THE IMPACT OF HYPERCALCEMIA: MORE THAN JUST A NUMBER

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DISCLOSURES

- Abbott nutrition: advisor and speaker's bureau
- Xeris Pharmaceuticals: speaker's bureau
- Sanofi: advisor

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OBJECTIVES

1. Review the physiology of calcium metabolism and homeostasis with an emphasis on the impact on neurological and musculoskeletal function and health.
2. Discuss diagnostic criteria versus misconceptions in the diagnosis of hypercalcemia and hyperparathyroidism.
3. Distinguish causes of hypercalcemia outside of hyperparathyroidism to appropriately manage and prevent unnecessary procedures.
4. Determine the appropriate role of parathyroid imaging in calcium disorders.
5. Demonstrate the specific surgical criteria for parathyroidectomy in hyperparathyroidism.

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CALCIUM METABOLISM AND HOMEOSTASIS

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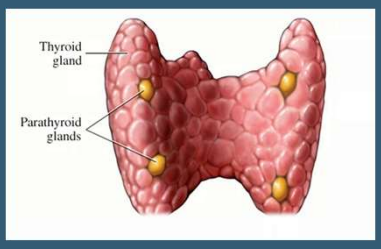
CALCIUM METABOLISM

Regulated primarily by

- Parathyroid hormone (PTH)
  - Half-life 5 minutes
- Calcitriol (1,25-dihydroxyvitamin D)
  - Half-life 5-8 hours



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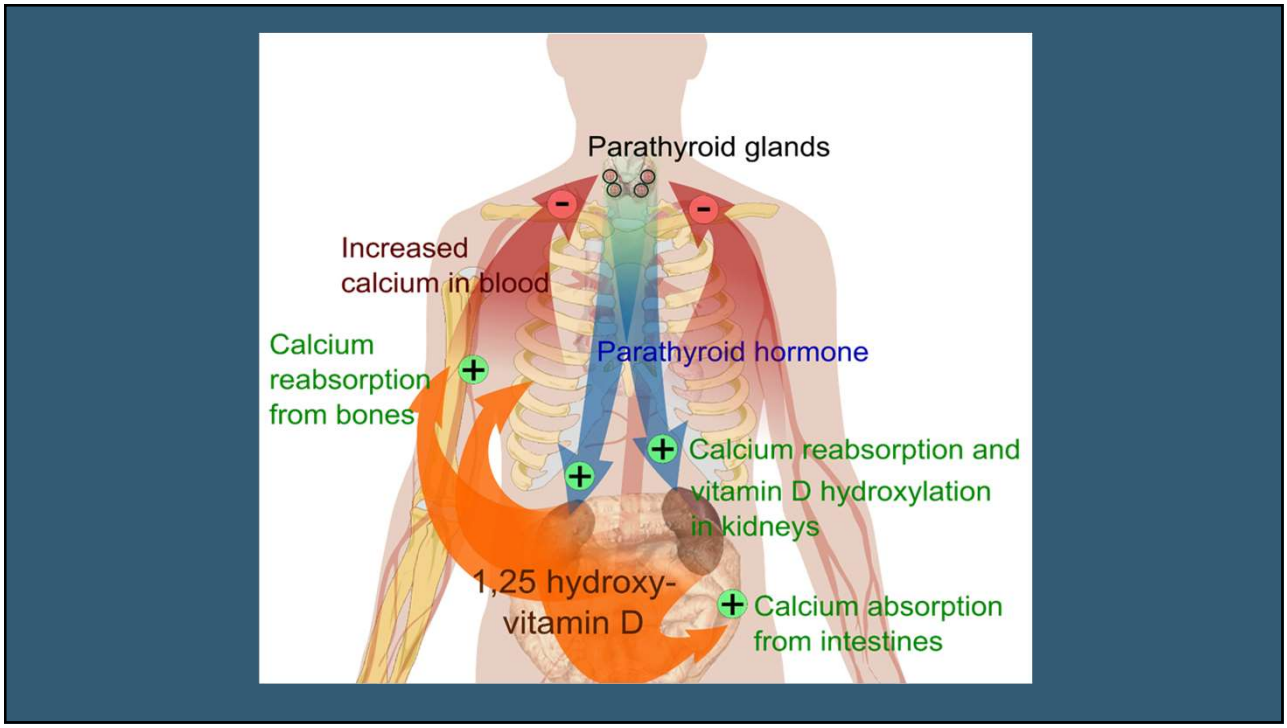
Parathyroid glands
Increased calcium in blood
Calcium reabsorption from bones
Parathyroid hormone
Calcium reabsorption and vitamin D hydroxylation in kidneys
1,25 hydroxy-vitamin D
Calcium absorption from intestines

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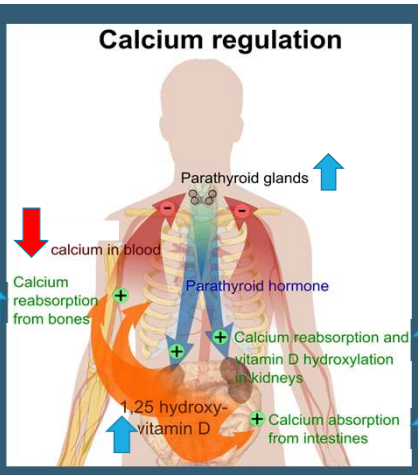
CALCIUM PHYSIOLOGY

- Decreased serum calcium → PTH is released
  - **Stimulates** renal tubular and bone calcium resorption
  - Promotes renal secretion of **1,25-dihydroxyvitamin D** (calcitriol) → increased intestinal calcium absorption and bone resorption
  - 1,25-dihydroxyvitamin D provides **negative feedback** to the parathyroid glands to deactivate PTH secretion
  - **Result:** net increase in serum calcium in an effort to reinstate normocalcemia



Peacock, Munro. Calcium Metabolism in Health and Disease. *Clinical Journal of the American Society of Nephrology*. 5: S23–S30, 2010.

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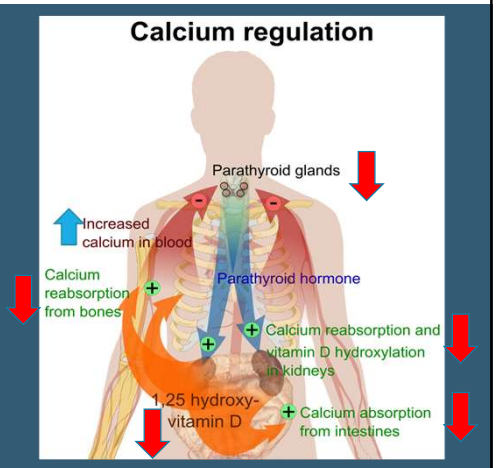
CALCIUM PHYSIOLOGY

- Elevated serum calcium → suppress PTH release
  - **Limits** renal tubular resorption, bone calcium resorption, and 1,25-dihydroxyvitamin D secretion
  - Lower 1,25-dihydroxyvitamin D further **decreases** bone resorption as well as intestinal calcium absorption
  - **Result:** net decrease in serum calcium in an effort to reinstate normocalcemia



Peacock, Munro. Calcium Metabolism in Health and Disease. *Clinical Journal of the American Society of Nephrology*. 5: S23–S30, 2010.

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CASE STUDY

Case 1: Symptomatic Cinderella

Case 2: Incidental Elsa

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CASE 1: SYMPTOMATIC CINDERELLA

- 52 year old female presents to discuss new diagnosis of osteoporosis on postmenopausal screening
- Past medical history: none
- Current medications: none
- OTC supplementation:
  - Calcium carbonate + D 500mg/400IU QD to BID when she remembers
  - Multivitamin from time to time

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CASE 1: SYMPTOMATIC CINDERELLA

- BMI 27, BP 124/80, Pulse 64
- Review of her annual labs is overall unremarkable except for serum calcium 10.8mg/dL (8.7-10.3mg/dL)
- She c/o feeling tired, moody, and achy for the last few years
- Upon further questioning, she is also symptomatic with constipation and nausea which limits how frequently she takes calcium and multivitamin supplements
- What is the most appropriate next step?

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CALCIUM *PATHO*PHYSIOLOGY

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CALCIUM AND PARATHYROID PATHOPHYSIOLOGY

- Typically manifests as an incidental elevated serum calcium level
- Calcium may be normal, elevated, or intermittently elevated
  - Most common cause in outpt setting: primary hyperparathyroidism (PHPT)

  *Serum intact PTH level may be inappropriately normal

Normal ≠ Physiologic!

AACE/AAES Task Force on Primary Hyperparathyroidism. The American Association of Clinical Endocrinologists and the American Association of Endocrine Surgeons Position Statement on the Diagnosis and Management of Primary Hyperparathyroidism. Endocrine Practice. Vol 11 No. 1 January/February 2005.

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When to refer?

Work up hypercalcemia in house or refer to endo

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INCIDENCE

- Hypercalcemia in gen pop: 1 in 1,000[1]
  - Between age 50 and 60
  - Women > men
  - Primary hyperparathyroidism
    - 80% due to single parathyroid adenoma
    - 15% due to multiple parathyroid gland hyperplasia
    - Rarely parathyroid neoplasm
- Hypercalcemia in malignancy: 1 in 5[1]
  - 80% due to PTH-related peptide[2]
    - Over-secreted by CA cells
    - Mimics PTH
    - Paraneoplastic syndrome: Humoral hypercalcemia of malignancy
  - 20% due to bony metastases/osteolytic hypercalcemia[2]

1. Jeremy J O Turner. Hypercalcemia – presentation and management. Clin Med (Lond). 2017 Jun; 17(3): 270–273. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6297576/
2. Mahendra Agraharkar, MD, MBBS, FACP, FASN. Hypercalcemia. Updated: Oct 03, 2018. https://emedicine.medscape.com/article/240681-overview#a5

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MANIFESTATIONS AND IMPLICATIONS

- Stones
  - Nephrolithiasis
  - Nephrocalcinosis
  - Renal impairment
- Bones
  - Osteopenia/osteoporosis/ pathological fx
  - Osteitis fibrosa cystica, osteomalacia
  - Bone tumors
  - Bone/joint pains
- (Abdominal) Groans
  - Constipation, indigestion, n/v
  - Peptic ulcers
  - Acute pancreatitis
- Moans
  - Lethargy, malaise, fatigue
  - Weakness
- (Psychiatric) Overtones
  - Depression, mood disturbances
  - Confusion, memory loss
  - Psychosis, delirium, coma

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HYPERCALCEMIA EVALUATION

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STOP! LOOK AT THE MEDS AND SUPPLEMENTS

- Hydrochlorothiazide/thiazide diuretics
- Lithium
- Calcium carbonate/OTC antacids
- Excessive vitamin D or vitamin A
- Over-replacement with thyroid hormone

Cleveland Clinic. Hypercalcemia. https://my.clevelandclinic.org/health/diseases/14597-hypercalcemia

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SEROLOGIC/UROLOGIC EVALUATION

- Serum calcium, iPTH
- Albumin: calcium binding protein
  - Corrected calcium = serum calcium in mg/dL + 0.8 × (4.0 − serum albumin in g/dL)
- Ionized calcium: helpful in normal/intermittently elevated serum calcium
- Renal functions: BUN, creatinine
- 25-hydroxyvitamin D
  - 1,25-dihydroxyvitamin D
- Phosphate, alkaline phosphatase
- Urine: calcium, creatinine and creatinine clearance

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CASE 1, CONT'D: SYMPTOMATIC CINDERELLA

Repeat calcium 10.9mg/dL (8.7-10.3mg/dL)	Albumin 4.2g/dL
iPTH 95pg/mL (12-65pg/mL)	Corrected calcium 10.7mg/dL
24 hour urine calcium 282mg (100mg-300mg)	25-OH vitamin D 23ng/mL (30-100ng/mL)
Renal functions normal	
Sestimibi scan: negative for localization	DXA scan: osteoporosis

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HYPERPARATHYROIDISM CLASSIFICATIONS

- Primary: over-secretion of PTH causing hypercalcemia
  - Most commonly due to parathyroid adenoma
- Secondary: increased PTH secretion in response to hypocalcemia
  - Vitamin D deficiency
  - End stage renal disease (ESRD) – decreased conversion 1,25-dihydroxyvitamin D
- Tertiary: autonomous PTH secretion following prolonged ESRD
  - ?impairment in calcium receptor
  - ?altered calcium set-point

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When to refer?

Confirmed diagnosis of hyperparathyroidism or unsure of dx

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FINDINGS IN HYPERPARATHYROIDISM

	Primary	Secondary:	Tertiary:
iPTH	Elevated or inappropriately normal	Elevated or normal	Elevated or inappropriately normal
Serum calcium	Normal, intermittently elevated, or elevated	Mid/low-normal or low	Normal, intermittently elevated, or elevated
Renal functions and/or 25-hydroxyvitamin D	Normal	Low	Low or normal
Phosphate	Low	Elevated	Elevated
24hr urine calcium	Elevated	Elevated	Elevated

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HYPERPARATHYROIDISM MISCONCEPTIONS

- Mildly elevated serum calcium level is a normal variation
- Elevated ionized calcium is required to diagnose hypercalcemia
- Normal iPTH level rules out hyperparathyroidism
- Urine calcium level is not important in the hypercalcemia w/u
- Normal urine calcium level rules out hyperparathyroidism
- Secondary hyperparathyroidism is hypercalcemia and hyperparathyroidism in the setting of low vitamin D or low renal function
- All patients with primary hyperparathyroidism require surgery

Normal ≠ Physiologic!

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CASE STUDY

Case 1: Symptomatic Cinderella

Case 2: Incidental Elsa

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CASE 2: INCIDENTAL ELSA

- 42 year old Caucasian female presents for annual exam
- She feels well overall without concerns
- Past medical history: hypothyroidism
- Current medication: levothyroxine 75mcg daily
  - No OTC supplementation
- BMI 24, BP 114/76, Pulse 70
- Annual labs are unremarkable except thyroid functions and calcium 10.6mg/dL (8.7-10.3mg/dL)

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CASE 2: INCIDENTAL ELSA

Repeat calcium 10.8mg/dL	Albumin 4.0g/dL
iPTH 15pg/mL (12-65pg/mL)	Renal functions normal
24 hour urine calcium 110mg (100mg-300mg)	25-OH vitamin D 15ng/mL (30-100ng/mL)

- What is the most appropriate next step?

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When to refer?

Work up for hyperparathyroidism is negative thus pt needs secondary work up

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CASE 2, CONT'D: INCIDENTAL ELSA

- Thyroid stimulating hormone (TSH) 0.20 mU/L (0.3-3.0 mU/L)
- Free T4 2.0ng/dL (0.7-1.9 ng/dL)

Repeat calcium 10.8mg/dL	Albumin 4.0g/dL
iPTH 15pg/mL (12-65pg/mL)	Renal functions normal
24 hour urine calcium 110mg (100mg-300mg)	25-OH vitamin D 15ng/mL (30-100ng/mL)

- What is Elsa's most likely diagnosis?

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ADDITIONAL CAUSES OF HYPERCALCEMIA

- Malignancy
  - PTH-related peptide
    - Humoral hypercalcemia of malignancy
  - Bony metastases/osteolytic hypercalcemia
- Genetic disorders
  - Familial hypocalciuric hypercalcemia (FHH)
  - Multiple endocrine neoplasia (MEN) 1 or 2A
- Hyperthyroidism
- Addison's disease (dehydration)
- Medication effects
- Immobility
- Sarcoidosis (increased calcitriol synthesis)

1. Muls E, et al. Etiology of hypercalcemia in a patient with Addison's disease. Calcif Tissue Int. 1982;34(6):5236.https://www.ncbi.nlm.nih.gov/pubmed/6819071
2. AACE/ACE. Primary Hyperparathyroidism. Copyright © 2019 American Association of Clinical Endocrinologists. https://www.aace.com/sites/default/files/2019-02/Primary_Hyperparathyroidism_formatted.pdf

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PHPT VS FHH

	PHPT	FHH
iPTH	Elevated or inappropriately normal	Elevated or normal
Serum calcium	Normal, intermittently elevated, or elevated	Normal, intermittently elevated, or elevated
Renal functions and/or 25-hydroxyvitamin D	Normal	Normal
24hr urine calcium	Elevated or high-normal	Low or low-normal
Symptoms or manifestations	Yes or no	No

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THE ROLE OF IMAGING

- DXA scan:
  - Assessment of hypercalcemia manifestations/surgical criteria
  - Include distal 1/3 radius
  - Preferential loss of cortical bone
- Consider abdominal imaging
  - Assess for nephrolithiasis or nephrocalcinosis
- Parathyroid imaging:
  - NOT for diagnosis
  - Localization for surgery only

"Imaging has no utility in confirming or excluding the diagnosis of PHPT[1]"

1. Wilhelm, Scott MD; et al. The American Association of Endocrine Surgeons Guidelines for Definitive Management of Primary Hyperparathyroidism. *JAMA Surg.* 2016;151(10):959-968. doi:10.1001/jamasurg.2016.2310

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CASE STUDIES: CINDERELLA & ELSA

- Which imaging studies would you recommend for Cinderella (if any)?

Repeat calcium 10.9mg/dL	Albumin 4.2g/dL
iPTH 95pg/mL (12-65pg/mL)	Corrected calcium 10.7mg/dL
24 hour urine calcium 282mg (100mg-300mg)	25-OH vitamin D 23ng/mL (30-100ng/mL)
Renal functions normal	

- For Elsa?

Repeat calcium 10.8mg/dL	Albumin 4.0g/dL
iPTH 15pg/mL (12-65pg/mL)	Renal functions normal
24 hour urine calcium 110mg (100mg-300mg)	25-OH vitamin D 15ng/mL (30-100ng/mL)
TSH 0.20 mU/L (0.3-3.0 mU/L)	Free T4 2.0ng/dL (0.7-1.9 ng/dL)

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TO TREAT OR NOT TO TREAT?

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LONG-TERM RISKS OF HYPERCALCEMIA AND HYPERPARATHYROIDISM

- BMD loss/fracture
- Kidney stone, renal impairment
- CVD/Premature death: severity of the hypercalcemia

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TREATMENT OPTIONS

- Parathyroidectomy
  - Preferred for those who meet surgical criteria
- Observation[1,2]
  - Not a surgical candidate/refuse surgery
    - Biochemical markers annually
    - BMD Q1-2 years
    - Up to 10 years
  - Additional considerations:
    - Dietary calcium: no restriction
    - Vitamin D: optimize
    - Bisphosphonate: tx of low BMD

1. AACE/ACE. Primary Hyperparathyroidism. Copyright © 2019 American Association of Clinical Endocrinologists.
2. Bilezikian, John P; et al. Guidelines for the Management of Asymptomatic Primary Hyperparathyroidism: Summary Statement from the Fourth International Workshop. *The Journal of Clinical Endocrinology & Metabolism*, Volume 99, Issue 10, 1 October 2014, Pages 3561–3569.

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SURGICAL CRITERIA FOR PARATHYROIDECTOMY

	Calcium	BMD	Age	Renal	Symptoms
Endocrine Society	Serum calcium >1.0 mg/dL	-OP by DXA Scan -Vertebral fx	<50	-Cr Clearance <60cc/min -24hr urine calcium >400mg/dL and increased stone risk -Nephrolithiasis or nephrocalcinosis on imaging	(did not assess)
AAES/AACE	Serum calcium >1.0 mg/dL	-OP by DXA Scan -Vertebral or fragility fx	<50	-eGFR <60 mL/min -24hr urine calcium >400mg/dL and increased stone risk -Nephrolithiasis or nephrocalcinosis on imaging	Confidently attributable to PHPT

*Pt preference or pt unable/unwilling to comply with observation

1. AACE/ACE. Primary Hyperparathyroidism. Copyright © 2019 American Association of Clinical Endocrinologists.
2. Bilezikian, John P; et al. Guidelines for the Management of Asymptomatic Primary Hyperparathyroidism: Summary Statement from the Fourth International Workshop. *The Journal of Clinical Endocrinology & Metabolism*, Volume 99, Issue 10, [illegible] 2014, Pages 3561–3569.

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When to refer?

Considering parathyroidectomy

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ALTERNATIVE TREATMENT OPTIONS: MEDICATION THERAPY

- Cinacalcet (Sensipar) [1, 2]
  - Effective in normalizing calcium in 70-80% of cases
    - No evidence of improvement in BMD, symptoms, or nephrolithiasis
  - AEs: QT prolongation, cardiac arrhythmias, heart failure, and hypotension
- Vitamin D: optimize
- Bisphosphonate: tx of low BMD

1. AACE/ACE. Primary Hyperparathyroidism. Copyright © 2019 American Association of Clinical Endocrinologists.
2. Wilhelm, Scott MD; et al. The American Association of Endocrine Surgeons Guidelines for Definitive Management of Primary Hyperparathyroidism. *JAMA Surg.* 2016;151(10):959-968. doi:10.1001/jamasurg.2016.2310

CASE STUDIES: CINDERELLA & ELSA

- What treatment would you recommend for Cinderella (if any)?

Repeat calcium 10.9mg/dL	Albumin 4.2g/dL
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TSH 0.20 mU/L (0.3-3.0 mU/L)	Free T4 2.0ng/dL (0.7-1.9 ng/dL)

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PROGNOSIS AND LONG-TERM EFFECTS

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POSTOP COMPLICATIONS

- Overall low (1-3%)[1]
- Hypocalcemia[2]
  - 5% - 47%
  - Typically transient
- Hypoparathyroidism
  - Rare (0%-3.6%)
- Recurrent laryngeal damage
  - Typically transient but can be permanent

1. AACE/ACE. Primary Hyperparathyroidism. Copyright © 2019 American Association of Clinical Endocrinologists.
2. Wilhelm, Scott MD; et al. The American Association of Endocrine Surgeons Guidelines for Definitive Management of Primary Hyperparathyroidism. *JAMA Surg.* 2016;151(10):959-968. doi:10.1001/jamasurg.2016.2310

RISK OF RECURRENCE

- Surgery is curative in >95%
- Repeat surgery in 5%
  - Due to incomplete resection
- True recurrence in 8%
  - >6 months postop

Rule out other causes, especially FHH!

IMPROVEMENT IN SYMPTOMS AND MANIFESTATIONS

- After parathyroidectomy
  - Bone mineral content/remodeling improves
  - Risk of nephrolithiasis improves
  - Possible improvement in CV and fx risks
  - Possible improvement in symptoms

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CME QUESTIONS

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CME QUESTION 1

1. The most common cause of hypercalcemia in the general population is:

a) Familial hypocalciuric hypercalcemia
b) Parathyroid adenoma
c) Multiple parathyroid gland hyperplasia
d) Humoral hypercalcemia of malignancy
e) Bony metastases

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CME QUESTION 2

2. Parathyroid imaging should be used to:

a) Rule out parathyroid carcinoma
b) Rule in parathyroid adenoma
c) Localize parathyroid adenoma/hyperplasia for surgery
d) Monitor hyperparathyroidism when surgery has been deferred

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CME QUESTION 3

3. Which of the following is true in primary hyperparathyroidism?

a) Parathyroid hormone level may be elevated or normal
b) Urine calcium level will be low
c) All patients should proceed with parathyroidectomy
d) Parathyroidectomy will not impact BMD

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CME QUESTION 4

4. A 32 year old female presents for a follow up after her annual labs showed an incidental elevated calcium of 10.6mg/dL (8.7-10.3mg/dL). She is asymptomatic and DXA scan is normal. Follow up testing shows:

Repeat calcium 10.7mg/dL	iPTH 70pg/mL (12-65pg/mL)
Albumin 4.4g/dL	25-OH vitamin D 18ng/mL (30-100ng/mL)
Corrected calcium 10.4mg/dL	Renal functions normal
24hour urine calcium 32mg (100mg to 300mg)	

What is the dx?

a) Primary hyperparathyroidism
b) Secondary hyperparathyroidism
c) Calcium oversupplementation
d) Familial hypocalciuric hypercalcemia

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QUESTIONS?

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