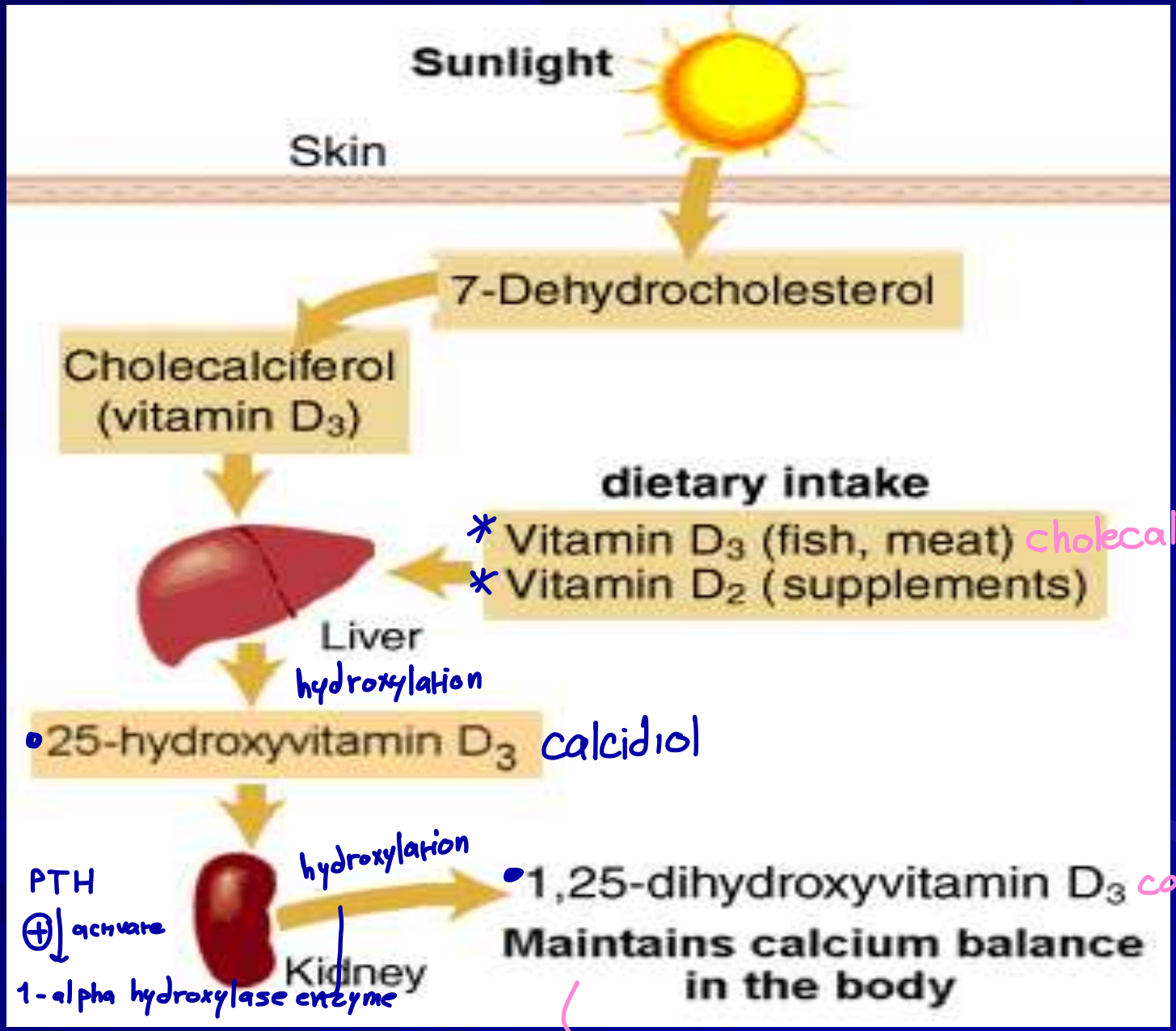
# Hypercalcemia and management

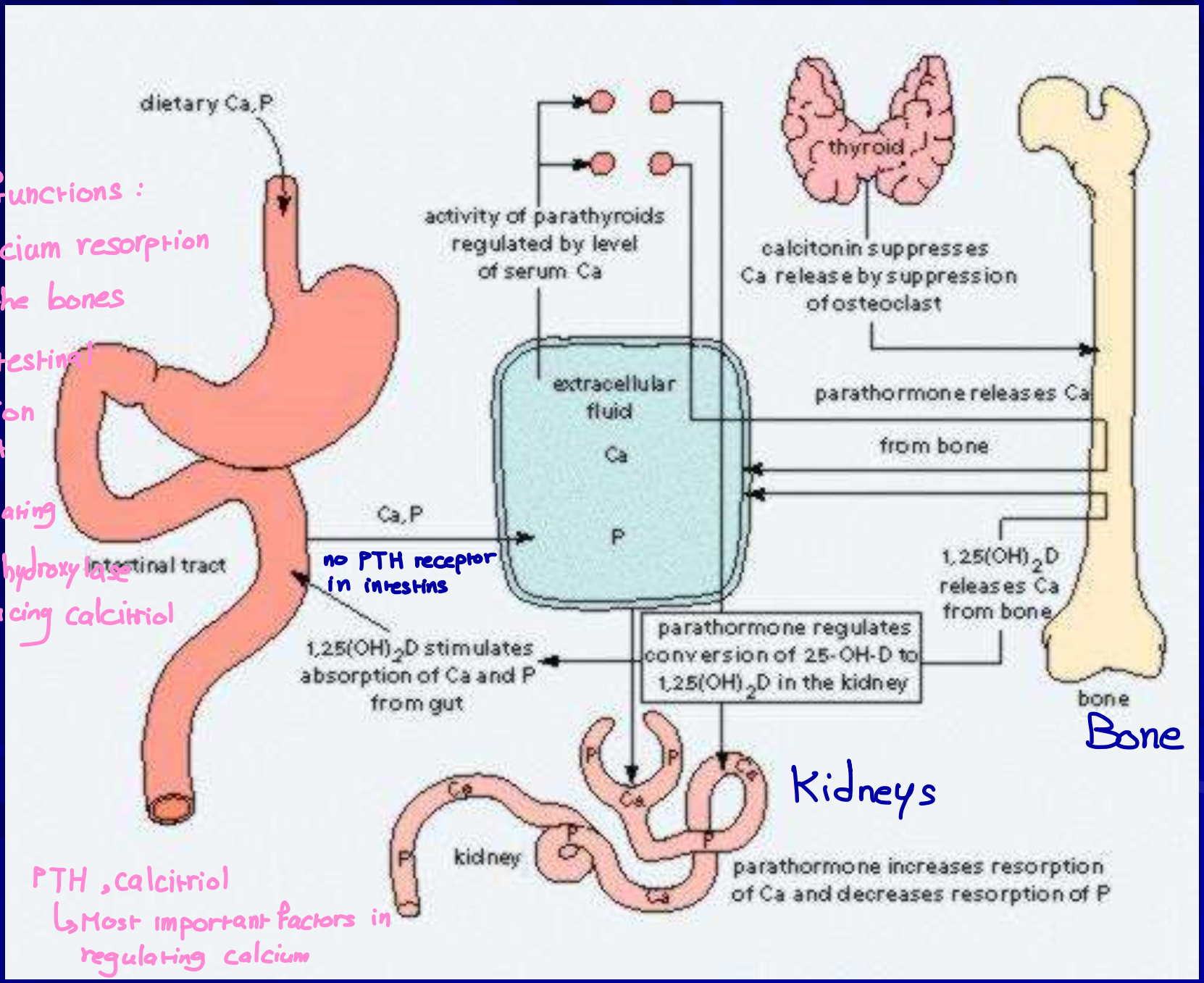
*Edited by: Ruaa Hdeib*


Sunlight
Skin
7-Dehydrocholesterol
Cholecalciferol
(vitamin D3)
dietary intake
* Vitamin D3 (fish, meat) cholecalciferol
* Vitamin D2 (supplements)
Liver
hydroxylation
• 25-hydroxyvitamin D3 calcidiol
PTH
activate
1-alpha hydroxylase enzyme
Kidney
hydroxylation
• 1,25-dihydroxyvitamin D3 calcitriol
Maintains calcium balance in the body
Most active

PTH functions :

① ↑ calcium resorption from the bones

② ↑ intestinal absorption of $Ca^{++}$ by activating 1-alpha hydroxylase & producing calcitriol




PTH, calcitriol
↳ Most important factors in regulating calcium

# Ca balance

Ca entry (circulation) > Ca excretion or deposition (urine) (bone)

Causes:

1. Accelerated bone resorption
2. Excessive GI absorption
3. Decreased renal excretion. or ↑renal reabsorption

# Causes of Hypercalcemia????????

## I. PTH-mediated:

PTH → high
PTH → high - normal (inapropriately normal)
↳ should be negative feed back from kidney & parathyroid gland

1. **Primary hyperparathyroidism**
2. Familial MEN-I and -IIa
   ↳ isolated hyperpara
   ↳ syndromatic hyperpara
3. FHH
   familial hypocalciuric hypercalcemia
4. Tertiary hyperparathyroidism
   ↳ pt. has chronic renal failure

high → بالنسبة لـ hypercalcemia

PTH – non mediated

# II. PTH-independent Hypercalcemia:

1. **Hypercalcemia of malignancy**
2. Vitamin D intoxication
3. Chronic granulomatous disease (↑ extrarenal 1 α-hydroxylase)
4. Medications (HCTZ, Lithium, Teriparatide). hydrochlorothiazide
5. Excessive Vitamin A vitamin A toxicity
6. Theophylline toxicity
7. Miscellaneous: Hyperthyroidism, Acromegaly, Pheochromocytoma, Adrenal insufficiency, Immobilization, Parenteral nutrition, Milk alkali syndrome

↳ calcium carbonate oral antacid

PTH - mediated

non PTH - mediated

# Hyperparathyroidism & malignancy

## accounts for > 90% of cases

- **Primary hyperparathyroidism —**

  PTH -mediated activation of osteoclasts

  → **↑ bone resorption**

  → Serum Ca is usually < 12 mg/dL (values > 13 mg/dl are unusual)

  → Parathyroid adenoma, hyperplasia, carcinoma (very rare)

autonomus (out of control) synthesis & secret-ion of PTH

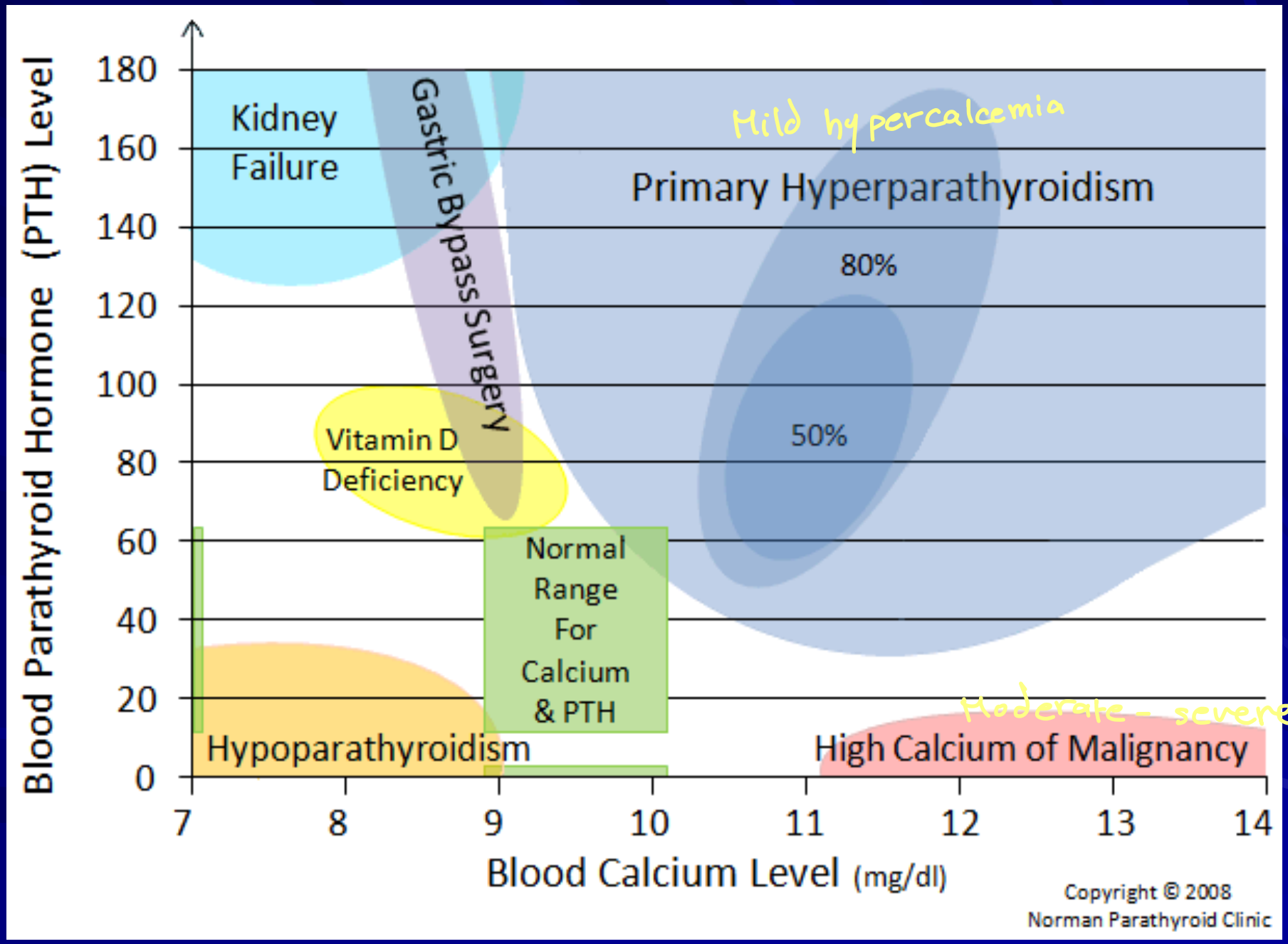
hyperkalemia

| | |
|---|---|
| | 8.2 – 10.2 |
| Mild | 10.2 — 12 |
| Moderate | 12 - 14 |
| severe | >14 |

- **Malignancy** — non PTH-mediated
  - → Solid and hematologic tumors.
  - → Usually > 12 mg/dl severe, needs emergency, symptomatic

**2 possible mechanisms:**

1. Bone metastases → ↑ osteolysis (Cytokines such as TNF and IL-1 stimulates the differentiation of osteoclast precursors into mature osteoclasts).
2. In non-metastatic solid tumors → PTHrP activates extrarenal 1 α-hydroxylase similar to PTH; bind same receptor / do the same action
3. Ectopic non-parathyroid cancers that secreted PTH, not PTH-rP, have been reported (v. rare)


Blood Parathyroid Hormone (PTH) Level
180
160
140
120
100
80
60
40
20
0
7
8
9
10
11
12
13
14
Blood Calcium Level (mg/dl)
Kidney Failure
Gastric Bypass Surgery
Mild hypercalcemia
Primary Hyperparathyroidism
80%
50%
Vitamin D Deficiency
Normal Range For Calcium & PTH
Hypoparathyroidism
Moderate - severe
High Calcium of Malignancy
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# Thyrotoxicosis —

Thyroid hormone (T4) ↑ bone resorption

Mild hypercalcemia in up to 15-20%

Typically resolves following correction of hyperthyroidism

- **O**ther less common causes of hypercalcemia due to increased bone resorption include:

- Immobilization ↑ osteoclast activity & bone resorption
- Paget disease of bone (mainly with bed rest). also
- Hypervitaminosis A. Retinoic acid causes a dose-dependent increase in bone resorption (mech. Downregulation of IL-6 receptors → ↑ IL-6.).

determine osteoclast activity

- **CALCIUM ABSORPTION — .**

A High Ca intake alone is a rare cause of hypercalcemia (may be if there is Kidney problem)

**↑ Ca inhibits PTH and calcitriol synthesis.**

Only when urinary Ca excretion is decreased then the increased Ca intake can cause hypercalcemia.

**2 situations:**

**- CKD**

**- Milk-alkali syndrome (causes CKD).**

# Milk-alkali Syndrome -

High intake of milk or Caco3

(Ex. supplementation to treat osteoporosis or dyspepsia) → **Hypercalcemia**, **Metabolic alkalosis**, & **Renal insufficiency**

Metabolic alkalosis → ↑ Ca reabsorption in the distal tubule → ↓ renal Ca excretion → a Ca-induced decline in renal function, due to renal vasoconstriction & hypercalcemia (structural injury) → inability to excrete the excess calcium.

Renal function usually returns to baseline after cessation of milk or calcium carbonate intake, but irreversible injury can occur in patients who have prolonged hypercalcemia.

- **Hypervitaminosis D —**

  - High serum concentrations of 25-OH-D (calcidiol) or 1,25-OH-D (calcitriol) can cause hypercalcemia (↑ Ca absorption & bone resorption). 1,25-OH-D is a more potent stimulator of Intestinal Ca transport

**Examples:**

- High doses of either vitamin D or calcidiol (t½ several days)
- Topical calcinriol (Rx of dermatologic disorders).
- Calcitriol in the Rx of hypoparathyroidism or hypocalcemia and secondary hyperparathyroidism of renal failure (Calcitriol t½ is 1-2 days)

Other causes:

↑ endogenous production of 1,25-OH-D as in:

- Malignant lymphoma

↑ calcitriol level

- Chronic granulomatous disorders like sarcoidosis and less frequently Wegener's granulomatosis.

crohn's disease

# Other rare causes of Hypercalcemia:

- **Lithium —** Li Induced hyperparathyroidism
- **Thiazide diuretics —** lower urinary calcium excretion, rarely causes hypercalcemia in otherwise normal persons but can lead to hypercalcemia in patients with an underlying increase in bone reabsorption, such as those with hyperparathyroidism.
- **Pheochromocytoma —** It can be due to concurrent hyperparathyroidism (in MEN, type II) or to the pheochromocytoma itself . In the latter → tumora production of PTHrp. Serum PTHrp can be ↓ by α-adrenergic blockers.
- **Adrenal insufficiency —** (? increased bone resorption, volume contraction, increased proximal tubular calcium reabsorption, hemoconcentration, and increased binding of calcium to serum proteins. Cortisol administration reverses the hypercalcemia within several days.
- **Rhabdomyolysis & ARF —** during the diuretic phase of ARF, primarily due to the mobilization of calcium that had been deposited in the injured muscle. Correction of hyperphosphatemia (induced by the rise in glomerular filtration rate), mild secondary hyperparathyroidism induced by the renal failure, and an unexplained increase in serum calcitriol concentrations all appear to contribute to the hypercalcemia.
- **Theophylline toxicity —** hypercalcemia usually subsides in response to administration of a beta-adrenergic antagonist.
- **Familial hypocalciuric hypercalcemia (FHH) —** autosomal dominant (mild hypercalcemia and hypocalciuria). A loss-of-function mutation in the calcium-sensing sensor on the parathyroid cells and in the kidneys so that higher than normal serum calcium concentrations are needed to suppress PTH release.

# Hyperparathyroidism & malignancy

## accounts for > 90% of cases

# Diagnostic approach???

- 40 to 45% of calcium in serum is bound to protein (principally albumin)
- Pseudohypercalcemia → ↑ protein binding can cause an elevation in the serum total Ca without any rise in the serum ionized Ca →

  Example: hyperalbuminemia due to severe dehydration and patients with MM who have a calcium-binding paraprotein
- Hypoalbuminemia → total serum Ca may be normal when serum ionized calcium is elevated.

  **(if albumin ↓ 1 g/dl → total Ca ↓ by 0.8 mg/dl)**

paraproteinemia → multiple myloma

normal albumin → 4 g/dL

**→ Calcium concentration should be corrected for the abnormality in albumin, some authorities prefer to measure the serum ionized calcium in this situation.**

- A single elevated serum Ca should be repeated.

corrected

- Review previous values for serum Ca → request outside records if needed

- The degree of hypercalcemia also may be useful diagnostically.

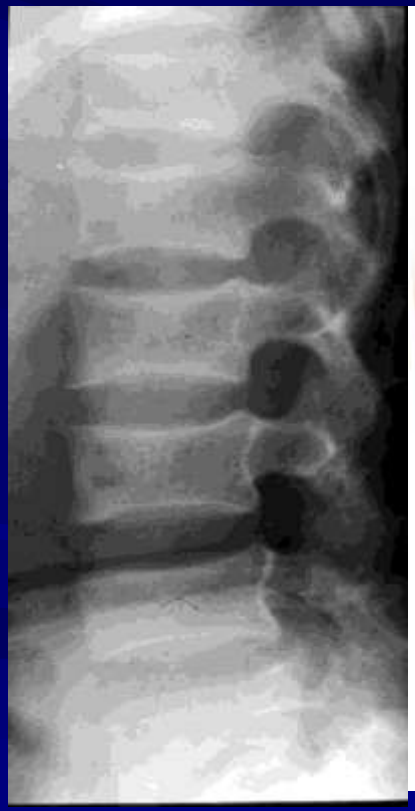
# CLINICAL EVALUATION — History ☺

Direct symptoms of hypercalcemia

depression

Mood disturbances

**Bones** pain



Renal **Stones**


Abdominal **Groans**

pain

Psychic **Moans**

**CNS:**

- Lethargy
- Weakness
- Confusion
- Coma

**Renal:**

- Polyuria
- Nocturia

bcs of nephrogenic Diabetes insipidus
$K^+$ affects ADH action

- Dehydration
- Renal stones
- Renal failure

**GI:**

- Constipation
- Nausea
- Anorexia
- Pancreatitis
- Gastric ulcer

**Cardiac:**

- Syncope, arrhythmias.

A review of diet and medications (prescription and nonprescription drugs, herbal preparations, calcium and vitamin supplements).

- **Primary hyperparathyroidism →** Mild asymptomatic chronic

  Asymptomatic chronic hypercalcemia, normal PE, earthy look pt.

  No other obvious cause of hypercalcemia (such as sarcoidosis), a family history of hyperparathyroidism, and evidence of multiple endocrine neoplasia
- **Hypercalcemia of malignancy →**

  Higher concentrations of and more rapid ↑ in serum Ca → more symptomatic.

  A sign of advanced disease and a poor prognosis ☹

# LABORATORY EVALUATION —

repeat خطوة أول

**Once hypercalcemia is confirmed ☺ remember**

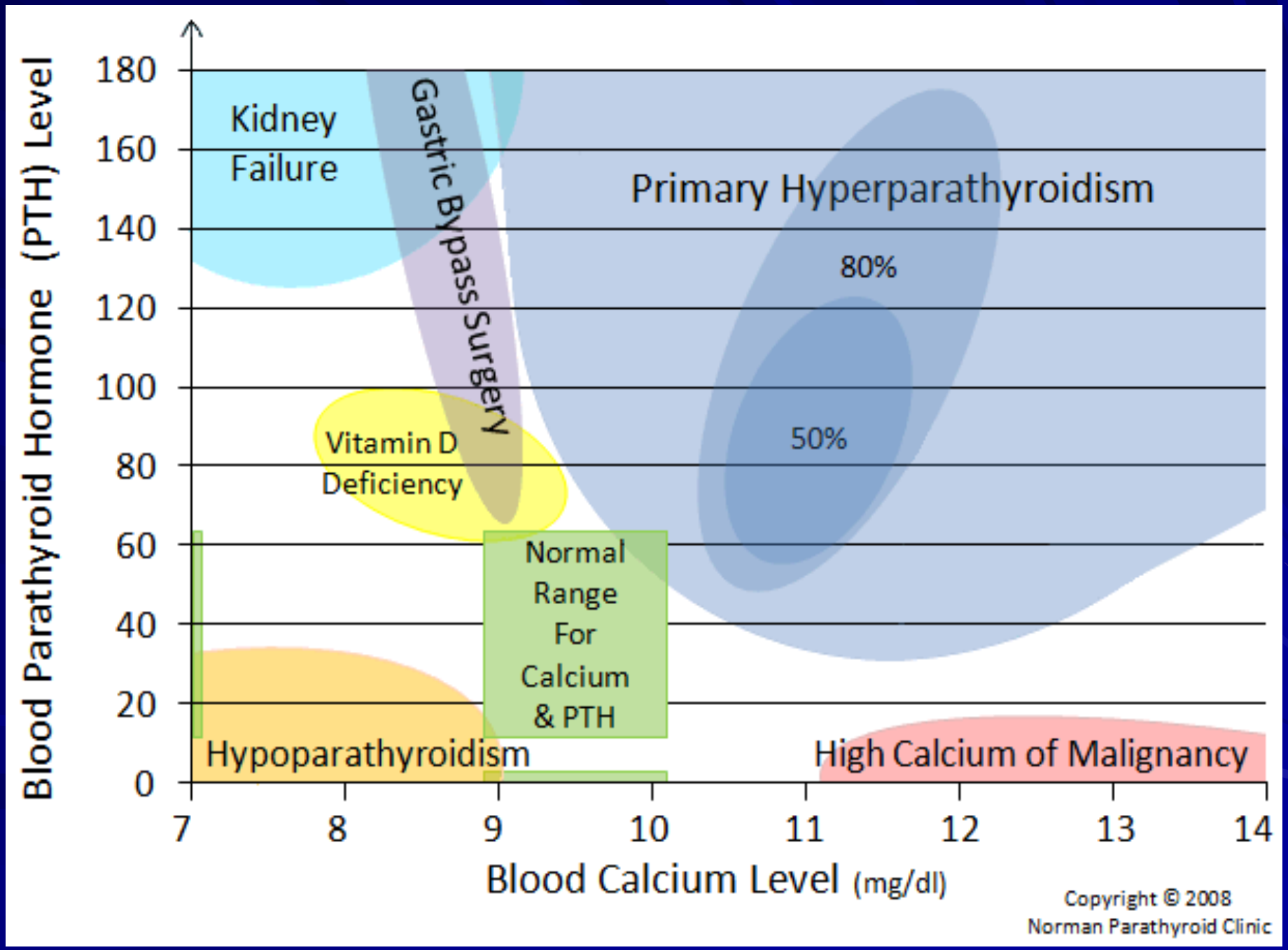
1. **Check serum PTH**

   Even in a patients with known malignant disease (higher incidence of hyperparathyroidism in patients with malignancy than in the general population)

2. **Check PTHrp, 25-OH-D and 1,25-OH-D** Vitamin D metabolites

   (If serum PTH is <20 pg/mL)

in malignancy


Blood Parathyroid Hormone (PTH) Level
180
160
140
120
100
80
60
40
20
0
Kidney Failure
Gastric Bypass Surgery
Primary Hyperparathyroidism
80%
50%
Vitamin D Deficiency
Normal Range For Calcium & PTH
Hypoparathyroidism
High Calcium of Malignancy
7
8
9
10
11
12
13
14
Blood Calcium Level (mg/dl)
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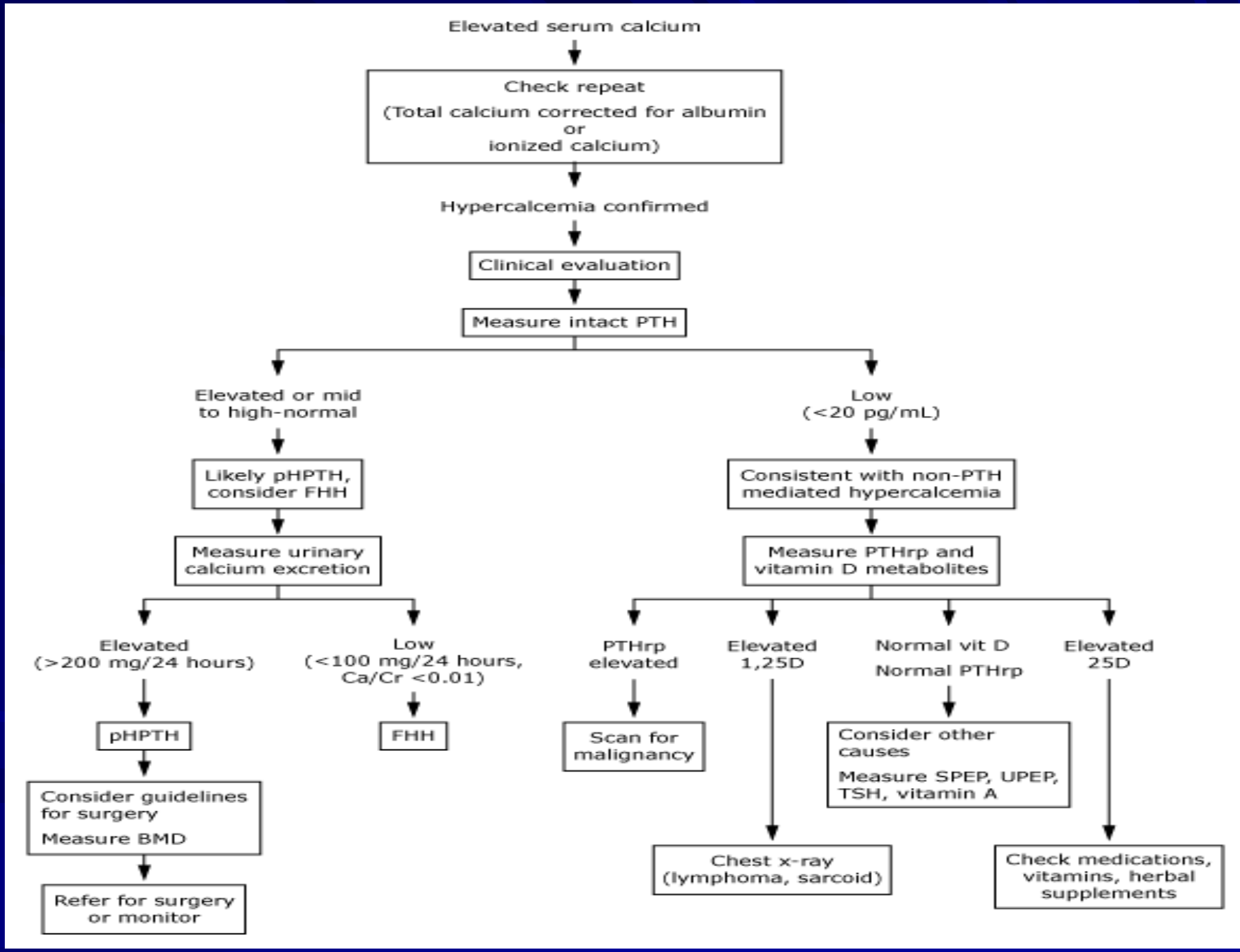
# Urinary calcium excretion??

- Is usually high or high-normal in hyperparathyroidism and hypercalcemia of malignancy.

- Is usually decreased (relative hypocalciuria when <100 mg/day) → secondary to ↑ renal calcium reabsorption: **JUST 3 CAUSES ☺**

1. **The milk-alkali syndrome**
2. **Thiazide diuretics**
3. **FHH** (Fractional execretion of Ca < 1%, family history of hypercalcemia, few or no symptoms.


Elevated serum calcium
Check repeat
(Total calcium corrected for albumin
or
ionized calcium)
Hypercalcemia confirmed
Clinical evaluation
Measure intact PTH
Elevated or mid
to high-normal
Low
(<20 pg/mL)
Likely pHPTH,
consider FHH
Consistent with non-PTH
mediated hypercalcemia
Measure urinary
calcium excretion
Measure PTHrp and
vitamin D metabolites
Elevated
(>200 mg/24 hours)
Low
(<100 mg/24 hours,
Ca/Cr <0.01)
PTHrp
elevated
Elevated
1,25D
Normal vit D
Normal PTHrp
Elevated
25D
pHPTH
FHH
Scan for
malignancy
Consider other
causes
Measure SPEP, UPEP,
TSH, vitamin A
Consider guidelines
for surgery
Measure BMD
Chest x-ray
(lymphoma, sarcoid)
Check medications,
vitamins, herbal
supplements
Refer for surgery
or monitor

- Serum Ca should be corrected for albumin, and an elevated concentration should be confirmed by repeat sampling.

- Clinical evaluation, including duration of hypercalcemia, presence or absence of symptoms, family history, and medications, may help determine the etiology of hypercalcemia.

- Measurement of intact PTH is important to distinguish PTH-mediated from non-PTH-mediated causes of hypercalcemia. A frankly elevated PTH concentration or a PTH value in the upper half of the normal range in the setting of hypercalcemia is likely the result of primary hyperparathyroidism.

- PTH concentrations < 20 pg/mL in the setting of hypercalcemia are not consistent with primary hyperparathyroidism and indicate the need for evaluation for other causes of hypercalcemia. This evaluation should include measurement of PTHrp and vitamin D metabolites.

- If the diagnosis is still not clear, other tests should be considered, including TSH, SPEP, UPEP, and Vitamin A.

serum protein electrophoresis
↳ hyperthyroidism
thyrotoxicosis
↳ multiple myloma
↳ urin protein electrophor-esis test

# Treatment?

1. To lower serum Ca
2. Treat the underlying disease
   (If possible)

- **INDICATIONS FOR TREATMENT** — the degree of hypercalcemia & the rate of rise of serum Ca

  → determine symptoms and the urgency of therapy.

- Asymptomatic or mildly symptomatic (calcium <12 mg/d) do not require immediate treatment. Similarly, a serum calcium of 12-14 mg/dL may be well-tolerated chronically, and may not require immediate treatment.

- An acute rise to 12-14 mg/dl may cause marked changes in sensorium.

- Serum Ca >14 mg/dl does require treatment

## Mild hypercalcemia —

- ✓ Avoid hypercalcemia aggrevating factors, including thiazide, Li therapy, volume depletion, prolonged bed rest or inactivity, and a high calcium diet (>1000 mg/day).
- ✓ Adequate hydration (at least 6-8 glasses of water per day) is recommended to minimize the risk of nephrolithiasis.
- ✓ Additional therapy depends mostly upon the cause of the hypercalcemia.

# 1. ISOTONIC SALINE HYDRATION —


Hypovolemia exacerbates hypercalcemia by impairing the renal clearance of calcium. IV saline restores intravascular volume and ↑ urinary Ca excretion by inhibiting proximal and loop sodium reabsorption.

↑fluid → ↑ renal excretion

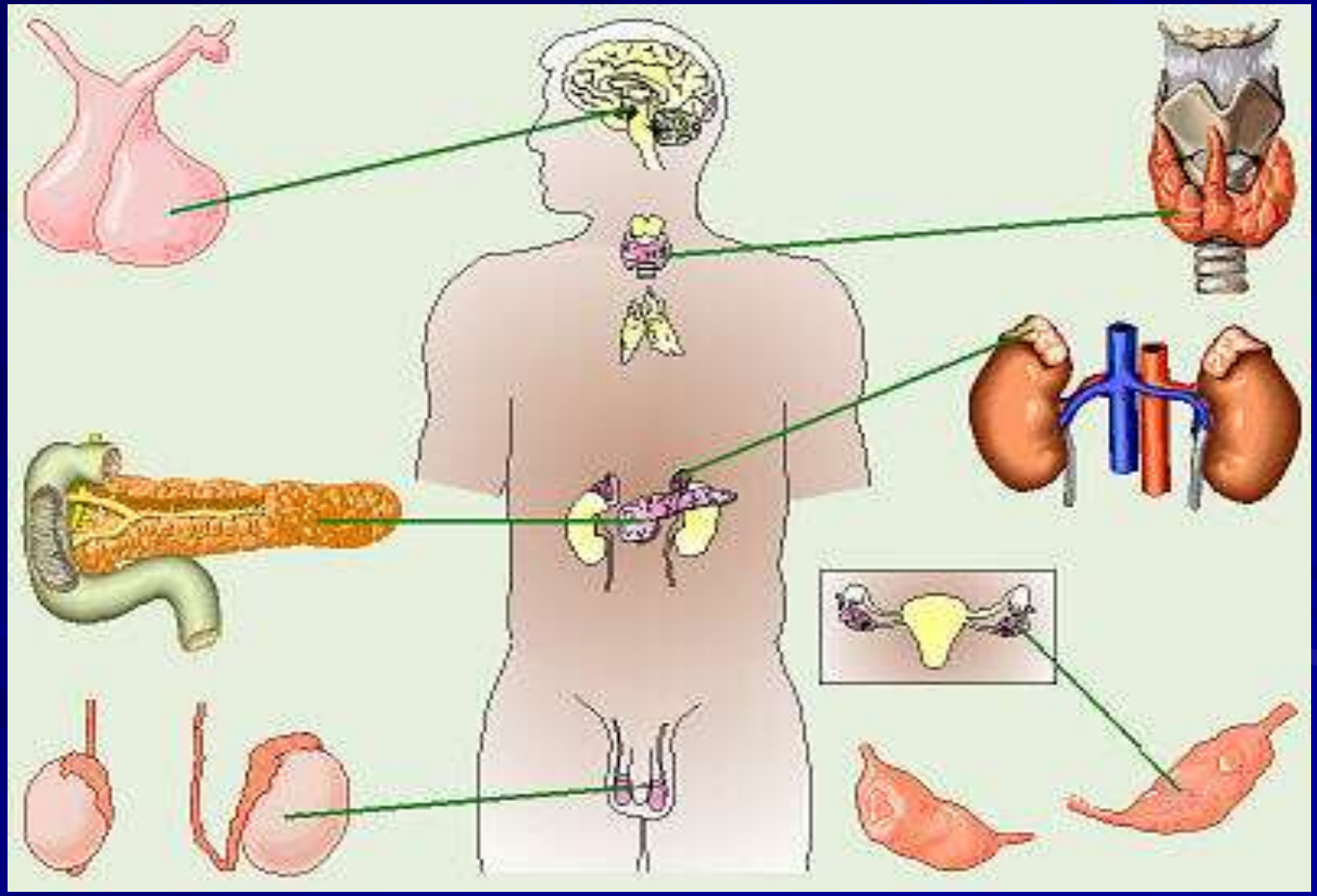
**The rate ?** →severity of hypercalcemia, the age, presence of comorbid conditions → 200 to 300 mL/h, monitor VS and urine output (100 to 150 mL/h).

2. **Lasix?** Saline therapy alone rarely normalizes moderate or severe hypercalcemia. In the past, administration of a loop diuretic was initiated routinely once fluid repletion had been achieved to further increase urinary calcium excretion.

   This approach has fallen out of favor for two reasons:

- ✓ The availability of drugs such as the bisphosphonates and calcitonin.
- ✓ The potential fluid and electrolyte complications resulting from a massive saline infusion and furosemide-induced diuresis such as hypokalemia, hypomagnesemia, and, even volume depletion if the diuretic-induced losses are not replaced.

# 2. Endo Consult ☺



## 3. BISPHOSPHONATES —

- ✓ Θ osteoclast-mediated bone resorption.
- ✓ More potent than NS and calcitonin.
- ✓ The preferred agents for hypercalcemia secondary to excessive bone resorption
- ✓ IV zolendronic acid or pamidronate are the most commonly used.

# 4. CALCITONIN —

- ✓ ↓ Bone reabsorption (Θ osteoclast maturation) & ↑ renal Ca excretion
- ✓ Salmon calcitonin (4 IU/kg) IM or SC q12 hours, can be ↑ up to 6 to 8 IU/kg q 6 hours.
- ✓ Nasal application of calcitonin is not efficacious for treatment of hypercalcemia.
- ✓ Safe and relatively nontoxic (mild nausea and rare hypersensitivity reaction). Although a relatively weak agent, it works rapidly, lowering the serum Ca by a maximum of 1 to 2 mg/dL within 4-6 hrs.
- ✓ Efficacy is limited to the first 48 hrs (tachyphylaxis & receptor downregulation) rapid correction
- ✓ Most beneficial in symptomatic patients with calcium >14 mg, when combined with hydration and bisphosphonates. Calcitonin and hydration provide a rapid reduction in serum Ca, while a bisphosphonate provides a more sustained effect.

# 5. GLUCOCORTICOIDS —

- ✓ Glucocorticoids ↓ calcitriol production by the activated mononuclear cells in the lung and lymph nodes.
- ✓ ↑ Calcitriol production can occur in chronic granulomatous diseases (eg, sarcoidosis) and in lymphoma.
- ✓ Glucocorticoids (Ex. prednisone 20-40 mg qd) will usually ↓ serum Ca within 2-5 days

# 6. GALLIUM NITRATE —

- ✓ Θ Osteoclastic bone resorption & Θ PTH secretion.
- ✓ It is effective in both PTHrP-mediated, and non-PTHrP-mediated hypercalcemia
- ✓ More potent than Etidronate, pamidronate and calcitonin.
- ✓ Potential for nephrotoxicity, and the need for continuous infusion over five days.

# 7. Calcimimetics —

يعمل حاجه كالسيوم

- ✓ Calcimimetics (such as cinacalet) has been shown to ↓ serum Ca in cases of severe hypercalcemia due to parathyroid carcinoma.

- ✓ ↓ PTH levels and the calcium-phosphorous product in hemodialysis patients with secondary hyperparathyroidism.

# 8. Dialysis —

- ✓ Use as a last resort in severe malignancy-associated hypercalcemia and CKD or heart failure, in whom hydration cannot be safely administered.

# Case# 1

- 45 y/o WM presented to outpatient clinic for routine follow up visit. He has history of HTN and GERD. PE is unremarkable.

Labs:

- Repeat serum Ca
- Review previous values for serum Ca if available
- Assess the degree of hypercalcemia.

- Repeat serum Ca → 11
- Previous values for serum Ca:

2003:  10.6 mg/dl

2005: 11.0 mg/dl

2009: 10.9 and 11 mg/dl

→ Mild hypercalcemia, stable since at least 2003

## Primary Hyperparathyroidism?

- Check PTH and 24 hour urine calcium
- Check BMD bone mineral density
- Results:
  - PTH: 117 (mildly elevated)
  - 24 hour urine calcium: 300 mg/24 hours
  - BMD with Z-Scores within normal for matched controls

- Consulted endo and patient was referred for parathyroid surgery???

1. Age < 50 y/o
2. Total calcium of 1 mg/dl above normal range
3. Low BMD
4. CKD (if no other CKD risk factors and think that CKD is mainly secondary to hypercalcemia)

→ **SURGERY**

# Case # 2

- 78 y/o WW was admitted with acute mental status changes. She has history of SCLC diagnosed 4 months ago and has been receiving chemotherapy and radiaiton since it was inoperable.

small cell lung cancer

- Labs:

Total Calcium: 11 mg/dl

Albumin: 1.0 g/dl

- Recheck Ca → 11.0 mg/dl
- Correct for low serum albumin

Remember:

**(if albumin ↓ 1 g/dl → total Ca ↓ by 0.8 mg/dl)**

Corrected calcium will be:

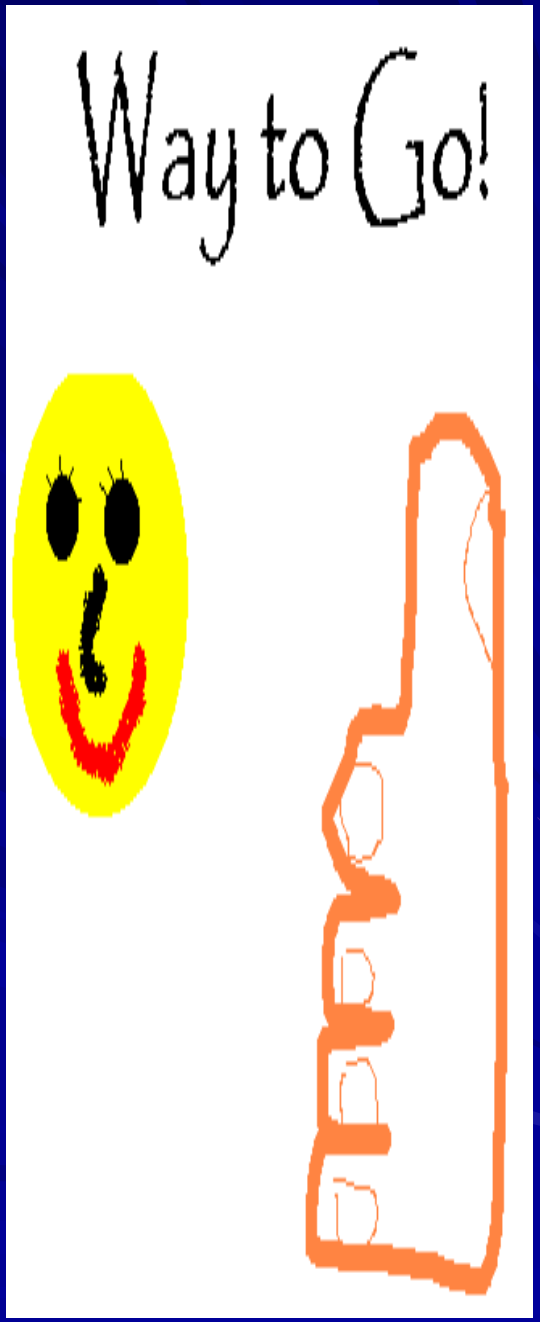
13.4 mg/dl

- Previous values for serum Ca:

2003: 8.0 mg/dl

2005: 8.6 mg/dl

2009: 11 and 11 mg/dl



Hypercalcemia of Malignancy ?

– poor prognosis ☹

- Check PTHrp, Skeletal surveys
- Treatment – see previous slides ☺


THANK YOU