HYPERCALCEMIA

BRRH Grand Rounds

24th January, 2017

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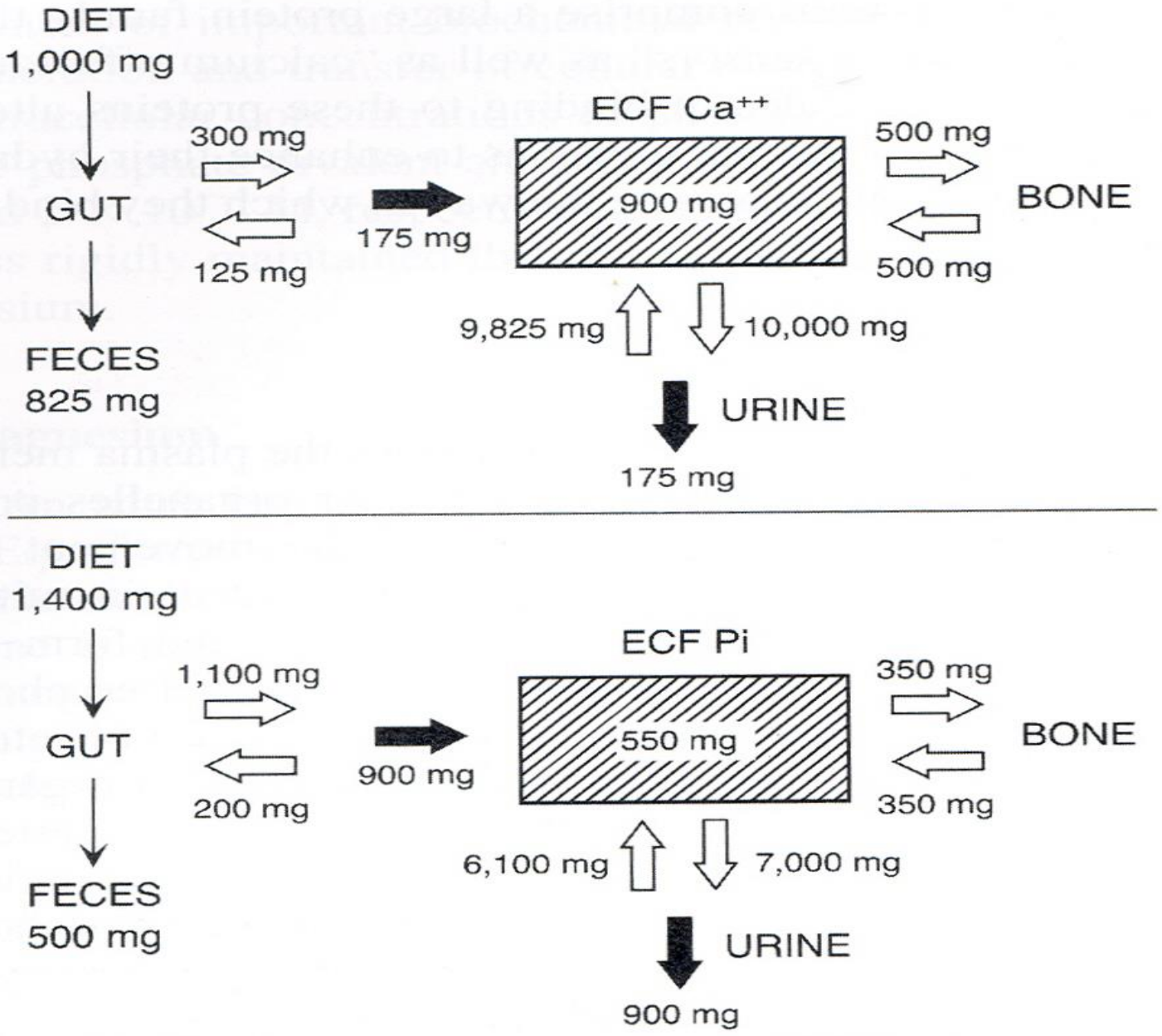
Hypercalcemia: Lecture Objectives

- 1. Mechanisms: calcium metabolism
- 2. Signs, Symptoms and Comorbidities
- 3. Differential dx and Evaluation Process
- 4. Treatment: general and specific

Distribution of minerals in the body

	CALCIUM	PHOSPHORUS
Total Body	1,100 gram	600 gm total. Makes up 50% of skeletal mass
Bone	99% of total Ca++ Also in teeth	85% in skeleton
Plasma fraction	4.8 mg/dL (48%) ionized 4.4 mg/dL (44%) protein bound-albumin 0.8 mg/dL (8%) complexed to citrate,PO4	1.9 mg/dL (55%) Ionized 0.4 mg/dL (11%) protein-bound 1.2 mg/dL (34%) complexed
Dietary intake	1,000 – 1,500 mg day	800-1500 mg day

Calcium and Phosphorus Fluxes



[Primer Metabolic Bone Diseases, 5th Edition]

Correcting the calcium for albumin concentration

Each g/dl of albumin binds 0.8 mg/dl of calcium

Corrected calcium = Calcium + (4.0 - albumin) X 0.8

If measured calcium = 8.0 and albumin + 3.0, then

Corrected calcium = 8.0 + (4.0 – 3.0) X 0.8

= 8.0 + 0.8 = 8.8 (normal)

Calcium and pH

- Calcium bound mostly to carboxyl groups on albumin
- Highly pH dependent

Acute acidosis → ↓ binding → ↑ ionized calcium

Acute alkalosis → ↑ binding → ↓ ionized calcium

Example – hyperventilation causes paresthesias

1,25 Vit D actions

Intestine

Increase fractional absorption Ca, Mg, Phos

Kidney

Increases distal tubule reabsorption of Ca,

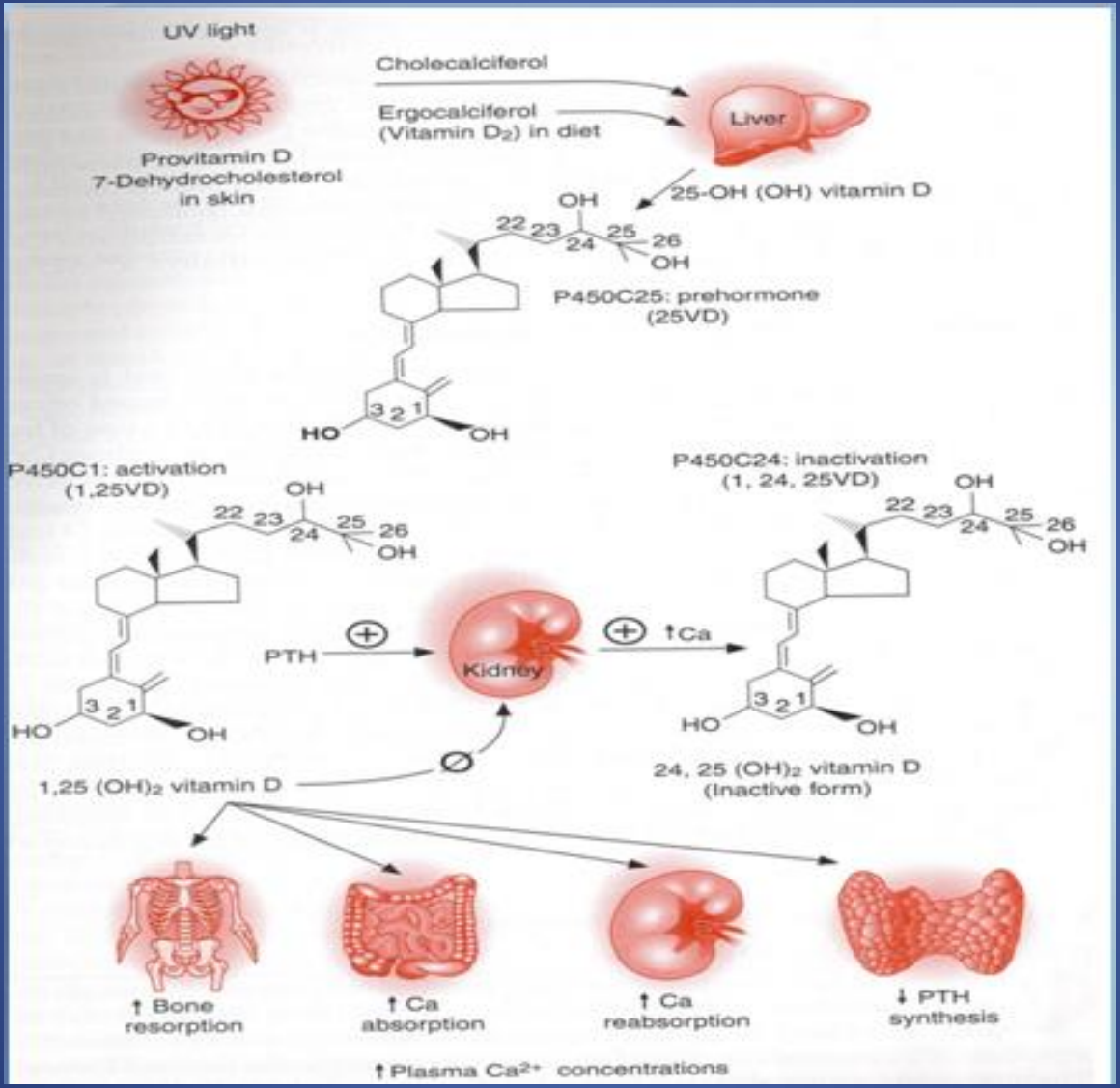
Bone

Osteoid mineralization, ↑ bone resorption, ↓ osteoblast

Parathyroid gland

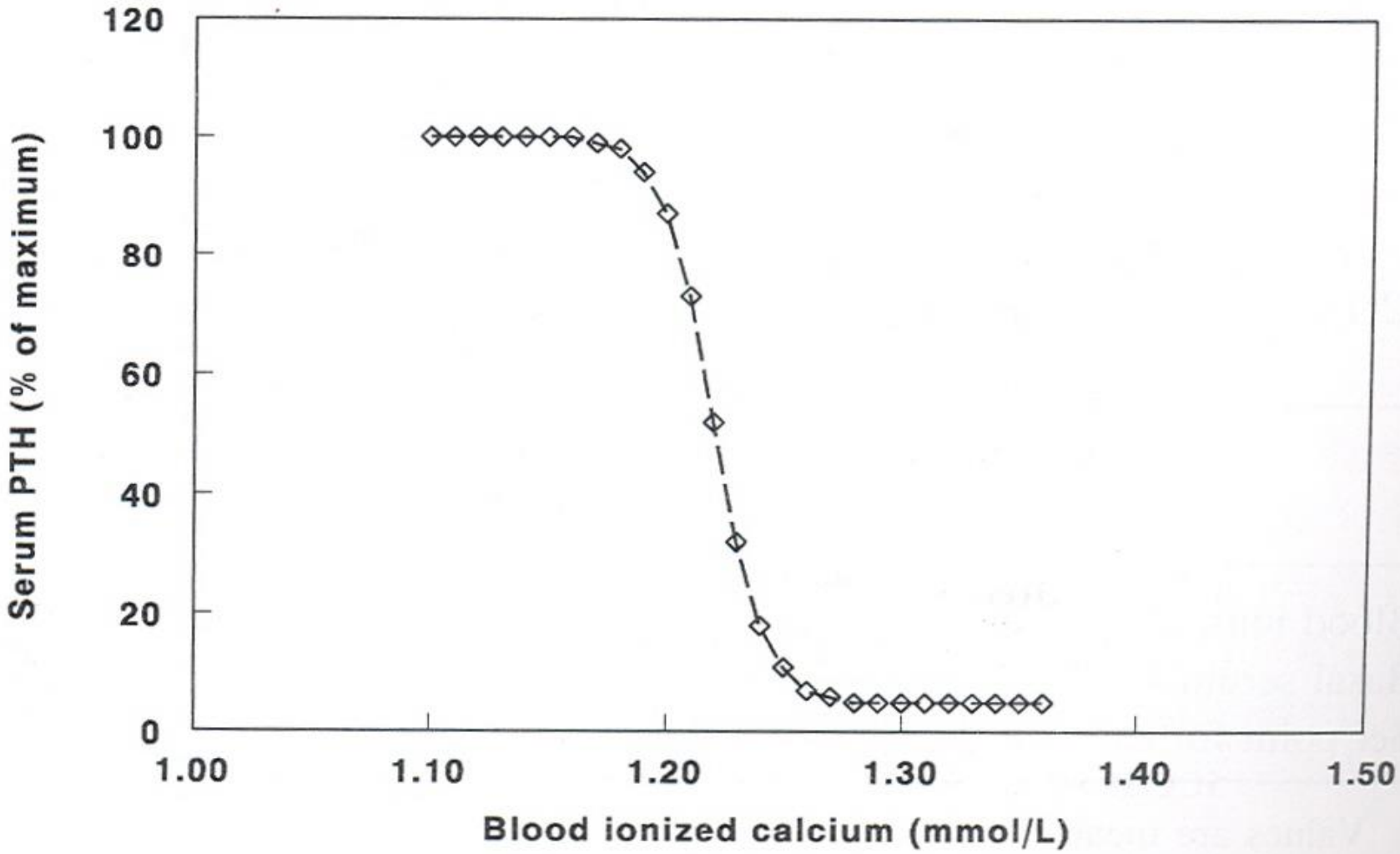
Suppresses PTH gene transcription, cell proliferation

Vitamin D Metabolism



Lange Physiology Series

Calcium is maintained in a narrow range by PTH



Primer on the Metabolic Bone Diseases

PTH and PTH Receptors

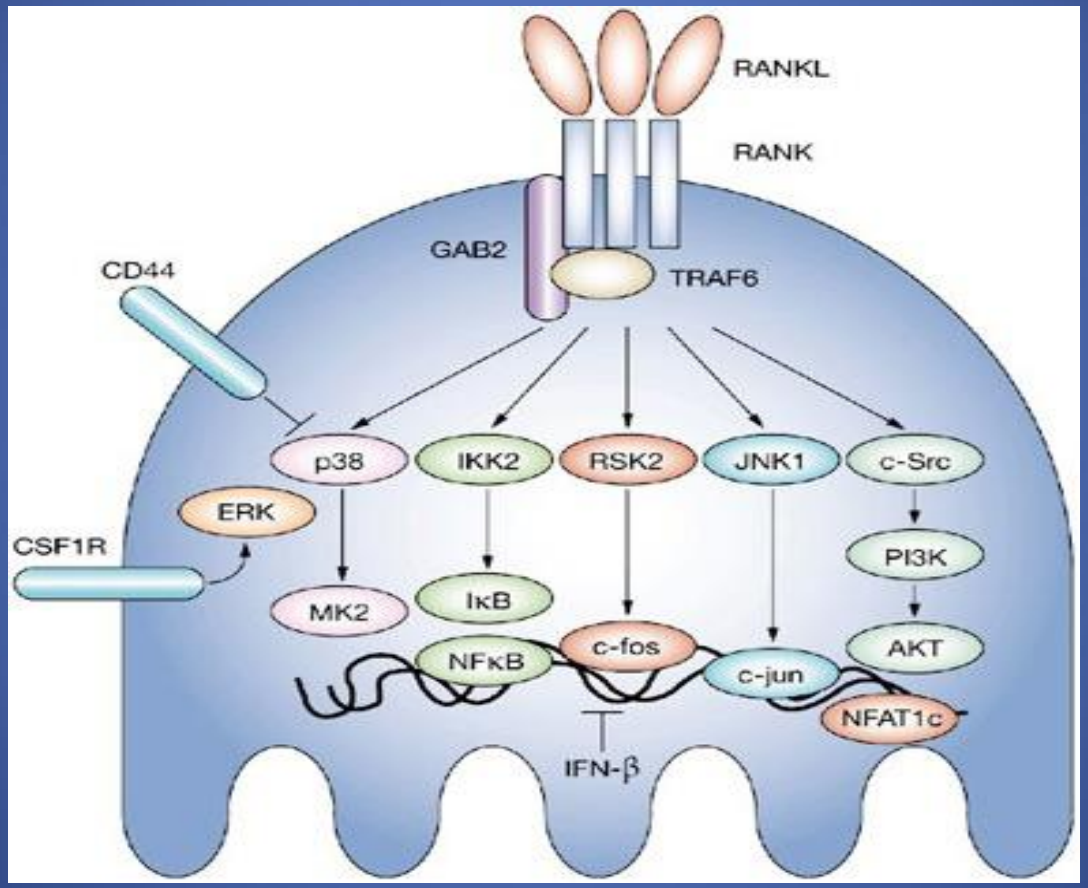
- PTH/PTHrp – same receptor for both
- PTH receptor 1 (MAJOR), 2 and 3 (?importance)
- Found in bone osteoblasts and kidney
- HIGH concentrations in growth plate chondrocytes
- (probably PARA/AUTOcrine PTHrp effect for cartilage)
- PTH2 receptor found in pancreas, placenta and blood vessels, testis and brain. ? Role in regulation of blood flow.
- PTH effect is to stimulate RANK-ligand

  (Receptor Activator of NF-κB)

RANKL is Expressed by Osteoblasts in Response to:

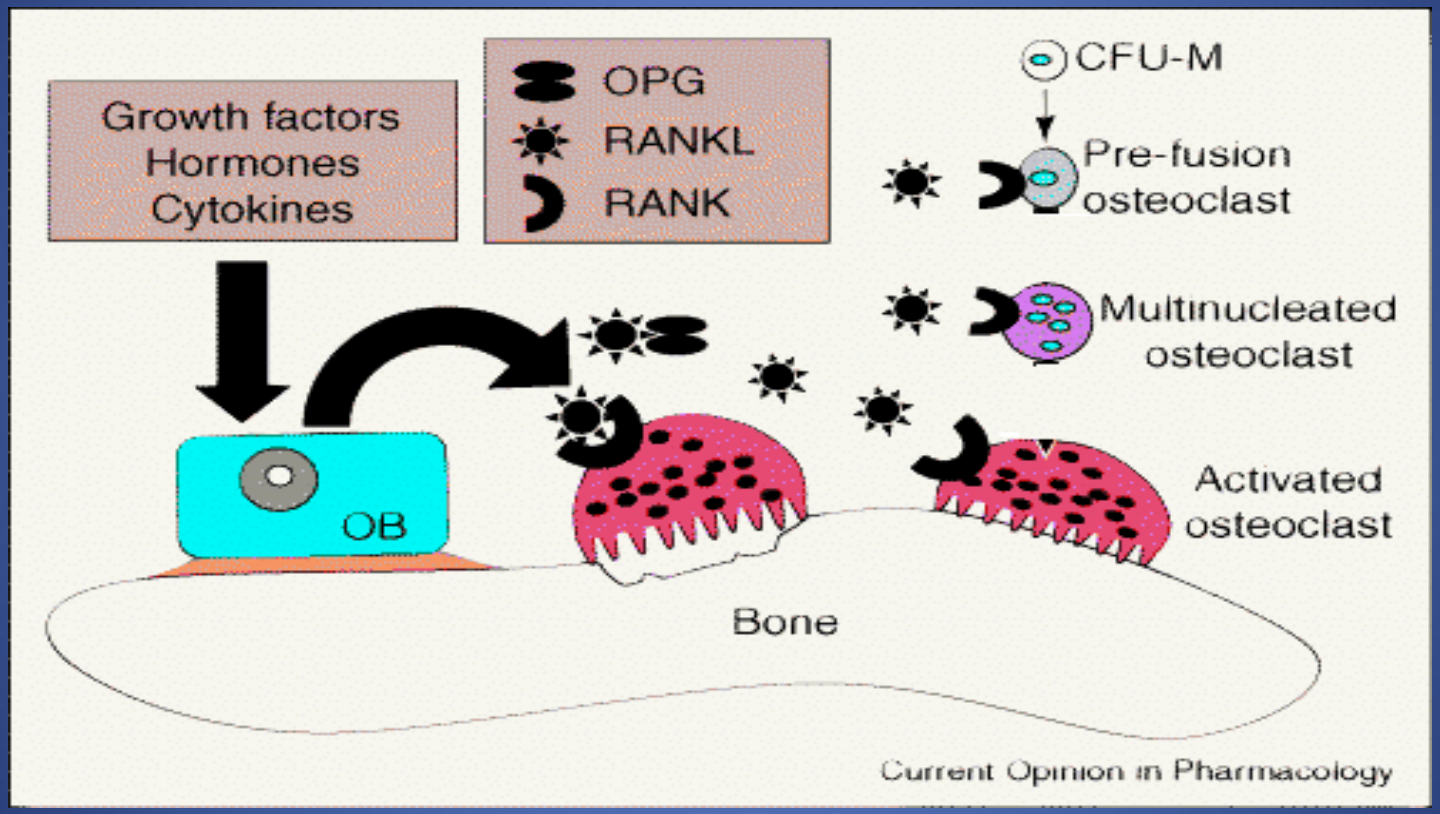
- **PTH, PTHrP, 1,25 D**
- **Various Cytokines:**
- PGE2,
- IL-1β,
- IL-6,
- IL-11,
- TNF-α

RANKL Stimulates Osteoclasts to cause Bone Resorption



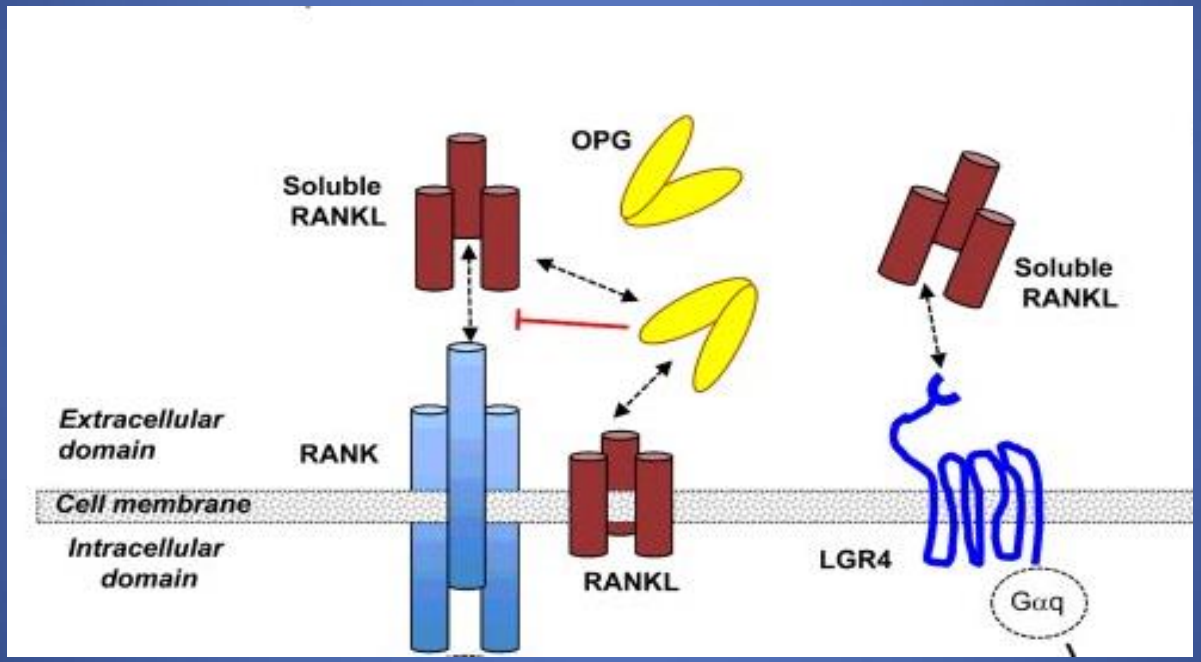
Schett G *et al. (2005) Nat Clin Pract Rheumatol* ***1:*** 47–54

Osteoprotegerin counterbalances RANK activation



Modified from Kostenuik PJ, Curr Opin Pharmacol. 2005 Sep 23

LGR4 is a Second Receptor for RANKL That Negatively Regulates Osteoclast Activity



from Renema, N.*et al Biosci Rep.*2016 Aug; 36(4): e00366

Balance between RANKL and OPG Governs Osteoclast Activity and Bone Resorption

Bone Markers

- Osteocalcin

Marker for osteoblast activity

Elevated in active bone loss

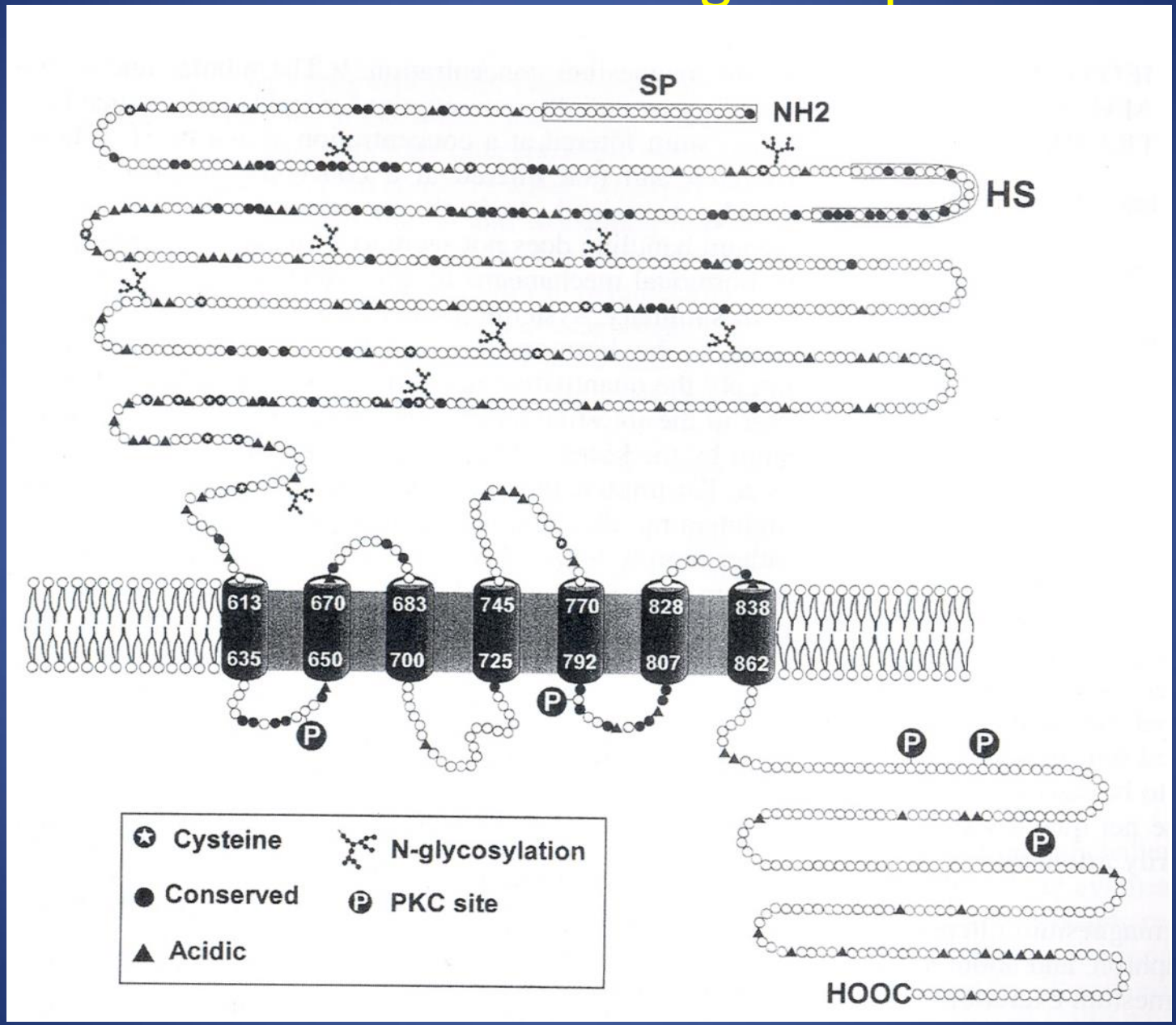
- CTx/NTx/Pyrilinks

Marker for osteoclast activity

Elevated in active bone loss

Measurable collagen loss from bone turnover

The Calcium Sensing Receptor



Primer on the Met Bone Diseases, 5th Ed.

Distribution of Calcium Sensing Receptors

- Parathyroid CHIEF cells--determines PTH response to ambient calcium levels
- Kidney: (distal) tubule cells-- determines % calcium in urine
- Thyroid C-cells (make calcitonin)

Hypercalcemia: Clinical Manifestations

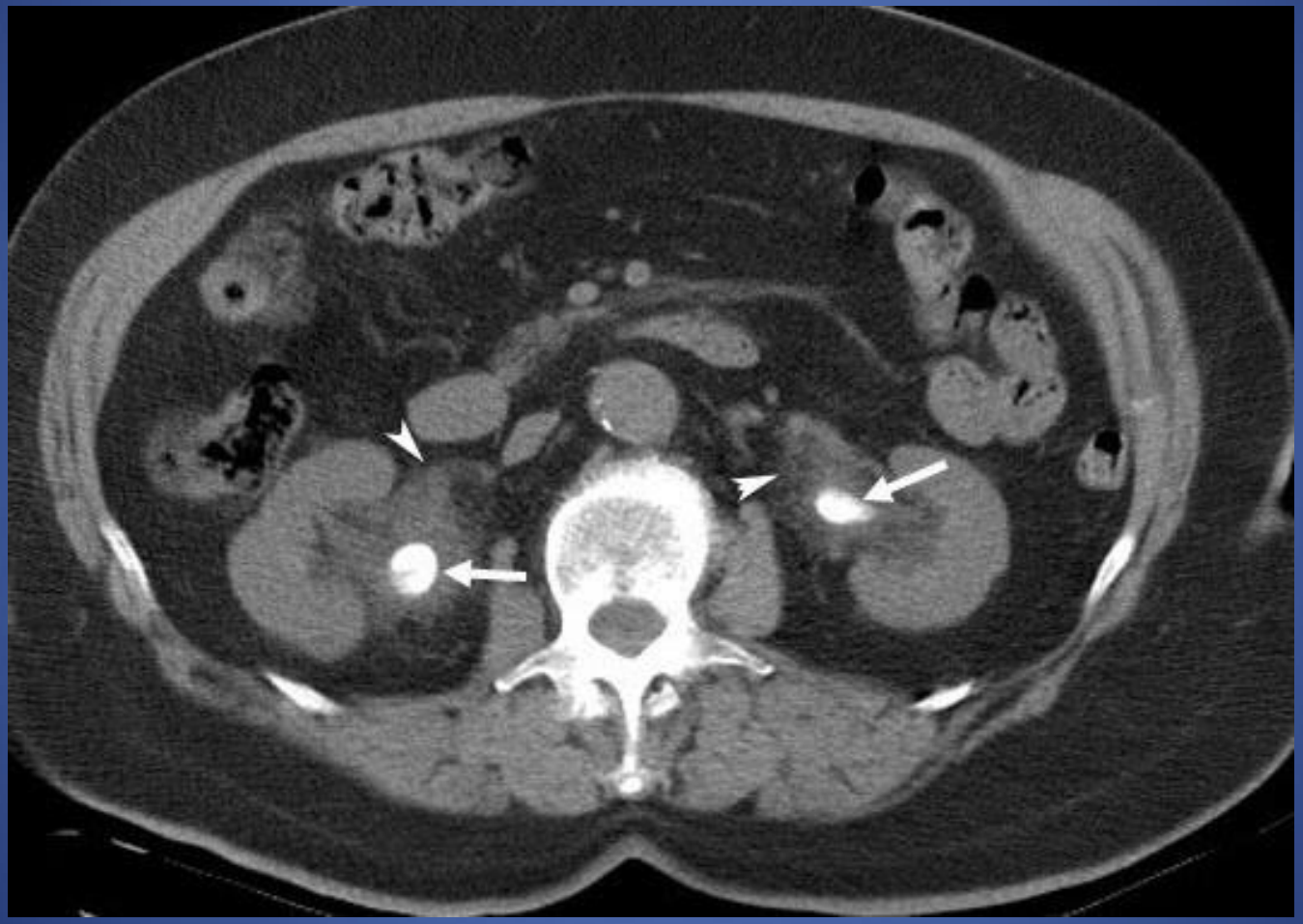
"Bones, Stones and Abdominal Groans"

- Fatigue, lethargy, poor memory and concentration, stupor, coma
- Personality change
- Nausea, anorexia, constipation
- Peptic ulcer disease
- Pancreatitis
- Polyuria, nephrolithiasis, nephrocalcinosis
- Hypertension
- Bradycardia, short QT interval, AV block
- Bone pain, pathologic fractures
- Muscle weakness, arthralgias

Gastrointestinal manifestations of hypercalcemia

- Hypercalcemia depresses autonomic nervous system
- Smooth muscle hypotonicity
- Increased gastric residual volume
- Constipation

Renal manifestation of hypercalcemia: Nephrolithiasis



Bilateral Renal Pelvis Calculi

Mechanisms of Hypercalcemia

- 1. Increased bone resorption
- 2. Increased intestinal absorption
- 3. Decreased renal excretion

Causes of Hypercalcemia

Primary Hyperparathyroidism

- 90% of all cases of hypercalcemia
- Inappropriately elevated PTH for given Ca level
- Usually a single adenoma (80-85%)
- Several DNA deletions have been described
- Altered “set point” vs. cell mass
- Also 4 gland hyperplasia (10%), 2 adenomas (4%)
- RARELY parathyroid carcinoma (1%)

Causes of Hypercalcemia
Hyperparathyroidism-MEN Syndrome

- MEN Type 1
  - 2/100,000 prevalence
  - Tumors in Parathyroid, anterior Pituitary and Pancreatic islet cell
  - Primary HPT has nearly 100% penetrance
  - Accounts for 2% of HPT cases
  - Also gastrinomas, carcinoids, enterochromaffin-like tumors, adrenocortical tumors, lipomas, angiofibromas, colalgenomas and spinal cord ependymomas.
  - HPT presents EARLIER if associated with MEN
  - More likely multiple gland involvement
  - High recurrence rate following (successful) surgery

Causes of Hypercalcemia
Hyperparathyroidism-MEN Syndrome

- MEN Type 2
  - 2A, 2B and familial medullary cancer (FMTC)
  - 75% are 2A
  - 2A only type that manifests HPT
  - Autosomal dominant, RET protooncogene
  - Medullary CA, HPT, pheochromocytoma
  - Penetrance of HPT only 20-30% (90% for medullary)
  - Rule out pheo prior to parathyroidectomy
  - Usually multiglandular (2,3, or 4)

Causes of Hypercalcemia

Familial Hypocalciuric Hypercalcemia -FHH

- Inactivating mutation in CaSR
- HYPOcalciuria (Ca Cl/Creat CL < 0.01)
- Family history
- Autosomal dominant
- 100% penetrance—Patient will have lifetime Hx of hypercalcemia

Causes of Hypercalcemia

Malignancy

- PTHrp
- Osteolytic metastases (KOTLTB)
- Cytokines and other Humoral Factors
- 1-alpha-hydroxylase production
  - Lymphomas
- Poor prognosis <6 month survival

Hypercalcemia is a frequent complication of malignant disease (% of total cases)

Bronchus	26
Breast	22
ENT	7
Urologic	7
Myeloma	7
Cervix	7
Esophagus	6
Unknown primary	5
Lymphoma	4
Kidney	3
Colon	2
Thyroid	2

Hematologic Malignancies Associated with Hypercalcemia (%)

Adult T-cell lymphoma/ leukemia	50 - 90
Multiple myeloma	20 - 40
Malignant lymphoma	< 10
Hodgkin's disease	< 1
Chronic lymphocytic leukemia	< 1
Chronic myelogenous leukemia	< 1
Acute leukemia	< 1

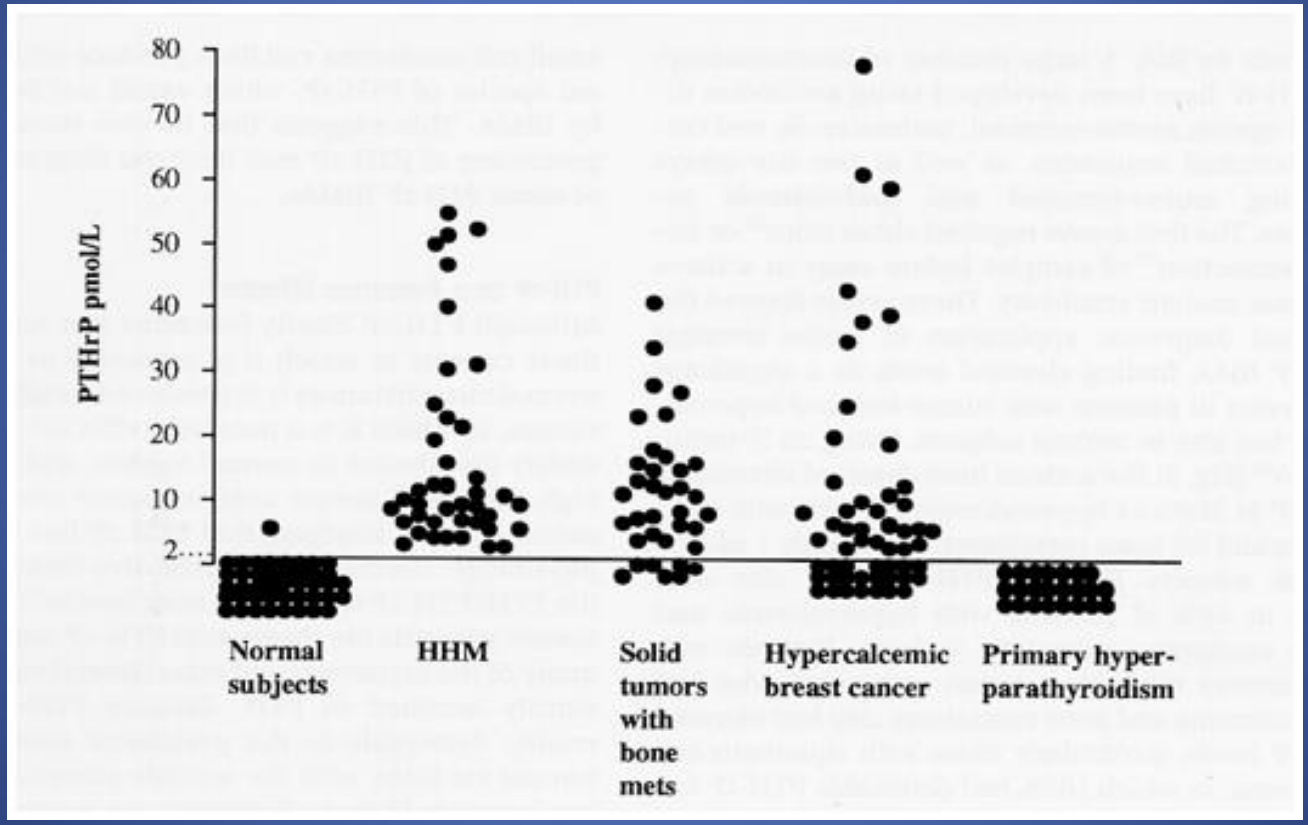
Characteristics of PTHrp

- Similar structure to PTH (8 of 1st 13 are identical)
- Similar biologic effects
- Chromosone 12
- More complicated than PTH gene
- Functions LOCALLY (para/autocrine)
- 3 isoforms from alternative splicing
- EQUIVALENT binding affinities for PTH/PTHrp receptor
- Also causes elevated Ca, decreased Phos, but NOT elevated 1,25 Vit D
- Major cause of hypercalcemia of malignancy
- Mostly squamous, renal, breast cancer and others

Parathyroid hormone-related protein PTHrP

- PTHrp 1---13 ----34 ----------141
- PTH 1---13 ----34 ----------84
- PTH bioactivity: binds to PTH-1 receptors
- Principal Mediator of HHM
- Autocrine and Paracrine actions
- Humoral actions (placental calcium transport, HHM)
- Knockout of PTHrP in mice: lethal

Circulating PTHrP in various neoplastic conditions



Grill V, *et al J Clin Endocrinol Metab. (1991) v.73 :pp. 1309-15.*

Causes of Hypercalcemia

Medications

- Thiazides
- Lithium
- Vit D excess
- Milk alkali
- Vit A excess
- Aminophylline
- Tamoxiphen
- Growth Hormone
- TPN
- Thyroid Hormone
- Foscarnet

Causes of Hypercalcemia

Medications

LITHIUM

Interferes with CaSR

Mild, persistent hypercalcemia

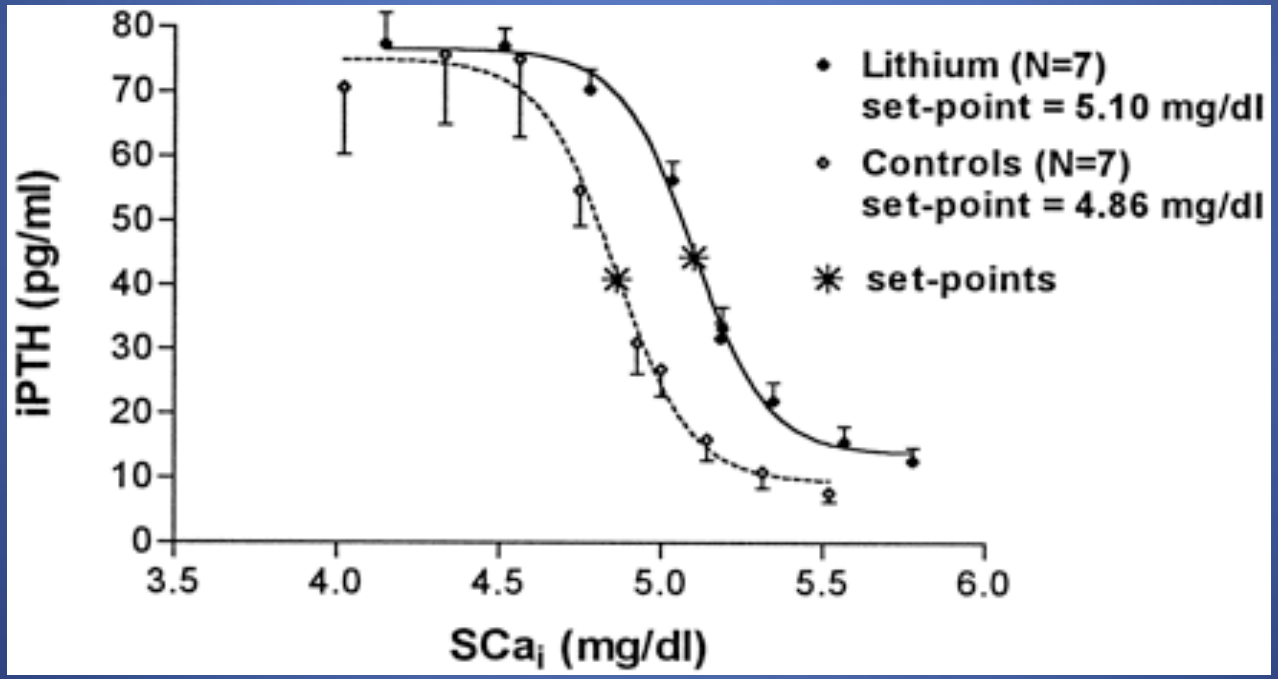
Elevated PTH after years of therapy

Ca normalizes few months after stoppping Rx

Rarely hyperplasia after stopping Lithium

Lithium Shifts the Set-Point for Calcium-Regulated PTH Release

Clinical condition resembles FHH



J Clin Endocrinol Metab. 1997 Sep; 82(9): pp. 2844-8

Hypercalcemia and Thiazide Diuretics

- Thiazides enhance calcium reabsorption in the distal renal tubule
- + Extracellular volume depletion
- Decreased urinary calcium excretion

Milk-Alkali Syndrome

- Classical Triad:Hypercalcemia + Metabolic alkalosis + Renal failure
- Classical setting: pts with peptic ulcer disease treated with absorbable antacids (bicarbonate) and large quantities of milk and cream

Hypercalcemia from Hypervitaminosis A

- Vitamin A Ingestion > 50,000 IU
- Other retinoids: Retin A, Accutane

1. Vitamin A directly stimulates osteoclast- mediated bone resorption (mechanism?)
2. Associated with ↓ PTH and ↓ 1,25 diOH vitamin D
3. Can be prolonged due to vitamin A fat solubility
4. Usually responds to general measures and glucocorticoids

Causes of Hypercalcemia

Infectious (granulomatous)

- TB or leprosy
- Coccidiomycosis or histoplasmosis
- Cryptococcus
- CMV
- HIV

Causes of Hypercalcemia

NON-Infectious (granulomatous)

- Sarcoidosis
- Silicone
- Eosinophilic granuloma
- Wegener's granulomatosis

Calcitriol-mediated hypercalcemia

Table 1. Frequency of Identified Etiologies of Calcitriol-Mediated Hypercalcemia

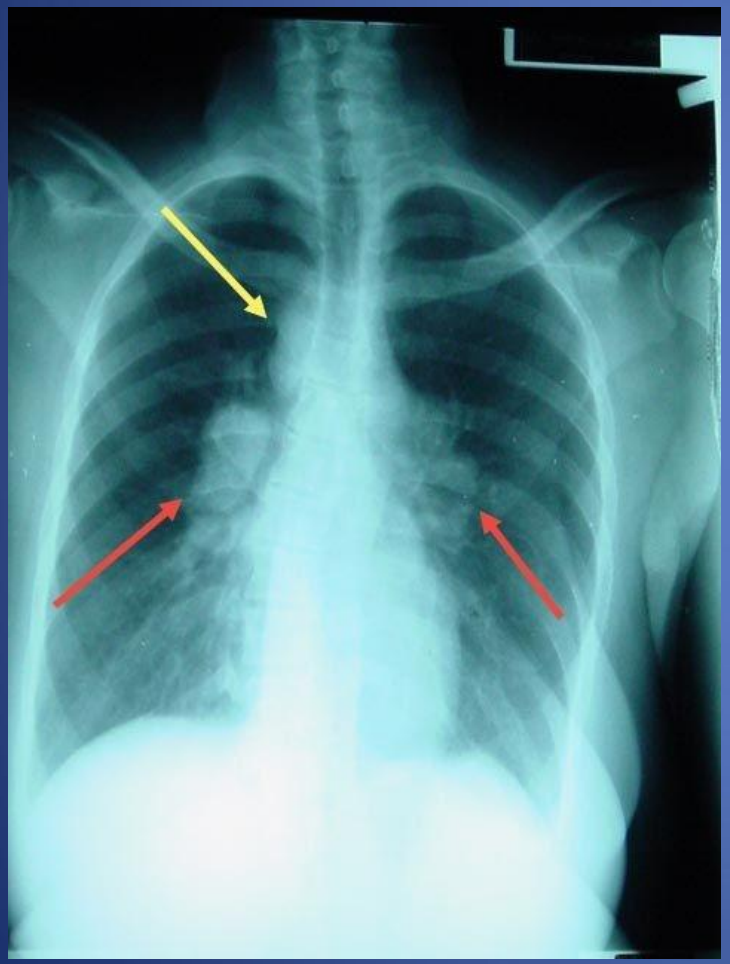
Etiology	n (%)
Sarcoidosis	49 (49)
Hematological malignancy	17 (17)
Non-Hodgkin's lymphoma	
Diffuse large B cell lymphoma	8 (8)
Follicular lymphoma	2 (2)
T cell lymphoma	1 (1)
Subtype unknown	3 (3)
Hodgkin's lymphoma	2 (2)
Chronic lymphocytic leukemia	1 (1)
Infectious	8 (8)
Mycobacterium tuberculosis infection	4 (4)
Mycobacterium avium complex	2 (2)
Mycobacterium bovis variant BCG	1 (1)
Invasive histoplasmosis	1 (1)
Solid organ malignancy	5 (5)
Ovarian clear cell cystadenocarcinoma	1 (1)
Seminoma	1 (1)
Metastatic squamous cell carcinoma of tongue	1 (1)
Metastatic adenocarcinoma of unknown primary	1 (1)
Non-small-cell lung carcinoma	1 (1)
Other granulomatous conditions	4 (4)
Foreign body granulomatosis	2 (2)
Granulomatous disease of unknown cause	2 (2)
Idiopathic	3 (3)
Unknown or no diagnosis made	15 (15)
Treated empirically before diagnosis established	9 (9)
Insufficient information to make diagnosis	3 (3)
Resolved spontaneously before diagnosis established	3 (3)
Total cases	101

Calcitriol-Mediated Hypercalcemia: Causes and Course in 101 Patients

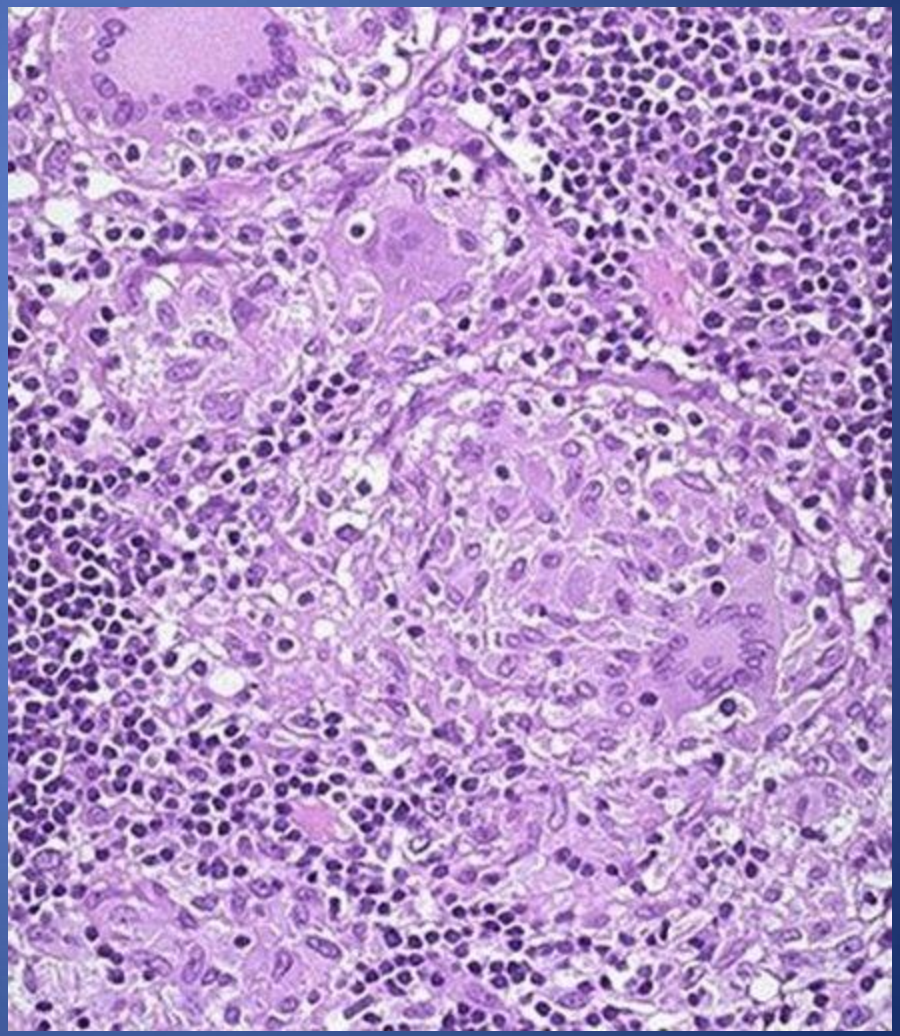
Peter J. Donovan, Lana Sundac, Carel J. Pretorius, Michael C. d'Emden, and Donald S. A. McLeod

(*J Clin Endocrinol Metab* 98: 4023–4029, 2013)

Pulmonary sarcoidosis



bilateral hilar lymphadenopathy



non-caseating granulomas

Causes of Hypercalcemia

Miscellaneous

- Recovery phase rhabdomyolysis
- Aluminum
- William's syndrome (infants)
- Jansen syndrome (PTH receptor protein)
- Immobilization
- Renal failure (acute and chronic)

Immobilization-associated hypercalcemia

- 1. The skeleton can sense mechanical stress and adjust bone mass to meet the physical load: skeletal “mechano-sensing”
- 2. Bone mass is lost with physical unloading of bone: e.g. prolonged bed rest, weightlessness in space
- 3. Mechanism of such bone loss is “uncoupling” of bone turnover: ↓ bone formation, ↑ bone resorption
- (low PTH and 1,25 OH2-Vit D, like PTHrp mediated)
- 4. This can lead to net efflux of calcium from bone, hypercalciuria, and hypercalcemia

Causes of Hypercalcemia

Other Endocrine Causes

- Hyperthyroidism
- Adrenal Insufficiency
- Pheochromocytoma
- VIPoma

Thyrotoxicosis is associated with Hypercalcemia

Hypercalcemia has been documented in:

- Graves' disease
- Toxic MNG
- Toxic adenoma
- Subacute thyroiditis

50% of patients with thyrotoxicosis present with hypercalcemia (Ca 10.5- 11.5 mg/dL)

Association of hypercalcemia with pheochromocytoma:

1. In many cases reflects concomitant primary HPT in patient with known or occult MEN2A.
2. Elevated catecholamines may increase bone turnover
3. Pheochromocytomas, like other neoplasms, can secrete PTHrP

Hypercalcemia present in up to 20% of patients with acute Primary Adrenal Insufficiency

- Infection
- Metastases
- Autoimmunity

1. Often with concurrent hypovolemia and renal insufficiency
2. Can also be seen in secondary adrenal insufficiency
3. Associated with ↓ PTH and ↓ 1,25 diOH vitamin D
4. Responds well to IV fluids and corticosteroids

Evaluation of Hypercalcemia

- History, Family History, Medication, vitamin history (include OTC)
- a. PTH-intact - two site antibody sandwich method (IRMA, ICMA)
- b. ionized calcium
- c. SPEP, UPEP, ESR
- d. Vitamin D metabolites: 25-OH; 1,25-diOH
- e. Lytes, glucose, BUN, creatinine, alk phos, phos
- f. Other: ostase, BSAP, urine NTx or serum CTx, ACE level, calcitonin, genetics
- g. Imaging: CXR, Neck USN, Sestamibi—may need chest CT, consider renal USN, Bone Density

Therapy of Hypercalcemia

General vs. Specific measures:

- - increase urinary excretion
- - decrease intestinal absorption
- - decrease bone resorption

Treatment of Hypercalcemia

- HYDRATION – almost all pts. dehydrated
- +/- loop diuretics
- Calcitonin (immediate response)
- IV bisphophonates
  - 48-96 hour response
  - Zolendronic acid, pamidronate, etidronate
- Gallium, plicamycin
- Corticosteroids
- Dialysis
- Intravenous phosphate (toxic)

Therapy of Hypercalcemia:

Hydration

- Intervention: Normal saline 3 to 6 liters IV daily for 1 to 3 days (125 to 250 ml/hr)
- Onset of action: Hours
- Benefits: Rehydration; enhanced filtration and excretion of calcium
- Risks: Congestive heart failure; volume overload

* Consider Furosemide additionally

Therapy of Hypercalcemia:
Dialysis

- Intervention: Hemodialysis against low or zero calcium dialysate (in patients with renal failure:
- GFR < 20 ml/min)
- Onset of action: Hours
- Benefits: Rapid onset; no volume overload
- Risks: Hypotension; invasive procedure

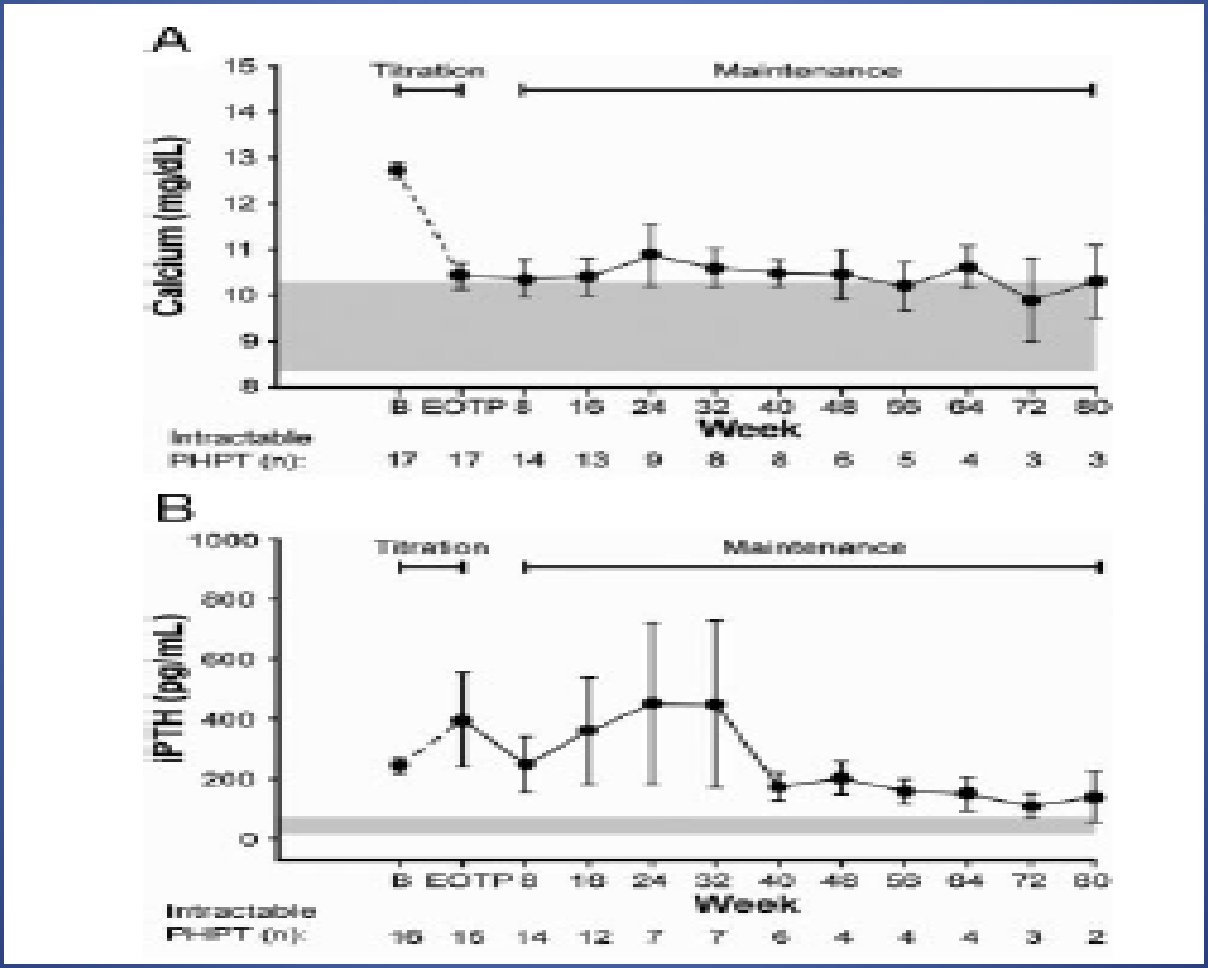
Therapy of Hypercalcemia: Calcitonin

- Intervention: 4 to 8 IU per kg calcitonin, IM or subcutaneously every 12 hrs
- Onset of action: Hours
- Benefits: Rapid acting, minimal toxicity
- Risks: Flushing, nausea—use test dose; effectiveness limited by tachyphylaxis

Therapy of Hypercalcemia: Cinacalcet

- Used primarily in patients refusing surgery or with contraindications to surgery
- Usual dose is 30-90 mg PO daily
- Side effects: nausea and vomiting
- Does NOT protect bones from PTH induced bone loss

Cinacalcet Reduces Serum Calcium Concentrationsin Patients with Intractable PrimaryHyperparathyroidism



(JCEM 94:2766-72, 2009)

Therapy of Hypercalcemia: Bisphosphonates

- Creat Cl > 35 for safe use
- Used essentially to prevent bone loss
- Can be used in conjunction with Sensipar
- Alendronate, Ibandronate and Residronate
- Should suppress markers of bone turnover
- GI sxs are potentially limiting

Therapy of Hypercalcemia: Pamidronate

- Intervention: Pamidronate (Aredia) 60 to 90 mg IV over 2 hrs in 50 to 200 ml D5W or NS
- Onset of action: 1 to 3 days
- Benefits: Potent anti-resorptive agent; less expensive than zoledronic acid
- Risks: Renal failure, transient fever, aches, chills; mild hypophosphatemia; ONJ, possibly atrial fibrillation

Therapy of Hypercalcemia: Zoledronate

- Intervention: Zoledronic acid (Zometa) 4 mg IV over 15 min in 50 ml D5W or NS
- Onset of action: 1 to 3 days
- Benefits: Most potent bisphosphonate; longer acting than pamidronate
- Risks: Renal failure, transient fever, aches, chills; mild hypophosphatemia; ONJ, possibly atrial fibrillation

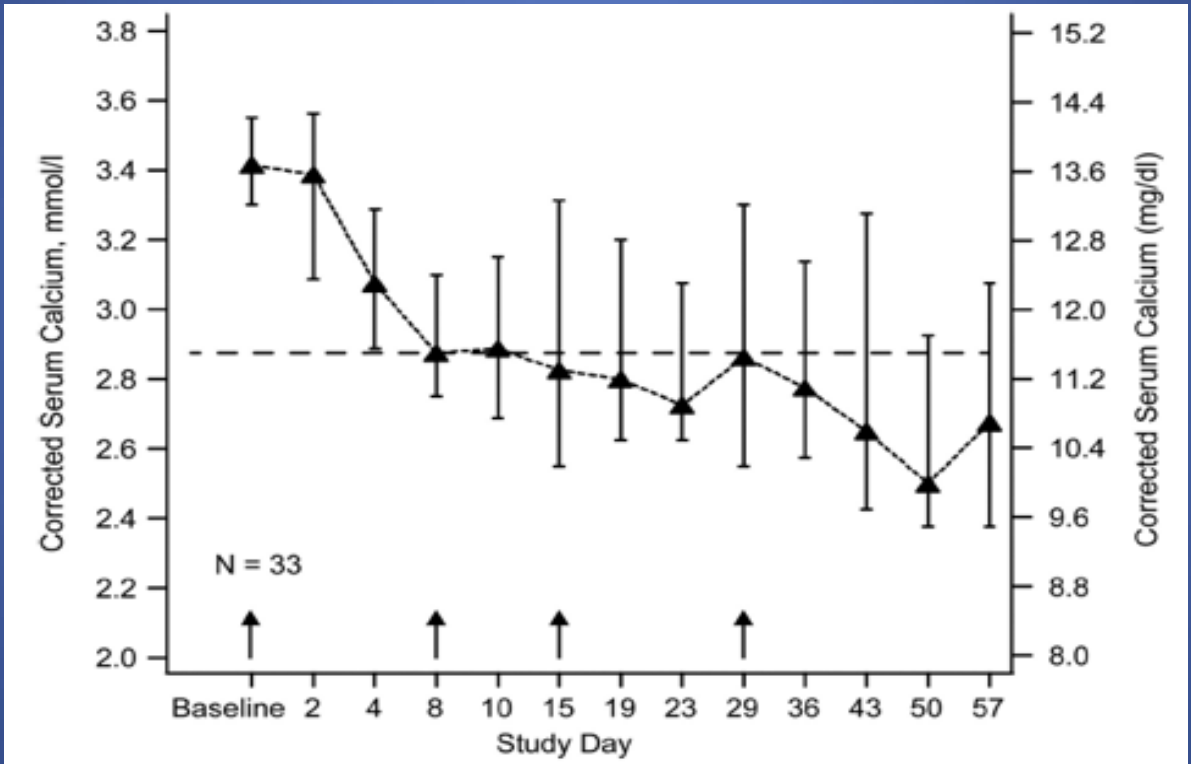
Therapy of Hypercalcemia: Glucocorticoids

- Intervention: Hydrocortisone 100 mg IV q 8 hrs, or prednisone 60 mg daily, for 3 to 10 days
- Onset of action: Days
- Benefits: Useful in setting of lymphoma, sarcoidosis, or vitamin D intoxication
- Risks: Cushing's syndrome, HTN, Hyperglycemia

Therapy of Hypercalcemia: Mithramycin

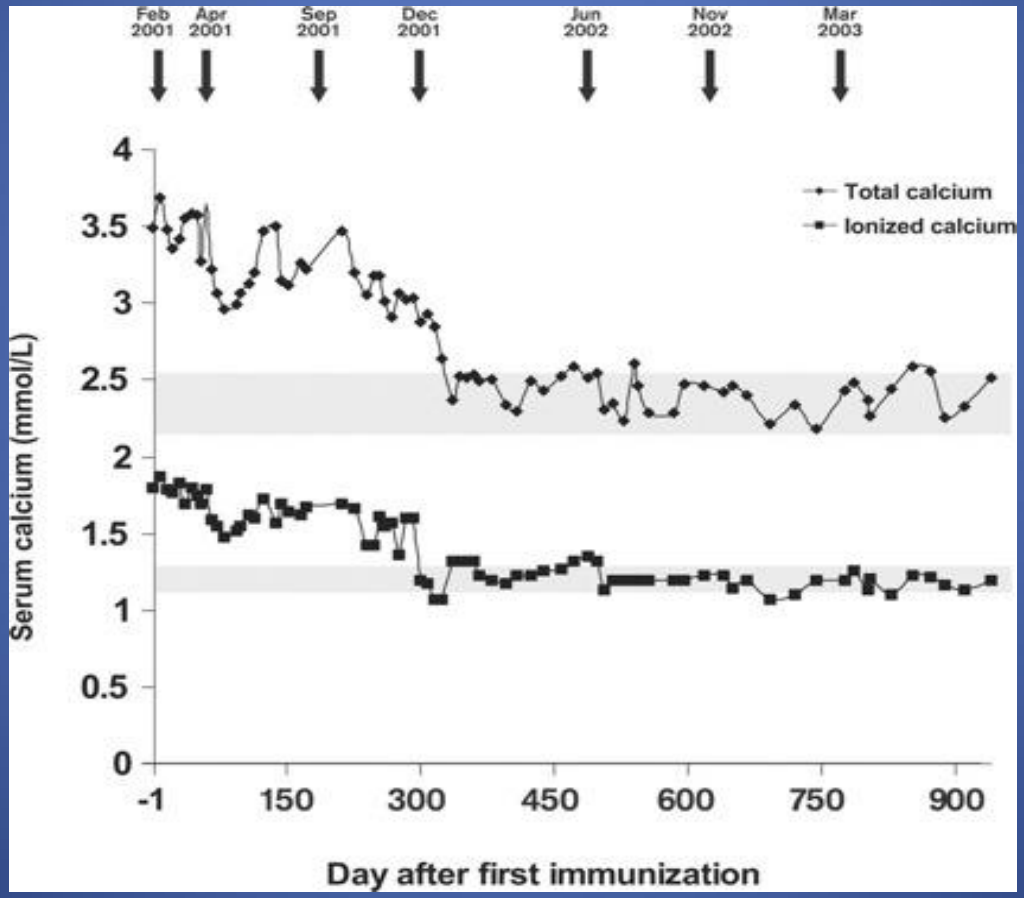
- Intervention: Single dose of 25 mcg / kg mithramycin in 1 liter NS IV over 4 to 6 hours
- Onset of action: 1 to 2 days
- Benefits: Decreases bone resorption
- Risks: **Thrombocytopenia, anemia, renal failure, hepatitis**

Denosumab for Treatment of Hypercalcemia of Malignancy—not FDA approved



Hu et al, JCEM July 2014

Treatment of malignancy-associated hypercalcemia with anti-PTHrp-antibody--not FDA approved



Treatment of Hypercalcemia

Primary Hyperparathyroidism

Surgical criteria (2002 NIH conf--updated JAMA 2016)

- Calcium >1 point above normal
- Life threatening hypercalcemia
- Kidney stones
- Hypercalciuria (>400 mg/24 hour)
- Reduced creat clear <70% age
- Osteoporosis (T score <-2.5)
- Young age <50

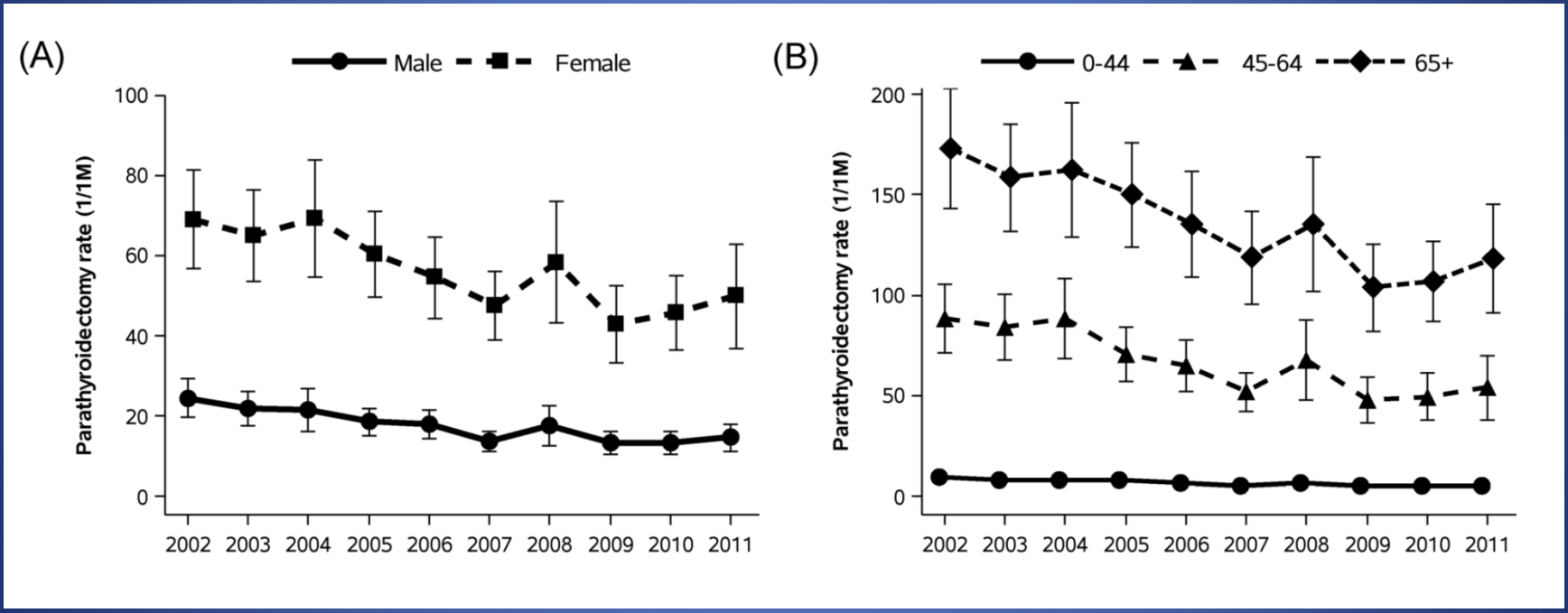
Treatment of Hypercalcemia

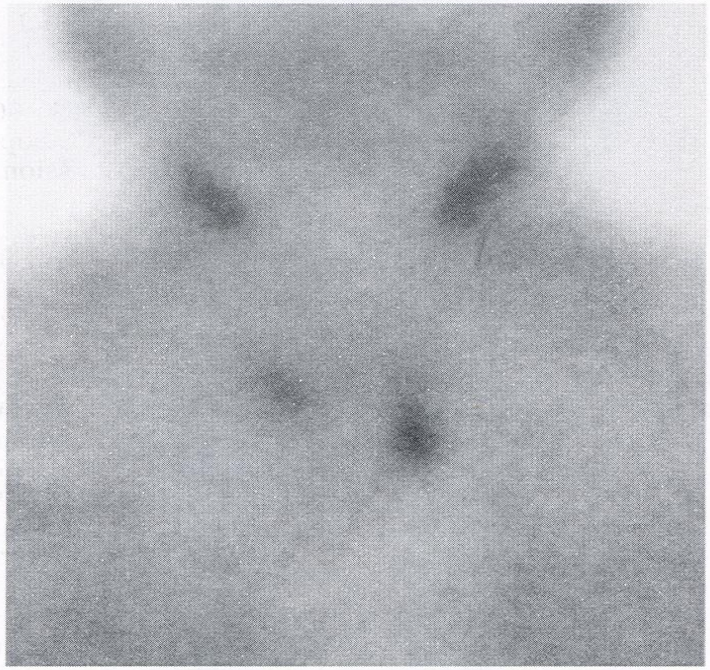
Primary Hyperparathyroidism

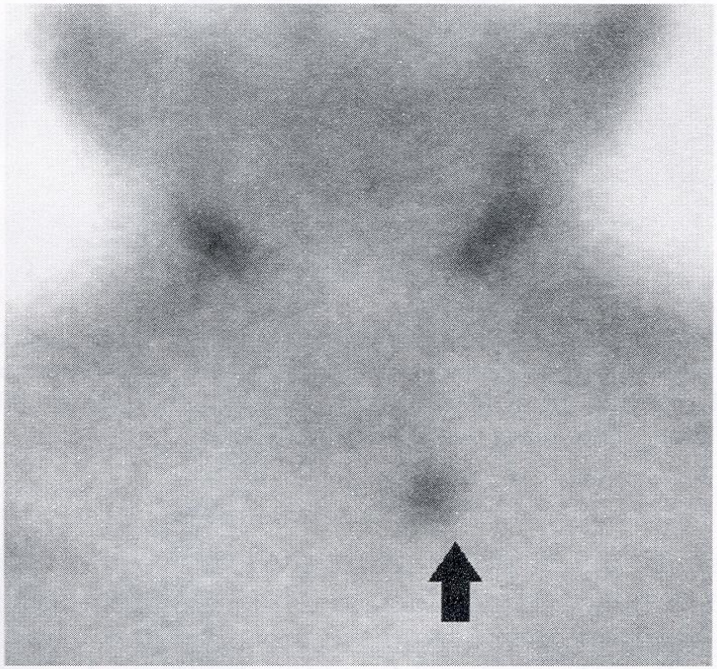
Traditional surgery—best if Dx or preop localization unclear or suspect hyperplasia (3.5 gland resection)

Minimally invasive procedure--can be done outpatient--best with intaoperative Sestamibi and rapid PTH assay

Parathyroidectomy Rates are Declining







Positive Sestamibi Scan in HPT

Primer on the Metabolic Bone Diseases

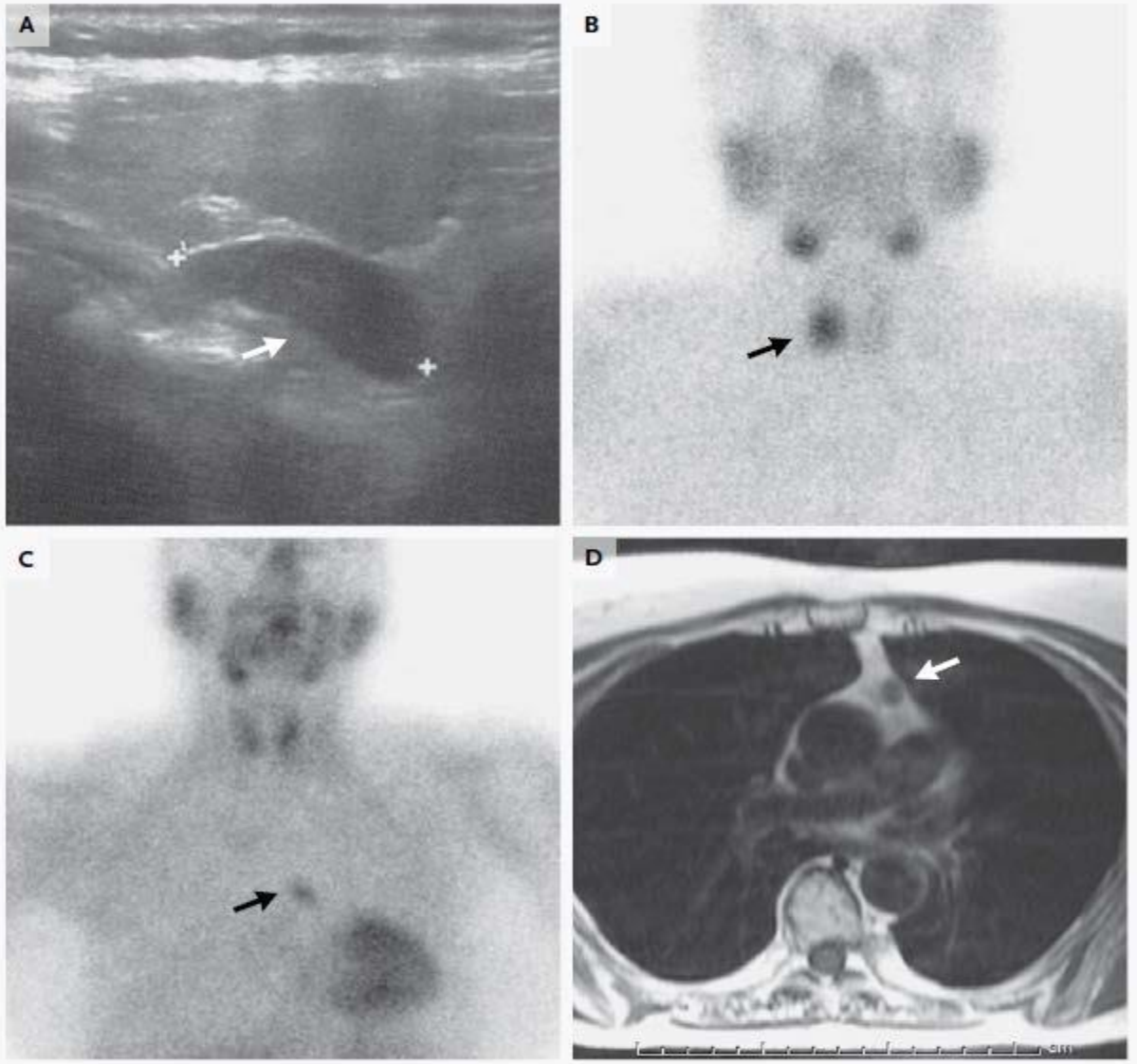


Figure 1. Parathyroid Imaging.

Panel A shows a longitudinal ultrasonographic image of the right thyroid lobe of the patient described in the vignette. An enlarged parathyroid gland appears homogeneously solid and markedly more hypoechoic than the adjacent thyroid tissue (arrow). Panel B shows a delayed-phase planar sestamibi scan indicating a marked uptake at the level of the right thyroid lobe, where the ultrasound localized the parathyroid lesion (arrow) in the patient described in the vignette. Panels C and D show a mediastinal parathyroid adenoma in a 65-year-old woman with primary hyperparathyroidism. In Panel C, a delayed-phase sestamibi scan shows a marked uptake at the level of the middle mediastinum (arrow). In Panel D, a magnetic resonance imaging scan (T_1-weighted image) of the chest shows a lesion in the aortopulmonary window (arrow). The patient underwent a sternotomy, and a parathyroid adenoma was excised.

Asymptomatic Primary Hyperparathyroidism

- Monitor DEXA for bone loss even within the osteopenic range
- Monitor for changes in renal function (GFR)
- Monitor for development of renal calculi
- Treat associated deficiency of Vitamin D to a minimum level of 20 ng/dl
- Risk of developing symptoms or complications ranges from 23-62%

THANK YOU !