Calcium and Bone Disorders
Hyperparathyroidism
Hypoparathyroidism

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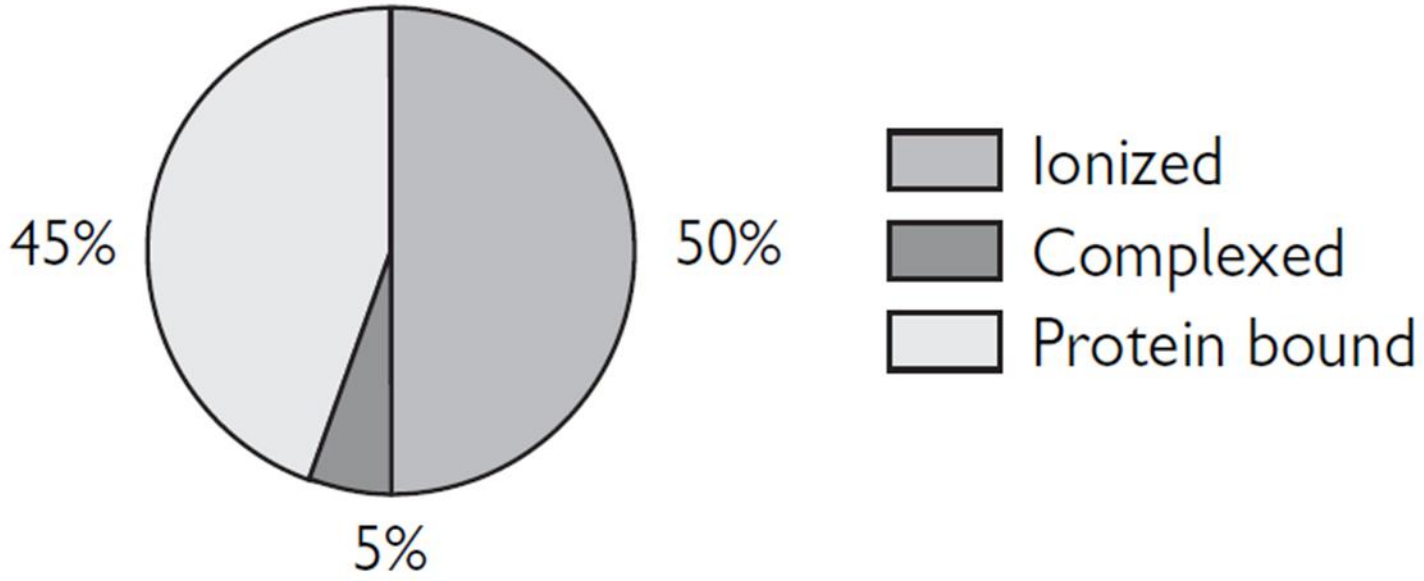
Factors involve in calcium and phosphate hemostasis

- Calcium
- Phosphate
- Albumin
- PTH
- 25-OH-vitamin D
- 1,25-dihydroxycholecalciferol(1,25-dihydroxyvimtain D3).
- Calcitonin
- Bone
- Kidney
- Bowel

Calcium in the circulation

Circulating calcium exists in several forms:

- Ionized—biologically active.
- Complexed to citrate, phosphate, etc.—biologically active.
- Bound to protein, mainly albumin—inactive.



Total Calcium **Normal laboratory values** (adult patients)

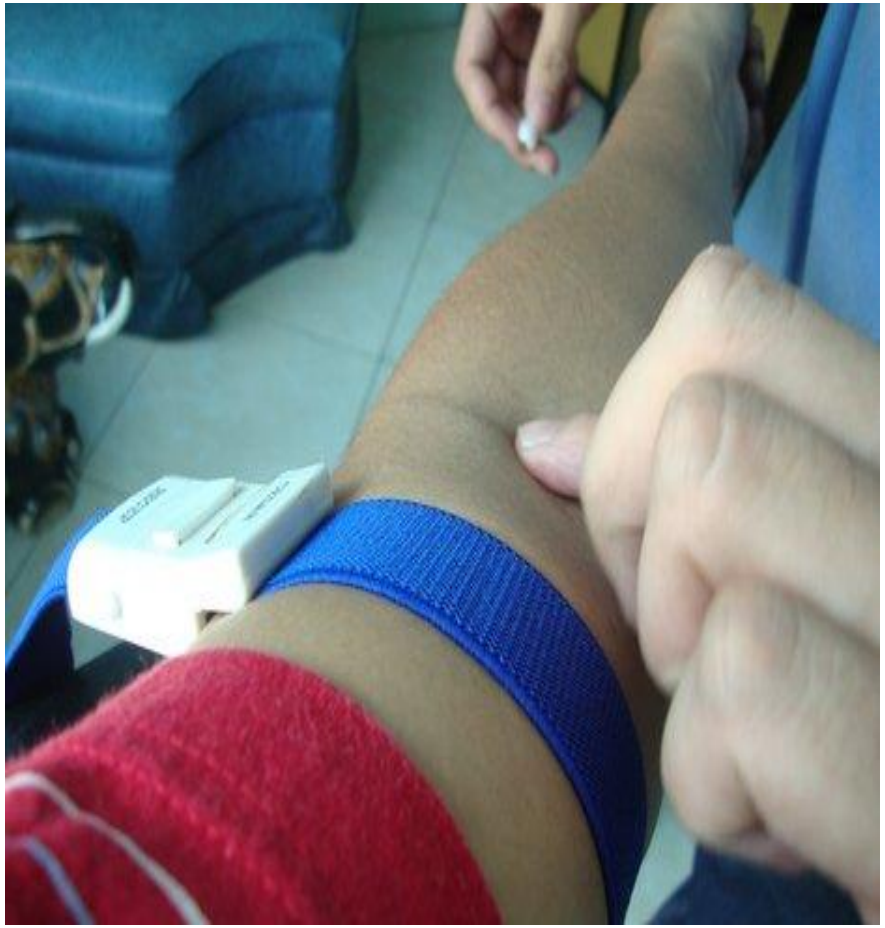
- Calcium is the most abundant mineral in the body; the bones and teeth accounting for about 99% of the total body stores.

- Calcium (Serum): 8.5 - 10.5 mg/dL (2.1 - 2.6 mmol/L)
- Calcium (Ionized) Serum: 4.5 - 5.6 mg/dL (1.1-1.4 mmol/L)
- Convert mmol/L to mg/dL multiply by 4.

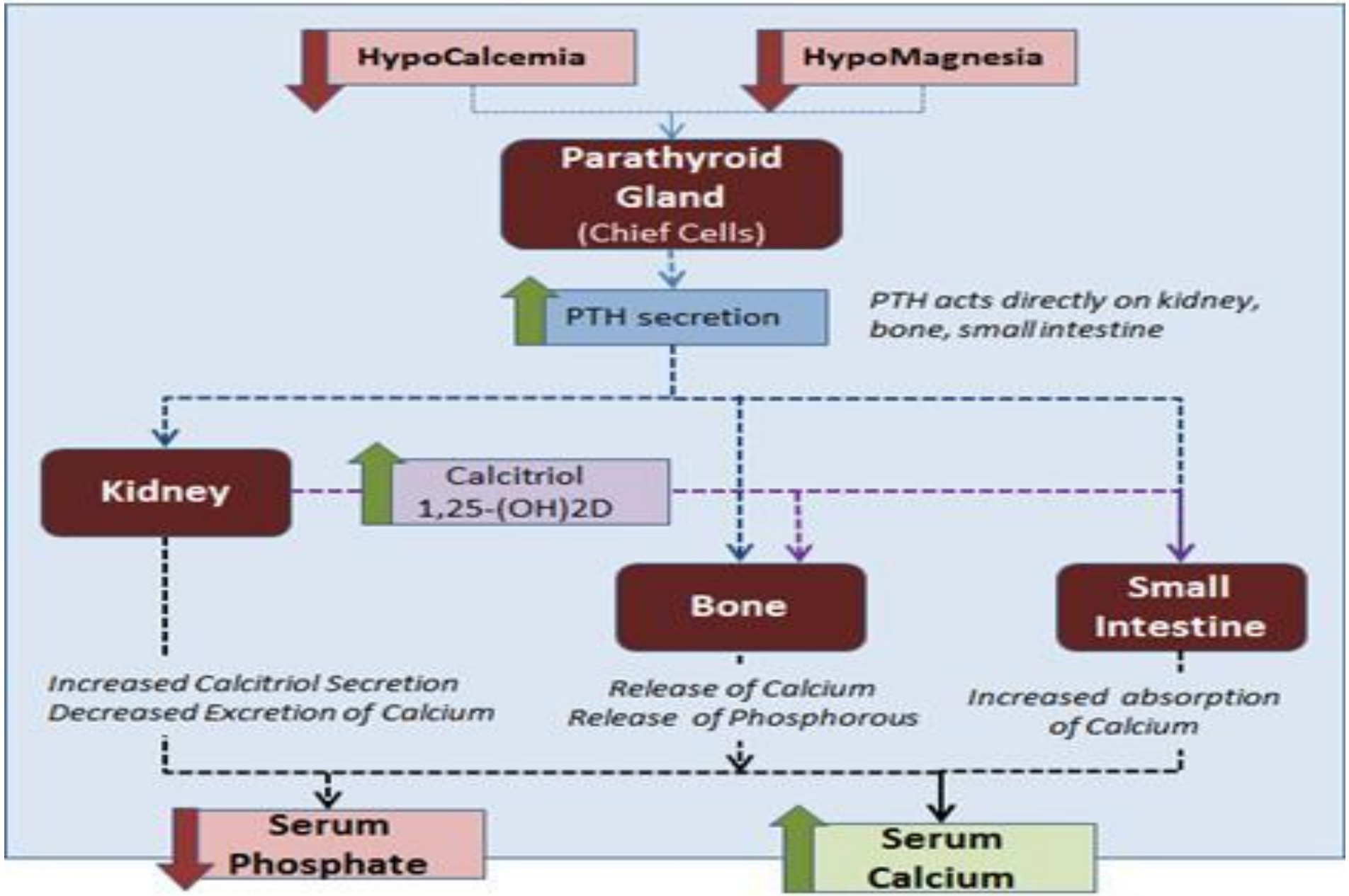
For serum Calcium blood sample should be obtained without applying a tourniquet .

- The blood test should be taken without a tourniquet or if it is difficult to locate a ‘good’ vein remove the tourniquet 30 seconds after the insertion of the needle in the vein but before the blood sample is drawn.

- The reason for this is because prolonged tourniquet pressure while drawing blood can spuriously increase total calcium.



PTH Pathway


HypoCalcemia
HypoMagnesia
Parathyroid Gland (Chief Cells)
PTH secretion
PTH acts directly on kidney, bone, small intestine
Kidney
Calcitriol 1,25-(OH)2D
Bone
Small Intestine
Increased Calcitriol Secretion
Decreased Excretion of Calcium
Release of Calcium
Release of Phosphorous
Increased absorption of Calcium
Serum Phosphate
Serum Calcium

Summary of the Hormones Regulating Ca

	PTH	Vitamin D	Calcitonin
Stimulus for secretion	↓ serum [Ca^{2+}]	↓ serum [Ca^{2+}] ↑ PTH ↓ serum phosphate	↑ serum [Ca^{2+}]
Actions on:			
Bone	↑ resorption	↑ resorption	↓ resorption
Kidney	↓ P reabsorption (↑ urinary cyclic AMP) ↑ Ca^{2+} reabsorption	↑ P reabsorption ↑ Ca^{2+} reabsorption	
Intestine	↑ Ca^{2+} absorption (via vitamin D)	↑ Ca^{2+} absorption (vitamin D-dependent Ca^{2+} -binding protein) ↑ P absorption	
Overall effect on:			
Serum [Ca^{2+}]	↑	↑	↓
Serum [phosphate]	↓	↑	

Actions of PTH

1. PTH increases bone resorption/absorbtion.
2. PTH inhibits renal phosphate reabsorption.
3. PTH increases renal Ca reabsorption in the distal tubule.
4. PTH increases intestinal Ca absorption indirectly by stimulating the production of 1,25-dihydroxycholecalciferol(1,25-dihydroxyvimtain D3).

Classification of parathyroid gland disorders

	Primary	Secondary
Hormone excess	Primary hyperparathyroidism Parathyroid adenoma Parathyroid carcinoma[1] Parathyroid hyperplasia[2] Tertiary hyperparathyroidism Following prolonged secondary hyperparathyroidism	Secondary hyperparathyroidism Chronic kidney disease Malabsorption Vitamin D deficiency
Hormone deficiency	Hypoparathyroidism Post-surgical Autoimmune Inherited	
Hormone hypersensitivity	Autosomal dominant hypercalciuric hypocalcaemic (CASR-activating mutation)	
Hormone resistance	Pseudohypoparathyroidism Familial hypocalciuric hypercalcaemia	
Non-functioning tumours	Parathyroid carcinoma[1]	

[1]Parathyroid carcinomas may or may not produce parathyroid hormone. [2]In multiple endocrine neoplasia (MEN) syndromes (p. 688).
(CASR = calcium-sensing receptor)

Hypercalcemia

With normal or elevated parathyroid hormone (PTH) levels

- Primary or tertiary hyperparathyroidism
- Lithium-induced hyperparathyroidism
- Familial hypocalciuric hypercalcaemia

With low PTH levels

- Malignancy (lung, breast, myeloma, renal, lymphoma, thyroid)
- Elevated 1,25-dihydroxyvitamin D (vitamin D intoxication, sarcoidosis, human immunodeficiency virus, other granulomatous disease)
- Thyrotoxicosis
- Paget's disease with immobilisation
- Milk-alkali syndrome
- Thiazide diuretics
- Glucocorticoid deficiency

Hyperparathyroidism

- Hyperparathyroidism is an endocrine disorder caused by excessive secretion of parathyroid hormone (PTH) from the parathyroid glands.

Primary

Autonomous inappropriate production of PTH resulting in hypercalcemia defines primary hyperparathyroidism.

Secondary

When the parathyroid glands appropriately increase PTH production in response to low calcium states.

Primary hyperparathyroidism

- is characterized by the following:
- ↑ serum [Ca2+]
- ↓ or normal serum [phosphate]
- ↑ urinary phosphate excretion (phosphaturic effect of PTH)
- ↓ urinary Ca2+ excretion (caused by ↑ Ca2+ reabsorption)
- ↑ bone resorption

Epidemiology & demographics

- Incidence: 2 cases/100,000 person-yr
- Prevalence: 1 case/1000 persons
- Women:Men 2:1,
- Peaks 50 to 60 yr.

Physical findings & clinical presentation

- The majority of patients with primary hyperparathyroidism are asymptomatic.

- The development of symptoms varies with severity and rapidity of disease progression and reflects both the hypercalcemic and hyperparathyroid components of the disease process.

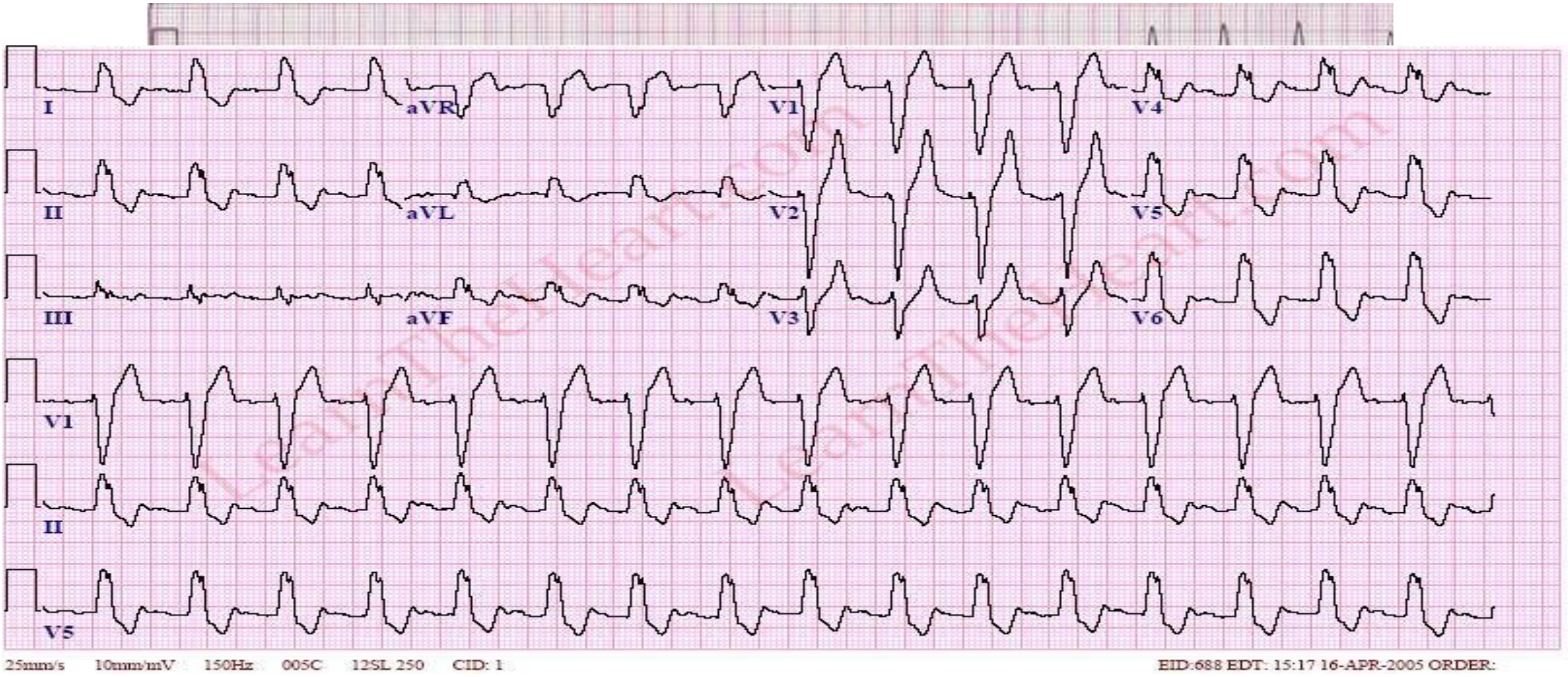
Physical findings & clinical presentation

Cardiovascular: hypertension, shortened QT interval, arrhythmia, valvular calcification

GI: anorexia, nausea, vomiting, constipation, abdominal pain, peptic ulcer disease, pancreatitis

GU: nephrolithiasis, nephrocalcinosis, renal insufficiency, polyuria, nocturia, nephrogenic diabetes insipidus, renal tubular acidosis

shortening of the QT interval (0.33 and 0.44 seconds)



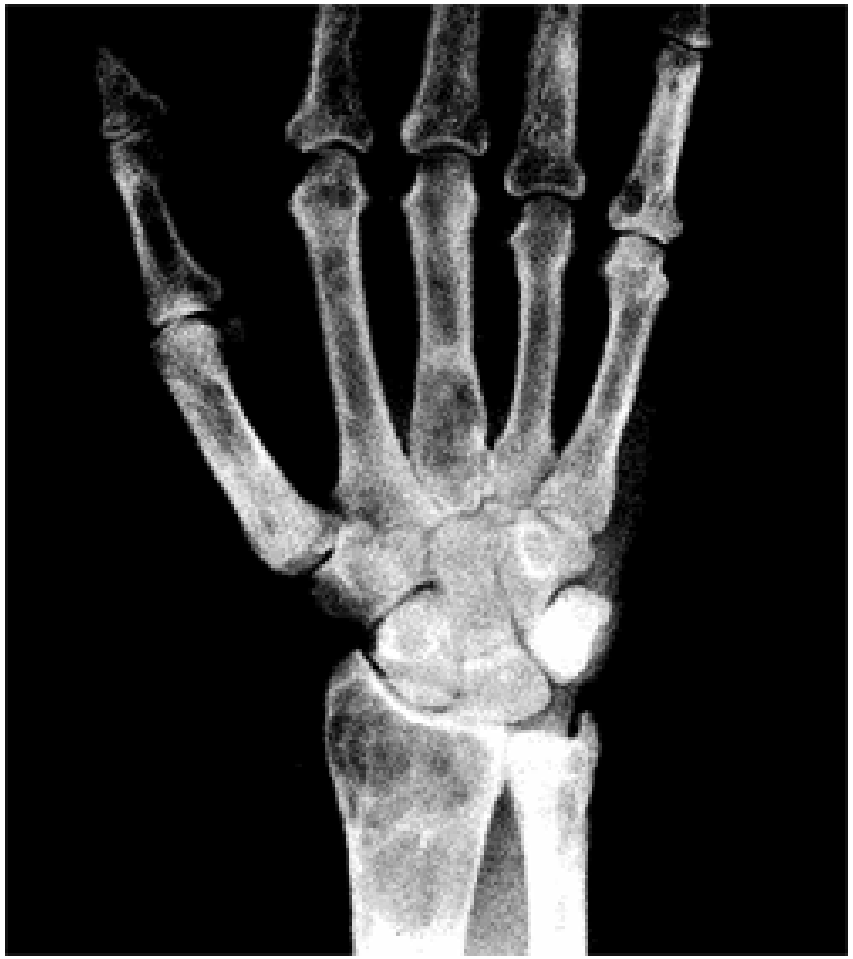
Physical findings & clinical presentation

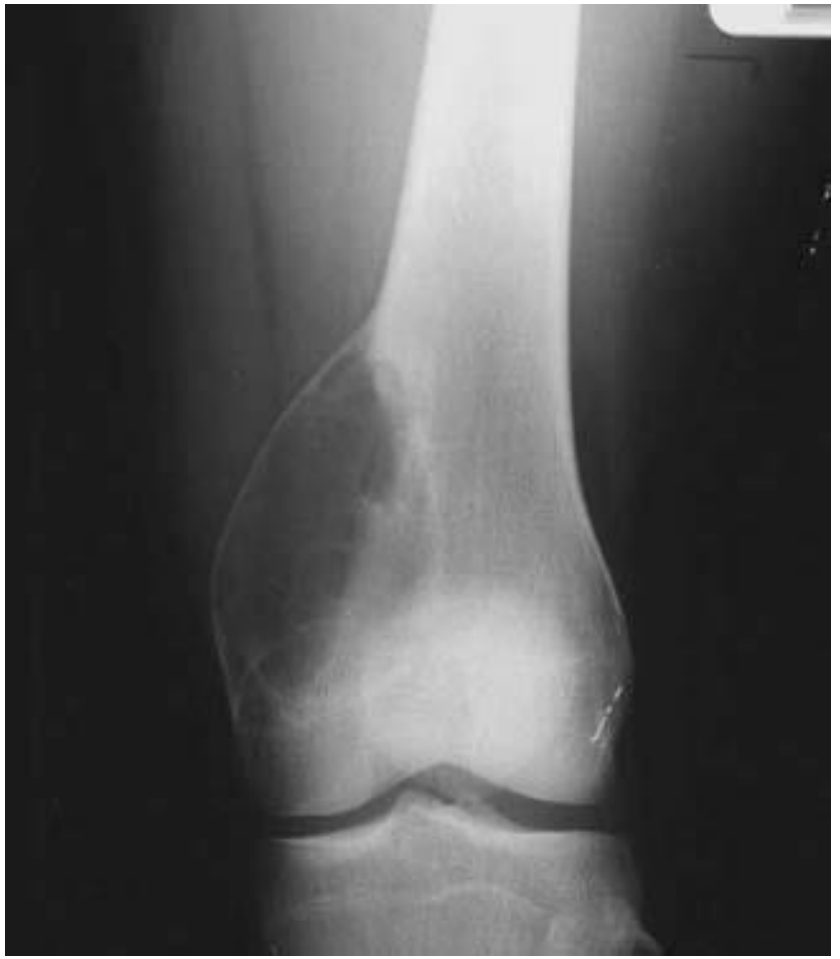
Musculoskeletal: weakness, myopathy, bone pain, osteoporosis, gout, pseudogout, chondrocalcinosis, osteitis fibrosa cystica

CNS: confusion, anxiety, fatigue, obtundation, depression, coma

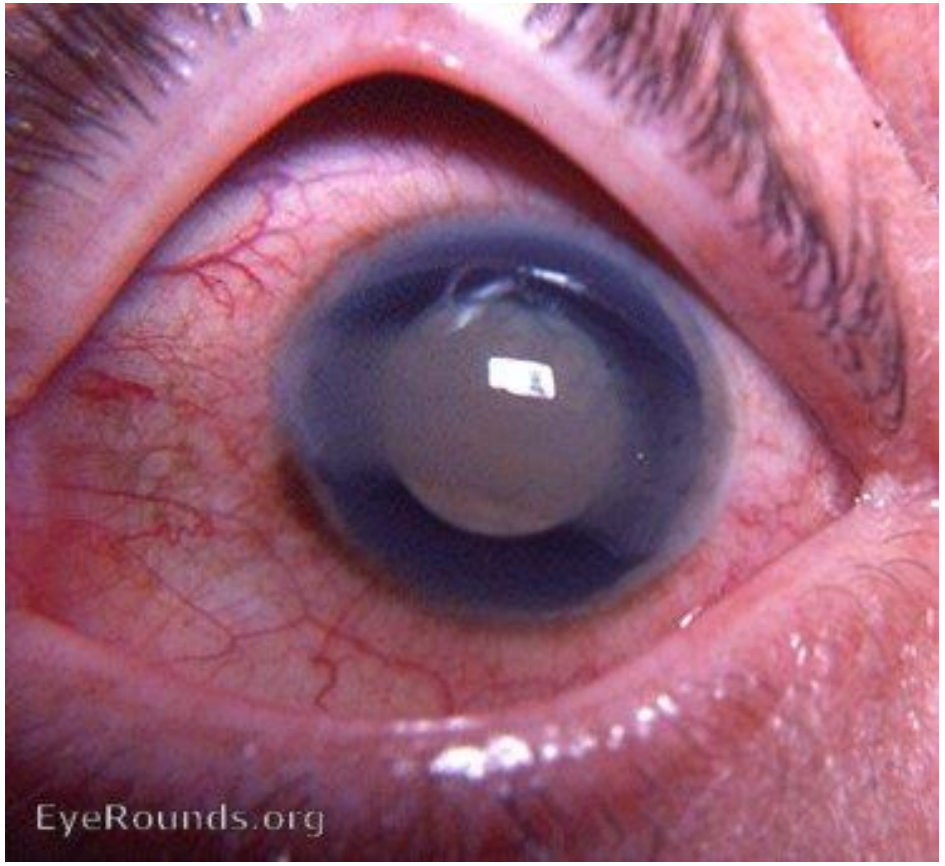
Other: hypomagnesemia, hypophosphatemia, pruritus, metastatic calcifications, band keratopathy.

Osteitis fibrosa cystica





Band keratopathy



Etiology

Pathologic characteristics include

- Adenoma (89%)
- Hyperplasia (10%)
- Carcinomas (1%)
- Inherited as a part of multiple endocrine neoplasia 1 and 2 (MEN 1 or 2), usually as hyperplasia.

Investigations: Laboratory

Primary hyperparathyroidism is confirmed with an elevated serum calcium and PTH level.

Serum Ca	Intact PTH	PO4
24 hr urine Ca	25-OH D	1,25-OH D

Investigations: Laboratory

Serum Ca

Two measurements of serum calcium are required for the confirmation of hypercalcemia.

- Total calcium should be corrected for low albumin utilizing the formula:
- Corrected Calcium = measured total Ca (mg/dL) + 0.8x (4.0 - serum albumin [g/dL]), where 4.0 represents the average albumin level in g/dL.
- In other words, for each 1 g/dL decrease of albumin, 0.8 must be added to the measured Calcium to get a corrected Calcium value.
- If a reliable laboratory is available, an ionized calcium should be considered especially in condition associated with acid-base disturbances or low albumin states.

Investigations: Laboratory

iPTH

Elevated PTH

- PTH is elevated in hyperparathyroidism and decreased in most other conditions associated with elevated calcium.

Ph

- Low or low-normal serum phosphorus

24-hr urine calcium

- Evaluate risk for renal stones and
- To rule out FHH

PTHrp — Parathyroid hormone related peptide

- Rule out other etiologies for hypercalcemia (malignancy)

25-OH D — 25 hydroxy-vitamin D

- Is recommended in all patients with hyperparathyroidism. Vitamin D deficiency can decrease calcium and increase PTH levels. Due to the clinical impact of vitamin D deficiency, normalization is required prior to making any diagnostic and therapeutic decisions.
- Assess hypercalcemia secondary to glaucomatous diseases or lymphomas

1,25-OH D — 1,25 dihydroxy-vitamin D

Investigations: Laboratory

U & C Serum urea and Creatinine

- For chronic renal failure as a secondary cause for hyperparathyrodism
- Complications of primary hyperparathyroidism

Other

- Multiple myeloma and bone secondaries

ECG

Diagnosis

Elevated serum calcium (ionized or corrected calcium)

Low or low-normal serum phosphorus

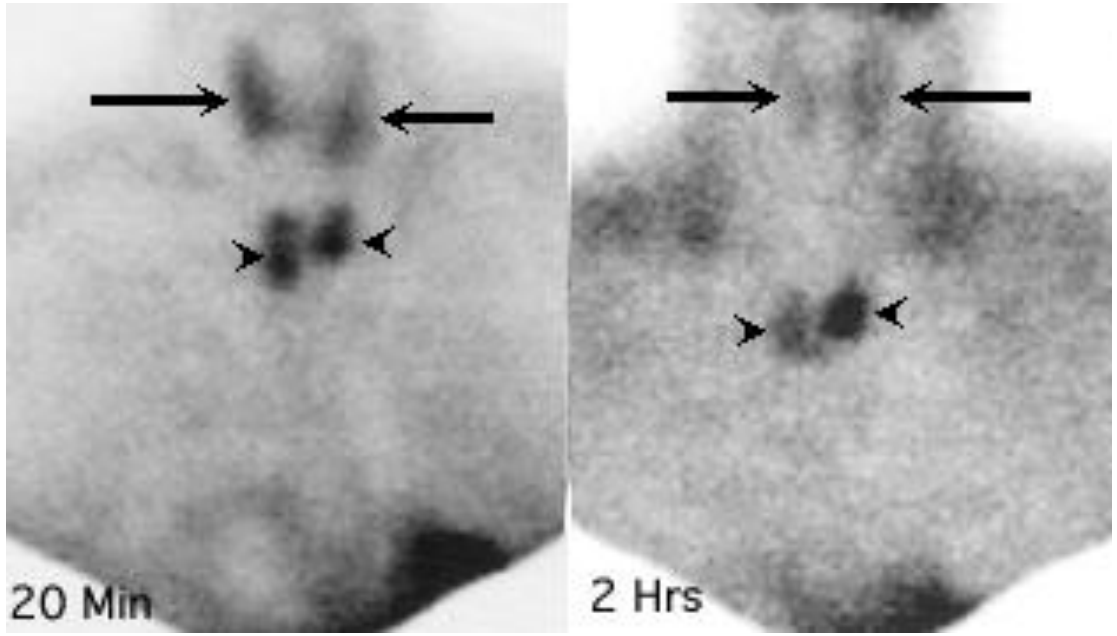
Elevated iPTH

24-hr urine calcium to evaluate risk for renal stones and to rule out FHH.

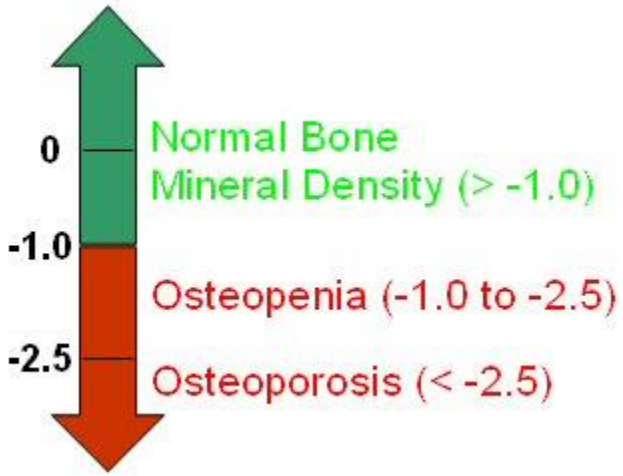
Imaging

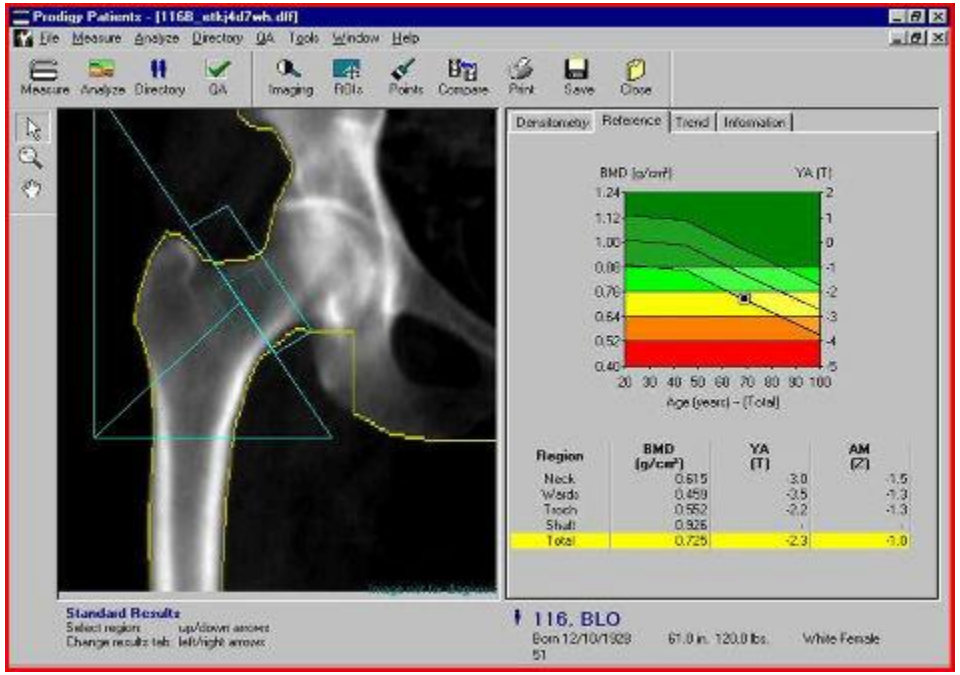
- Parathyroid ultrasound /CT
- Parathyroid localization with technetium99m sestamibi can identify potential adenomas.
- Bone mineral density is recommended for all patients with hyperparathyroidism in order to assess the risk for osteoporosis and fragility fractures.
- Renal ultrasound can be considered to assess asymptomatic renal stones.
- Plain X ray for skeletal lytic lesions

- Parathyroid localization with technetium99m sestamibi can identify potential adenomas.



Bone mineral density of the spine, hip, and forearm is recommended for all patients with Hyperparathyroidism in order to assess the risk for osteoporosis and fragility fractures.





Treatment: surgery

- Surgery is the only definitive treatment for symptomatic primary hyperparathyroidism.
- Indications for parathyroidectomy:

1. All patients younger than 50 yr
2. Hypercalcemia (Ca >1 mg/dl above upper limit normal)
3. Creatinine clearance <60 ml/min
4. Osteoporosis (T-score >2.5 or fragility fracture)
5. Symptomatic hyperparathyroidism such as nephrolithiasis

Medical management

1. Avoid medications that precipitate hypercalcemia (e.g., thiazide or lithium)

2. Since inadequate calcium and vitamin D status stimulates PTH, calcium and vitamin D intake should be the same as for patients without hyperparathyroidism (i.e., 1000 mg of elemental calcium and 600 to 800 IU of vitamin D daily).

3. Encourage physical activity since immobilization increases bone resorption.

4. Recommend adequate hydration (at least 2 L) to minimize the risk of nephrolithiasis.

Pharmacologic therapy

- Include symptomatic hyperparathyroidism or osteopenia associated with an increased fracture risk.
- Not surgical candidate:

Agents that inhibit bone resorption such as bisphosphonates (e.g., alendronate, pamidronate, zoledronate)

Cinacalcet is an oral calcimimetic agent that activates the calcium sensing receptor in the parathyroid gland. It decreases PTH and serum calcium levels.

Acute hypercalcemia treatment

- Severe and/or symptomatic hypercalcemia may require hospitalization especially if serum calcium >12 mg/dl.

Vigorous hydration with IV normal saline (2 to 4 L/day). Fluid status must be monitored in patients with cardiac or renal insufficiency in order to avoid fluid overload.

Bisphosphonates can effectively decrease calcium levels.

Zoledronate (4 mg IV over 15 min). Onset of action after 24 to 48 hr.

Calcitonin (IM/SC every 12 hr) may be used with bisphosphonates to achieve a more rapid reduction of calcium levels. Onset of action is within hours.

Tachyphylaxis ?

Monitoring

- Asymptomatic patients
- Serum creatinine
- Serum Calcium
- Bone mineral density measurements.

Hypocalcemia

	Total serum calcium	Ionised serum calcium	Serum phosphate	Serum PTH
Hypoalbuminaemia	↓	↔	↔	↔
Alkalosis	↔	↓	↔	↔ or ↑
Vitamin D deficiency	↓	↓	↓	↑
Chronic renal failure	↓	↓	↑	↑
Hypoparathyroidism	↓	↓	↑	↓
Pseudohypoparathyroidism	↓	↓	↑	↑
Acute pancreatitis	↓	↓	↔ or ↓	↑
Hypomagnesaemia	↓	↓	Variable	↓ or ↔

Hypoparathyroidism

- A decrease in parathyroid hormone (PTH) secretion or function results in hypoparathyroidism.

Primary

Absence or dysfunction of the parathyroid gland results in inadequate PTH secreation and subsequent hypocalcemia and hyperphosphatemia.

Impaired function of PTH (i.e., **PTH resistance or pseudohypoparathyroidism**) can also cause hypocalcemia and hyperphosphatemia but the measured PTH level is elevated in this circumstance.

Etiology: Primary hypoPTH

- Postoperative hypoparathyroidism is the most common etiology and has an incidence as high as 3.8% in patients undergoing total or near Total thyroidectomy.

- Autoimmune disorders are more common in women (female:male ratio of 1.4:1.0). Autoimmune polyglandular syndrome Typically, patients with this syndrome present in childhood.

- Failure of parathyroid development, e.g. Di George syndrome

- Failure of PTH secretion: Magnesium deficiency, Overactivity of calcium-sensing receptor.

Physical findings & clinical presentation

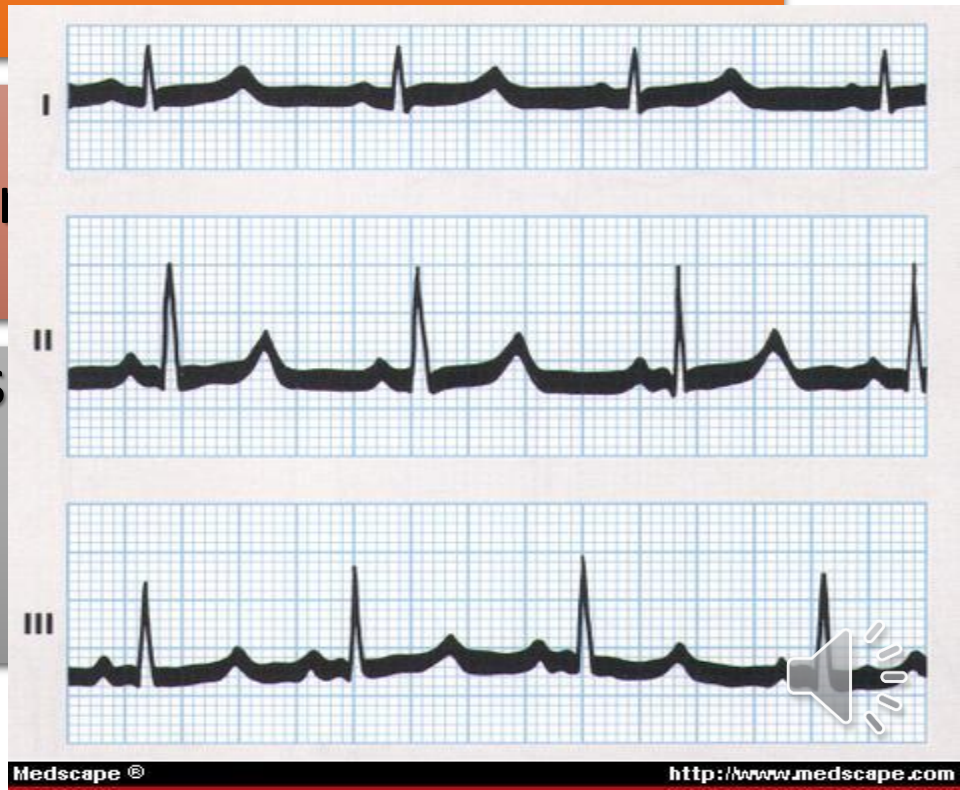
- The symptoms of primary hypoparathyroidism are primarily related to hypocalcemia. The presentation of symptoms varies with the severity and duration of illness.

Physical findings & clinical presentation

Cardiovascular: prolonged QT intervals, QRS and ST segment changes, ventricular Arrhythmias.

Musculoskeletal: muscle cramps, laryngospasm

CNS: tetany (Chvostek's sign and Trousseau's s
paresthesias, visual impairment from cataract
mental status, papilledema, and basal ganglia
longstanding disease.



Eliciting Chvostek's sign

Begin by telling the patient to relax his facial muscles. Then stand directly in front of him, and tap the facial nerve either just anterior to the earlobe and below the zygomatic arch or between the zygomatic arch and the corner of his mouth. A positive response varies from twitching of the lip at the corner of the mouth to spasm of all facial muscles, depending on the severity of hypocalcemia.

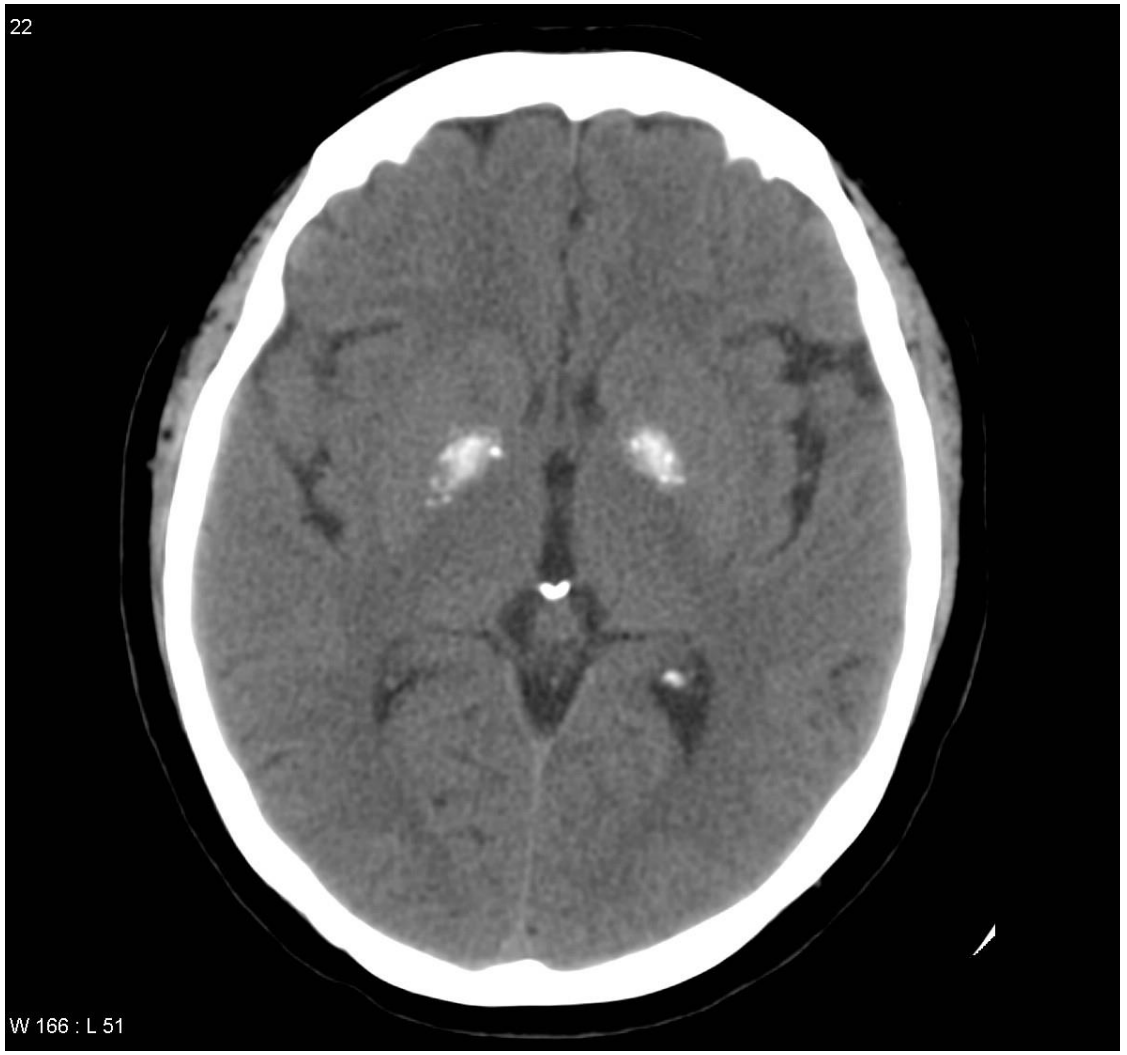
Trousseau's sign

EXAMINATION TIP

Recognizing carpopedal spasm

In the hand, carpopedal spasm involves adduction of the thumb over the palm, followed by flexion of the metacarpophalangeal joints, extension of the interphalangeal joints (fingers together), adduction of the hyperextended fingers, and flexion of the wrist and elbow joints. Similar effects occur in the joints of the feet.

Basal ganglia calcifications



Physical findings & clinical presentation

GI: abdominal pain

Renal: hypercalciuria and nephrolithiasis

Other: dry scaly skin, brittle nails, dry hair

Differential diagnosis(Low PTH + high calcium)

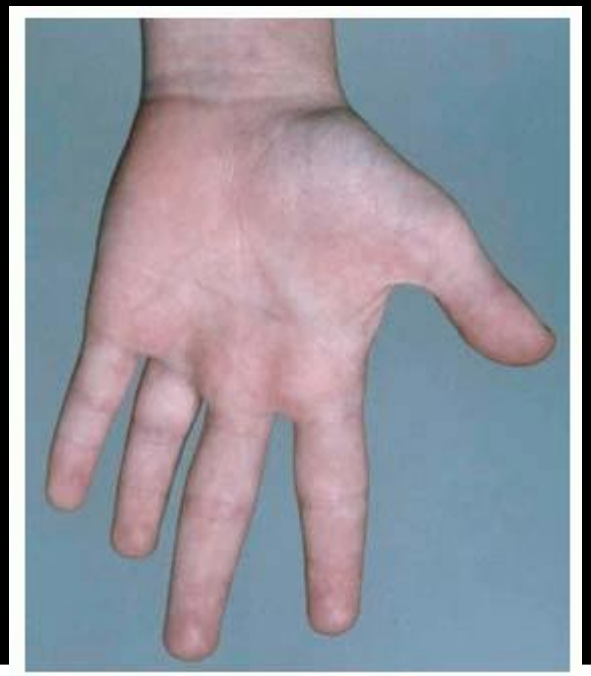
?

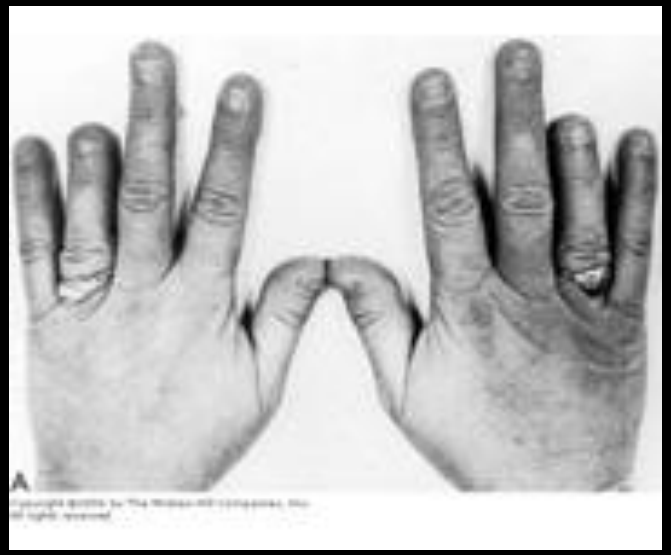
High PTH +Low calcium

- Pseudohypoparathyroidism (PTH resistance) hyperphosphatemia and elevated PTH levels.
- Secondary hyperparathyroidism
- Hypomagnesemia (The PTH will be low)

Pseudohypoparathyroidism

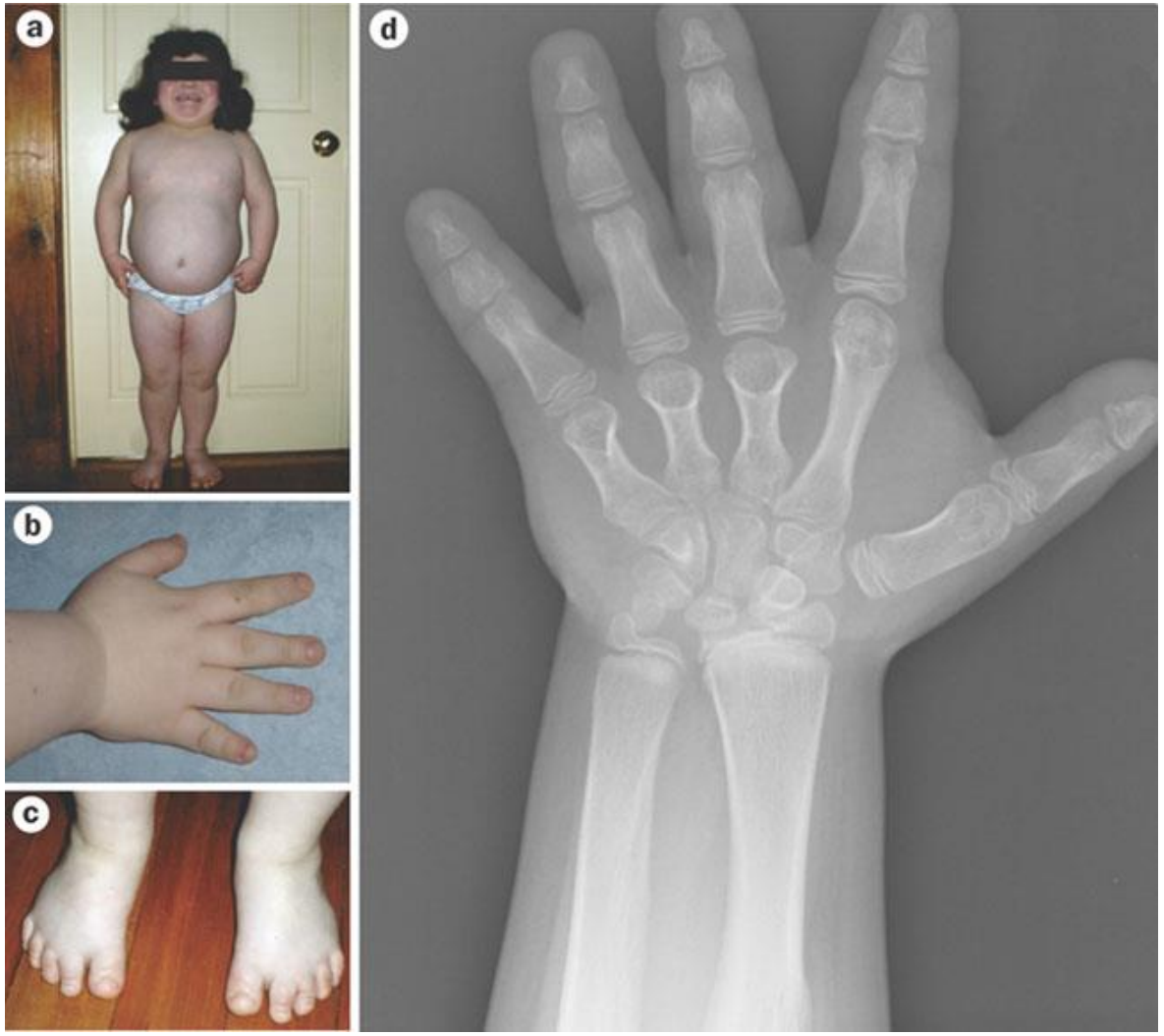
- including short fourth and fifth metacarpals and a rounded facies. Most patients have associated mental retardation and obesity





- They are associated with hypocalcemia, hyperphosphatemia, and increased circulating PTH.

- Target tissue unresponsiveness to the hormone manifests as a lack of increased phosphate and, in some cases, cAMP excretion in response to PTH administration



Laboratory investigations

Serum Ca

Two measurements of serum calcium are required for the confirmation of hypocalcemia.

- Total calcium will be low in primary and pseudo hypoparathyroidism
- Correct Calcium with albumin.

Laboratory investigations

iPTH

Low PTH

- PTH is low in primary and secondary hypoparathyroidism, high in PTH resistance states like pseudohypoparathyroidism.

PO4

- high-normal or high in primary and pseudo hypoparathyroidism

Mg

Low Mg

- Both hypomagnesemia and hypermagnesemia can cause Hypoparathyroidism.

Laboratory investigations

24 hr urine Ca high

- To evaluate the risk for renal stones

ECG

Others

- 25-OH D, 1,25-OH D, creatinine, and amylase
- According to DDx

Diagnosis of primary hypoparathyroidism

Low serum calcium (ionized or corrected calcium)

High or High-normal serum phosphorus

Low iPTH

Medical management

- Calcium and vitamin D supplementation.
- The aim should be to obtain low-normal serum calcium, 24-hr urinary calcium ,300 mg/day, and a calcium-phosphorus product <55.

1,25(OH) Vitamin D3 (calcitriol) 0.25 to 0.5 mg twice daily

Calcium carbonate or calcium citrates

Thiazide diuretics

(urine calcium >250 mg/day)

Acute hypocalcemia treatment

- Severe and/or symptomatic hypocalcemia requires hospitalization. Acute management of hypocalcemia includes:

IV infusion of calcium gluconate 10 ml of 10% solution to receive a bolus of 90 mg of elemental calcium followed by an infusion of 0.5 to 2 mg/kg/hr .

	Primary hyperPTH	Secondary hyperPTH	Primary hypoPTH	Pseudo hypoPTH	Secondary hypoPTH	FHH
Calcium	H	N\L	L	L	H	H
Phosphorus	L\LN	L\N\H*	H\HN	H\HN	Variabe	L\LN
iPTH	H	H	L	H	L	H
24-Hr urine Ca	H	L	Variable\H on Ca Rx	Variable\H on Ca Rx	H	L
PTHrP	L	L	L	L	H (malignant causes)	L