



## DIAGNOSIS AND TREATMENT OF HYPERCALCEMIA

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## Introduction

- The skeleton contains 99 percent of total body calcium; the remaining 1 percent circulates throughout the body
- One half of circulating calcium is free (ionized) calcium, the only form that has physiologic effects.
- The remainder is bound to albumin, globulin, and other inorganic molecules
- Corrected calcium =  $(4.0 \text{ mg/dl} - [\text{plasma albumin}]) \times 0.8 + [\text{serum calcium}]$



## Definition

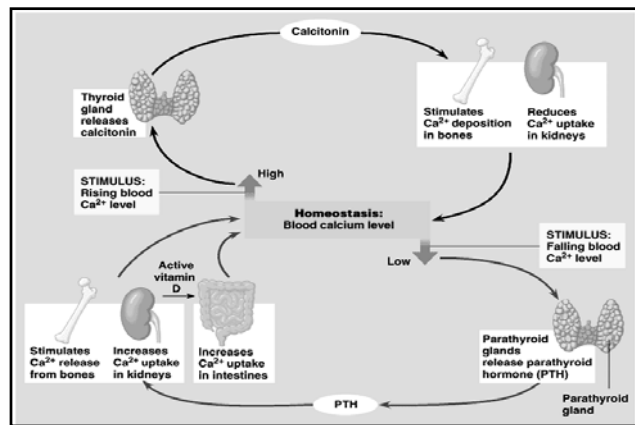
- **Normal serum calcium levels** are 8.5 to 10 mg/dL (2.0 to 2.5 mmol/L)
- **Normal ionized calcium levels** are 4 to 5.6 mg /dL (1 to 1.4 mmol per L)
- **Hypercalcemia** is defined as total serum calcium > 10 mg/dl (>2.5 m mol/L ) or ionized serum calcium > 5.6 mg/dl (>1.4 m mol/L )

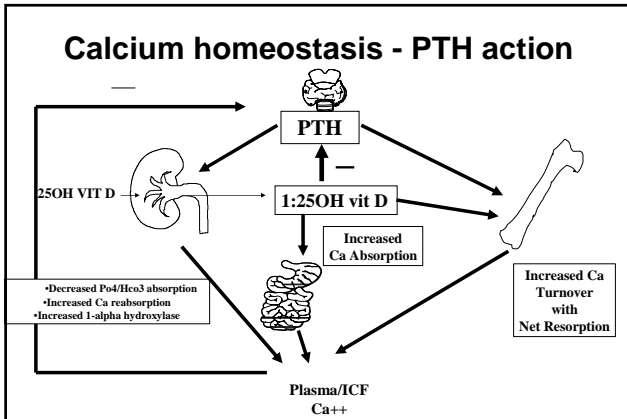
## Definition

- **Severe hypercalcemia is defined as total serum calcium > 14 mg/dl (> 3.5 mmol/L)**
- **Hypercalcemic crises (no definite definition) severe neurological symptoms or cardiac arrhythmias are present in a patient with a serum calcium > 14 mg/dl (> 3.5 mmol/L) .**

## CALCIUM HOMEOSTASIS 3 Hormones-3 Organs

- PTH
- ACTIVATED VITAMIN D (1,25 OH vit D)
- CALCITONIN
  
- BONE
- KIDNEY
- SMALL INTESTINE





### Hypercalcemia 3 Mechanisms

- **Hypercalcemia is caused by**
- Increased bone resorption
- Increased gastrointestinal absorption of calcium
- Decreased renal excretion of calcium

### Clinical Manifestations

- Patients with levels of calcium between 10.5 and 12 mg/dl can be asymptomatic.
- Renal : polyuria , nephrolithiasis
- GI : anorexia , nausea , vomiting , constipation , Pancreatitis , PUD
- Neuro- psychiatric : weakness , fatigue , confusion , stupor , coma
- Cardiovascular : Shortened QT interval on electrocardiogram, bradyarrhythmias . heart block and cardiac arrest
- Cornea : band keratopathy

### Etiology of hypercalcemia

(based on pathophysiology)

<ul style="list-style-type: none"> <li>• <b>Bone resorption</b></li> <li>• Primary hyperparathyroidism</li> <li>• Tertiary hyperparathyroidism</li> <li>• Malignancy</li> <li>• Thyrotoxicosis</li> <li>• Immobilization</li> <li>• Hypervitaminosis A</li> </ul>	<ul style="list-style-type: none"> <li>• <b>Miscellaneous</b></li> <li>• Lithium</li> <li>• Thiazide diuretics</li> <li>• Pheochromocytoma</li> <li>• Adrenal insufficiency</li> <li>• Rhabdomyolysis</li> <li>• Acute renal failure</li> <li>• Theophylline</li> <li>• Familial hypocalciuric hypercalcemia</li> </ul>
<ul style="list-style-type: none"> <li>• <b>Calcium absorption</b></li> <li>• Milk Alkali syndrome</li> <li>• Hypervitaminosis D</li> </ul>	

### Etiology of Hypercalcemia

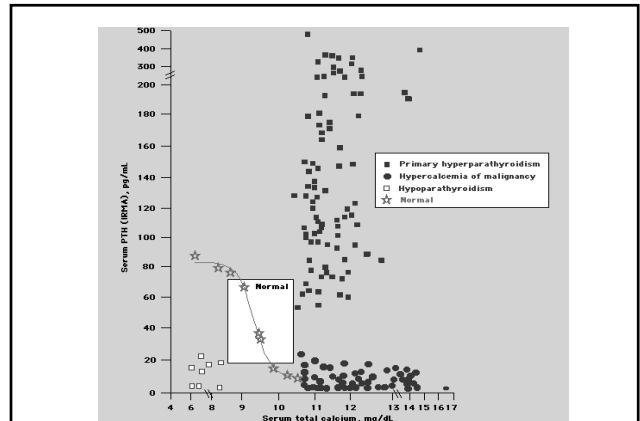
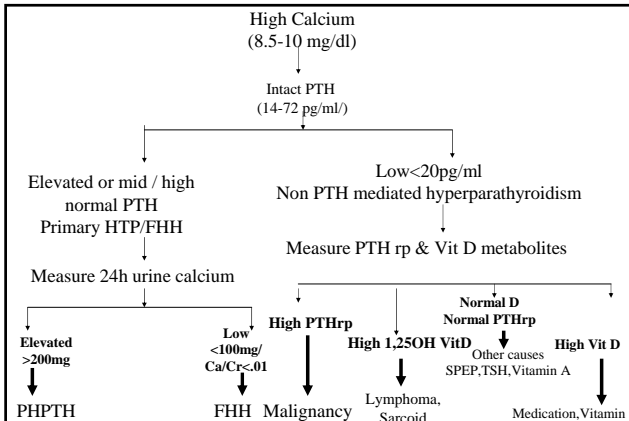
(Practical approach-Based on Intact PTH)

<ul style="list-style-type: none"> <li>• <b>PTH Dependent</b></li> <li>• Primary hyper-PTH</li> <li>• Tertiary hyper-PTH</li> <li>• Familial hypocalciuric hypercalcemia</li> <li>• Lithium toxicity</li> </ul>	<ul style="list-style-type: none"> <li>• <b>PTH Independent</b></li> <li>• Malignancy</li> <li>• Vitamin D excess</li> <li>• Sarcoidosis</li> <li>• Thyrotoxicosis</li> <li>• Adrenal insufficiency</li> <li>• Immobilization</li> <li>• Drugs</li> <li>• Milk Alkali Syndrome</li> </ul>
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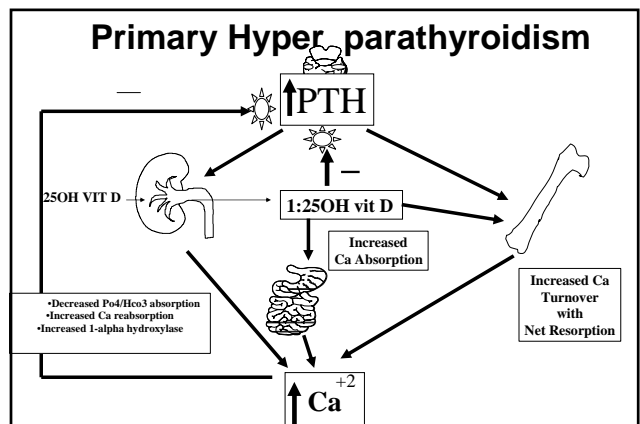
Calcium

### Evaluation

- Evaluation of a patient with hypercalcemia ( should include a careful history and physical examination focusing on clinical manifestations of hypercalcemia
- risk factors for malignancy
- causative medications, and
- family history of hypercalcemia-associated conditions



- ### Primary Hyperparathyroidism
- Hypercalcaemia with an elevated PTH or inappropriately normal PTH
  - PTH suppressed in other forms of hypercalcaemia.
  - Primary hyperparathyroidism
    - Most common etiology in outpatients
    - 1 in 500 to 1 in 1000
    - Most common in 6th decade
    - Women > men, 3:2 ratio
    - Many patients found on routine screening with minimal symptoms



- ❖ 80% due to solitary adenoma
- ❖ 4 gland hyperplasia
  - MEN I
    - Pancreatic tumors (gastrinoma, insulinoma)
    - Pituitary tumors
  - MEN 2a
    - Medullary thyroid cancer
    - Pheochromocytoma
    - Parathyroid hyperplasia or adenoma
- ❖ 5% are carcinoma

Labs - ↑ Ca<sup>++</sup>, ↓ PO<sub>4</sub>  
 ↑ PTH  
 ↑ urinary calcium excretion

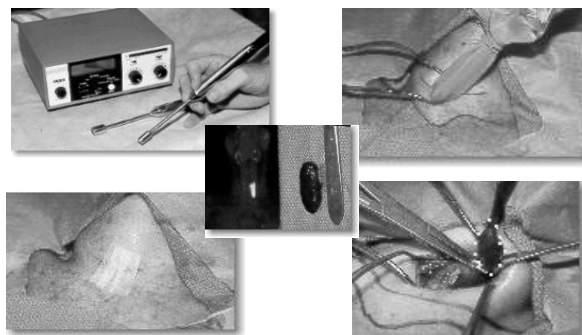
- ### Work-Up
- Intact PTH and chemistry panel
    - PTH elevated despite elevated serum calcium
    - Serum phosphate in the low-normal to mildly decreased range
    - Look at the serum creatinine to evaluate for CRI/CRF
  - Rule out lithium or thiazide use
  - 24-hour urine calcium excretion
    - Used to rule out familial hypocalciuric hypercalcemia
    - Values below 100mg/24 hours or a calcium creatinine clearance ratio of <0.01 are suggestive of FHH
  - Wrist, spine and hip DEXA
  - Consider KUB, IVP or CT to evaluate for kidney stones
  - Ionized calcium versus serum calcium
    - CORRECTED SERUM CALCIUM
      - Serum calcium (mg/dL)+(0.8X[4-albumin (g/dL)])

### Guidelines for Parathyroid surgery

Measurement	1990	2002	2008
calcium(>upper N)	1-1.6 mg/dl	1.0 mg/dl	1.0mg/dl
24 hr urine ca	>400mg/d	>400mg/d	Not indicated
Cr Clearance	Reduced by 30%	Reduced by 30%	Reduced to <60ml/min
BMD	Z score<-2.0 forearm	T-score<-2.5 at any site	T-score<-2.5 at any site or h/o fracture
Age	<50	<50	<50

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### Intra-operative Gamma probe



### Guidelines of Asymptomatic Primary Hyperparathyroidism not to undergo surgery

Measurement	1990	2002	2008
Serum Ca	Biannually	Biannually	Annually
24 hr urine ca	Annually	Not recommended	Not recommended
Cr Cl	Annually	Not recommended	Not recommended
Serum Ce	Annually	Annually	Annually
Bone density	Annually(forearm)	Annually(3 sites)	Every1-2y(3 sites)
Abdominal X-ray	Annually	Not recommended	Not recommended

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### Case

- 30 year old female with history of hypertension comes to establish her care. No known family history.
- Physical examination is normal
- Her initial labs showed hypercalcemia
- Further work up showed
- Calcium 10.3 mg /dl (8.5-10)
- Intact PTH 70 pg/ml (14-72)
- 1,25 OH vit D 67 ng/ml( 19-57)
- 24 hr urine calcium 60 mg/dl
- Any other information needed to help reach the diagnosis?

### What is the diagnosis?

- A.Primary hyperparathyroidism
- B.Familial hypocalciuric hypercalcemia
- C.Malignancy
- D.Sarcoidosis

### Familial hypocalciuric hypercalcemia

- **Inactivating mutation of Calcium sensor:**
  - Parathyroid cell: higher serum Ca needed to shut off PTH secretion
  - Renal tubular cell: increase urinary Ca reabsorption
- **Autosomal dominant inheritance**
  - Homozygous: severe neonatal hypercalcemia
  - Heterozygotes: asymptomatic mild hypercalcemia
- **Distinguish HPT from FHH by  $FE_{Ca}$** 
  - FHH:  $FE_{Ca} < 0.01$
  - HPT:  $FE_{Ca} > 0.01-0.02$
$$FE_{Ca} = \frac{CaU \times Cr \cdot S}{CrU \times Ca \cdot S}$$

## Factors to decide for treatment

- Degree of hypercalcemia
- Rate of rise of calcium
- Symptomatic/asymptomatic
- Acute vs Chronic

## Treatment outline

- Mild hypercalcemia
- Moderate hypercalcemia
- Severe hypercalcemia
- Volume expansion with NS
- Loop diuretics ?
- Salmon calcitonin
- Bisphosphonate(Pamidronate/Zoledronic acid)
- Treat underlying cause

## Hypercalcemic Crisis: Rx

1. Volume: IV NS 200-300 cc/h (slower if elderly, cardiac or renal disease), urine output 100-150ml/hr
2. Loop diuretic: Only if ECFv overloaded. Lasix 20-40 mg IV q4-6h. Monitor I/O carefully, keep patient in positive fluid balance
3. Replace electrolyte depletion from saline diuresis as needed (K, Mg, )
4. Calcitonin 4iu/kg IM/SC -Tachphylaxis

## Bisphosphonates

1. Inhibit calcium release by interfering with osteoclast bone resorption
  2. Potent/Preferred
- Pamidronate-60-90 mg IV over 2 hrs
  - Zoledronic acid-4 mg IV in 15 minutes
  - Ibandronate 2-4 mg IV over 2 hrs

## Treatment of Hypercalcemia

Intervention	Mode of action	Onset of action	Duration
NS hydration	Restores I / V volume	Hrs	During infusion
Loop diuretic	Increase Ca excretion	Hrs	During Rx
Calcitonin	Inhibits bone resorption(BR)	4-6 hrs	48 hrs
Bisphosphonates	Inhibits bone reso	24-72 hrs	2-4 wks
GIO	↓ 1,25 OH vit d	2-5 days	Days to weeks
Gallium nitrate	Inhibits BR	3-5 days	2 weeks
Calcimimetics	Ca sensing receptor A	2-3 days	During Rx
Dialysis	Low or no calcium Dialysate	Hrs	During Rx

## Cinacalcet: a 2<sup>nd</sup> Generation Calcimimetic

- The only FDA approved calcimimetic
- In three large randomized controlled clinical trials, cinacalcet given in doses of 30-180mg orally each day was associated with:

- effective decrease in PTH levels over 26 weeks compared with placebo
- decrease in Ca, P and Ca X P

### Indications

- Parathyroid carcinoma
- Hemodialysis patients to control hyperparathyroidism

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 Quarles, et al., *J Am Soc Nephrol* 14: 575-583, 2003  
 Lindberg, et al., *Kidney International*, Vol 63 (2003), pp 248-254  
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 Drugs in Res and Dev, 2003, 41(6):349-351

### **Take home points !**

- Family history, medication history.
- Calcium, Intact PTH and Vit D to be measured in the same specimen
- 24 hr urine for calcium to be checked.
- Further diagnostic workup depending upon calcium and intact PTH levels.