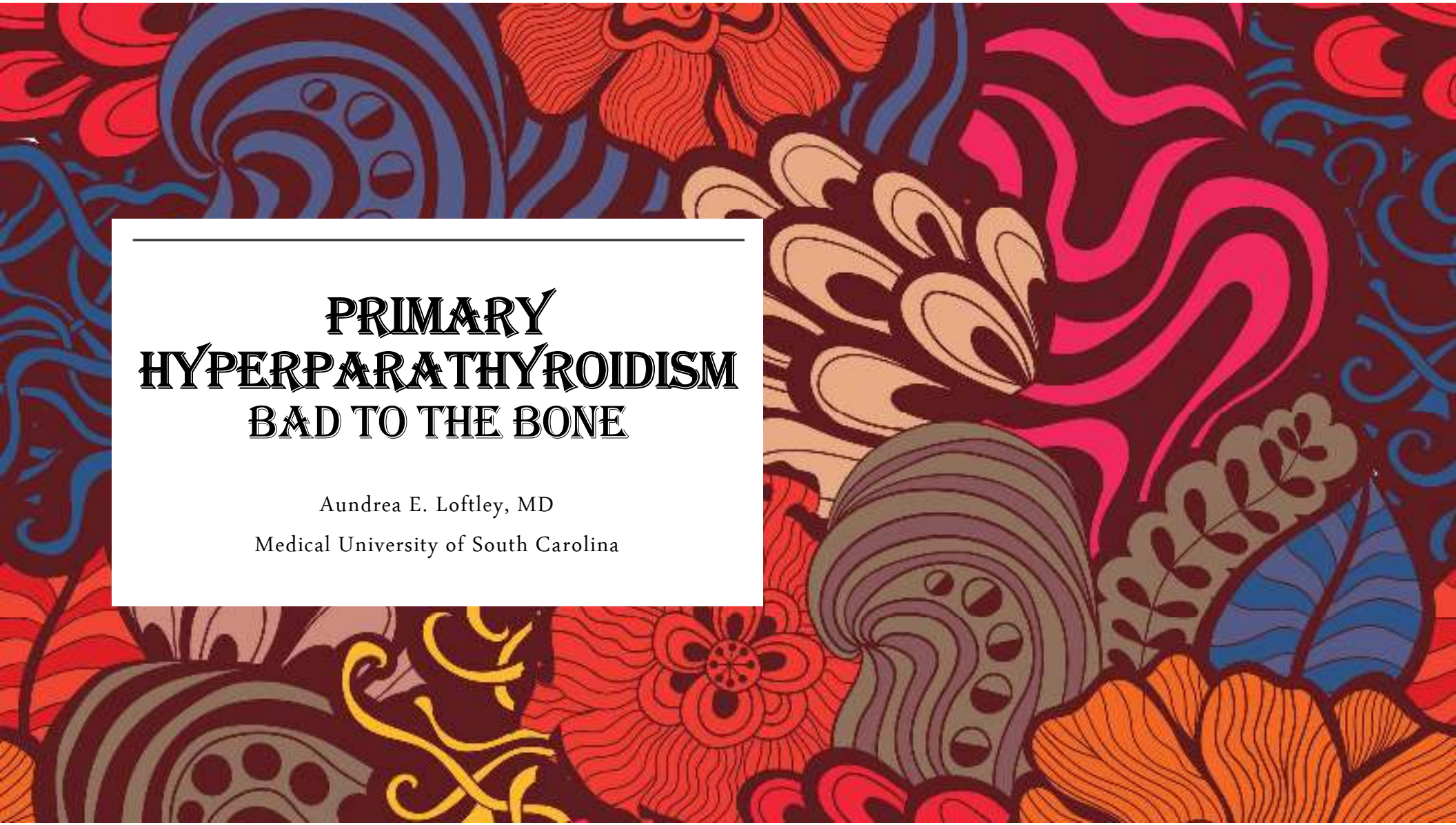

PRIMARY HYPERPARATHYROIDISM
BAD TO THE BONE

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Medical University of South Carolina

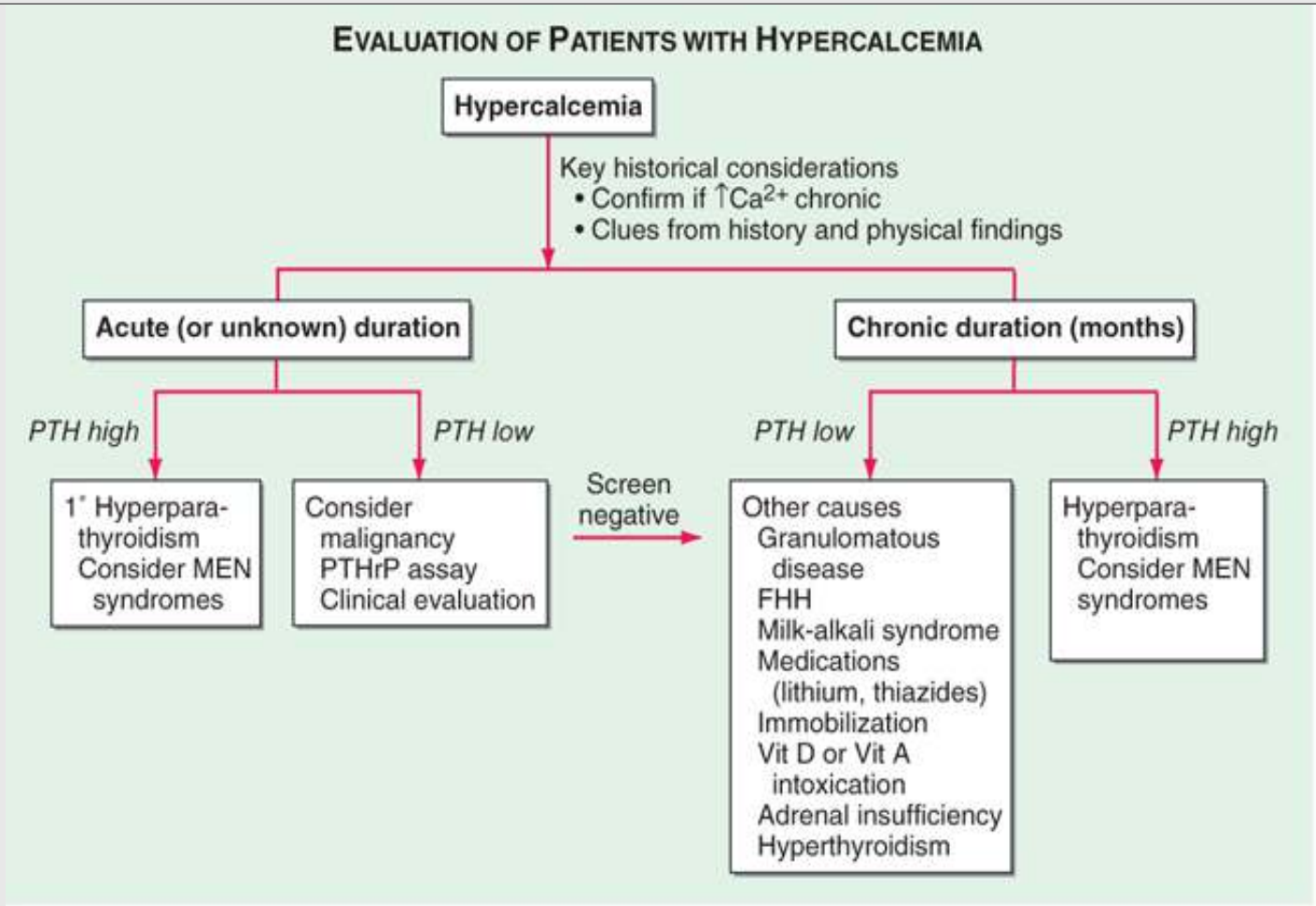
Disclosures

I have no actual or potential conflicts of interest in relation to this program/presentation

Objectives

- Discuss the typical and atypical presentations of primary hyperparathyroidism
- Discuss work-up, diagnostic evaluation and biochemical findings
- Review the major manifestations/complications associated with primary hyperparathyroidism

EVALUATION OF PATIENTS WITH HYPERCALCEMIA



TABLE

Differential diagnosis of primary hyperparathyroidism[2]

Diagnosis	Serum calcium	PTH	25(OH) vitamin D	Serum phosphorous
PHPT	High/Normal	High/Normal	Normal	Low/Normal
FHH	High/Normal	Normal/Mildly high	Normal	Normal/Low
Vitamin D deficiency	Low/Normal	High/Normal	Low	Normal/Low
Humoral hypercalcemia of malignancy	High	Low	Normal	Normal/Low
Milk alkali syndrome	High	Low	Normal	Normal/High

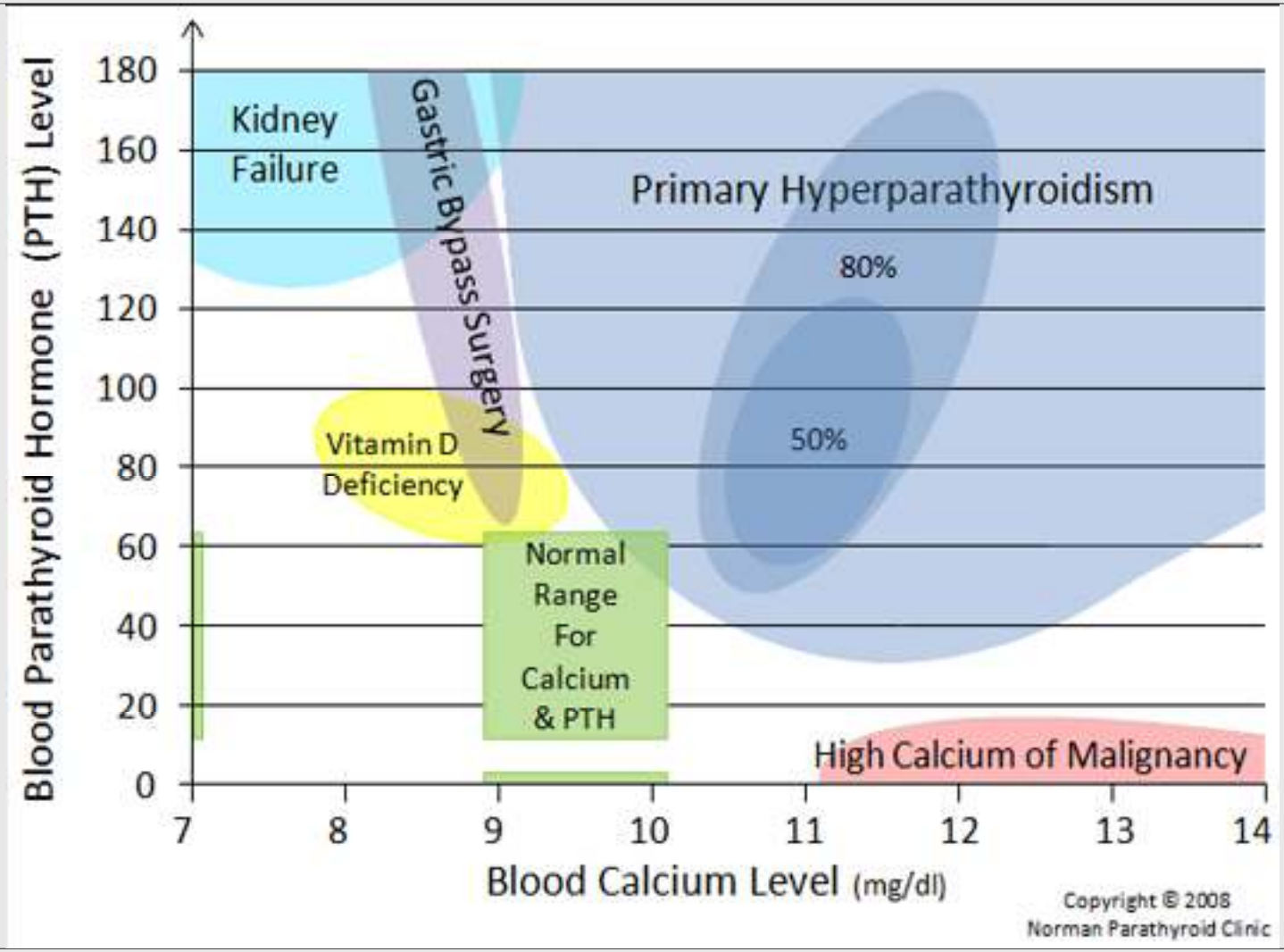
FHH, familial hypocalciuric hypercalcemia; PHPT, primary hyperparathyroidism; PTH, parathyroid hormone.

Table 1. Typical Findings in Hyperparathyroidism.

Finding	Primary Hyperparathyroidism	Normocalcemic Hyperparathyroidism	Secondary Hyperparathyroidism	Tertiary Hyperparathyroidism	Familial Hypocalciuric Hypercalcemia
Family history of hypercalcemia	No	No	No	No	Yes; sometimes with a history of unsuccessful parathyroid surgery
Lifelong hypercalcemia	No	No	No	No	Yes
Parathyroid hormone level	High	High	High	High	Normal to high-normal (approximately 75%) or high (approximately 25%)
Calcium	High	Normal	Low or low-normal	High	Normal or high
Phosphorus	Normal or low-normal	Normal or low-normal	Variable; can be high with renal insufficiency	Usually high owing to renal failure	Normal
25-hydroxyvitamin D	Normal	Normal	Normal or more often low, depending on cause (e.g., <20 ng/ml in vitamin D deficiency)	Normal	Normal
1,25-dihydroxyvitamin D	Often high or high-normal	Variable but not low	Variable; often low in renal insufficiency, high in calcium malabsorption	Low	Normal
Bone mineral density	Can be low, particularly at cortical sites	Can be low, particularly at cortical sites	Can be low with long-standing disease	Often low, particularly at cortical sites	Normal
24-hr urine calcium	Normal or high	Normal or high	Very often low	Low	Low, with calcium:creatinine clearance ratio <0.010*

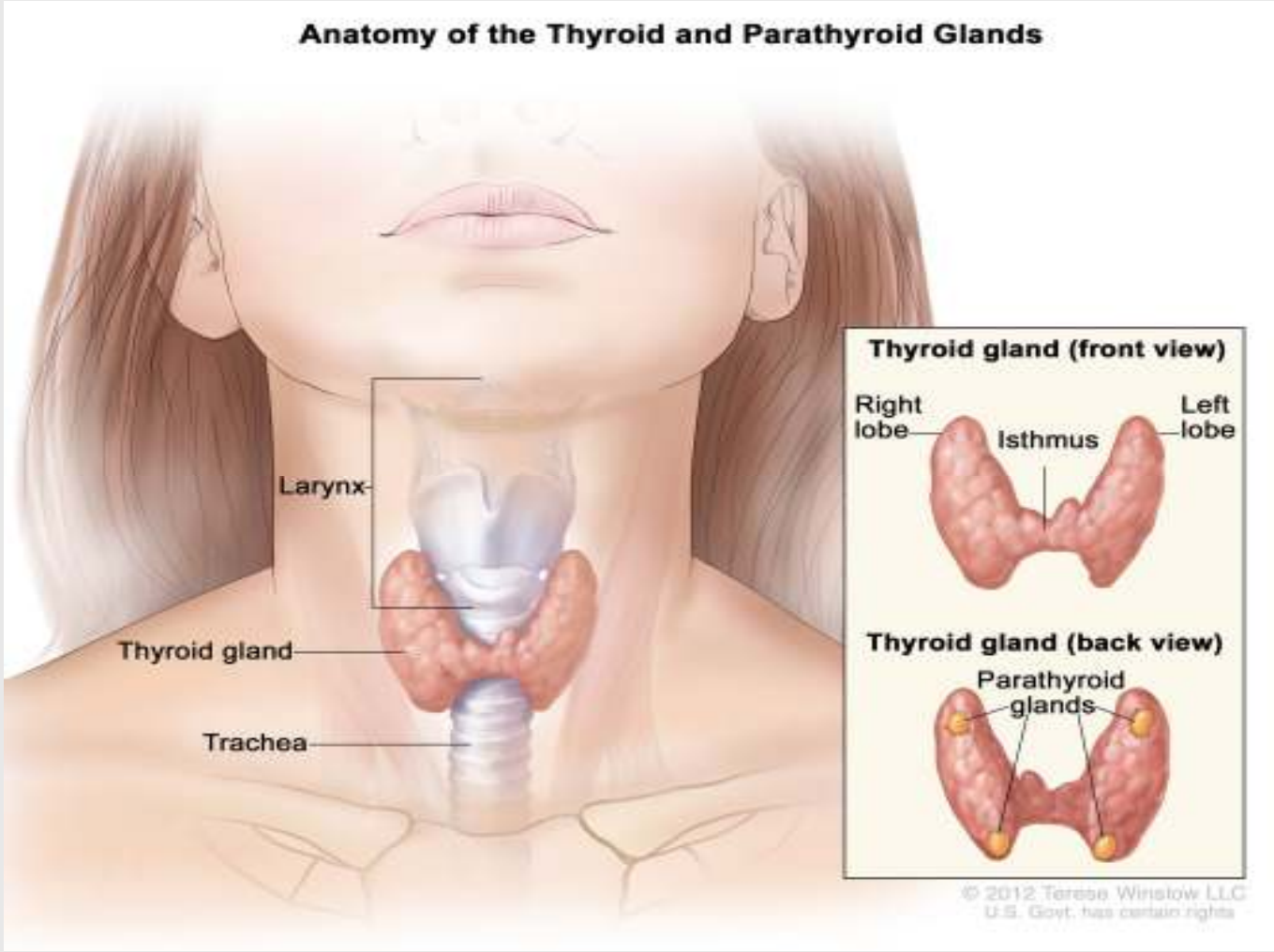
* The calcium:creatinine clearance ratio is calculated as (urine calcium × serum creatinine)/(urine creatinine × serum calcium), with all measurements in the same units (i.e., millimoles per liter or milligrams per deciliter).

https://www.nejm.org/doi/full/10.1056/NEJMcp1714213


Blood Parathyroid Hormone (PTH) Level
180
160
140
120
100
80
60
40
20
0
Kidney Failure
Gastric Bypass Surgery
Primary Hyperparathyroidism
80%
50%
Vitamin D Deficiency
Normal Range For Calcium & PTH
High Calcium of Malignancy
7
8
9
10
11
12
13
14
Blood Calcium Level (mg/dl)
Copyright © 2008
Norman Parathyroid Clinic

ORIGIN OF DISEASE

PATHOPHYSIOLOGY


Anatomy of the Thyroid and Parathyroid Glands
Larynx
Thyroid gland
Trachea
Thyroid gland (front view)
Right lobe
Isthmus
Left lobe
Thyroid gland (back view)
Parathyroid glands
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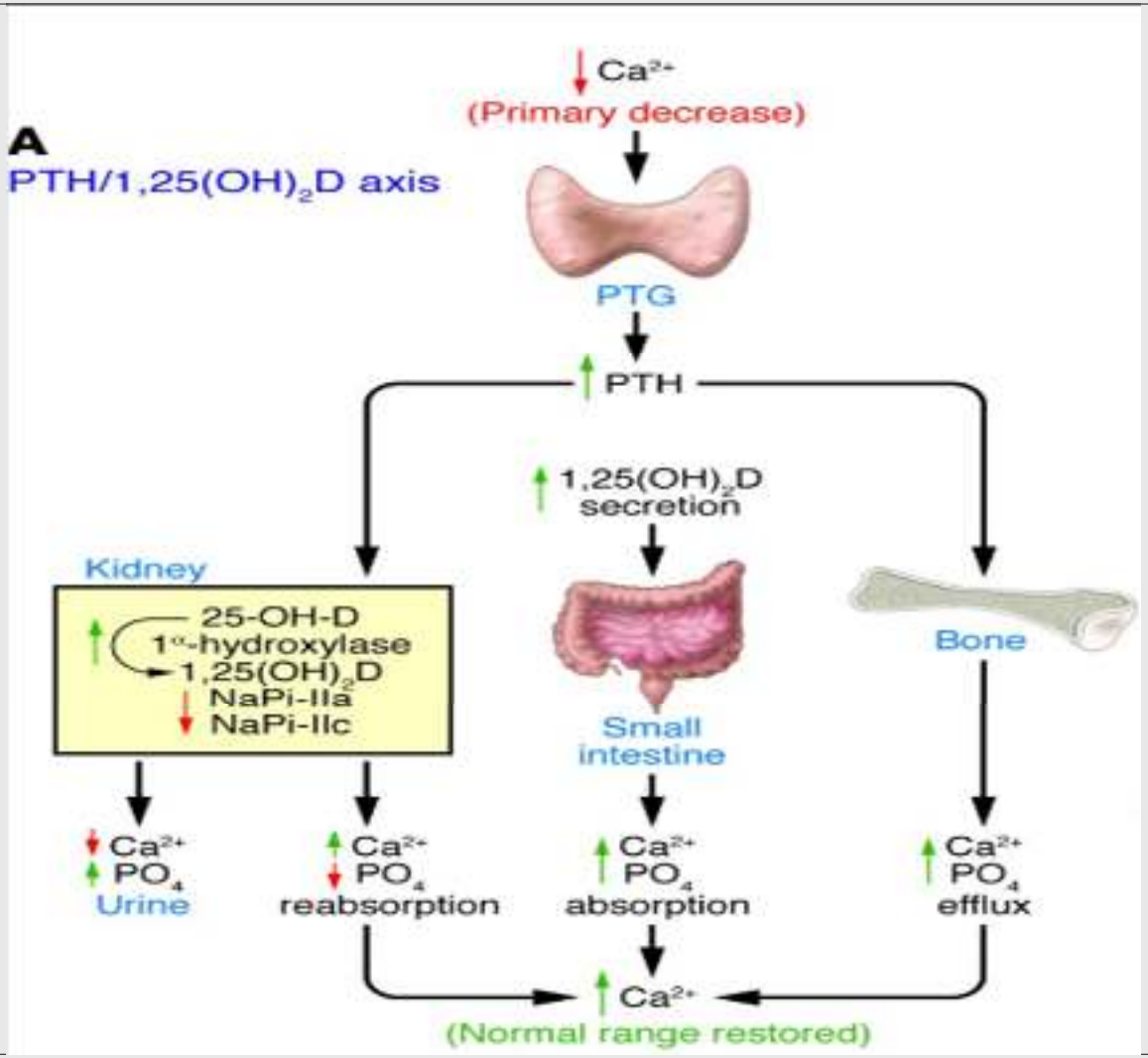
- In primary hyperparathyroidism (PHPT), an enlargement of one or more of the parathyroid glands causes overproduction of parathyroid hormone (PTH).
- PTH regulates the level of calcium in the body, including the release of calcium from bones and the excretion of calcium in the urine. It also increases calcium absorption in the duodenum by changing 25(OH)D to the active form of vitamin D: 1,25(OH)2D.
- Abnormally high parathyroid hormone levels typically result in hypercalcemia.
- The most common cause of PHPT is parathyroid adenoma, found in 80% of patients.
- Hyperplasia is involved in most other cases, and carcinoma is a rare cause.

Wilhelm SM et al. The American Associa7on of Endocrine Surgeons Guidelines for Defini7ve Management of Primary Hyperparathyroidism. JAMA Surg2016;151(10):959-968. Na7onal Ins7tute of Diabetes and Diges7ve and Kidney Diseases. Primary Hyperparathyroidism. Available at hXps://www.niddk.nih.gov/health-informa7on/endocrine-diseases/primary-hyperparathyroidism. Accessed August 28, 2018. Mayo Clinic. Hyperparathyroidism. Available at hXps://www.mayoclinic.org/diseases-condi7ons/hyperparathyroidism/symptoms-causes/syc-20356194. Accessed August 28, 2018. Velez RP et al. Simplifying the Complexity of Primary Hyperparathyroidism. The Journal for Nurse Prac55oners2016; 12(5): 346–352.



J Clin Invest. 2008;118(12):3820-3828.

EPIDEMIOLOGY

- Most common cause of hypercalcemia
- 100,000 people per year develop primary hyperparathyroidism (PHPT) in the US
- Women are 3-4 times more likely to develop PHPT
- Postmenopausal women more likely to develop PHPT
- African Americans are most affected, followed by Caucasians and Asians
- Most often affects people between 50-60 years of age

Bilezikian JP. Primary hyperparathyroidism. In: De Groot LJ, Chrousos G, Dungan K, et al., eds. *Diseases of Bone and Mineral Metabolism*. South Dartmouth, MA: MDTEXT.COM, Inc. 2000-2018. https://www.ncbi.nlm.nih.gov/books/NBK278923/

Typical and Atypical Presentations

TABLE

Differential diagnosis of primary hyperparathyroidism[2]

Diagnosis	Serum calcium	PTH	25(OH) vitamin D	Serum phosphorous
PHPT	High/Normal	High/Normal	Normal	Low/Normal
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Vitamin D deficiency	Low/Normal	High/Normal	Low	Normal/Low
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Milk alkali syndrome	High	Low	Normal	Normal/High

FHH, familial hypocalciuric hypercalcemia; PHPT, primary hyperparathyroidism; PTH, parathyroid hormone.

J Fam Pract. 2018 November;67(11):E16-E21

CASE 1

A 62-year-old woman is referred for management of primary hyperparathyroidism. She was noted to have a serum calcium concentration of 10.7 mg/dL (8.2-10.2 mg/dL) on routine chemistry panel. A previous serum calcium measurement from 2 years ago was 10.0 mg/dL. She feels well and has no symptoms of hypercalcemia. She has no history of fractures or kidney stones.

Her medical history is notable for mild hypertension. Current medications are hydrochlorothiazide 12.5 mg daily (for the past 4 years) and cholecalciferol, 1000 IU daily. Her family history is noncontributory.

Question Adapted from Endocrine Board Review

CASE 1 continued

On physical examination her blood pressure is 120/72 mm Hg

Laboratory test results:

Serum calcium = 11 mg/dL (8.2-10.2 mg/dL)

Albumin, normal

Creatinine, normal

Phosphate = 3.0 mg/dL (2.3-4.7 mg/dL)

Intact PTH = 60 (10-65 pg/mL)

25-Hydroxyvitamin D = 35 ng/mL (30-80 ng/mL)

Urinary calcium (adequate collection) = 105 mg/24 h (100-300 mg/24 h)

Question Adapted from Endocrine Board Review

CASE 1 continued

Which of the following is the best next step?

A. Calculate the calcium-to-creatinine clearance ratio

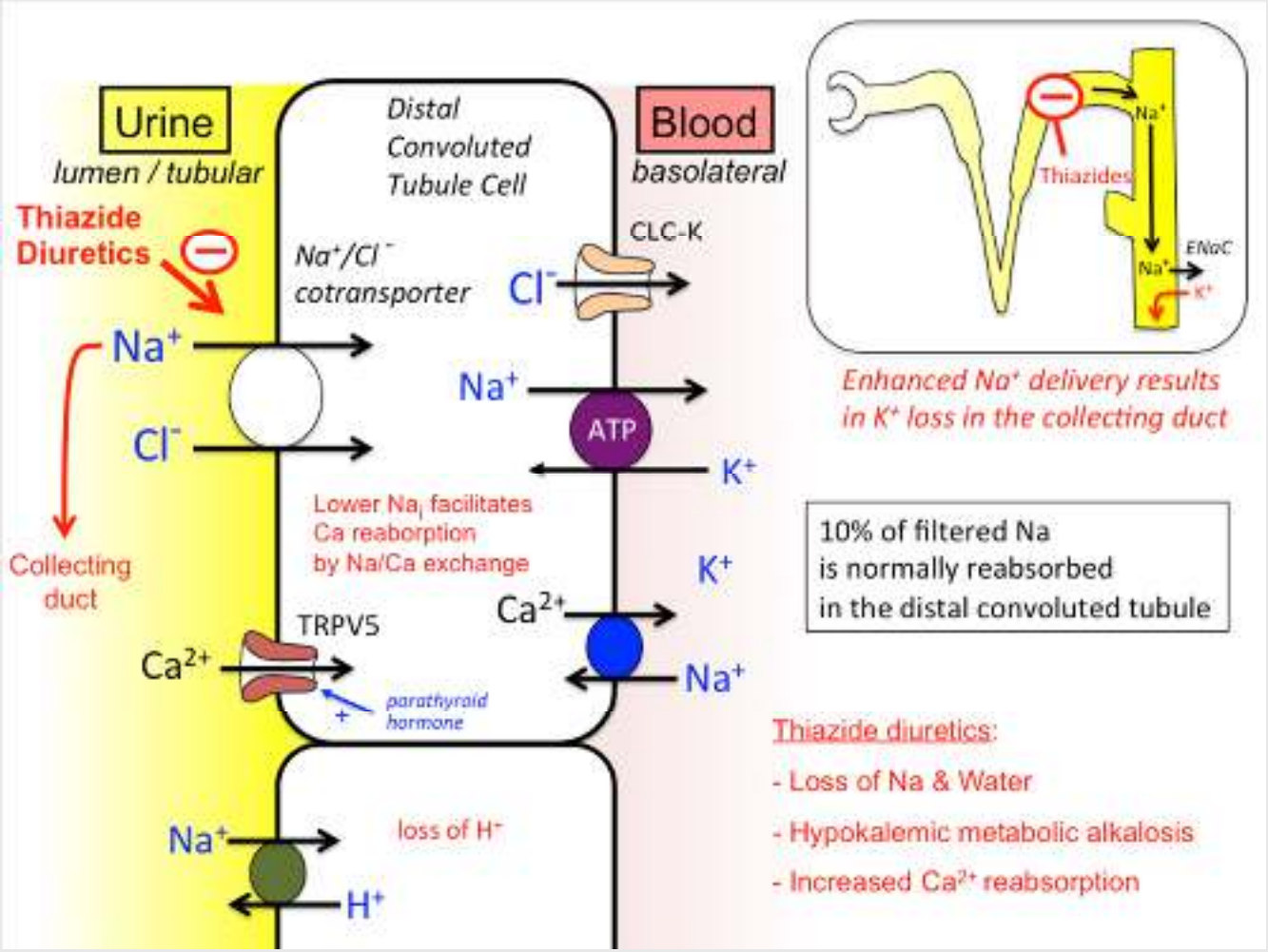
B. Order DXA, including one-third distal radius

C. Measure 1,25-dihydroxyvitamin D

D. Measure calcium and PTH after stopping hydrochlorothiazide for 3 months

E. Order sestamibi parathyroid scan

Question Adapted from Endocrine Board Review



http://tmedweb.tulane.edu/pharmwiki/doku.php/thiazides

Typical Presentation

- **Nephrolithiasis**: 15% to 20% of patients with PHPT present with kidney stones, due to high calcium levels in the glomerular filtrate.

Renal, musculoskeletal, gastrointestinal, and psychiatric symptoms.

("Stones, bones, abdominal groans, psychiatric moans.")

- Anorexia
- Nausea/vomiting
- Constipation
- Insomnia
- Depression
- Fatigue/muscle weakness
- Arthritis
- Bone and/or joint pain
- Bone demineralization/ fractures
- Polydipsia and polyuria

Khan AA et al. Primary hyperparathyroidism: review and recommenda7ons on evalua7on, diagnosis, and management. A Canadian and interna7onal consensus. Osteoporosis Interna-onal2017; 28 (1):1–19 Wilhelm SM et al. The American Associa7on of Endocrine Surgeons Guidelines for Defini7ve Management of Primary Hyperparathyroidism. JAMA Surg 2016;151(10):959-968. Velez RP et al. Simplifying the Complexity of Primary Hyperparathyroidism. The Journal for Nurse Prac--oners2016; 12(5): 346–352.

- Hypercalcemia + abnormally elevated or inappropriately normal PTH levels makes PHPT the most likely diagnosis.
- Calcium and parathyroid hormone levels should be tested simultaneously
- Measurement of serum calcium should be adjusted for albumin
  - 40% of calcium is bound to serum proteins, predominantly albumin.
- If the adjusted serum calcium is normal but parathyroid hormone is elevated, serum ionized calcium should be measured.
- PHPT can present with an elevated ionized calcium despite a normal albumin-adjusted serum calcium.

Khan AA et al. Primary hyperparathyroidism: review and recommenda7ons on evalua7on, diagnosis, and management. A Canadian and interna7onal consensus. Osteoporosis Interna-onal2017; 28 (1):1–19 Wilhelm SM et al. The American Associa7on of Endocrine Surgeons Guidelines for Defini7ve Management of Primary Hyperparathyroidism. JAMA Surg 2016;151(10):959-968. Velez RP et al. Simplifying the Complexity of Primary Hyperparathyroidism. The Journal for Nurse Prac--oners2016; 12(5): 346–352.

CASE 2

A 60-year-old postmenopausal women is found to have osteoporosis on DXA scan with the lowest T-core of -2.8 at the femoral neck. She has no history of fractures, but her mother had a hip fracture at age 75 years. A workup for secondary causes of osteoporosis shows a normal serum calcium concentration but elevated PTH concentration. She has taken cholecalciferol, 1000 IU daily, for many years, along with at least 1000 mg elemental calcium daily (diet plus a supplement).

Question Adapted from Endocrine Board Review

CASE 2 continued…

Laboratory test results:

Serum total calcium (3 measurements) = 9.5 mg/dL, 9.8 mg/dL, 9.7 mg/dL (8.2-10.2 mg/dL)

Ionized calcium, normal

Intact PTH (3 measurements) = 87 pg/mL, 78 pg/mL and 85 pg/mL (10-65 pg/mL)

Urinary calcium = 180 mg/24 h (100-300 mg/24h)

Serum creatinine = 0.8 mg/dL (0.6-1.1 mg/dL)

Phosphate = 2.6 mg/dL (2.3-4.7 mg/dL)

25-Hydroxyvitamin D = 48 ng/mL (30-80 ng/mL)

Question Adapted from Endocrine Board Review

CASE 2 continued…

Which of the following is the most appropriate next step?

A. Perform DXA of the one-third distal radius
B. Perform preoperative parathyroid imaging
C. Perform renal ultrasonography
D. Double the calcium supplementation and measure calcium and PTH again in 3 months
E. Measure serum calcium and PTH again in 6 months

Question Adapted from Endocrine Board Review

Atypical Presentation

Normocalcemic Hyperparathyroidism

- Mild PHPT: high levels of parathyroid hormone but normal levels of calcium
- Secondary causes of elevated parathyroid hormone should be excluded:
  - Primary hypercalciuria
  - Vitamin D deficiency
  - Malabsorption syndromes (i.e celiac disease)
  - Use of loop diuretics or thiazide diuretics
  - Bisphosphonates or denosumab therapy
  - Chronic kidney disease (estimated GFR <60 mL/min per 1.73 m2)

Khan AA et al. Primary hyperparathyroidism: review and recommenda7ons on evalua7on, diagnosis, and management. A Canadian and interna7onal consensus. Osteoporosis Interna-onal2017; 28 (1):1–19 Wilhelm SM et al. The American Associa7on of Endocrine Surgeons Guidelines for Defini7ve Management of Primary Hyperparathyroidism. JAMA Surg 2016;151(10):959-968. Velez RP et al. Simplifying the Complexity of Primary Hyperparathyroidism. The Journal for Nurse Prac--oners2016; 12(5): 346–352.

Normocalcemic Hyperparathyroidism

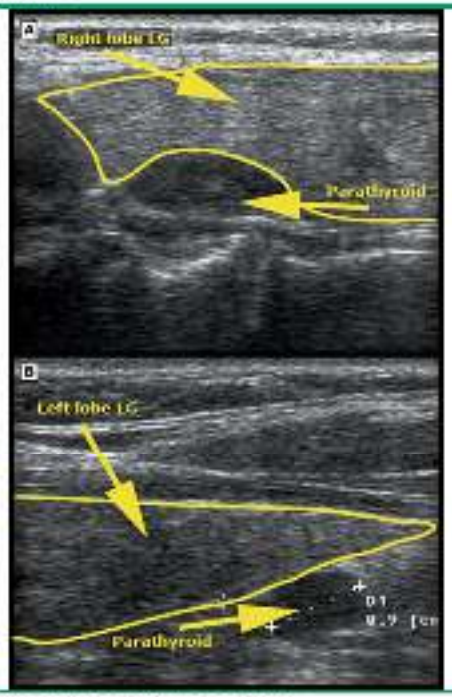
- Elevated serum parathyroid hormone with consistently normal albumin-adjusted calcium and ionized calcium, normal serum 25-hydroxyvitamin D, and preserved renal function (eGFR >60 mL/min/1.73 m2)
- Normocalcemic HPT can develop in to PHPT
- Same criteria for surgical intervention are used for normocalcemic HPT and asymptomatic PHPT

Khan AA et al. Primary hyperparathyroidism: review and recommenda7ons on evalua7on, diagnosis, and management. A Canadian and interna7onal consensus. Osteoporosis Interna-onal2017; 28 (1):1–19 Wilhelm SM et al. The American Associa7on of Endocrine Surgeons Guidelines for Defini7ve Management of Primary Hyperparathyroidism. JAMA Surg 2016;151(10):959-968. Velez RP et al. Simplifying the Complexity of Primary Hyperparathyroidism. The Journal for Nurse Prac--oners2016; 12(5): 346–352.

Preoperative parathyroid imaging

- Parathyroid ultrasound and/or sestamibi scan
- Imaging detects 80% of abnormal parathyroid tissue
  - False negative results
- Imaging studies may be less sensitive in normocalcemic HPT
- Multiglandular disease may be more common in patients with normocalcemic HPT

Sonographic characteristics of parathyroid adenomas

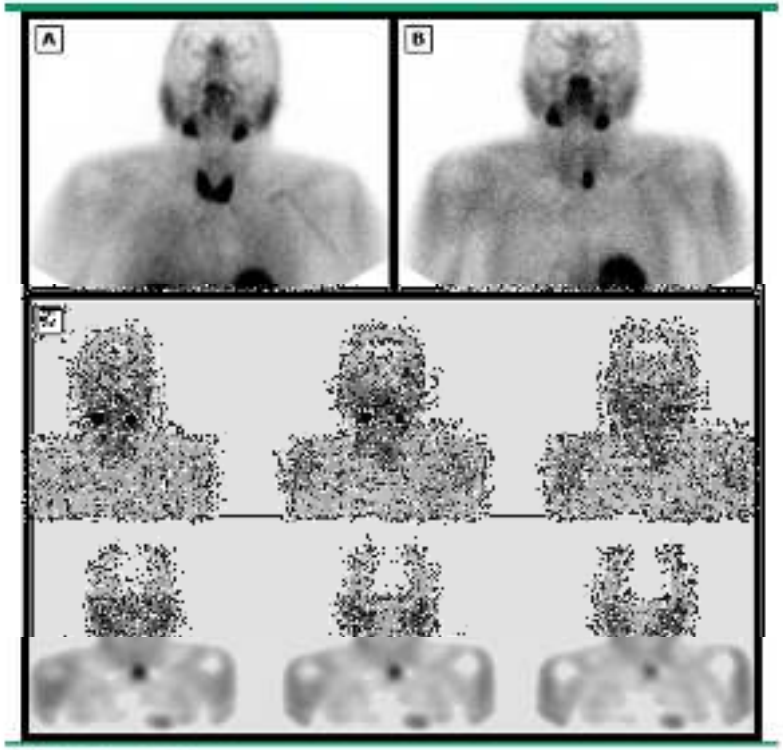


Ultrasound views of parathyroid adenomas.
(A) Sagittal image of the upper pole of the right lobe of the thyroid gland, demonstrating a hypoechoic parathyroid adenoma posterior to the thyroid parenchyma.
(B) Sagittal image of the lower pole of the lower pole of the left lobe of the thyroid gland with an adjacent hypoechoic parathyroid adenoma measuring 9 mm in greatest dimension.

Reproduced with permission from: Mulholland, MW, Maier, RV. Greenfield's Surgery: Scientific Principles And Practice, Fourth edition. Philadelphia: Lippincott Williams & Wilkins, 2006. Copyright © 2006 Lippincott Williams & Wilkins.

UpToDate

MIBI SPECT images of parathyroid adenoma



(A) Anterior 10 min.
(B) Anterior delayed.
(C) SPECT.

MIBI-SPECT: methoxyisobutyl isonitrile single-photon emission computed tomography; SPECT: single-photon emission computed tomography.

Courtesy of Pierre J Sasson, MD.

UpToDate

EVALUATION AND MANAGEMENT

Guidelines for surgery in asymptomatic PHPT: A comparison of current guidelines with the previous one*

Measurement¶	2008	2014
Serum calcium (>upper limit of normal)	1.0 mg/dL (0.25 mmol/L)	1.0 mg/dL (0.25 mmol/L)
Skeletal	1. BMD by DXA: T-score <−2.5 at any site¶ 2. Previous fragility fracture△	1. BMD by DXA: T-score <−2.5 at lumbar spine, total hip, femoral neck, or distal 1/3 radius¶ 2. Vertebral fracture by radiograph, CT, MRI, or VFA
Renal	1. eGFR <60 mL/min 2. 24-hour urine for calcium not recommended	1. Creatinine clearance <60 mL/min 2. 24-hour urine for calcium >400 mg/day (>10 mmol/day) and increased stone risk by biochemical stone risk analysis◇ 3. Presence of nephrolithiasis or nephrocalcinosis by radiograph, ultrasound, or CT
Age (years)	<50	<50

Patients need to meet only one of these criteria to be advised to have parathyroid surgery. They do not have to meet more than one.

PHPT: primary hyperparathyroidism; BMD: bone mineral density; DXA: dual-energy x-ray absorptiometry; CT: computed tomography; MRI: magnetic resonance imaging; VFA: vertebral fracture assessment; eGFR: estimated glomerular filtration rate; ISCD: International Society for Clinical Densitometry.

* Surgery is also indicated in patients for whom medical surveillance is neither desired nor possible and in patients opting for surgery, in the absence of meeting any guidelines, as long as there are no medical contraindications.

¶ Consistent with the position established by the ISCD, the use of Z-scores instead of T-scores is recommended in evaluating BMD in premenopausal women and men younger than 50 years[1].

△ The history of a fragility fracture at any site would define someone as having a complication of PHPT, and thus, the individual would be automatically considered to be a surgical candidate.

◇ Most clinicians will first obtain a 24-hour urine for calcium excretion. If marked hypercalciuria is present (>400 mg/day [>10 mmol/day]), further evidence of calcium-containing stone risk should be sought by a urinary biochemical stone risk profile, available through most commercial laboratories. In the presence of abnormal findings indicating increased calcium-containing stone risk and marked hypercalciuria, a guideline for surgery is met.

References:

1. *Lewiecki EM, Bolm S, Langman CB, Bilezikian JP. The official positions of the International Society for Clinical Densitometry: perceptions and commentary. J Clin Densitom 2009; 12:267.*

Republished with permission of The Endocrine Society, from: Bilezikian JP, Brandi ML, Eastell R, et al. Guidelines for the management of asymptomatic primary hyperparathyroidism: summary statement from the Fourth International Workshop. J Clin Endocrinol Metab 2014; 99:3561. Copyright © 2014 The Endocrine Society; permission conveyed through Copyright Clearance Center, Inc.

Guidelines for Surgery in Asymptomatic PHPT

Nonoperative Management

- When surgery is not recommended:
  - Long-term surveillance for worsening hypercalcemia, renal failure and reduction in bone mineral density
  - Check calcium and creatine levels q 12 months
  - Check bone density q 1-2 years (hip, spine, forearm)
  - If there is disease progression, surgery is indicated

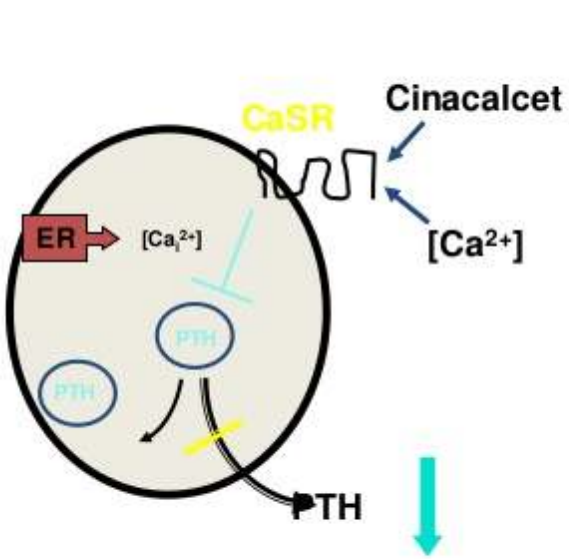
Prevention of Disease Progression

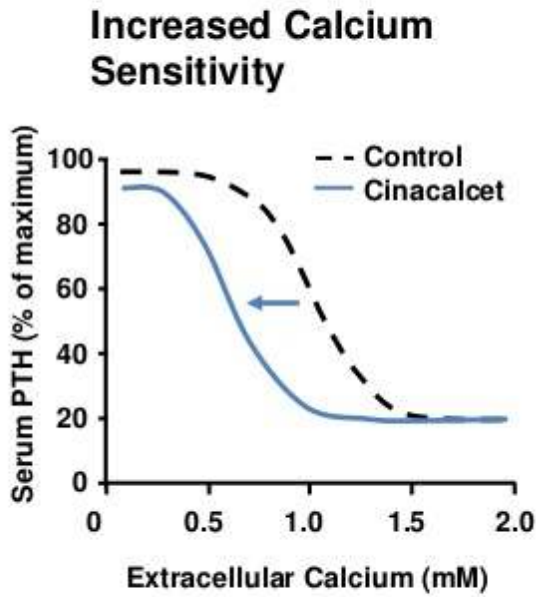
- Promote physical activity (beneficial impact on bone resorption).
- Avoid prolonged inactivity
- Avoid thiazides and lithium
- Avoid hypovolemia
- Avoid high-calcium diets (>1000 mg/day)
- Avoid calcium restricted diets
- Avoid vitamin D deficiency (400-800 IU daily)

Management of Symptomatic Patients

- Nephrolithiasis, fractures, symptomatic hypercalcemia: PARATHYROIDECTOMY
- Minimally invasive surgery vs. 4-gland exploration
- For those who are not appropriate surgical candidates:
  - CINACALCET (Recommended if BMD is normal)
  - BISPHOSPHONATES (Consider if BMD is low)

Cinacalcet Acts at the Calcium-Sensing Receptor to Decrease PTH Secretion





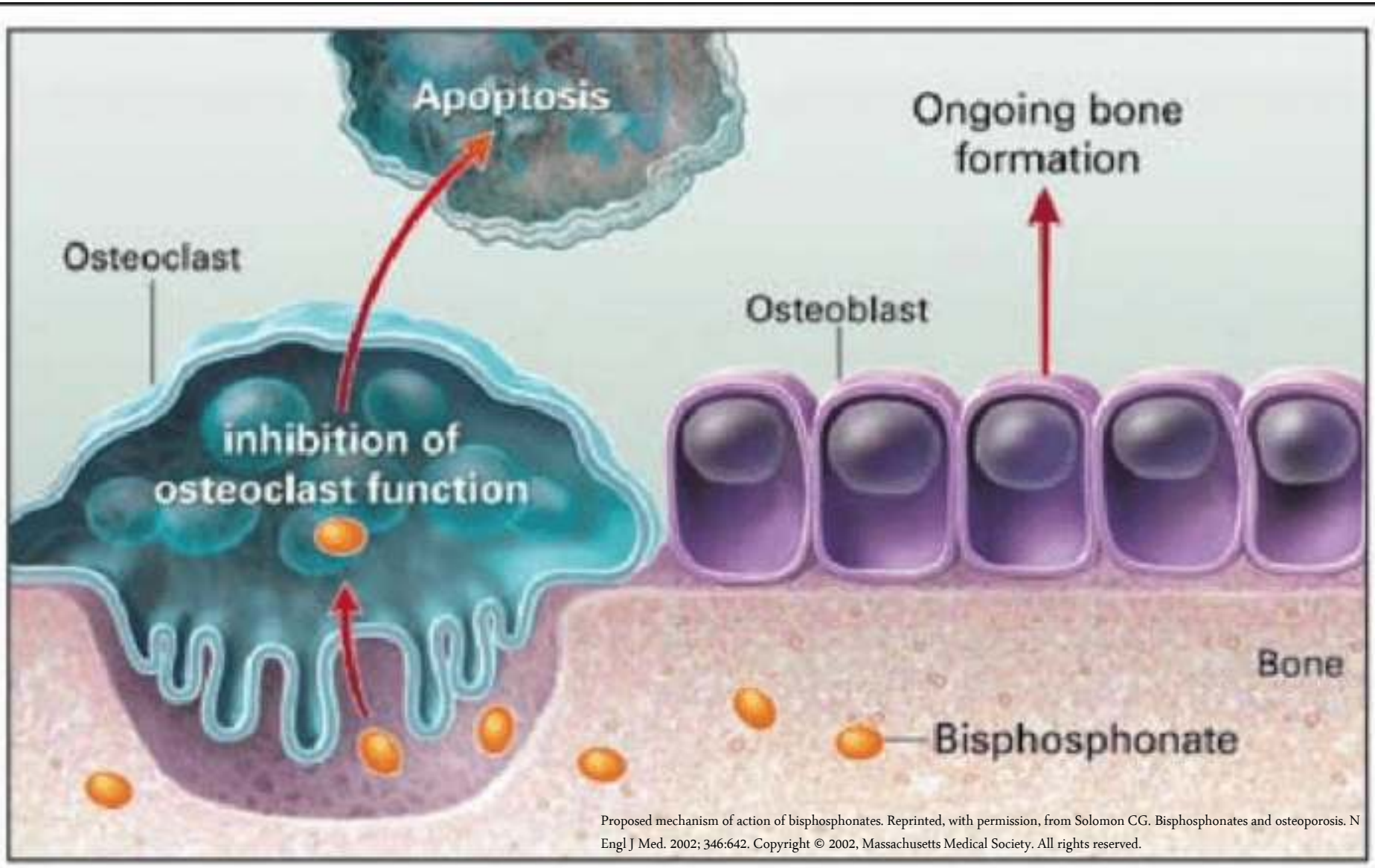
Adapted from Nemeth EF, et al. *J Pharmacol Exp Ther.* 2004;308:627-635.

Cinacalcet

- Considered when primary indication for surgery is severe and/or symptomatic hypercalcemia
- Preferred when there is no evidence of osteoporosis
- Dosing: 30 mg po twice daily
- Monitor corrected calcium or ionized calcium levels frequently (q1 week after initiation and following dose adjustments) until normalized
- Not definitive therapy
- No beneficial effect on BMD

Cinacalcet – Side Effects

- Nausea 36%
- Joint Aches 30%
- Diarrhea 22%
- Muscle Aches 22%
- Paresthesias 22%

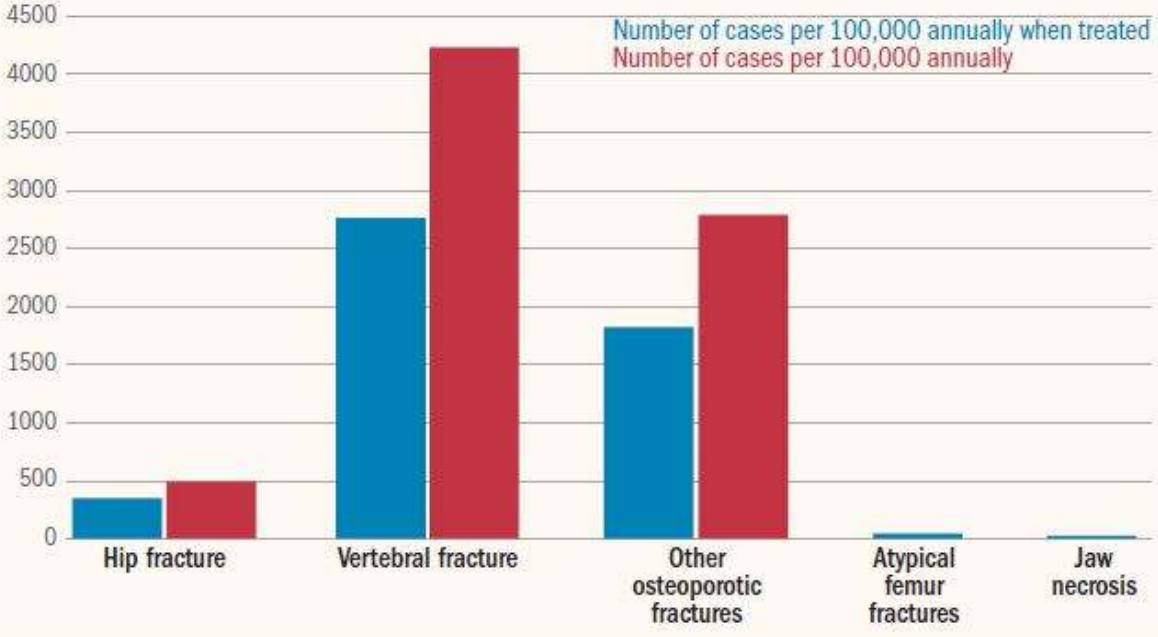


Proposed mechanism of action of bisphosphonates. Reprinted, with permission, from Solomon CG. Bisphosphonates and osteoporosis. N Engl J Med. 2002; 346:642. Copyright © 2002, Massachusetts Medical Society. All rights reserved.

Bisphosphonate

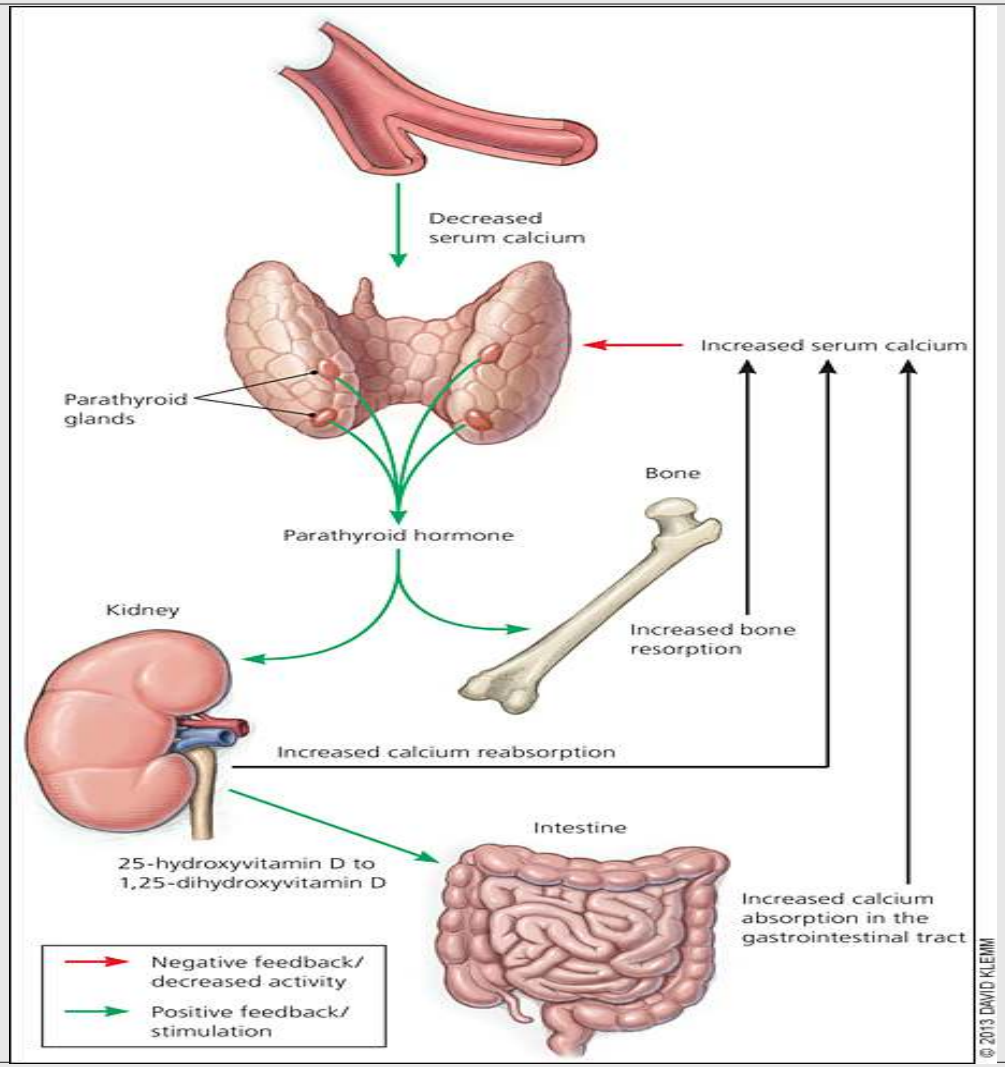
- Indicated in patients with PHPT and osteoporosis
- Improvement in BMD is equivalent to changes seen following parathyroidectomy at 2-year mark
  - Sankaran S, Gamble G, Bolland M, et al. Skeletal effects of interventions in mild primary hyperparathyroidism: a meta-analysis. J Clin Endocrinol Metab 2010; 95:1653.
- Unclear whether or not this benefit is maintained beyond 2-year mark
- Alendronate is best studied
- Not definitive therapy
- Increased risk of adverse effects with long-term use

Risks with and without bisphosphonate therapy



Source: Adapted from Adler RA et al. "Managing osteoporosis patients after long-term bisphosphonate treatment." *Journal of Bone and Mineral Research* (Jan. 2016), Vol. 31, No. 1, pp. 16–35.

CLINICAL MANIFESTATIONS



Am Fam Physician. 2013 Aug 15;88(4):249-257.

TABLE 2

Manifestations of Primary Hyperparathyroidism

System	Signs and symptoms	Mechanism
Renal	Nephrolithiasis, nephrocalcinosis, recurrent urinary tract infections, renal impairment	Hypercalcemia, hypercalciuria, and hyperphosphaturia
		Calcium phosphate precipitates in alkaline urine, calcium oxalate stones form; stones formed in the renal pelvis or collecting ducts are associated with increased risk of infection
	Polyuria, dehydration	Hypercalcemia has a direct effect on renal tubules, causing a decreased response to antidiuretic hormone
Musculoskeletal	Osteoporosis, osteitis fibrosa cystica, fractures, muscle weakness, myalgia	Excess PTH excretion leads to metabolic acidosis, bone resorption, and myopathic changes
	Arthralgia, arthritis	Hyperuricemia leads to gout, pseudogout
Gastrointestinal	Abdominal pain, constipation, anorexia, nausea, vomiting	Hypercalcemia decreases gastrointestinal motility, stimulates the central vomiting center, and increases gastrin secretion
	Peptic ulcer disease	Hypercalcemia stimulates elevated hydrochloric acid secretion
	Pancreatitis (less common)	Exact mechanism unknown; gastrin weakly stimulates pancreatic enzymes and gallbladder contraction
Neurologic/ psychiatric	Memory impairment, depression, anxiety, confusion, stupor, coma	Hypercalcemia induces neuropathy, electroencephalographic changes
Cardiovascular	Hypertension	Hypercalcemia has direct effect on arterial smooth muscle and elevates plasma renin activity

Sources: Brashers et al. *Pathophysiology.* 2015[6]; Michels and Kelly. *Am Fam Physician.* 2013[8]; Bilezikian et al. *J Clin Endocrinol Metab.* 2014.[19]

Mechanisms for cardiovascular disease

Hypertension	• Excess PTH-driven alterations in vasodilatory properties of endothelium • Hypercalcemia-driven atherosclerotic disease • Excess aldosterone due to PTH activation of RAAS
Left ventricular hypertrophy	• Hypertrophy of cardiac myocytes driven by PTH activation of PTH1R and subsequent upregulation of PKC
Heart failure	• Excess PTH-driven cardiac myocyte hypertrophy, dysfunction of endothelium and vasculature • Vitamin D deficiency: adverse cardiac myocyte remodeling, increased RAAS activity • Hypoparathyroidism: dilated cardiomyopathy due to chronic hypocalcemia and reduced cardiac contractility
Calcific disease	• Chronic hypercalcemia leading to calcium depositions
Arrhythmias	• PHPT: hypercalcemia leading to shortened QT intervals, prolongation of PR and QRS intervals, myocardial depression • Hypoparathyroidism: hypocalcemia-driven QT prolongation

Brown SJ, Ruppe MD, Tabatabai LS. The Parathyroid Gland and Heart Disease. *Methodist Debakey Cardiovasc J.* 2017;13(2):49–54. doi:10.14797/mdcj-13-2-49

Summary

- Hyperparathyroidism can present with hypercalcemia or normocalcemia
- Normocalcemic HPT and asymptomatic PHPT have the same criteria for surgical intervention
- For those who are not appropriate surgical candidates, consider bisphosphonate or cinacalcet use
- When surgery is not indicated, long-term surveillance for worsening hypercalcemia, renal failure and reduction in bone mineral density is recommended
- Untreated PHPT can adversely impact multiple organ systems: gastrointestinal, renal, musculoskeletal, neurologic and cardiovascular

Thank you for your time and attention

https://www.pinterest.cl/pin/517702919637793191/