CALCIUM METABOLISM, PHYSIOLOGY AND RELATED DISORDERS

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ENDOCRINOLOGY FELLOW PGY-4

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OBJECTIVES

- Where are the primary effects of vitamin D and PTH, respectively?
- Describe and draw the feedback loop between the GI track, parathyroids, bones, serum blood level, and kidneys.
- Describe the signs and symptoms of hypercalcemia.
- Describe the indications for parathyroidectomy in primary hyperparathyroidism.
- Describe the differential diagnosis for **hypOcalcemia**, and how the PTH, phosphorous, and vitamin D levels would be different.

CALCIUM (CA^{++})

- Involved in :
  - Excitation- contraction coupling in various muscles, including the heart
  - Synaptic transmission
  - Platelet aggregation and coagulation
  - Secretion of other hormones via acting as secondary messengers
  - Bone rigidity and mineralization
  - Cell division

QUESTION #1

29 y/o M with PMHx of Nephrotic Syndrome who present as a STAT direct admit by one of the attending from IMC clinic for Calcium of 7.2 mg/dL on BMP.

Upon admission, repeat BMP significant for Calcium of 7.0 (8.0 -10.2 mg/dL), Cr 0.9 mg/dL

Patient stated that he feels well and would like to go home since his Airpods Pro arrive today and need to do Youtube review.

Which of the following step would be the most useful to determine next course of action?

A. Check Magnesium Level
B. Check Vitamin D Level
C. Convert BMP to CMP
D. Check PTH level
E. Call endocrine for STAT consult

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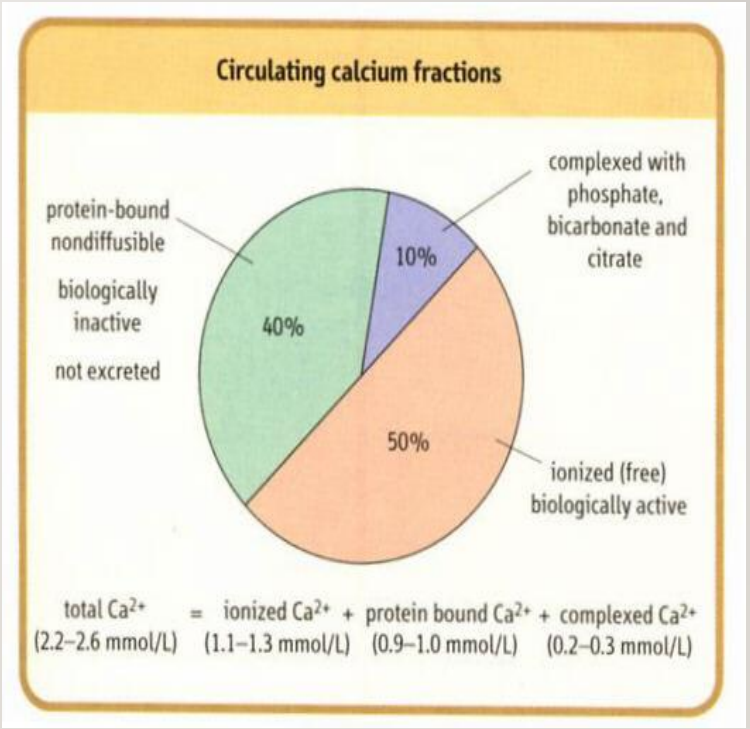
CORRECTING FOR CALCIUM

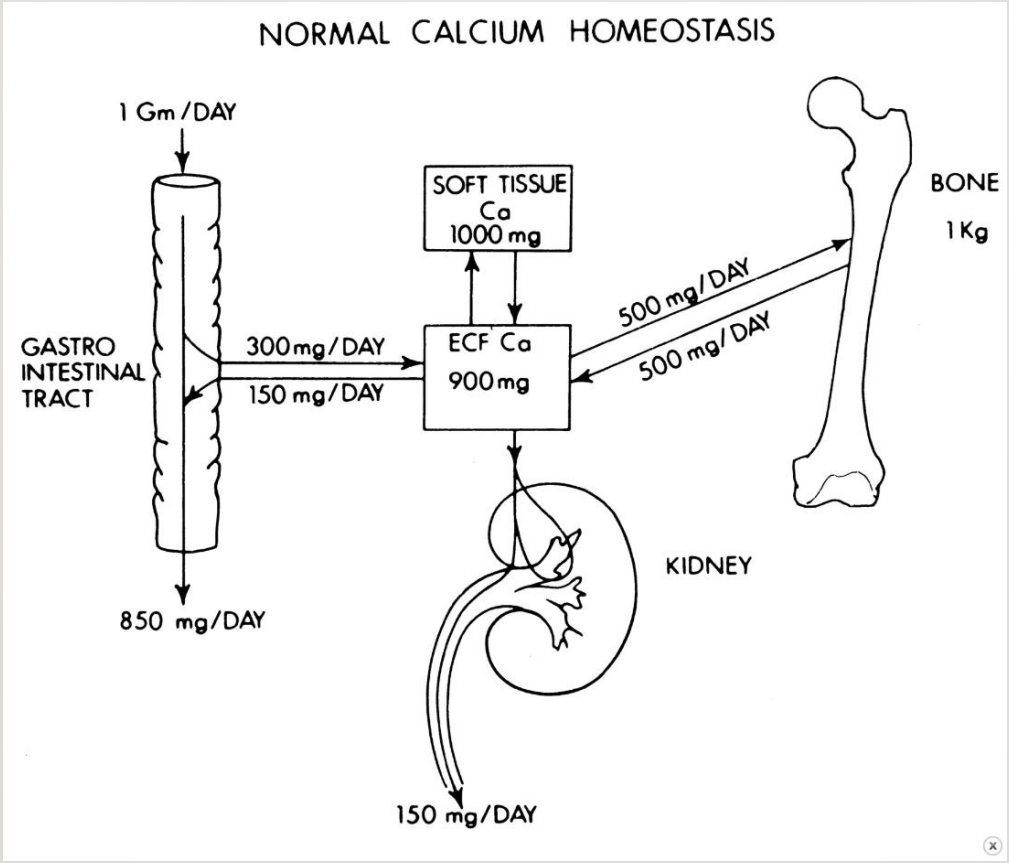
- The **biological actions of Ca are attributed to the ionized fraction**, which is readily exchangeable with pools of Ca in bone, blood, and intracellular sites.
- Calcium binds to albumin (90%).
- **Serum calcium measures <u>ALBUMIN BOUND</u> Calcium.**
  - Binding to albumin is pH dependent
  - Acidosis- decreases binding
  - Alkalosis- increases binding
  - 10 % bound to globulin
- **Corrected Ca = Serum calcium + [(4 –albumin) x 0.8]**

DISTRIBUTION IN THE BODY

- Total body Calcium in adults ~ 1000g
  - 98-99% exists as the hydroxyapatite $(OH)_2$ crystal in the mineral phase of bone.
  - 1-2% is found in soft tissue and the extracellular fluid (ECF) space including blood.



CALCIUM FLUXES



QUESTION #2

67 y/o F with PMHx of HTN, HLD, and Osteoporosis who present to the ED after found down at home. Per EMS report, she was found to have multiple of empty Forteo (Teriparatide) pen next to her.

What would be the expected labs?

A. High Calcium, High Phos, High 1,25 D
B. High Calcium, Low Phos, High 1,25 D
C. Low Calcium, High Phos, Low 1,25 D
D. Low Calcium, Low Phos, High 1,25 D
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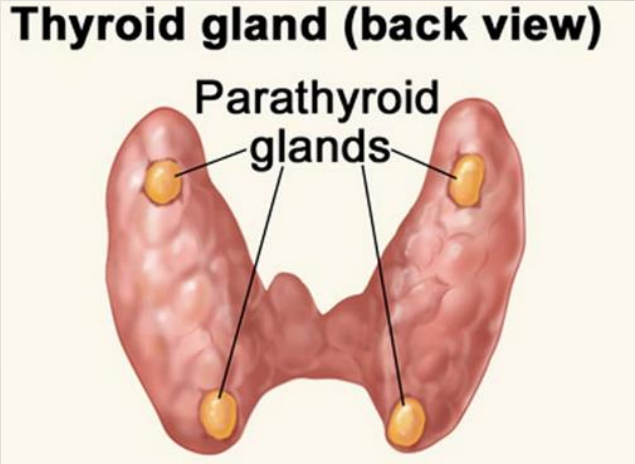
PARATHYROID HORMONE (PTH)

- Secreted from 4 parathyroid glands located adjacent to the thyroid.
  - 12-15% of the population have a 5th gland
- Provides for minute-minute regulation of serum ionized calcium
- Also involved in phosphate homeostasis
- Acts on 3 principal target organs
  - Bone
  - Intestinal Mucosa (indirect)
  - Kidney

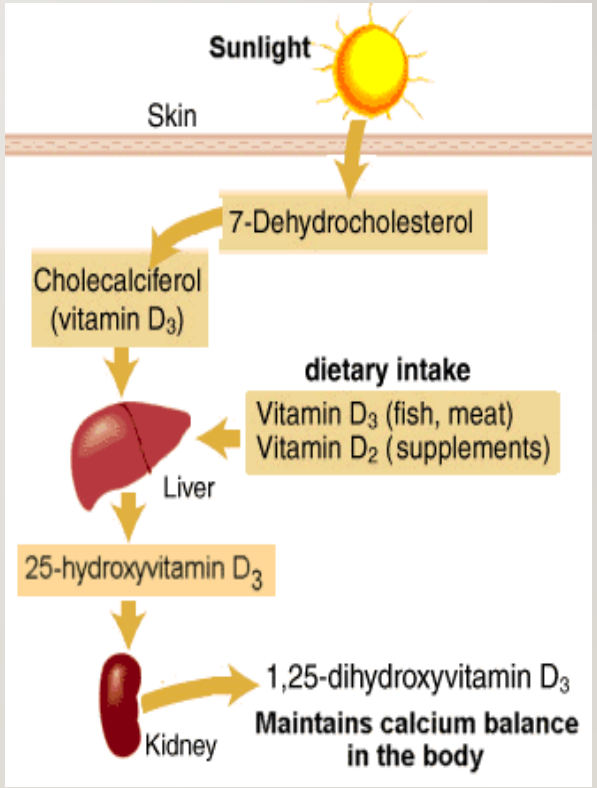


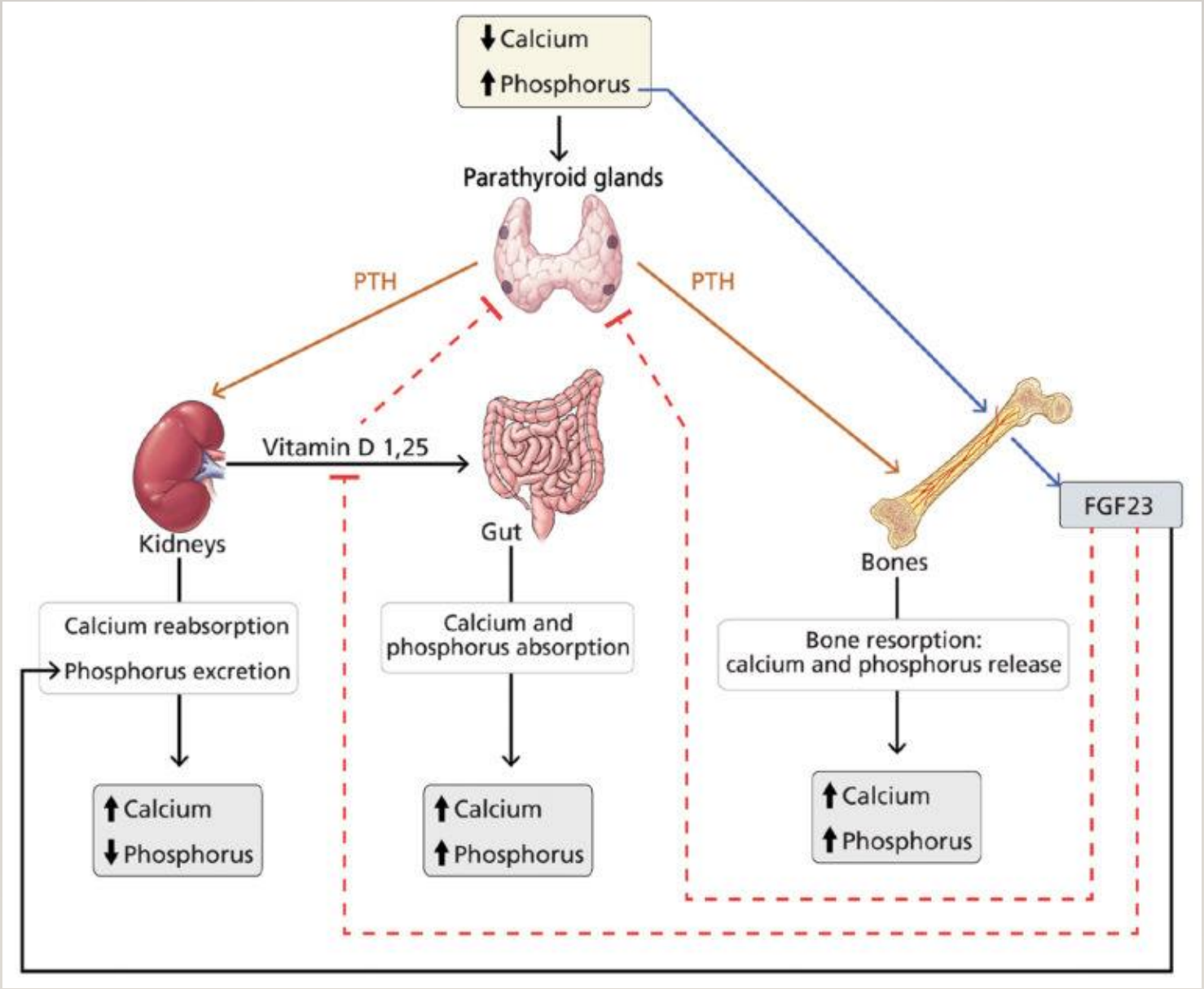
PTH AND CALCIUM

- PTH acts to increase Ca^{2+} by :
  - stimulating the release of Ca^{2+} from bone via **bone resorption**.
  - decreasing urinary loss of Ca^{2+} via increase in renal **Ca^{2+} reabsorption**
  - indirectly stimulating **Ca^{2+} absorption** in the small intestine via increase synthesis of $1,25(OH)_2D$ (calcitriol) by the kidney.

VITAMIN D

- Prohormone that regulates calcium and phosphate homeostasis
- Also known as calciferol,
  - comprises a group of fat-soluble sterols
- Can be synthesized on skin by UV sunlight or obtained by food/supplement
- Major forms (inactive)
  - D2 – Ergocalciferol (plants, yeast)
  - D3 – Cholecalciferol (UV rays, animal skin)




Calcium
Phosphorus
Parathyroid glands
PTH
PTH
Vitamin D 1,25
Kidneys
Gut
Bones
FGF23
Calcium reabsorption
Phosphorus excretion
Calcium and phosphorus absorption
Bone resorption: calcium and phosphorus release
Calcium
Phosphorus
Calcium
Phosphorus
Calcium
Phosphorus

SUMMARY OF PTH AND VITAMIN D EFFECT

- PTH
  - INCREASE calcium
  - DECREASE phosphate
- Calcitriol **(Active Vitamin D)**
  - INCREASE calcium
  - INCREASE phosphate

QUESTION #3

59 y/o M Orange team patient with PMHx of EtOH Cirrhosis present to hospital for Acute Encephalopathy.

CMP noted w/ Calcium of 10.5, Albumin of 2.0

What is the corrected Calcium?

A. 11.8

B. 11.9

C. 12.0

D. 12.1

E. 12.2

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What is the corrected Calcium?

10.5 + [0.8 x (4-2)] = 10.5 + 1.6 = 12.1

A. 11.8

B. 11.9

C. 12.0

D. 12.1

E. 12.2

QUESTION #4

- Which of the Lab results if present, **does not** explain his hypercalcemia?

A. TSH <0.001, FT4 7.6
B. PTH 196
C. Positive Quantiferon
D. Magnesium 9.6
E. ACTH-stim: 1.0 -> 1.8 -> 8.6

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D. Magnesium 9.6

E. ACTH-stim: 1.0 -> 1.8 -> 8.6

HYPERCALCEMIA

- Normal serum calcium: 8.5 to 10.5 mg/dl
- **Mild hypercalcemia: >10.5 but ≤ 12 mg/dl**
- **Moderate hypercalcemia: >12 but ≤ 14 mg/dl**
- **Severe hypercalcemia: >14 mg/dl**

HYPERCALCEMIA: ETIOLOGIES

- PTHrP-producing cancers→ squamous cell, breast cancer mets to bone, Non-Hodgkins lymphoma
- Granulomatous diseases
- Lymphoma
- Milk Alkali syndrome
  - (intake >5g calcium/day)
- Hypervitaminosis A and D
- Immobility
- Paget's disease
- Addison's disease (crisis)
- Thyrotoxicosis (can be seen in 15-20% of thyrotoxic pts)
- Medication induced (HCTZ- calcium-sparing diuretics, usually transient)
- Familial Hypocalciuric Hypercalcemia (FHH)

HYPERCALCEMIA: SYMPTOMS

"stones, bones, groans, psychiatric overtones"

- "Stones": Kidney stones
- "Bones": Bone pain, osteoporosis, fractures
- "Groans": Muscle weakness, nausea, constipation, polyuria
- "Psychiatric overtones": Anxiety, depression, cognitive dysfunction, lethargy
- In addition: Renal insufficiency, pancreatitis

COMMON CLINICAL PRESENTATION

- Mild hypercalcemia
  - Asymptomatic or nonspecific symptoms: constipation, fatigue, depression
- Moderate Hypercalcemia
  - Tolerated well chronically
  - Acute elevations → polyuria, polydipsia, dehydration, anorexia, and changes in mental status
- Severe Hypercalcemia
  - Worsening of symptoms

INITIAL ASSESSMENT

- If Ca <11 and only mildly symptomatic
  - No immediate treatment required, just do workup for etiology
  - Stop thiazides, keep well hydrated (at least 6-8 oz water/day),
  - keep active and keep Ca intake <1000mg/day
- Ca 11-14
  - If chronically elevated, usually well tolerated and may not be symptomatic
  - If symptomatic OR acute elevation, send to ED immediately for IVF hydration
- Ca >14 +/- symptoms
  - Send to ED immediately for IVF hydration

INITIAL WORK UP

- PTH mediated vs Non-PTH mediated
- Check
  - Serum calcium, albumin; CMP instead of BMP
  - Ionized calcium
  - PTH
  - Phosphate
  - 25-OH Vit D
  - Creatinine
- Get EKG – look for short QT, prolonged PR

HYPERCALCEMIA: INITIAL TREATMENT

- Place on telemetry
  - Short QT, prolong PR
- Aggressive IVF hydration
  - isotonic saline at an initial rate of 200 to 300 mL/hour
  - then adjusted to maintain the urine output at 100 to 150 mL/hour
- If hx heart failure or renal failure, also use loop diuretics to increase Ca excretion and reduce volume overload- but only once patient has been adequately hydrated.

HYPERCALCEMIA: ADJUNCT TREATMENT

- If aggressive IVF hydration is not improving Ca (target upper limit normal),
  - Calcitonin
  - Bisphosphonates
  - Steroids
  - Denosumab

QUESTION #5

3AM on Saturday, you are at VA-ICU admitting 67 y/o F with PMHx of Metastatic Breast CA, Afib on Coumadin, and CKD IV for Hypercalcemic crisis.

After IVF treatment, Her calcium remains elevated at ~12.3

Which of the following treatments can you use that would provide her with long term benefit for her hypercalcemia?

A. Zolendronic Acid
B. Calcitonin
C. Pamidronate
D. Denosumab
E. Furosemide

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CALCITONIN

- Pros
  - Fast acting
  - Lowers serum calcium by 1- 2 mg/dL within four to six hour
- Cons
  - Short acting; lasted ~48 hrs
  - Tachyphylaxis; Salmon

- Inhibits osteoclast resorption of bone and increases renal excretion of calcium and phosphate
- Usually used as a bridge to bisphosphonates

BISPHOSPHONATES

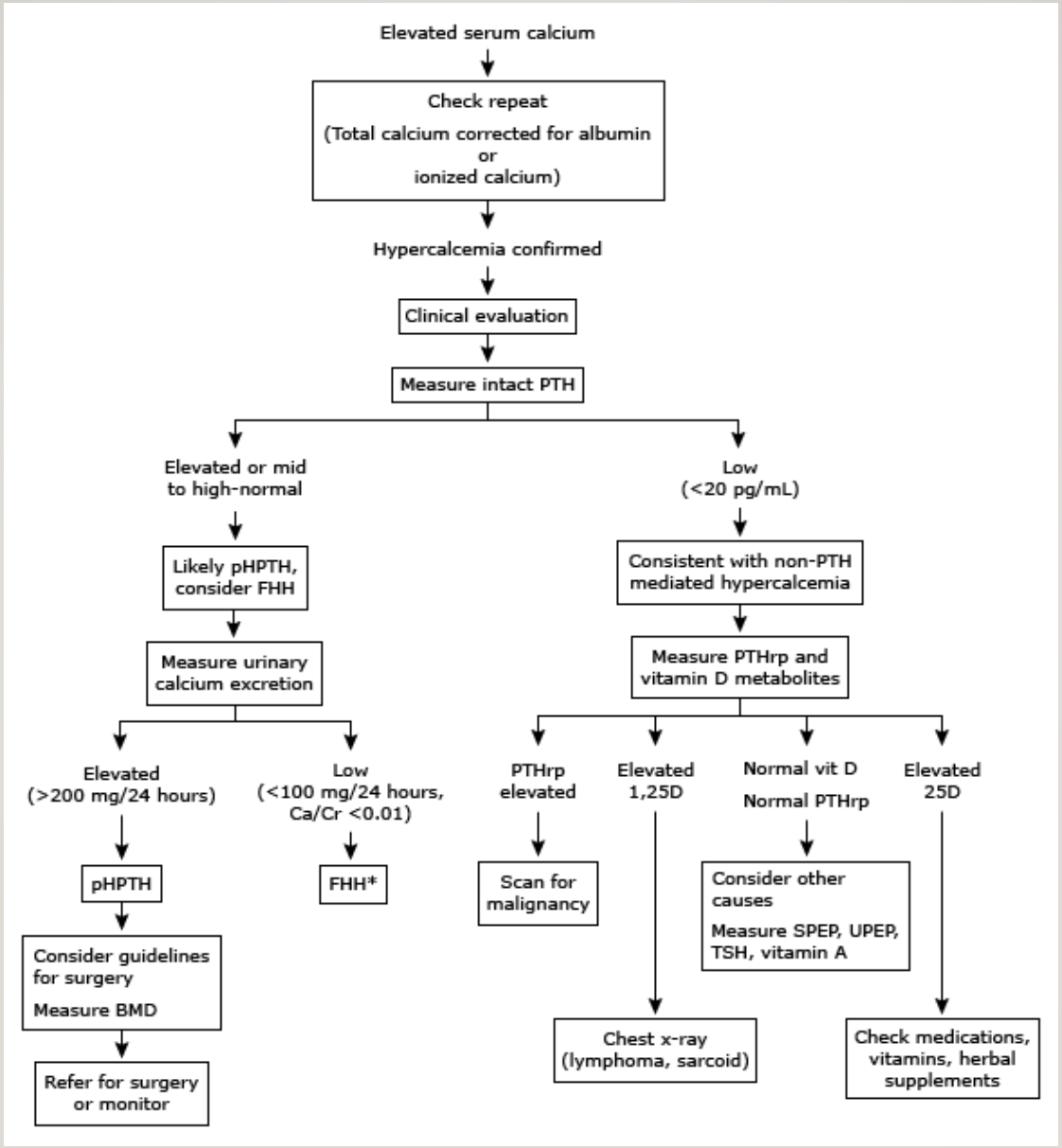
- Effective at treating decreasing HyperCa related to increased bone resorption
- Action: Bind to hydroxyapatite crystals → deposition into the bone. They are ingested by osteoclasts → decreased bone resorption
- Slow effect- takes 2-4 days to see max effect
- Options: IV Zoledronic Acid (ZA) or Palmidronate
- ZA is more potent and can be administered over a shorter period of time (15 min vs 2H)
- Palmidronate is associated with less adverse renal effects.
- **Contraindicated when GFR <35**

DENOSUMAB

- monoclonal antibody to RANK-L → inhibition of osteoclasts
- **Safe in Renal impairment**

GLUCOCORTICOIDS

- Use when cause of hypercalcemia is NOT due to increased bone resorption
  - Excessive Ca intake
  - Vit D toxicity
  - Chronic Granulomatous Diseases
    - The granulomas have 1-alpha hydroxylase so increase production of calcitriol
    - Sarcoidosis, Lymphoma, etc
- Decrease calcitriol production in mononuclear cells in the Lungs and LNs.
- Takes 2-5 days to act


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

QUESTION #6

- 53 y/o F who present to IMC clinic with anxiety for the past 6 months that has been progressively worse along with memory loss. She initially blamed her son who is currently a first year endocrinology fellow for all her symptoms as he complains about life everyday. However, symptoms persist when she stay in Thailand for almost 8 months.
- Reviewing her labs: CBC WNL, CMP noted for Ca 10.8 w/ Albumin of 4.0 with Calcium the year prior at 10.7
- Vitamin D and PTH were subsequently check which both were normal; 38 (20-100), and 36 (10-65)
- Which of the following is the best next step of management?

A. Check Vitamin D 1,25 level
B. Check PTHrP
C. Sestamibi/Parathyroid localization scan
D. Start Cinacalcet (Sensipar)
E. STAT Admit

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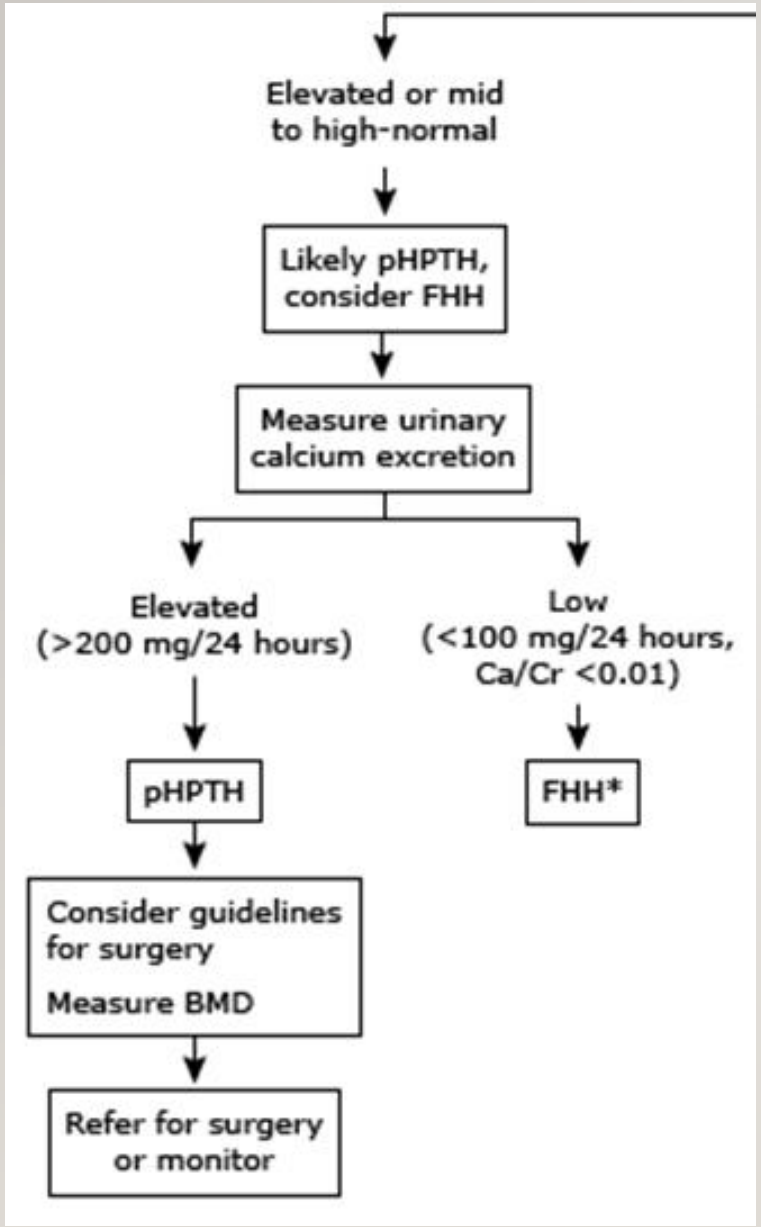

PTH-mediated
Primary hyperparathyroidism (sporadic)
Familial
MEN1 and -2a
FHH
Familial isolated hyperparathyroidism
Tertiary hyperparathyroidism (renal failure)

PRIMARY HYPERPARATHYROIDISM (PHPT)

- Definition: Inappropriate production of PTH from parathyroid gland(s) and presents with hypercalcemia
- Biochemical Diagnosis: **HIGH serum Ca with HIGH/NORMAL PTH and NORMAL/HIGH 24H Urinary Calcium**
- Note: Serum 1,25-D (calcitriol) may be normal to increased
  - **PTH → 1-alpha hydroxylase → increased conversion D2,D3 to calcitriol**

PHPT: CLINICAL FEATURES

- **Incidence**: as high as 1/500 to 1/1000 adults
- **Sex**: females>males (approximately 3:1)
- **Age**: especially in postmenopausal females between 50 and 60 years of age; rare before 15 yrs of age
- **Genetics/heritability**
  - *Sporadic*: most common!
  - *Familial*: MEN I, MEN II, non-MEN related, and familial hypocalciuric hypercalcemia

Pathological conditions related to familial/isolated PHPT*
Single adenomas (85%)
Hyperplasia and multiple adenomas (15%)
Carcinomas (0.5%)
Clinical conditions associated to familial PHPT*
MEN** type 1 and 2
Hyperparathyroidism-jaw tumor syndrome
Familial isolated hyperparathyroidism

* Primary hyperparathyroidism; ** Multiple endocrine neoplasia.

PHPT: CLINICAL MANIFESTATION

- most common clinical presentation = asymptomatic hypercalcemia
- symptomatic:
  - renal calculi, bone pain, pathologic fractures, bone shaft tumors,
  - proximal muscle weakness (especially of the lower extremities),
  - nonspecific symptoms such as depression, lethargy, and vague aches and pains

PHPT: TREATMENT

- Only treatment = Surgery
- 95% cure rate

*Medical management still considered experimental → Sensipar (Cinacalcet)

- Can be considered when not surgical candidate

QUESTOIN #7

- Sestamibi Scan showed
  Left Inferior Parathyroid adenoma
- Her son nags her everyday that she needs to get surgery done.
- Which of the facts would support her per guidelines that she should proceed with parathyroidectomy?

A. Daily phone call by his son
B. Age <55
C. Anxiety and memory loss symptoms
D. Ca 10.7
E. Female

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D. Ca 10.7
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PHPT: WHEN TO TREAT?

- **Symptomatic**
- Met any one of the criteria
  - Serum Ca concentration of 1.0 mg/dL (0.25 mmol/L) or more above the upper limit of normal
  - Bone density at the hip, lumbar spine, or distal radius with T-score <-2.5
  - Previous asymptomatic vertebral fracture ; from CT, MRI, VFA
  - eGFR <60 mL/min.
  - 24-hour Urine Calcium >400 mg/day (>10 mmol/day) or Nephrolithiasis/nephrocalcinosis by radiograph, US, or CT.
  - Age less than 50 year

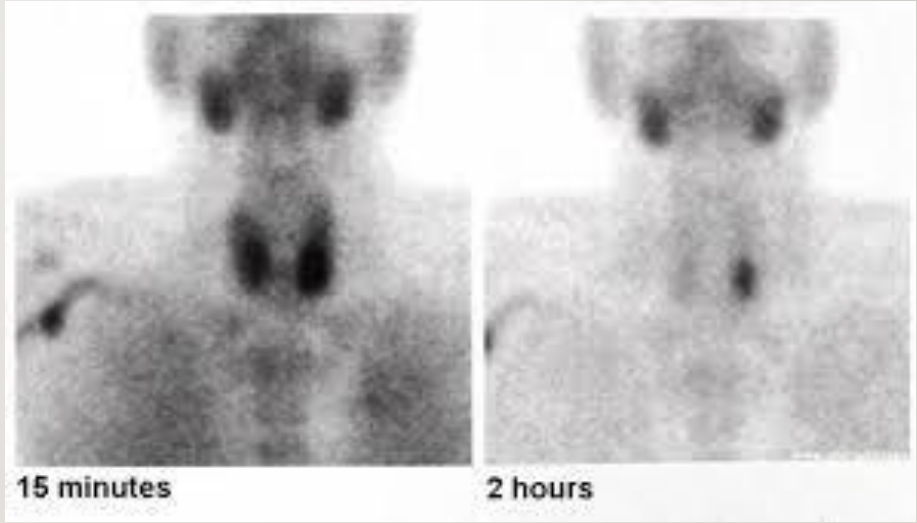
PHPT:
IMAGING STUDIES

Diagnostic accuracy of imaging modalities for preoperative parathyroid localization

Imaging modality	Sensitivity (percent)	Positive predictive value (percent)
Sestamibi	71-79	72-95
Sestamibi-SPECT	70-81	91-95
Ultrasound	64-91	83-96
4D-CT	83-95	88-99
MRI	40-85	N/A
MET-PET-CT scan	79-90	93-94

SESTAMIBI

- Technetium-99m bound to six (sesta=6) methoxyisobutylisonitrile (MIBI)
- lipophilic cation which



HYPOCALCEMIA

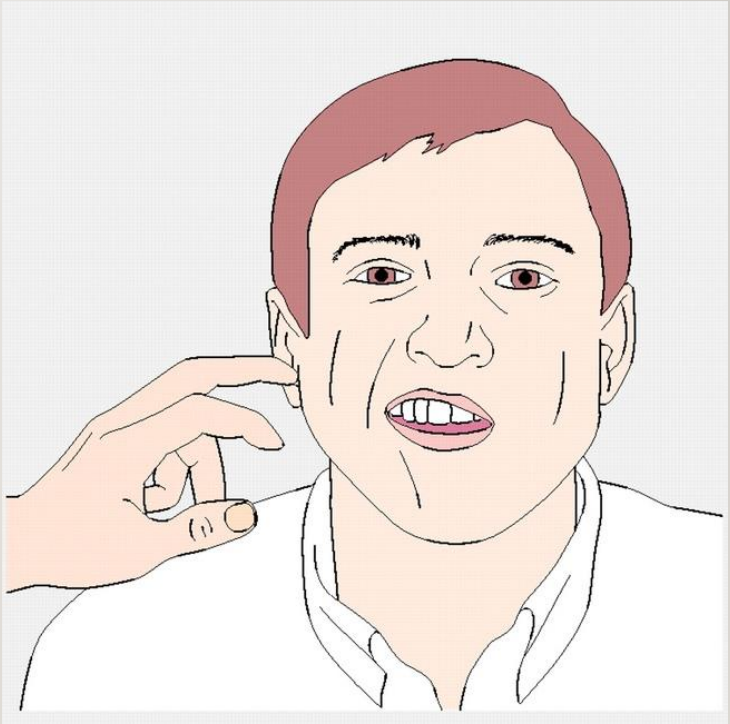
- Normal Total Ca: 8.5 and 10.5 mg/dL
- Normal range of ionized calcium
  - 4.65 to 5.25 mg/dL (1.16 to 1.31 mmol/L)
- Levels below these ranges are considered to be consistent with hypocalcemia.

CLINICAL MANIFESTATION

- Hallmark of acute hypocalcemia is "tetany"
  - Perioral numbness, facial twitching
  - Paresthesias of hands/feet
  - Muscle cramps
  - Carpopedal spasm
- Laryngospasm
- Seizures

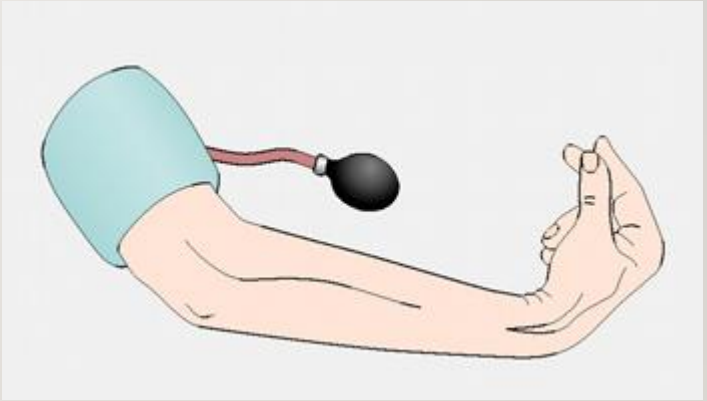
CHVOSTEK'S SIGN

- contraction of ipsilateral facial muscles elicited by tapping the facial nerve anterior to the ear
- Normal variant in 10% of normocalcemic subjects



TROUSSEAU'S SIGN

- induction of carpopedal spasm by inflation of sphygmomanometer 20 mmHg above systolic BP for 3 minutes



ETIOLOGY

- Hypoparathyroidism
  - Surgical vs Autoimmune
- Vitamin D deficiency (most common cause) or resistance
- Chronic kidney disease
- Hyperphosphatemia
- Impaired 1,25 dihydroxy vitamin D production
- PTH resistance / pseudohypoparathyroidism

Laboratory evaluation hypocalcemia

	PTH	Corrected serum calcium	Phos	Mag	25OHD	1,25 (OH) 2D	Creatinine
Hypoparathyroidism	Low	Low	Elevated	Normal	Normal	Normal or low	Normal
Activating mutation calcium sensing receptor	Normal or low	Low	Elevated	Normal	Normal	Normal	Normal
Hypomagnesemia	Normal or low	Low	Normal	Low	Normal	Normal	Normal
PTH resistance (pseudohypoparathyroidism)	Elevated	Low	Elevated	Normal	Normal	Normal	Normal
Vitamin D deficiency	Elevated	Low or normal	Low or normal	Normal	Low	Normal or high	Normal
Chronic kidney disease	Elevated	Low	Elevated	Elevated or normal	Normal or low*	Low	Elevated

* In individuals with concurrent nutritional deficiency.

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TREATMENT: IV CALCIUM

- Symptomatic patients (carpopedal spasm, tetany, seizures)
- Asymptomatic patients with an acute decrease in serum corrected calcium to ≤7.5 mg/dL
- prolonged QT interval

- IV calcium should be continued until the patient is receiving an effective regimen of oral calcium and vitamin D.
  - Calcitriol is the preferred preparation of vitamin D for patients with severe acute hypocalcemia because of its rapid onset of action (hours).

TREATMENT: PO CALCIUM

- For milder symptoms of neuromuscular irritability (paresthesia) and corrected Ca concentrations > 7.5 mg/dL
- If symptoms do not improve with oral supplementation, switch to IV calcium.

- Ca 1500 to 2000 mg of **elemental calcium** given as calcium carbonate or calcium citrate daily, in divided doses
  - Calcium Carbonate: needs to be taken with food for absorption, 40% elemental Ca
  - Calcium citrate: Not dependent on food for absorption, 20% elemental Ca

QUESTION #8

- 32 y/o F with PMHx of MNG s/p Total thyroidectomy complicated with iatrogenic hypoparathyroidism.
- Pt present to ED for muscle spasm, abdominal cramps along with tingling sensation down her throat after stop Natpara [PTH(1-84)] for 2 days due to Recall
- What would you expect in her labs?

A. Ca Low, Phos Low, 1,25 D Low
B. Ca High, Phos Low, 1,25 D High
C. Ca Low, Phos Low, 1,25 D High
D. Ca Low, Phos High, 1,25 D Low
E. Ca Low,, Phos High 1,25 D High

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THANK YOU!