

Wednesday, October 20, 2021

3:45 p.m. to 4:30 p.m.

Tennessee Academy of Family Physicians
72nd Annual Scientific Assembly
The Park Vista Doubletree Hotel, Gatlinburg, Tennessee
October 19-22, 2021

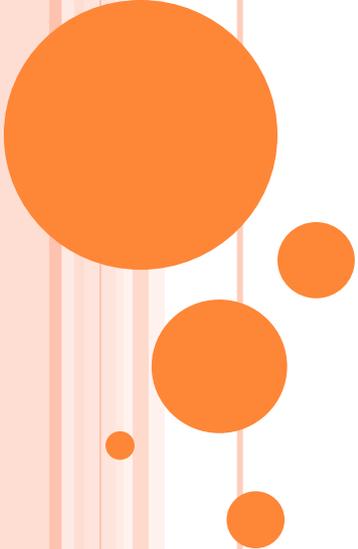
“Calcium Disorders”

AMIT C. VORA, M.D., FACE

Presentation Objectives:

- 1) Diagnostic approach and treatment of hypocalcemia.
- 2) Diagnostic approach and treatment of hypercalcemia both PTH mediated and non-PTH mediated.

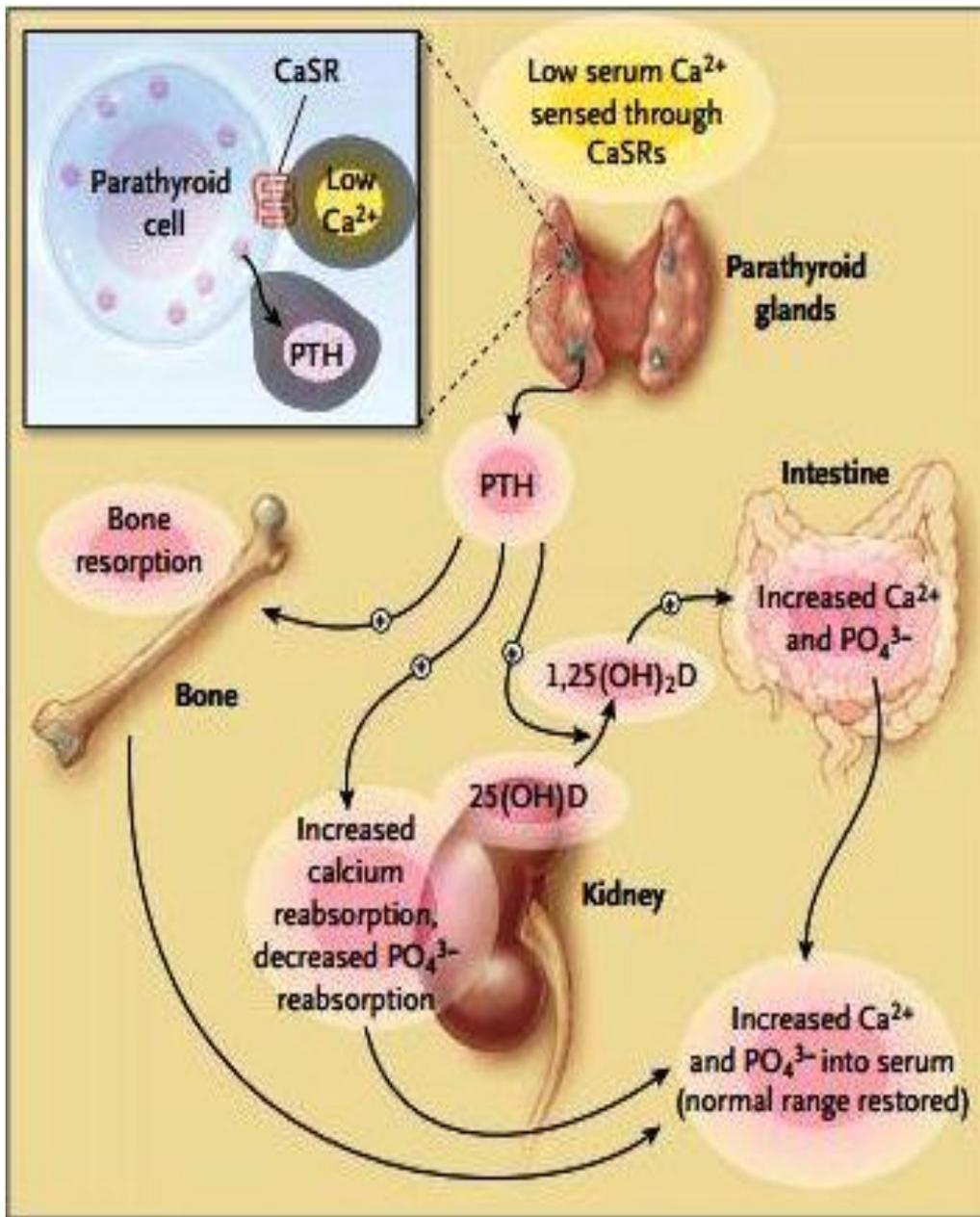




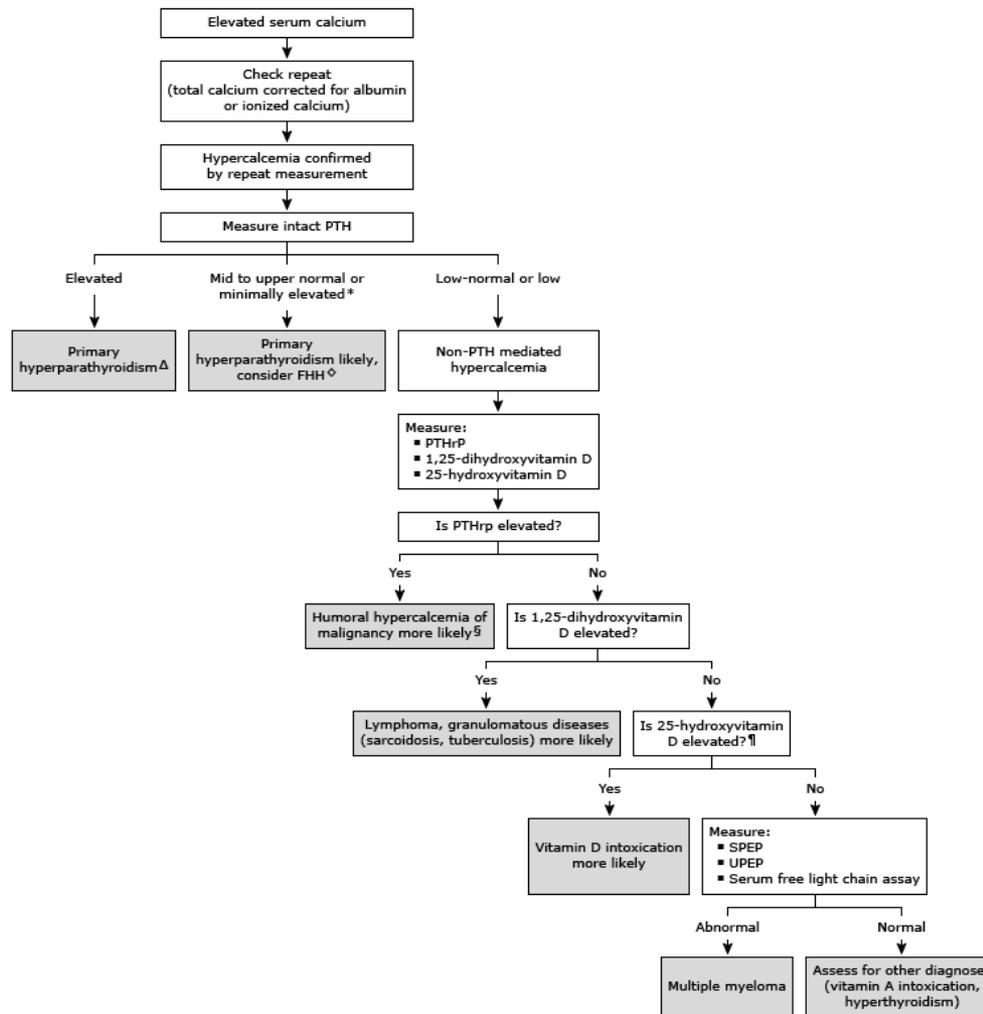
DISORDERS OF CALCIUM METABOLISM

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Diagnostic approach to hypercalcemia



PTH: parathyroid hormone; FHH: familial hypocalciuric hypercalcemia; PTHrP: parathyroid hormone-related peptide; SPEP: serum protein electrophoresis; UPEP: urine protein electrophoresis.

* Serum PTH typically ranging from 35 to 65 pg/mL in an assay whose normal range is 10 to 60 pg/mL.

¶ Serum 25-hydroxyvitamin D must be markedly elevated before hypercalcemia develops. Although the serum concentration of 25-hydroxyvitamin D at which hypercalcemia typically occurs is undefined, many experts define vitamin D intoxication as a value >150 ng/mL (374 nmol/L).

Δ Refer to UpToDate content on primary hyperparathyroidism.

† Refer to UpToDate content on primary hyperparathyroidism and familial hypocalciuric hypercalcemia for details.

§ Additional work-up is warranted to identify malignancy.

- A 67-year-old female is evaluated for a recent finding of an incidental elevated serum calcium level detected on laboratory testing. In hindsight, she has had some nausea and heartburn and her spouse has noticed some irritability and anxiety. Medical history is significant only for hypertension, and her only medication is ramipril.
- On physical examination, temperature is 35.8 °C (96.4 °F), blood pressure is 120/68 mm Hg, pulse rate is 62/min, and respiration rate is 14/min. BMI is 32. The remainder of her examination is unremarkable.
- Laboratory studies: Ca 11.3 (8.4-10.2 mg/dl), Intact PTH 130 (nl<72). 25 Vit D=18



SIGNS/SYMPTOMS OF HYPERCALCEMIA

- Neuro - Usually asymptomatic when calcium <12 mg/dl. Anxiety, depression, dementia
- GI – nausea, anorexia, constipation, PUD
- Renal – nephrolithiasis, nephrocalcinosis
- MS – muscle weakness, bone pain, osteoporosis
- CV – arrhythmia if severe hypercalcemia; calcification, cardiomyopathy



DIFFERENTIAL DX OF HYPERCALCEMIA

- PTH mediated
 - Primary hyperparathyroidism
 - Familial – MEN 1 and 2
 - Includes FHH (familial hypocalciuric hypercalcemia)
 - Genetic defect of calcium-sensing receptor at parathyroid level. Usually normal PTH; if elevated r/o coincident Vit D deficiency. (Urine calcium usually <100; low fractional excretion of calcium)
 - Tertiary (renal failure)



DIFFERENTIAL DX OF HYPERCALCEMIA

- Non-PTH mediated
 - Malignancy
 - Osteolytic
 - Myeloma/lymphoma/leukemia
 - PTHrp-related
 - Medications
 - Thiazides
 - Vit D and Vit A
 - Lithium
 - Theophylline



DIFFERENTIAL (CON'T)

- Non-PTH mediated continued
 - Endocrine
 - Hyperthyroid
 - Adrenal insufficiency
 - Pheochromocytoma
 - Acromegaly
 - Miscellaneous
 - Immobilization
 - Milk-Alkali syndrome
 - Parenteral nutrition



- A 67-year-old female with Ca 11.3, PTH 130 (nl<72). 25 Vit D=18
- GI upset, some anxiety for past 1 yr
- Repeat labs: Ca 11.4 (8.4-10.2), alb 4.3, PO4 3.5, PTH 109, Vit D 28 (after Rx)
- Sestamibi parathyroid scan positive left inferior (When to order? Best localizing study?)
- US-Probable 7 mm left inferior gland enlargement



ASYMPTOMATIC PRIMARY HYPERPARATHYROIDISM (2014 GUIDELINES)

- Consider surgery for:
 - Age < 50
 - Serum calcium > 1 mg/dl over upper normal
 - DEXA T-score <2.5 at any site, or vertebral fracture by imaging study
 - Reduced GFR (<60)
 - 24 hr urine calcium > 400 mg; increased stone risk by stone risk analysis
 - Nephrolithiasis or nephrocalcinosis on imaging



MONITORING ASYMPTOMATIC HYPERPARATHYROIDISM

- Annual serum calcium, creatinine and GFR
- DEXA every 1-2 years
- Maintain 25 Vit D above 20-30 ng/ml
- Bisphosphonates may treat/prevent bone loss
- Surgery if meet indications during followup
- Consider cinacalcet in limited situations



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- Sestamibi parathyroid scan positive left inferior.
- US- Probable 7 mm left inferior gland enlargement
- Surgical resection leads to mom being back and less anxiety and irritability.
- DEXA had shown a T score of -2.8 Hip, -3.3 Distal forearm and we decided to resume calcium and Vit D and start IV bisphosphonate for a few years



HYPERCALCEMIA

- 79 yo WM with nephrolithiasis x 3 episodes in 5 years. Dementia.
- Ca 10.6 (8.4 – 10.2), PTH 100 (<72), normal albumin, creat.
- Low BMD, -2.9 at Hip and -3.3 distal forearm
- 24 hour urine calcium 350 mg.
- Patient/Family wishes to avoid surgery
- Rx-
- Bisphosphonates over Cinacalcet for BMD, ?HCTZ (with careful monitoring of Ca)
- (Cinacalcet over Bisphosphonates for severe hypercalcemia)



- A 76-y/o woman is evaluated for hypercalcemia that was incidentally discovered on routine blood testing. She has no symptoms. Medical history is unremarkable. Her only medication is calcium carbonate taken as needed for occasional heartburn.
- Unremarkable physical examination.
- Laboratory studies: GFR over 60
- Calcium 10.6 mg/dL
- Phosphorus 3.1 mg/dL
- Parathyroid hormone 72 pg/mL (14–72)
- 25-hydroxy vitamin D normal at 35
- 24-hour urine calcium 240 mg/ 24 hr
- KUB- negative for stones and DEXA shows T score of -1.7 at the distal forearm and -1.4 at the lumbar spine.

Which of the following is the most appropriate management?

- A. Parathyroid sestamibi scan
- B. Reevaluate in 6 months
- C. Start alendronate
- D. Start cinacalcet



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HYPERCALCEMIA

- A 65-year-old woman is evaluated in the emergency department for a 2-month history of fatigue, anorexia, thirst, polydipsia, and polyuria. Squamous cell lung cancer was diagnosed 6 months ago; the patient has declined surgery and chemotherapy. She takes no medications.
- On physical examination, temperature is 37.5 °C (99.5 °F), blood pressure is 90/60 mm Hg, pulse rate is 118/min, respiration rate is 22/min, and BMI is 18. The patient appears cachectic. The remaining general physical examination findings are normal.
- Laboratory studies: Blood urea nitrogen-70 mg/dL
- Calcium 13.5 mg/dL
- Creatinine 1.8 mg/dL
- Parathyroid hormone Undetectable
- Aggressive volume replacement with intravenous normal saline is initiated.
- Which of the following drugs is likely to provide the most sustained benefit in decreasing this patient's calcium level?
 - A. Calcitonin
 - B. Cinacalcet
 - C. Prednisone
 - D. Zoledronate



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- A 32-year-old man is evaluated for increasing shortness of breath, fatigue, anorexia, and polyuria. He has a history of hypertension. His only medication is lisinopril.
- On physical examination, temperature is normal, BP is 120/80 mm Hg, HR is 98/min, RR is 22/min, and BMI is 30. Lungs are clear to auscultation.
- Laboratory studies: Calcium-12.0 mg/dL, Phosphorus-4.4 mg/dL, PTH- Undetectable. 1,25-Dihydroxy vitamin D-Elevated, 25-Hydroxy vitamin D-Low

What next test do you want and what's the diagnosis?

- PTH RP
- SPEP and UPEP
- Chest x-ray
- 24-hour urinary calcium



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- A chest radiograph shows bilateral hilar lymphadenopathy with prominent interstitial markings. Mediastinal biopsy shows granulomas consistent with sarcoidosis.

- Which of the following is the best initial treatment for this patient?
 - A. Calcitonin
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 - C. Plicamycin
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HYPERCALCEMIA MANAGMENT

- Malignancy is the most common cause of **non-parathyroid hormone (PTH)–mediated hypercalcemia** and the most frequent cause of hypercalcemia in hospitalized patients. (most common outpatient cause of hypercalcemia is PTH)
- 2 forms: local osteolytic hypercalcemia (classic associated tumor is multiple myeloma) and humoral hypercalcemia of malignancy (squamous cell carcinomas, such as those of the lung [as in this patient], esophagus, or head and neck)
- Humoral hypercalcemia of malignancy results from the systemic effect of a circulating factor produced by neoplastic cells. The hormone most commonly responsible for this syndrome is PTH-related protein (PTHrP).



HYPERCALCEMIA MANAGMENT

- Bisphosphonates powerfully inhibit osteoclast-mediated bone resorption. They very effectively lower the serum calcium level, with their maximum effect seen in 2 to 4 days. Their duration of effect is usually several weeks and varies between patients and between types of bisphosphonate. Zoledronate appears to have the longest-lasting effect (1-1.5 months) and a faster onset of action than other bisphosphonates; it is approved for use in patients with hypercalcemia of malignancy by the U.S. Food and Drug Administration.
- Because of the lag in the onset of effect, bisphosphonates should be combined with faster-acting therapeutic modalities, such as aggressive volume replacement with normal saline infusion and possibly calcitonin injections. However, calcitonin has a short-lived effect on hypercalcemia because of tachyphylaxis and therefore should only be used as an interim step.
- Cinacalcet is a calcimimetic agent that occupies the calcium sensing receptor and lowers serum calcium levels in patients with primary and tertiary hyperparathyroidism associated with chronic kidney disease. It is not effective and not approved for use in malignancy-associated hypercalcemia.
- Increased calcitriol production associated with activated macrophages (granulomatous diseases and lymphomas) can be diminished by using corticosteroids. However, prednisone does not lower PTHrP levels and therefore is not useful in humoral hypercalcemia of malignancy.



HYPOCALCEMIA

- A 52-year-old man is evaluated in the surgical intensive care unit for carpopedal spasm and tetany. He underwent a thyroidectomy and a modified radical neck dissection for follicular thyroid cancer 2 days ago and was extubated this morning. The patient reports perioral and fingertip paresthesias.
- On physical examination, vital signs are normal. A thyroidectomy scar and carpopedal spasms are noted. A Chvostek sign is elicited.
- Laboratory studies: Albumin-4.5 g/dL (45 g/L)
- Calcium-6.9 mg/dL (1.7 mmol/L)
- Phosphorus -3.9 mg/dL (1.3 mmol/L)
- Which of the following is the most appropriate acute treatment for this patient?
 - A. Intravenous calcitriol
 - B. Intravenous calcium gluconate (10%, 10 ml over 10 mins)
 - C. Oral calcium
 - D. Oral calcium and vitamin D



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HYPOCALCEMIA

- 60 y/o male physician with Ca 8.4 (8.4-10.2 mg/dl), PTH elevated at 100 pg/ml (14-72) , 25 Vit D 10. Normal renal function.
- No stones, normal renal function, vitiligo and h/o squamous cell skin cancer. H/o Gastric bypass Sx, no symptoms except for some aches and pains.

What are the causes of mild hypercalcemia and hyperparathyroidism? What treatment?

- Hypomagnesemia
- Vitamin D deficiency
- Hyperphosphatemia
- Decreased dietary calcium intake



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HYPOCALCEMIA

- 70 y/o female with Ca 8.0 (8.4-10.2 mg/dl), PTH elevated at 90 pg/ml (14-72) , 25 Vit D 20. Normal renal function.
- No stones, normal renal function, h/o osteoporosis getting IV risedronate once a year. Last infusion was a week ago and except for some flulike illness for 2 days, no major problems.

What are the causes of mild hypercalcemia and hyperparathyroidism? What treatment?

- Hypomagnesemia
- Vitamin D deficiency
- Risedronate
- Low calcium intake



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HYPOCALCEMIA

- 90 y/o female with history of postsurgical hypoparathyroidism has repeated hospitalizations for hypo and hypercalcemia and has chronic diarrhea.
- Labs: Ca 8.4 (8.9-10.5), alb 3.8, creat 1.6, PTH undetectable
- On Rocaltrol 0.25 once a day with calcium citrate 200 mg, 3 times a day

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What are the causes of mild hypercalcemia and hyperparathyroidism? What treatment?

- **Hypomagnesemia (which can cause PTH resistance and low PTH)**
- Vitamin D deficiency
- Risedronate
- Low calcium intake
- **Rx 300 BID/TID Magnesium and careful periodic lab monitoring to avoid ER/ Hospital visits**



HYPOCALCEMIA

- A 55-year-old woman is evaluated in the surgical recovery room for tetany. Two hours ago, she had a single large parathyroid adenoma removed. Preoperative skeletal radiographs showed subperiosteal bone resorption of the distal phalanges, femoral and spinal osteopenia, and osteoporosis in the radius.
- She is treated with intravenous calcium and improves.
- Laboratory studies (before calcium therapy):
- Albumin- 4.2 g/dL (42 g/L)
- Calcium- 6.0 mg/dL (1.5 mmol/L)
- Phosphorus-1.8 mg/dL (0.58 mmol/L)
- Parathyroid hormone-20 pg/mL (20 ng/L)
- Which of the following is the most likely diagnosis?
 - A. Hungry bone syndrome
 - B. Osteomalacia
 - C. Permanent hypoparathyroidism
 - D. Vitamin D deficiency



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Major causes of hypocalcemia

Low PTH (hypoparathyroidism)
Genetic disorders
Abnormal parathyroid gland development
Abnormal PTH synthesis
Activating mutations of calcium-sensing receptor (autosomal dominant hypocalcemia or sporadic isolated hypoparathyroidism)
Post-surgical (thyroidectomy, parathyroidectomy, radical neck dissection)
Autoimmune
Autoimmune polyglandular syndrome (associated with chronic mucocutaneous candidiasis and primary adrenal insufficiency)
Isolated hypoparathyroidism due to activating antibodies to calcium-sensing receptor
Infiltration of the parathyroid gland (granulomatous, iron overload, metastases)
Radiation-induced destruction parathyroid glands
Hungry bone syndrome (post parathyroidectomy)
HIV infection
High PTH (secondary hyperparathyroidism in response to hypocalcemia)
Vitamin D deficiency or resistance
Multiple causes
Parathyroid hormone resistance
Pseudohypoparathyroidism
Hypomagnesemia
Renal disease
Loss of calcium from the circulation
Hyperphosphatemia
Tumor lysis
Acute pancreatitis
Osteoblastic metastases
Acute respiratory alkalosis
Sepsis or acute severe illness
Drugs
Inhibitors of bone resorption (bisphosphonates, calcitonin, denosumab), especially in vitamin D deficiency
Cinacalcet
Calcium chelators (EDTA, citrate, phosphate)
Foscarnet (due to intravascular complexing with calcium)
Phenytoin (due to conversion of vitamin D to inactive metabolites)
Fluoride poisoning
Disorders of magnesium metabolism
Hypomagnesemia can reduce PTH secretion or cause PTH resistance and is therefore associated with normal, low, or high PTH levels

Data from: Thakker RV. Hypocalcemia: Pathogenesis, differential diagnosis, and management. In: Primer on the metabolic bone diseases and disorders of mineral metabolism, sixth edition, American Society of Bone and Mineral Research 2006; 35:213.



Treatment of hypoparathyroidism

Treatment	Dosage
Calcium	1.0-1.5 g elemental daily (total diet + supplement) in divided doses Adjust dose as needed to control symptoms and maintain low-normal serum calcium concentration
Vitamin D	
Calcitriol	0.5-1.0 micrograms daily (in divided doses)
Alfacalcidol	0.5-2.0 micrograms daily (in divided doses)
Ergocalciferol (D2)	25,000-100,000 International Units daily
Cholecalciferol (D3)	
Dihydroxycholesterol	0.2-1.2 mg daily
Thiazide diuretics (if required to control hypercalciuria)	25-100 mg daily

Data from: Goltzman, D, Cole, DEC. Hypoparathyroidism. In *Primer on the Metabolic Bone Diseases and Disorders of Mineral Metabolism*, American Society of Bone and Mineral Research 2006; 6:216.



Treatment of chronic hypoparathyroidism

1. Calcium and calcitriol
2. Maintain low normal calcium (8.0-8.5/9.0)
3. IF fluctuating/difficult consider recombinant human Parathyroid Hormone 1-84: (Natpara) (daily SQ, \$\$)



CREDITS/ACKNOWLEDGMENT/RESOURCES

- Goltzman, David. Diagnostic approach, causes and treatment of hypocalcemia. In: UpToDate, Post, TW (Ed), UpToDate, Waltham, MA, 2021.
- Elizabeth Shane, MD, Shonni J Silverberg, MD, Ghada El-Hajj Fuleihan, MD, MPH. Hypercalcemia and Hyperparathyroidism. In: UpToDate, Post, TW (Ed), UpToDate, Waltham, MA, 2021.
- Years of doing resident lectures on this topic by me and my colleague Daniel K. McCammon, M.D.

