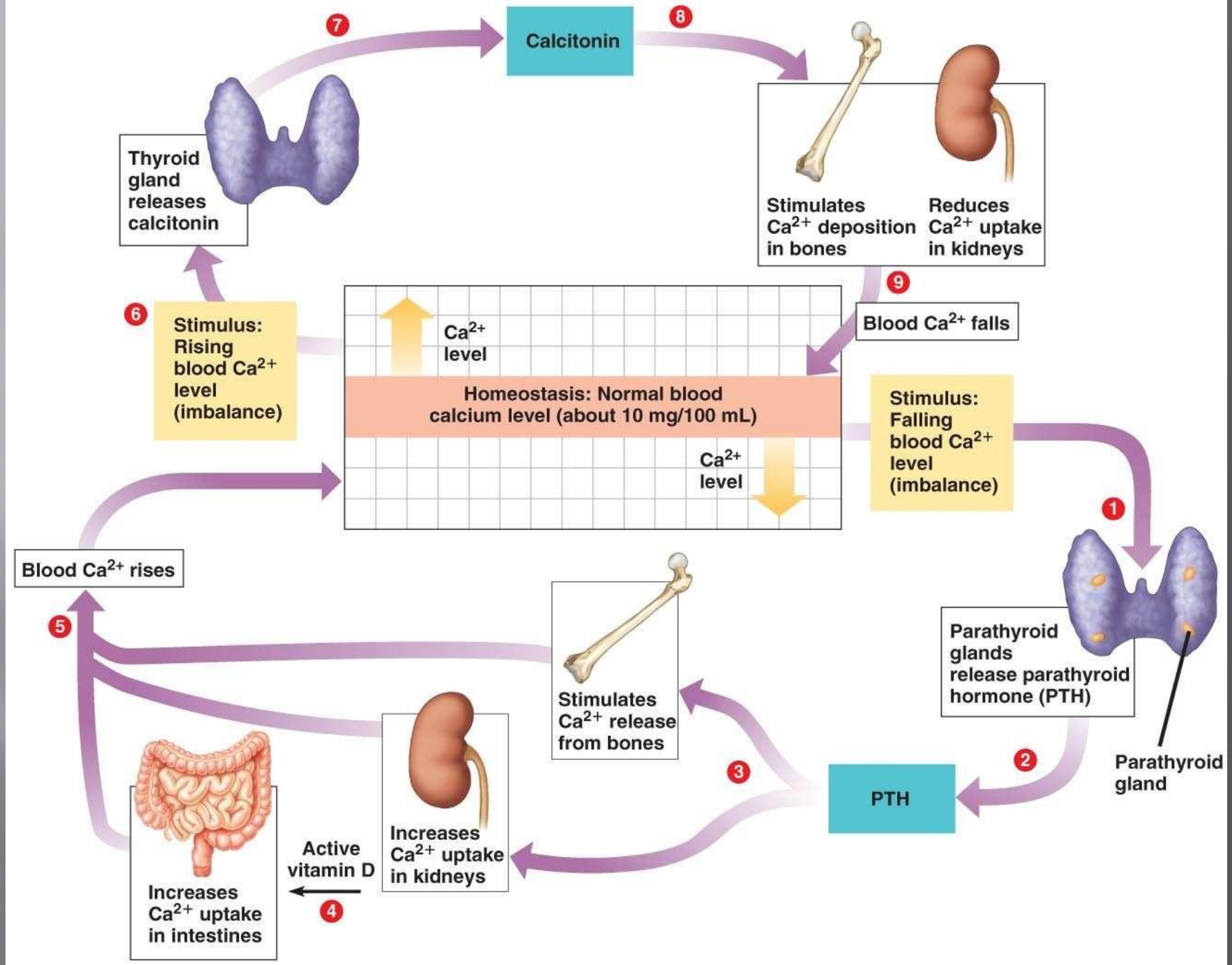


TABLE 1

Actions of the Hormones Involved in Calcium Homeostasis

Hormone	*Effect on bones*	*Effect on gut*	*Effect on kidneys*
Parathyroid hormone ↑Ca^{++}, ↓PO_4 levels in blood	Supports osteoclast resorption	Indirect effects via ↑calcitriol from 1-hydroxylation	Supports Ca^{++} resorption and PO_4 excretion, activates 1-hydroxylation
Calcitriol (vitamin D) ↑Ca^{++}, ↑PO_4 levels in blood	No direct effects Supports osteoblasts	↑Ca^{++} and PO_4 absorption	No direct effects
Calcitonin causes ↓Ca^{++}, ↓PO_4 levels in blood when hypercalcemia is present	Inhibits osteoclast resorption	No direct effects	Promotes Ca^{++} and PO_4 excretion

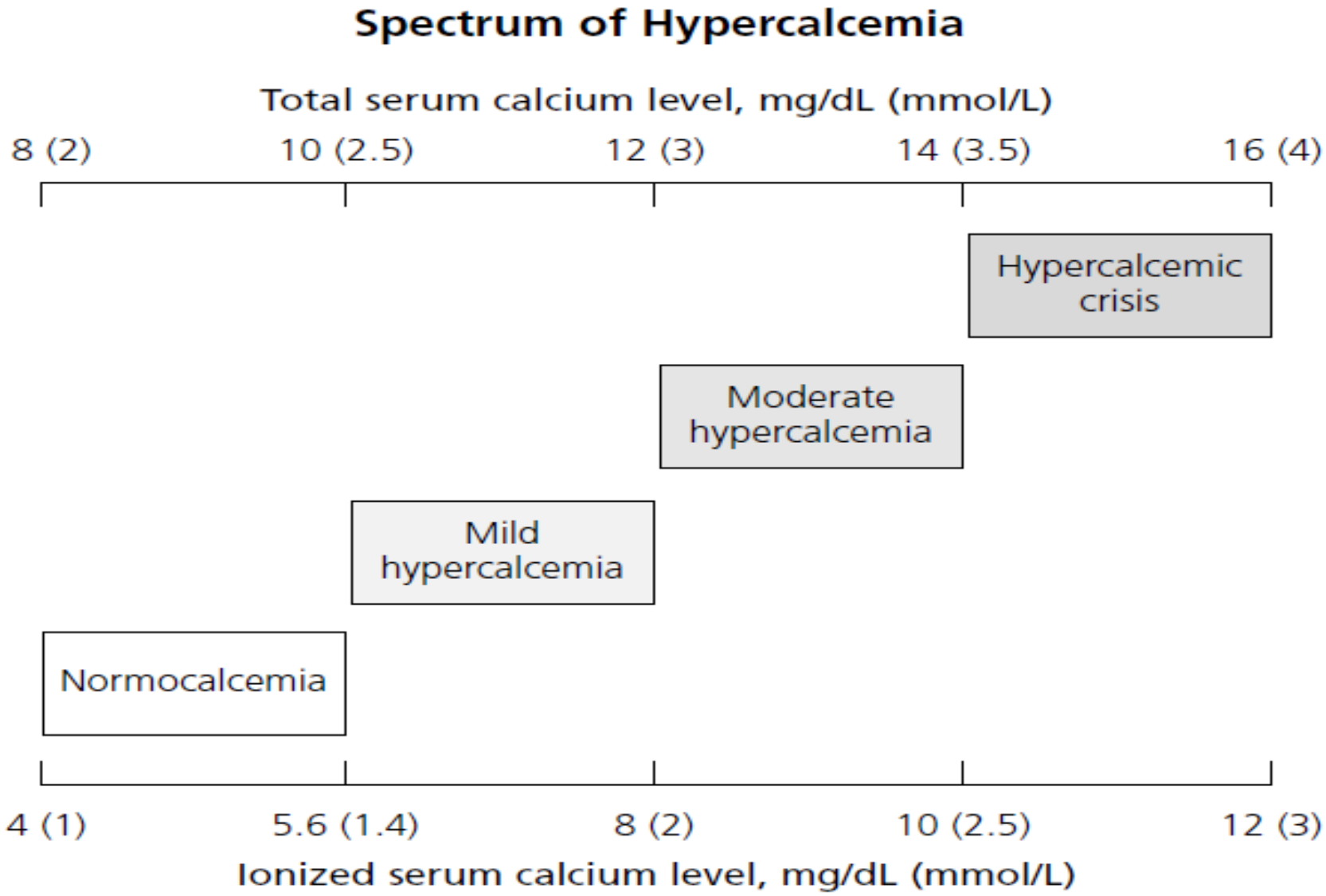
Ca^{++} = calcium; PO_4 = phosphate radical.

HYPERCALCEMIA

- **Hypercalcemia** is defined as total serum calcium >**10.2** mg/dl (>**2.5** mmol/L)
  or ionized serum calcium >**5.6** mg/dl (>**1.4** m mol/L)

- **Severe hypercalemia** is defined as total serum calcium > **14 mg/dl (> 3.5 mmol/L)**

- **Hypercalcemic crises** is present when severe **neurological symptoms** or **cardiac arrhythmias** are present in a patient with a serum calcium >14 mg/dl (> 3.5 mmol/L).


Spectrum of Hypercalcemia
Total serum calcium level, mg/dL (mmol/L)
8 (2)
10 (2.5)
12 (3)
14 (3.5)
16 (4)
Hypercalcemic crisis
Moderate hypercalcemia
Mild hypercalcemia
Normocalcemia
4 (1)
5.6 (1.4)
8 (2)
10 (2.5)
12 (3)
Ionized serum calcium level, mg/dL (mmol/L)

Clinical Manifestations of Hypercalcemia

Renal "stones"
Nephrolithiasis
Nephrogenic diabetes insipidus
Dehydration
Nephrocalcinosis

Skeleton "bones"
Bone pain
Arthritis
Osteoporosis
Osteitis fibrosa cystica in hyperparathyroidism (subperiosteal resorption, bone cysts)

Gastrointestinal "abdominal moans"
Nausea, vomiting
Anorexia, weight loss
Constipation
Abdominal pain
Pancreatitis
Peptic ulcer disease

Neuromuscular "psychic groans"
Impaired concentration and memory
Confusion, stupor, coma
Lethargy and fatigue
Muscle weakness
Corneal calcification (band keratopathy)

Cardiovascular
Hypertension
Shortened QT interval on ECG
Cardiac arrhythmias
Vascular calcification

Other
Itching
Keratitis, conjunctivitis

Causes of Hypercalcemia

Parathyroid hormone-related

- Primary hyperparathyroidism*
  Sporadic, familial, associated with multiple endocrine neoplasia I or II
- Tertiary hyperparathyroidism
  Associated with chronic renal failure or vitamin D deficiency

Malignancy

- Humoral hypercalcemia of malignancy* (mediated by PTHrP)
  Solid tumors, especially lung, head, and neck
  squamous cancers, renal cell tumors
- Local osteolysis* (mediated by cytokines)
  multiple myeloma, breast cancer

Vitamin D-related

- Vitamin D intoxication
- Granulomatous disease sarcoidosis, berylliosis, tuberculosis
- Hodgkin's lymphoma

Medications

- Thiazide diuretics (usually mild)*
- Lithium
- Milk-alkali syndrome (from calcium antacids)
- Vitamin A intoxication (including analogs used to treat acne)

Other endocrine disorders

- Hyperthyroidism
- Adrenal insufficiency
- Acromegaly
- Pheochromocytoma

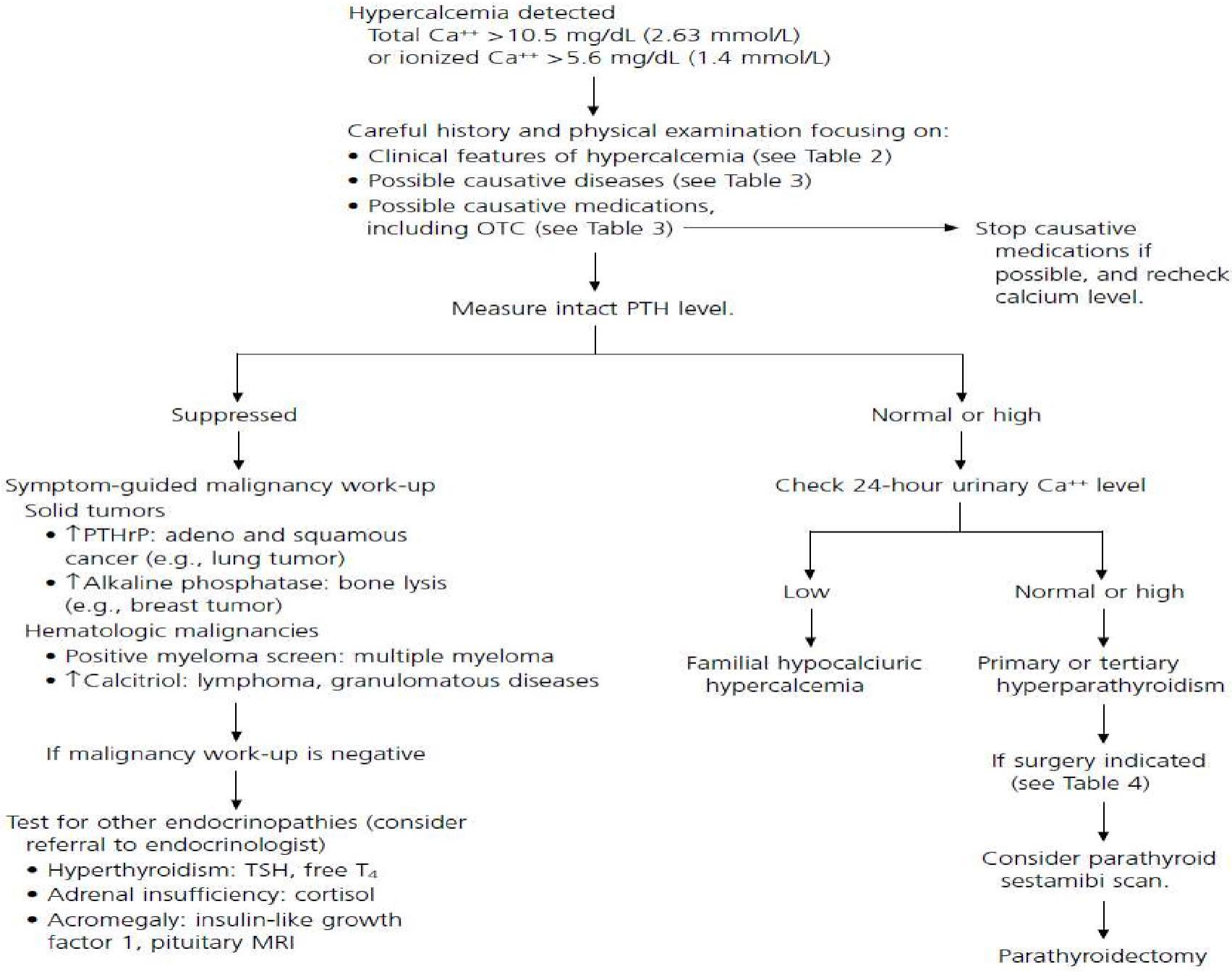
Genetic disorders

- Familial hypocalciuric hypercalcemia: mutated calcium-sensing receptor

Other

- Immobilization, with high bone turnover (e.g., Paget's disease, bedridden child)
- Recovery phase of rhabdomyolysis

Evaluation of Hypercalcemia



Among all causes of hypercalcemia, ***primary hyperparathyroidism and malignancy*** are the most common, accounting for greater than 90 percent of cases.

- Therefore, the diagnostic approach to hypercalcemia typically involves distinguishing between the two.
- Patients with hypercalcemia of malignancy usually have higher Ca concentrations and are more symptomatic from hypercalcemia than individuals with primary hyperparathyroidism.
- Serum Ca must be corrected for serum albumin before labelling it as a case of Hypercalcemia.

HYPERPARATHYROIDISM

- Measurement of intact PTH levels
- Normal or High i-PTH –Diagnosis of Primary or Tertiary HyperPTH
- 80% due to single parathyroid adenoma
- Hyperparathyroidism also can result from hyperplasia of the parathyroid glands or, rarely, parathyroid carcinoma

- 80 % cases: asymptomatic, diagnosed on routine lab finding of increased serum calcium

- 20-25% cases: chronic course with mild or intermittent hypercalcemia, recurrent renal stones, complication of nephrolithiasis

- 5-10% have severe and symptomatic hypercalcemia and overt osteitis fibrosa cystica; in these patients the parathyroid tumor is usually large (greater than 5.0 g).

- The diagnosis of PHPT is established by laboratory testing showing

- *hypercalcemia,
- normal or elevated PTH,
- hypercalciuria,
- hypophosphatemia,
- *-phosphaturia, and
- *increased urinary excretion of cyclic adenosine monophosphate.

- Chronic renal failure generally causes hypocalcemia.
- If untreated, prolonged high phosphate and low vitamin D levels can lead to increased PTH secretion and subsequent hypercalcemia ie ***Tertiary hyperparathyroidism.***

VITAMIN D-MEDIATED CAUSES

- Oral Vit D supplements consists of 25 OH Vit D2
- Ealvated levels of 25 OH Vit D levels are usually due to OTC medications (value >150 ng/mL (374 nmol/L)

- On the other hand, increased levels of ***1,25-dihydroxyvitamin D*** may be induced by
- direct intake of this metabolite,
- extrarenal production in granulomatous diseases or lymphoma, or
- increased renal production that can be induced by primary hyperparathyroidism but not by PTHrp

- In patients with elevated 1,25-dihydroxyvitamin D, chest radiograph (looking for malignancy or sarcoidosis) may be helpful

- Hypercalcemia mediated by excessive vitamin D responds to a short course of glucocorticoids if the underlying disease is treated.

HYPERCALCEMIA OF MALIGNANCY

- Humoral hypercalcemia of malignancy is one of the most common causes of non-PTH-mediated hypercalcemia.
- It should be particularly suspected if there is clinical evidence of malignancy, usually a solid tumor, and the hypercalcemia is of relatively recent onset.

- Have an elevated serum concentration of PTH-related protein (PTHrp) which mimics the bone and renal effects of PTH

- Low Levels of PTH and 1,25-dihydroxyvitamin D

- Multiple myeloma and metastatic breast cancer can present as Hypercalcemia due to extensive bonelysis

- Hodgkin's lymphoma causes hypercalcemia through increased production of calcitriol

Other Causes of Hypercalcemia

- ***Thiazide diuretics*:**
- Enhance ca reabsorption in the distal tubule➔ ↓urinary ca excretion.

Rarely causes ↑Ca in N persons, but lead to ↑Ca in pts with underlying ↑ bone resorption (eg in hyperparathyroidism)

Mild hypercalcaemia,↓/N PTH

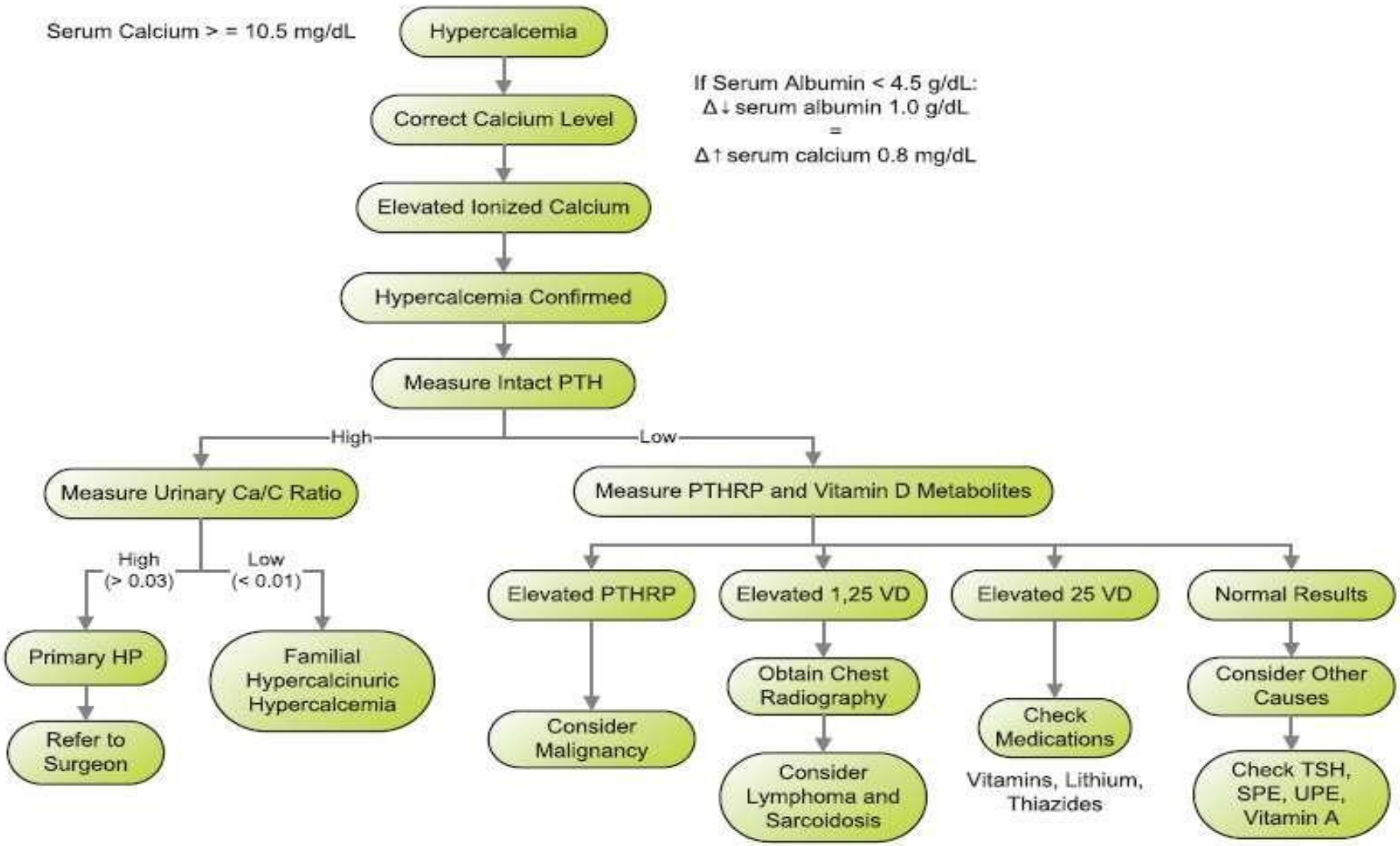
- ***Lithium therapy:***
- Increased PTH secretion → Increasing set point of PTH, hence higher [Ca] to switch off PTH
- Lab inv : high Ca, PTH, low urinary 24(h) calcium

- Milk Alkali Syndrome

  Consumption of large amounts of calcium carbonate via calcium-containing antacids can lead to hypercalcemia, alkalosis, and renal insufficiency

- Thyroid disorders
- Phaeochromocytoma
- Pagets disease

Diagnostic Approach to Hypercalcaemia - Summary



Diagnostic approach to hypercalcemia which is a modified algorithm published in UptoDate online.[6] PTH indicates parathyroid hormone; PTHRP, parathyroid hormone-related peptide; 1,25 VD; 1,25-dihydroxyvitamin D; 25 VD, 25-hydroxyvitamin D; Ca/C, calcium/creatinine; HP, hyperparathyroidism; SPE, serum protein electrophoresis; UPE, urine protein electrophoresis; and TSH, thyroid stimulating hormone.

DDX	Ca	PO4	PTH	PTHrP	1,25(OH)D	U Ca
Malignancy	↑	N/↑	↓	↑↑	↓/N	↓/N
Primary PTH	↑	↓	↑	N	↑	↑
Granulomatous disease	↑	↑	↓	N	↑↑	↑
Vit D excess	↑	↑	↓	N	↑↑	↑
Thiazide	↑/N	↑	↓/N	N	N	↓
Milk alkali syndrome	↑/N	↑	↓/N	N	N	↓

TREATMENT OF HYPERCALCEMIA

Aimed both at

- Lowering the serum calcium and, if possible,
- Treating the underlying disease.

- Main Principle of treatment aimed at reducing serum calcium by

1. Inhibiting bone resorption,
2. increasing urinary calcium excretion, or
3. decreasing intestinal calcium absorption

- Patients with mild hypercalcemia (<12 mg/dL) do not require immediate treatment. They should stop any medications implicated in causing hypercalcemia, avoid volume depletion and physical inactivity, and maintain adequate hydration.

- Moderate Hypercalcemia (12 to 14 mg/dL), especially if acute and symptomatic, requires more aggressive therapy.

- Patients with severe hypercalcemia (>14 mg/dL), even without symptoms, should be treated intensively.

SALINE HYDRATION

- Correction of the ECF volume is the first and the most important step in the treatment of severe hypercalcemia from any cause.
- Volume repletion can lower calcium concentration by approximately 1 to 3 mg/dL by increasing GFR and decreasing sodium and calcium reabsorption in proximal and distal tubules.

- . A reasonable regimen, in the absence of edema, is the administration of isotonic saline at an initial rate of 200 to 300 mL/hour that is then adjusted to maintain the urine output at 100 to 150 mL/hour

FUROSEMIDE 10- 20 mg iv as necessary after achieving adequate hydration

- Promotes calciuresis and prevents edema
- Lasix infusion not advisable due to complications

INTERVENTION	DOSAGE	ADVERSE EFFECT
Hydration or Calciuresis		
Intravenous saline	200-500 mL/hr, depending on the cardiovascular and renal status of the patient	Congestive heart failure
Furosemide	20-40 mg intravenously, *after rehydration has been achieved*	Dehydration, hypokalemia, hypomagnesemia

CALCITONIN

- Is Beneficial in symptomatic patients with serum calcium >14 mg/L (3.5 mmol/L),
- along with hydration and bisphosphonates.'

- It works rapidly, lowering the serum calcium concentration by a maximum of 1to 2 mg/dL (0.3 to 0.5 mmol/L) beginning within four to six hours

- It Acts by increasing Renal calcium excretion and, by decreasing bone resorption via interference with osteoclast function

- DOSING:

  Salmon calcitonin 4 IU/kg im or s/c every 12 hours; doses can be increased up to 6 to 8 international units/kg every six hours

- efficacy of calcitonin is limited to the first 48 hours, even with repeated doses, due development of tachyphylaxis, perhaps due to receptor downregulation

BISPHOSPHONATES –

- Are nonhydrolyzable analogs of inorganic pyrophosphate that adsorb to the surface of bone hydroxyapatite and inhibit calcium release by interfering with osteoclast-mediated bone resorption

- They are effective in treating hypercalcemia resulting from excessive bone resorption of any cause

- Maximum effect occurs in 2-4 days,

  so usually given in conjunction with saline and/or calcitonin, which reduce calcium concentration more rapidly.

- IV Zoledronic acid (ZA) or Pamidronate are bisphosphonates of choice

Bisphosphonates Pamidronate (Aredia), 60 to 90 mg IV over 4 hours Zoledronic acid (Zometa), 4 mg IV over 15 minutes	Inhibits osteoclast action and bone resorption	Hypercalcemia of malignancy	Nephrotoxicity, $\downarrow Ca^{++}$, $\downarrow PO_4$, rebound $\uparrow Ca^{++}$ in hyperparathyroidism Maximal effects at 72 hours

•Other Bisphosphonates that are in use are, ibandronate , clodronate , and etidronate

- Common complications of Bisphosphonate use are hypocalcemia, hypophosphatemia, impaired renal function, nephrotic syndrome, osteonecrosis of the jaw(Repetitive iv)

GLUCOCORTICOIDS:

- Increased calcitriol production occurs in patients with chronic granulomatous diseases (eg, sarcoidosis) and in occasional patients with lymphoma.

- eg, prednisone in a dose of 20 to 40 mg/day- reduces serum Ca concentrations within 2-5 days by decreasing calcitriol production by the activated mononuclear cells in the lung and lymph nodes.

GALLIUM NITRATE

- It Inhibits osteoclastic bone resorption, in part via inhibition of an ATPase dependent proton pump on the osteoclast ruffled membrane, without being directly cytotoxic to bone cells .
- It also inhibits PTH secretion from parathyroid cells in vitro
- Complications- Nephrotoxic and Bone Marrow suppresion

DIALYSIS -

- In severely hypercalcemic patients who are comatose, have ECG changes, in severe renal failure, or cannot receive aggressive hydration, hemodialysis with a low- or no-calcium dialysate is an effective treatment.
- Continuous renal replacement therapy can also be used to treat severe hypercalcemia.
- The effect of dialysis is transitory, and it must be followed by other measures.

- **Calcimimetic agent (cinacalcet)** reduces the serum Ca concentration in patients with severe hypercalcemia due to parathyroid carcinoma and in hemodialysis patients with an elevated calcium-phosphorous product and secondary hyperparathyroidism

- **Parathyroidectomy** curative in Hypercalcemic crisis resulting from Primary Hyperparathyroidism

- Denosumab (monoclonal antibody with affinity for RANKL) used in malignancy related hypercalcemia especially in renal failure.

THANK YOU