Calcium Disorders

- Calcium Ca has 3 forms in the circulation
  - ionized free b form
  - bound to proteins like albumin and globulins
  - Bound to anions (bicarbonate, phosphate, citrate)
- Parathyroid hormone PTH increases free Ca level in blood and decrease phosphate level
- PTH effect
  - Bone : increase osteoclast activity and bone resorption
  - Kidney : decreased Ca clearance / increase phosphate and bicarbonate excretion / increase vitamin D production
  - GI tract : increase Ca absorption by increase Vitamin D production
- Vitamin D
  - A fat soluble steroid obtained from diet or synthesized in skin in presence of UV light
  - Transported to the liver, where it is 25-hydroxylated to 25-OH D Then transported to kidney where it is 1-hydroxylated under the control of PTH to 1,25(OH)2D aka calcitriol the active form of vitamin D
  - it increases transport and absorption of Ca from GI tract and increase Ca and phosphate resorption from bone

Hypercalcemia

- Hypercalcemia develops when there are abnormalities in the movement of Ca between the ECF and these compartments : bone, intestines, kidney, serum binding proteins
- Hypercalcemia causes hyperpolarization of neuromuscular cell membranes, which result in several symptoms including neuropsychiatric disturbances, GI abnormalities, renal dysfunction, musculoskeletal symptoms and CVS disease
- Hypercalcemia is when absolute serum calcium is above 13 mg/dL and above 15 is severe
- Formula for correcting the total calcium for low serum albumin : Corrected calcium = total serum calcium + (0.8 * [4 – serum albumin])
- more in women
- The most common causes of hypercalcemia are hyperparathyroidism and malignancy
- other causes :
  - Chronic granulomatous disease that activate 1 alpha hydroxylase)
  - Medications : Lithium (in bipolar disorder) Hydrochlorothiazide
  - Excessive Vitamin A : retinoic acid
  - Theophylline toxicity

    - Hyperthyroidism, Acromegaly, Pheochromocytoma, Adrenal insufficiency, Immobilization
    - Paget Disease : Chaotic osteoclast function with bone remodeling (both formation and improve the quality of the bone resorption) / bowing of lower limb / cotton wool patches in the skull / Laboratory studies show an isolated increase in alkaline phosphatase
    - Milk Alkali syndrome : high intake of milk - metabolic alkalosis - more calcium absorption - hypercalcemia
    - Pseudohypercalcemia : increased protein binding can cause an elevation in the serum total Ca without any rise in the serum ionized calcium (hyperalbuminemia)
- clinical manifestations of acute hypercalcemia
    - GI : anorexia, nausea, vomiting, constipation (decreased GI motility)
    - CNS : confusion, weakness, lethargy, hyporeflexia, obtundation, coma, psychic moans
    - CVS : hypertension, shortened QT interval, occasional bradycardia, and first degree atrioventricular block
    - Renal : polyuria and polydipsia via interference with ADH action and inhibition of sodium resorption
    - Stones, osteoporosis with bone pain, pancreatitis
    - Band keratopathy (deposition of calcium phosphate in sun exposed cornea)
- Diagnosis : by intact PTH iPTH
    - High : primary hyperparathyroidism
    - normal : maybe primary hyperparathyroidism or familial hypocalciuric hypercalcemia FHH (check 24 hour urine calcium level .. it is low in FHH, milk syndrome and thiazide diuretics and it is high in hyperparathyroidism)
    - Low : other tests (iPTH is low in malignancy)
        - PTHrp : high in hypercalcemia of malignancy (Squamous cell carcinoma of the lung) which activates alpha 1 hydroxylase
        - Calcitriol : high in vitamin D intoxication
        - Thyroid hormones : thyrotoxicosis can cause
        - ACTH for adrenal insufficiency
    - 25(OH)D : is the major circulating form of vitamin D and is the best measure of vitamin D status for most patients
- Treatment for acute hypercalcemia :
    - IV Saline with diuretics : loop diuretics (Furosemide) enhance sodium excretion and protect against volume overload (Calcium follows sodium in the proximal tubule the more sodium excreted, the more calcium excreted)

- Mobilization (immobility increases bone resorption)
- Bisphosphonates :
  - gold standard
  - slow but more durable response
  - Pamidronate or zoledronic acid are drugs of choice
  - Adverse effects include transient mild increase in temperature, myalgias and transient increase in serum creatinine
- Calcitonin
  - rapid but short but lived (Efficacy is limited to the first 48 hours due to tachyphylaxis & receptor downregulation
  - Inhibits bone resorption and increases renal excretion
  - safe and non toxic
- Glucocorticoids : Most useful in treating vitamin D mediated hypercalcemia
- Gallium Nitrate
  - decreases osteoclastic activity and PTH secretion
  - effective in both PTHrP mediated and non mediated
  - More potent than Etidronate, pamidronate and calcitonin
  - Potential for nephrotoxicity
  - need for continuous infusion over five days
- Calcimimetics : severe cases due to parathyroid carcinoma
- Dialysis

Hypocalcemia

- Causes
  - PTH related
    - Hypoparathyroidism (after neck surgery, autoimmune, infiltrative diseases)
    - Resistance to action of PTH : high PTH (pseudohypoparathyroidism)
  - Vitamin D deficiency (often low-normal calcium values)
    - Inadequate oral intake
    - GI malabsorptive disorders (celiac disease, pancreatic insufficiency, ileal bypass)
    - End stage liver or renal disease
    - osteomalacia
  - Large volume blood transfusions (citrate in transfused blood can bind calcium)
  - Magnesium depletion (decreased PTH release)
  - Acute respiratory alkalosis (increases binding of calcium to albumin)

    - Acute pancreatitis
    - candidiasis
    - polyglandular autoimmune syndrome type 1
    - Disorders of Magnesium
        - Mg depletion : cause PTH resistance
        - hypermagnesemia : suppress PTH secretion
- Osteomalacia
    - Undermineralized bone
    - Caused usually by calcium and phosphorus deficiency
    - Clinical symptoms : Fatigue / Diffuse bone pain / Muscle weakness
    - Diagnosis : Laboratory results often reveal low calcium, significant hypophosphatemia, mildly elevated alkaline phosphatase, low vitamin D levels
    - Diagnosis confirmed by bone biopsy (with tetracycline labeling) showing undermineralization
    - Treatment : Repletion of calcium and vitamin D and phosphorus if necessary
- Clinical Presentation
    - CNS : Numbness, paresthesias (perioral), tetany
    - Chvostek sign : spasm of the facial nerve when tapped
    - Trousseau sign : carpopedal spasm elicited by inflating blood pressure cuff above systolic pressure
    - CVS : hypotension / prolonged QT
- Treatment : IV repletion with calcium gluconate or calcium chloride slowly and with magnesium

Hyperparathyroidism

- caused by Radiation exposure to the head and neck 20-40 years earlier
- Genetic mutations associated :
    - Cyclin D1 / PRAD1 protooncogene gene : parathyroid adenoma
    - MEN 1 (tumor suppressor gene) : sporadic nonfamilial parathyroid adenomas
    - HRPT2 : parathyroid carcinoma
- Most common complications : Nephrolithiasis (most common) and Osteitis Fibrosa Cystica
- Osteitis Fibrosa Cystica
    - coupled increases in osteoclastic bone resorption and osteoblastic osteoid synthesis
    - accelerated rates of bone mineralization accompanied by microcysts in the cortex and trabeculae and increased numbers of fibroblasts and marrow stroma

    - The radiologic hallmarks are
        - salt and pepper demineralization of the skull cap
        - resorption of the tufts of the terminal phalanges and tapering of distal clavicles
        - subperiosteal resorption of the radial aspect of the cortex of the second phalanges associated with brown tumors (osteoclasts) that might be also found in the pelvis
- CVS manifestations : Hypertension / carotid intima and media thickness was significantly higher