Calcium (8.5-10.5mg/dL)

- 99/100 in Bone
  - Calcium / Phosphate / OH Mineral aka Hydroxyapatite
- 1/10000 Intracellular and 1/100 Extracellular
  - 50% **ionized** (active form)
  - 40% **bound** to anionic proteins like albumin, etc (inactive form)
  - 10% **complexed** with anionic non-proteins like citrate, PO_4, SO_4, etc (inactive form)
  - NB the calcium that labs measure is ionized + bound NOT complexed
    - Acidosis increases iCa b/c the H+ ions bind to the negatively charged bindings sites on albumin that would otherwise bind calcium, therefore all pH does is alter the ratio of bound to ionized calcium therefore the calcium measured in the lab is read as normal when the ionized form could be lower or higher depending of pH
      - You can't really correct for calcium all you do is assess pH to see if pt actually has low active calcium or check iCa
    - Low Albumin has no effect on iCa b/c the calcium that is not bound to albumin complexes with anions rather than remaining ionized, therefore changes in albumin alter total measured levels of calcium but do not alter iCa therefore you must correct for albumin changes
      - for every 1g decrease in albumin total calcium increases by 0.8g but this correction equation is inaccurate therefore measure iCa if suspicious

Stimulant		Renal	GI	Bone	Other	Effect
↓Ca↑ PO_4↓Mg	**PTH**	↑Ca ↓PO_4	X	↑Ca ↑PO_4	↑VitD	↑Ca ↓PO_4
↓Ca↓ PO_4	**VitD**	↑Ca ↑PO_4	↑Ca ↑PO_4	↓Ca ↓PO_4	↓PTH	↑Ca ↑PO_4
↑Ca↑ PO_4	**Calcitonin**	↓Ca ↓PO_4	X	↓Ca ↓PO_4		↓Ca ↓PO_4
↑ PO_4	**Phosphatonins**	↓PO_4	X	X	↓VitD	↓PO_4

- **PTH**
- **VitD**
  - cholesterol converted to ergocalciferol ($VitD_2$) via sun VS cholecalciferol ($VitD_3$) in diet → **(via liver 25α-hydroxylase)** 25-hydroxyergo/cholecalciferol (25-OH-$VitD_{2/3}$) (nl 30-80ng/mL, reserve form) → **(via kidney 1α-hydroxylase)** 1,25-dihydroxyergo/cholecalciferol (1,25-OH_2-$VitD_{2/3}$) aka Calcitriol (nl ?, active form, 1,25 is 1000x more potent than 25)
  - NB has autocrine/paracrine functions: cell differentiation/proliferation, inhibit inflammatory cytokines, decreased vascular tone, decreased RAAS, decreased myocardial fibrosis, affects breast/prostate cancer, pancreatic islet cells, synovium cells, etc
- **Calcitonin**
  - Overall effect is very mild so not clinically important
- **Phosphatonins aka FGF-23**
  - increase urinary PO_4 and lowers VitD, its mutation is the cause of unusual disorders like XLHR/ADHR/TIO
- Approach
  - iCa, albumin, pH, intactPTH aka iPTH (measures the entire protein not just the N or C terminus), 25-VitD (you want 25 b/c this is the storage form while 1,25 is the active form that exists in a very small quantity, when you order 25 you get total and the breakdown of how much is D2 and D3 but it doesn't matter what the fraction is just look at the total), Mg, Phos, 24hr Urine Ca/Phos, RFTs, LFTs
  - look at serum Ca/Phos and then the hormones and see if the hormones are appropriate/in-appropriate for the serum electrolyte level
  - remember Mg looks like Ca therefore hypo/hyper causes hypo/hyper

HypoCa

90% of cases are 2/2 VitD deficiency, HypoMg, HyperPhos

Hormone Problem

↑ Calcitonin (rare)

↓ PTH

- HypoPTH
  - Iatrogenic usually surgery (Parathyrodectomy, Thyroidectomy or any neck surgery 2/2 accidental removal or ischemia but the effect only lasts a few weeks)
  - PGA Type I
  - Genetic (DiGeorge Syndrome aka 22q2 Deletion)
  - Infiltration (Hemochromatosis, Wilson's, Sarcoid, TB, et al)
- PTH Receptor Resistor
  - **HypoMg** (also inhibits PTH secretion)
  - PsuedoHypoPTH "Albright's Hereditary Osteodystrophy" AR end organ PTH receptor mutation such that PTH has no effect even though it is present such that there is low Ca and high Phos and you would assume low PTH but it is actually elevated, Other S/S: short stature/neck, round face, fat, MR, Archibald's Sign aka short $4^{th}/5^{th}$ metacarpals/metatarsals 2/2 missing knuckles, subcutaneous calcification (when these symptoms but nl calcium then called pseudo-psuedo-hypoparathyroidism)
- Gain of Function Calcium Sensing Receptor Mutation on PT

↓ VitD

- Deficiency VitD
  - Dietary Deficiency: Children (Rickets) vs Adult (Osteomalacia)
  - Poor Sunlight Exposure
  - Malabsorption
  - Bad Liver
  - Bad Kidney
  - Drugs that interfere with enzymes (Anticonvulsant Therapy, Rifampin, Ketoconazolem, 5-FU, Leucovorin)

Primary End Organ Problem

Bone

- Consuming Calcium (Osteoblastic Activity)
  - Tumor: Breast, Prostate, Lung (Dx: bone scan)
  - Osteoblastic Phase of Paget's Dz
  - "Hungry Bone Syndrome" (pts w/ long-standing 1/3° hyperPTH result in large amounts of Ca/PO4 being pulled out of bone and when they undergo PTHectomy the bone subsequently sucks up Ca/PO4)
  - Bisphosphonate Therapy

GI

- Malabsorbing Calcium
  - Drugs that bind Ca
  - Typical GI Malabsorption Issues

Kidney

- Renal Failure (not just VitD (NB measure 25 b/c often nutritionally deficient and 1,25 b/c the enzyme is not functioning) but also increase in Phos binds Ca)
- Secreting Calcium
  - Loop Diuretics / Bartter's

Serum

- Binding Free Calcium
  - HyperPO4 (refer to specific causes)
  - Pancreatitis via fat saponification
  - Transfusions (citrate used to keep blood uncoagulated also binds Ca)

NB any non-PTH cause for HypoCa results in 2° HyperPTH

HyperCa

90% of cases are 2/2 Cancer (Severe/Acute/Inpt) or HyperPTH (opposite)

Hormone Problem

↓ Calcitonin (rare)

↑ PTH

- HyperPTH
  - 1°: 85% solitary adenoma, 15% four gland hyperplasia (2/2 MEN Syndromes), <1% solitary carcinoma (w/ neck pain and recurrent laryngeal paralysis, +hCG, h/o radiation) 3°: after you treat longstanding secondary hyperPTH (causes of non-low-PTH hypoCa) the PTH gland becomes so autonomous (hyperplastic) that it does not respond to negative feedback anymore and you then begin having hypercalcemia
  - PTHrP (related protein) Tumor: Any Squamous Cell Carcinoma (Skin, Head & Neck, Esophagus, Lung), Renal, Pheo, Prostate, Bladder, Pancreas, Ovarian, Breast, Lymphoma, Carcinoid (NB not detected by PTH assays)
- PTH Receptor Stimulator
  - Lithium
  - **HyperMg**
- Loss of Function Calcium Sensing Receptor Mutation on PT aka Familial Hypocalciuric Hypercalcemia (FHH)
  - AD mutation of Ca sensing receptor on PTH gland and kidney such that they cannot respond to rising calcium by lowering PTH release and raising Ca absorption, respectively, PTH is usually normal therefore must measure U_{Ca} to make Dx**,** b/c pt had since birth they are usually asymp or present at a very young age, usually benign/mild requiring no Tx

↑ VitD

- Excess VitD
  - Tumor: T-cell Lymphoma
  - Granulomatous Dz
  - Iatrogenic from Meds

Primary End Organ Problem

Bone

- Releasing Calcium (Osteolytic Activity)
  - Tumor: Breast, Multiple Myeloma (Dx: Skeletal X-ray Survey)
  - Osteolytic Phase of Paget's Dz
  - Osteoporosis
  - Prolonged Immobilization
  - HyperTH
  - VitA

GI

- Hyperabsorbing Calcium
  - Milk Alkali Syndrome (hyperCa and alkalosis 2/2 excessive intake of Ca containing antacids)
  - Milk Ingestion

Kidney

- Absorbing Calcium
  - Thiazide Diuretics / Gittleman's

Serum

- Releasing Free Calcium
  - Addison's

<u>Severe/Acute</u>
Neurotransmitter (Ca is involved in signal transmission b/t neurons and b/t neuron and muscle)
• CNS Failure
  ○ seizures, full spectrum of mood changes from depression to hallucinations
• Skeletal Muscle Failure
  ○ muscle weakness/cramping
  ○ circumoral and fingers/toes paresthesia
  ○ *Chvostek's Sign* (tapping facial nerve elicits twitching of facial muscle but nonspecific)
  ○ *Trousseau's Sign* (inflating BP cuff to a pressure higher than pts SBP for 3min elicits flexion of wrist and extension of fingers but insensitive)
  ○ hyperactive DTRs
• Cardiac Muscle Failure
  ○ heart doesn't pump as well (CHF, hypotension, angina, et al)
  ○ conduction is impaired (arrhythmias esp prolong QT which can deteriorate into VT and VFib)
• Smooth Muscle Failure
  ○ laryngobronchospasm w/ SOB/stridor
  ○ dysphagia
 	
<u>Mild/Chronic</u>
Skin/CNS/Bone
• basal ganglia calcifications resulting in Parkinsonism
• calcification of lens resulting in cataracts
• atrophy, brittleness, ridging of nails
• dryness and scaling of skin
• hypoplasia of teeth
	<u>Severe/Acute</u>
	• Bone: "Bones": osteopenia, fractures, etc
	• Renal: "Stones": nephrolithiasis (even though PTH increases Ca reabsorption there is still so much Ca that it spills into kidney causing CaOxalate stones), nephrocalcinosis, nephrogenic DI, Type 1 RTA, polyuria
	• GI: "Ab Groans": ab pain 2/2 pancreatitis/PUD/constipation, anorexia w/ weight loss, N/V
	• "Moans": full spectrum of mood changes, fatigue, sleep disturbances, weakness, AMS, lethargy
	• Other: shortened QT, calcification of skin vessels = skin necrosis, HypoMg, corneal calcifications aka band keratopathy
	• Hypercalcemic Crisis: occurs when Ca >13, extreme of everything above w/ AKI, coma, etc
	
	<u>Mild/Chronic</u>
	• Usually asymptomatic occasionally mild neurocognitive impairment

- **HypoCa**
  - Mild/Asymptomatic: PO Ca+VitD w/ 1000mg/400IU Qd (women <50yo and men <65yo), 1200/800IU Qd (adolescents), 1500/1000IU Qd (women>50yo, men >65yo, pregnant/lactating)
    - Ca
      - **CaCO4** (Tums/Rolaids/Os-Cal/Caltrate, 1g tablet = 500mg of elemental Ca, less GI SEs and better absorption without food)
      - **CaCitrate** (Citracel, 1g tablet = 200mg of Elemental Ca, more GI SEs and better absorption with food)
      - **Milk** (1 glass of milk = 300mg of calcium)
    - VitD
      - **OTC VitD3**, if mild nutritionally deficient, 125,400,800,1000IU/tab
      - **Rx VitD2**, if severe nutritionally deficient, 50000U/tab PO Qwk x3-12mo
      - Rx 25-$VitD_{2/3}$, if liver dz, (no commercial form is available)
      - Rx 1,25-$VitD_{2/3}$ aka calcitriol (Rocatrol) if kidney dz, 0.25,0.5mcg/cap = 250,500 IU/cap
      - NB if you want to give VitD but for it to have more effect reducing PTH than increasing Ca GI absorption then give VitD analogues Hectoral/Zemplar (used in CKD pts who have high PTH but also hyperCa)
    - **NB Best Drug is Os-Cal-D (250mg of CaCO4 thus 125mg of elemental Ca + 0.2mcg of VitD3 thus 125IU of VitD) = *Os-Cal-D 250mg/125IU PO 2tabs TID***
    - NB goal is to bring Ca back to normal but to the low end of normal range to avoid hypercalciuria and subsequent stones, etc b/c even when Ca is normal if low PTH is the cause Ca is not being reabsorbed so is at high concentrations in the tubules
  - Severe/Symptomatic: IV Ca+VitD
    - Ca: **CaGluconate** (Kalcinate, used for NON cardiac arrest issues) vs **CaCl** (?, used for cardiac arrest issues) give 1amp IV (central line b/c causes vasoconstriction resulting in tissue necrosis and extravasation is very irritating) over 10min = 10mL of a 10% solution ~ 9-27mg/mL (CaGluconate/Cl) = 90-270mg of elemental calcium followed by a drip at 1-2mg/kg/hr
    - 25OH-VitD-total
      - If <5ng/mL then give 1tab Qwk x12wks then 1tab Qmo x3mo and then recheck level
      - If 5-15ng/mL then give 1tab Qwk x4wks then 1tab Qmo x5mo and then recheck level
      - If 15-30ng/mL then give 1tab Qmo x6mo and then recheck level
- **HyperCa**
  - Temporary Stabilization

        - Aggressive NS: simply dilutes calcium also hypercalcemic pts are volume depleted 2/2 calcium induced diuresis
        - Loop Diuretics: start ONLY after volume repletion, inhibits resorption thus immediate excretion, NB a recent Annals article indicates that diuretics should NO LONGER be used in hypercalcemia!!!
    - Chronic
        - General: correct other electrolytes esp PO4, low Calcium diet, stay hydrated
        - Treat underlying cause!!!
        - Calcitonin: refer above, quick acting but tachyphylaxis quickly develops w/in few days, no serious toxicity except for allergic reaction, has analgesic effects in pts with bone metastasis
        - RRT: good for RF/CHF pts in which aggressive hydration is prohibited
        - Bisphosphonates: inhibits osteoclasts, main ones used are Zoledronate and Pamidronate, takes a few weeks to work (NB Plicamycin/Mithramycin are similar to bisphosphonates but rarely used anymore b/c of SEs)
        - Glucocorticoids: inhibits VitD/osteoclast production, takes a week to work
        - Calcimimetics (cinacalcet (Sensipar)): increases sensitivity of calcium receptor on PTH gland so that it becomes more sensitive to Ca thus inhibiting PTH release, only FDA approved for secondary hyperPTH (though some try it for primary hyperPTH when surgery is not an option), very expensive and SEs of nausea and headache
        - Parathyroidectomy
            - 1° hyperPTH **(Indications: Symptomatic, Ca>1ULN, Nephrolithiasis, GFR <50, T-Score <-2.5, or <50yo and if you decide to not undergo surgery then follow Ca Q6mo, DEXA Qyr and Cr Qyr)**
                - Adenoma: partial (only 1 gland) –ectomy w/ incisional Bx of other glands if they appear enlarged b/c 5% adenomas are >1
                - Hyperplasia: progressive parathyroidectomy where you take out one gland then check intraoperative PTH, then two, then three, usually pts need 3½ out to achieve normal levels with the last ½ placed in nondominant forearm muscle or SCM
                - Carcinoma: partial (only 1 gland) –ectomy w/ ipsilateral thyroidectomy and LN removal
            - 2° hyperPTH: treat underlying cause
            - 3° hyperPTH: treat like hyperplasia
            - NB Technitium-99m **Sestamibi** (assesses mitochondrial activity) scan and **high-resolution US** can be used to characterize anatomy
            - NB Surgical Complications: (1) superior/recurrent laryngeal nerve palsy (2) hematoma (3) hypoCa
            - NB parathyroidectomy surgery has advanced over the years where now it is done under local anesthesia with a minimal access incision scheduled as a day surgery