Management of Asymptomatic Hyperparathyroidism

Faculty

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Relevant Financial Relationship(s): None

Off Label Usage: None

Outcome Objectives

- Comprehend basic concepts of calcium physiology
- Discuss the diagnosis of primary hyperparathyroidism, including the various subtypes of primary hyperparathyroidism
- Examine current evidence and guidelines for management of primary hyperparathyroidism
- Review the current evidence regarding surgery and alternative therapies for primary hyperparathyroidism

Primary Hyperparathyroidism Fundamental Concepts

Parathyroid Glands

- Usually four glands (15% of people have 2, 3, or 5)
- Ectopic glands occur in 20% of people
- Small (20-40 mg): about the size of a “grain of rice”

Usually located posterior to/or imbedded in the thyroid gland either mediastinum, tracheoesaphogeal groove, or thymus

Parathyroid Hormone (PTH)

- Peptide hormone secreted by chief and oxyphil cells
- 84 amino acids: first few amino acids contain biologic activity
- Half-life of two to four minutes
- Acts at a G-protein coupled cell membrane receptor

  (PTH/PTHrP* shared receptor) located primarily in kidney and bone

*Parathyroid hormone-related protein

Importance of Calcium Homeostasis

- Cell membrane stability
- Neuromuscular stability in particular
  - Nerve function
  - Skeletal muscle function
  - Cardiac conduction
- We require adequate concentrations to allow for skeletal mineralization and avoid precipitation in soft tissue
- Intracellular calcium important for intracellular signaling

Regulation of PTH: Ionized Calcium

- Acute hypocalcemia causes PTH secretion from secretory vesicles within seconds
  - Intracellular degradation of PTH reduced within hours
  - Increased gene expression of PTH over hours to days
  - Enhanced proliferative activity of parathyroid cells over weeks to months
- Hypercalcemia inhibits PTH secretion, gene expression, and cellular proliferation

PTH Action on Extracellular Fluid, Calcium, and Phosphorus

↑ serum calcium level in extracellular fluid (ECF) by:

- ↑ calcium reabsorption in kidney (distal convoluted tubule)
- Liberating calcium from bone (↑ bone resorption)
- ↑ 1,25-dihyroxyvitamin D production in kidney
  - ↑ intestinal calcium absorption

↓ Phosphorus level in ECF by

- Inhibiting reabsorption of phosphorus at proximal renal tubule, thereby increasing phosphorus excretion

Primary Hyperparathyroidism Diagnosis

Primary Hyperparathyroidism Classical Laboratory Results

- PTH
  - Normal (20%) or elevated (80%)
  - Normal = usually upper 1/2 to 1/3 of reference range
- Phosphorus
  - Low in 25% in referral populations
- Calcium creatinine clearance ratio
  - $(U_{Ca} x S_{Cr})/(S_{Ca} x U_{Cr})$ ‹ 0.01 suggests familial benign hypocalciuric hypercalcemia
  - › 0.02 essentially rules out FBHH
- 25-D low in 50% – worse hyperparathyroidism if severe

Differential Diagnosis of Confirmed Hypercalcemia

Mid-High Normal or Elevated PTH	
Primary hyperparathyroidism	Medications
• Sporadic	• Thiazide diuretics
-Adenoma (80-85%)	• Lithium
-Hyperplasia/multiple glands (15-20%)	Chronic renal failure
-Carcinoma (‹ 1%)	Aluminum
Familial	Tertiary hyperparathyroidism
• Isolated	Autoimmune hypocalciuric hypercalcemia
• MEN 1	
• MEN 2A	
• MEN4	
• Jaw Tumor Syndrome (CDC73)	
Familial benign hypocalciuric hypercalcemia	

Calcium-Sensing Receptor (CaSR)

- Cell surface membrane, G-protein coupled receptor
  - Parathyroid chief cells
  - Kidney (cortical thick ascending limb of the Loop of Henle)
  - Others
- Primary ligand is Ca^{2+}
  - "Senses" extracellular serum Ca^{2+} concentration

Calcium-Sensing Receptor (CaSR)

- Action is independent of PTH
  - As calcium rises
    - Impairs reabsorption of calcium
    - Impairs reabsorption of water
  - As calcium falls
    - Enhances reabsorption of calcium

Familial Benign Hypocalciuric Hypercalcemia

- Clues of FBHH to remember:
  - + Family history
    - Autosomal dominant; high penetrance
  - Longstanding hypercalcemia
    - Was there ever a “really” normal calcium?
  - Young individual
  - Lack of complications
  - Persistent primary hyperparathyroidism after surgery
- Always consider if you’re thinking about surgery
  - Do concomitant 24-hour urine calcium and creatinine

Primary Hyperparathyroidism (PHPT) Subtypes

- Classic
- Mild PHPT
  - Normoparathyroid PHPT
  - Normocalcemic PHPT
- Thiazide-associated PHPT
  - More multigland disease

Primary Hyperparathyroidism (PHPT) Subtypes

- Hypercalciuric PHPT
  - Cured (single gland disease) vs persistent hypercalciuria (multigland disease)
- Lithium-associated PHPT
- Familial (genetic) PHPT
- Recurrent PHPT
- Persistent PHPT

Hereditary States of Hyperparathyroidism

Disorder	Responsible gene	Pathogenic mechanism	Associated clinical features
MEN type 1*	*MEN1, CDKN1B*	Loss-of-function mutation	Pituitary and gastroenteropancreatic tumors; less frequently, adrenal tumor, facial angiofibroma, collagenoma and lipoma
MEN type 2A	*RET*	Gain-of-function mutation	Medullary thyroid cancer, pheochromocytoma, cutaneous lichen amyloidosis
Hyperparathyroidism – jaw tumor syndrome	*CDC73*	Loss-of-function mutation	Fibromas in mandible or maxilla, renal and uterine tumors, ↑ rate of parathyroid carcinomas (15-20%)
Familial hypocalciuric hypercalcemia	*CASR*	Loss-of-function mutation	Rare pancreatitis, relative hypocalciuria (24-hr urinary calcium:creatinine ratio ‹0.01)
Neonatal severe primary hyperparathyroidism	*CASR*	Loss-of-function mutation	Life-threatening condition with marked hypercalcemia, hypotonia and respiratory distress
Familial isolated hyperparathyroidism	*MEN1, CDC73, CASR, CDKN1B*	Loss-of-function mutation	Lack of specific features of other syndromic forms

*Multiple endocrine neoplasia (MEN) type 1, a syndrome associated with a *CDKNB1* gene mutation, is also referred to as MEN type 4.

Marcocci C and Cetanin F: NEJM 365:2389, 2011.

MEN-1* PHPT
Clinical Expression vs. Sporadic

- Younger age (present 2nd to 4th decade)
- Lower PTH
  - Age ‹ 50 years and normal PTH levels with hypercalcemia, may consider MEN1 genetic testing
- Higher severity of bone involvement on BMD
- Same degree of nephrolithiasis
- Lower serum phosphorus

* multiple endocrine neoplasia, type 1

Eller-Vainicher C et al: JCEM 24:1404, 2009.

Normocalcemic PHPT

Normal serum calcium and elevated PTH without secondary cause of elevated PTH

- 25-D ≥ 20 ng/mL (49.92 nmol/L)
- eGFR ≥ 40 ml/min
- Urinary calcium ‹ 350 mg per 24 hour

Lowe H et al: J Clin Endocrinol Metab 92:3001, 2007.

Normocalcemic PHPT Clinical Features

- Women (35/37) and postmenopausal (29) with mean calcium 9.4 mg/dL (2.35 mmol/L)
- 7/37 (19%) became hypercalcemic upon yearly evaluation
  - ✓Higher baseline calcium (9.7 mg/dL) (2.43 mmol/L)
  - ✓Older
  - ✓Higher baseline 24-hour urine calcium
- 3/7 (43%) surgery patients – **multi-gland disease**

Lowe H et al: J Clin Endocrinol Metab 92:3001, 2007.

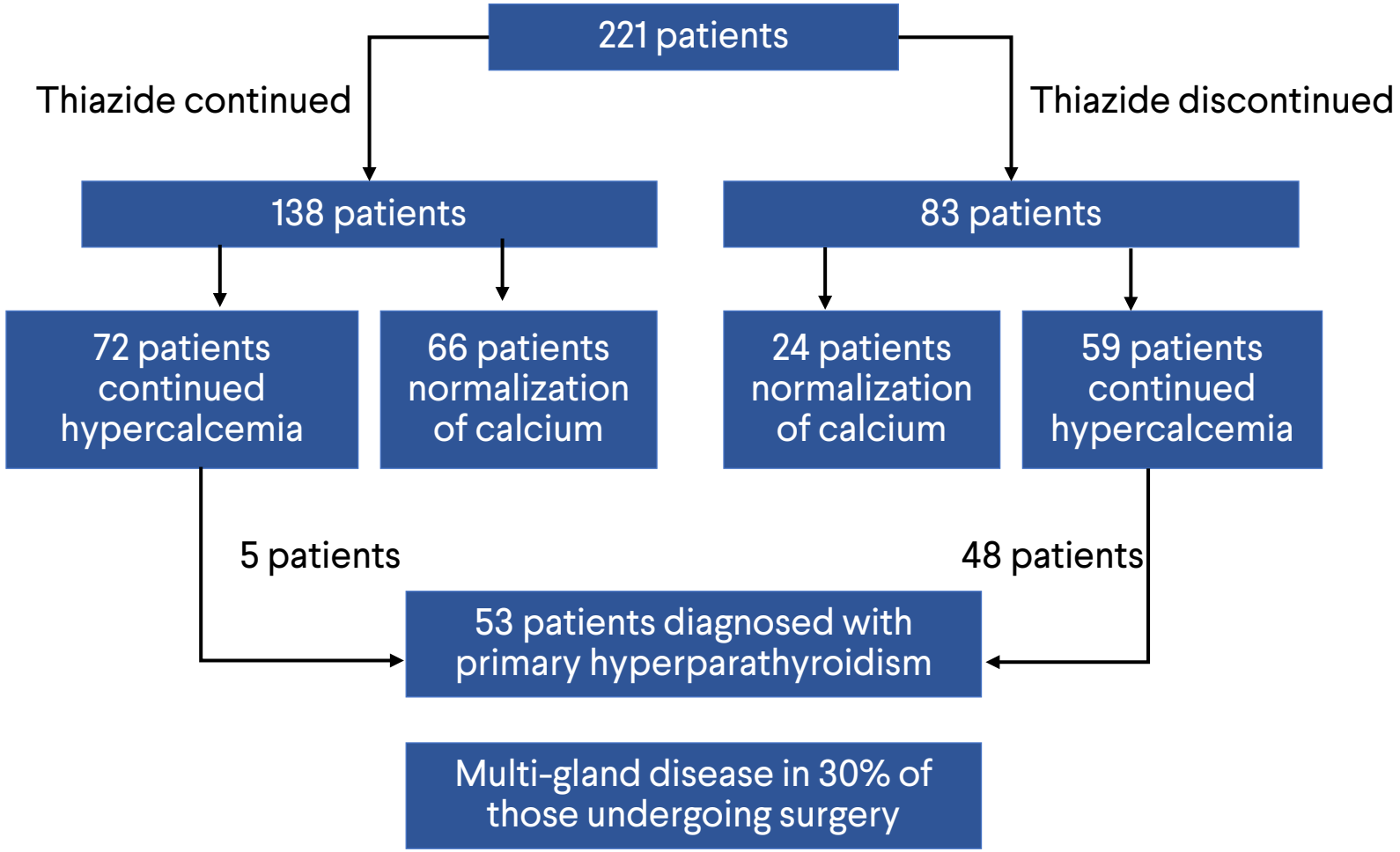
"Mild PHPT"

Normal PTH with high calcium or normal calcium with high PTH

- Increasing number of surgical patients with "mild PHPT"
  - 27% from 2001-2012 at referral center
    - 31.4% normocalcemic PHPT and 68.6% with normal PTH
- More likely to have multigland disease
- More than twice the number of kidneys stones
- Higher likelihood of negative localization (18% vs. 5%) persistent PHPT after surgery (12% vs. 4%)

Schneider DF et al: Ann Surg Oncol 20:4205, 2013.
Orr LE et al. World J Surgery 2018.

Thiazide-Associated Hypercalcemia



Griebeler et al: J Clin Endocrinol Metab 101:1166, 2016.

Other Unique PHPT Patients

- Persistent hypercalciuric PHPT after parathyroidectomy
  - Increased hyperplasia (50% estimate)

Palmieri S et al: JCEM 100:2734, 2015.

- Lithium-associated PHPT
  - 10-15% develop PHPT
    - Younger women (mean age 41 years)
  - Altered set point (FBHH-like) – Short term
  - Stimulates PTH secretion – Long term
    - Chronically leads to multigland disease

Mc Henry CR, Lee K: Endocr Pract 2:103,1996.

Primary Hyperparathyroidism Surgery

Asymptomatic PHPT

4th International Workshop on Asymptomatic Primary Hyperparathyroidism

Criteria for surgery:

- Age ‹ 50 years
- Serum calcium ›1 mg/dL (0.25 mM) upper limit of normal (ULN)
- Overt complication (Stones/Bones) includes radiographic stones (imaging recommended)
- 24-hour U-Ca ›400 mg (10 mmol) and increased stone risk by biochemical stone risk analysis

Bilezikian JP et al: J Clin Endo Metab, 2014.

Asymptomatic PHPT
4th International Workshop

Criteria for surgery:

- Calculated creatinine clearance ‹60 ml/min
- BMD with Z-score of ≤2.5 in premenopausal women or men ‹50 years or worse or T-score ≤2.5 in postmenopausal women and men over 50 years
- Vertebral fracture (morphometric) or fragility fracture

Bilezikian JP et al: J Clin Endo Metab, 2014.

Surgery is the only definitive therapy for PHPT and is always an option, even among those not meeting guidelines.

The American Association of Endocrine Surgeons (AAES) Guidelines for Definitive Management of Primary Hyperparathyroidism

- Not limited to asymptomatic PHPT
- Differences from 4th International Workshop exist but weakness of evidence acknowledged

Wihlem, SM et al. JAMA Surgery 2016;151:959-968.

AAES PHPT Evaluation

- Blood tests: calcium, PTH, creatinine, and 25- hydroxyvitamin D, albumin
- 24-hour urine calcium should be considered
- BMD hip, spine, radius
- In asymptomatic, renal imaging for stones (weak recommendation, low quality evidence)
- Obtain family history

Wihlem, SM et al. JAMA Surgery 2016;151:959-968.

AAES Indications for Parathyroidectomy

- “Symptomatic” disease
- Calcium › 1 mg/dL ULN
- Kidney stones and 24-hour urine calcium › 400 mg
- eGFR ‹ 60 mL/min
- Osteoporosis or vertebral fracture

Wihlem, SM et al. JAMA Surgery 2016;151:959-968.

AAES Indications for Parathyroidectomy

- Age ‹ 50 years
- Unwilling or unable to comply with observation
- Neurocognitive symptoms, heart disease, muscle weakness, functional capacity, sleep abnormality
- Consider in fibromyalgia, GERD

Wihlem, SM et al. JAMA Surgery 2016;151:959-968.

Meta-Analysis:
Surgery vs. Observation Asymptomatic PHPT

	Randomized clinical trials	Observational studies	
Outcome*	Comparative studies of surgery vs active surveillance	Active surveillance cohorts	Surgery cohorts
Fracture risk	No difference	Unknown (108 pts followed with no reported fractures)	NA
Kidney stones risk	No difference	Unknown (108 pts followed without symptomatic stones)	NA
Hypercalcemic crisis	NA	Unknown (108 pts followed without crisis)	NA
QOL/NPS	Clinical significance not clear (statistically significant treatment advantage for surgery in specific subdomains)	NA	No clear effect
Cardiovascular events	No difference	NA	NA
Mortality	NA	NA	NA
BMD changes	Clinical significance not clear (statistically significant treatment advantage for surgery)	No clear effect	NA

Singh Ospina N et al: Osteoporos Int 27:3395, 2016.

Primary Hyperparathyroidism Persistent and Recurrent Disease

Definitions

- Persistent PHPT
  - Fail of biochemical cure within six months after parathyroid surgery with hypercalcemia and inappropriate PTH
- Recurrent PHPT
  - Initial biochemical cure (normocalcemia) followed by hypercalcemia ›six months after surgery with inappropriate PTH

Reoperation for Persistent or Recurrent PHPT

Clinical Considerations:

- Does not have PHPT
  - Secondary HPT (especially in normocalcemic)
  - FBHH
  - Non-PTH mediated hypercalcemia
- Multiple gland disease
  - Family history important
  - PHPT subtype

Reoperation for Persistent or Recurrent PHPT

Clinical Considerations:

- Ectopic parathyroid adenoma
- Parathyroid carcinoma or parathyromatosis
- Surgeon did not find disease
  - Review operative report including intraoperative parathyroid hormone (IOPTH)
  - Review pathology report

Value of IOPTH in Parathyroidectomy

- Accurately predicted cure with a sensitivity of 98.6%
  - Single gland disease = 98.8%
  - Multi-gland disease = 96.7%

- If IOPTH would have not been utilized, only 517 (83.7%) of patients would have been cured (P ‹0.05).

Shawky M et al. Clin Endocrinol 2019;90:277-284.

Reoperative Parathyroidectomy

Patient Outcomes

- Imaging
  - Parathyroid sestamibi (89%), US (56%), CT (5%), SVS (1%)
- 89% cured (vs 97% without prior surgery)
  - Solitary gland 57%; Multigland 43%
    - Mediastinal 9%
  - Solitary gland disease and a single prior operation predictive of cure
- IOPTH 99% sensitive
  - Reduced risk of hypoparathyroidism (2% vs 9%)
- Hypoparathyroidism 3%; vocal cord paralysis 0.4%

Richards et al. Am J Surg 2008;196:937-943.

Primary Hyperparathyroidism Localization

Primary Hyperparathyroidism Imaging

- Main benefit is to allow minimal access parathyroidectomy
- Not necessary for the diagnosis, only do if surgery is planned
- Parathyroid nuclear imaging or US are sensitive tests (identify 75-85%) for identifying the abnormal gland but institutional dependent based on skill/methods of team
- 4D Parathyroid CT
- 11C Choline PET CT
  - Showing emerging benefit in localization

Liu Y et al J Nucl Med 2019.

Primary Hyperparathyroidism Non-Surgical Management

Primary Hyperparathyroidism Dietary Treatment

Maintain calcium intake: calcium intake of 1000 mg/day can suppress PTH and $1,25(D)_2$

Insogna KL et al. NEJM 1985.

Repleting with vitamin D when ‹ 20 ng/mL reduced PTH levels and urinary and serum calcium did not change

Grey A et al. JCEM 2005.

Non-Surgical Treatment of PHPT

	BMD	Serum calcium	PTH	Turnover markers
Alendronate	↑	0	0	↓
Estrogen	↑	↓	0	↓
Raloxifene	No data	↓	0	↓
Cinacalcet	0	↓	↓/0	↑/0
Cinacalcet + Alendronate	↑	↓	↓/0	↓

Cinacalcet in Primary Hyperparathyroidism

- Calcimimetic that directly reduces PTH secretion by binding to the calcium-sensing receptor on parathyroid cells increasing their sensitivity to extracellular calcium
- FDA approved in adults with:
  - Parathyroid carcinoma
  - Primary hyperparathyroidism unable to undergo parathyroid surgery

Cinacalcet in Parathyroid Carcinoma

- Starting dose 30 mg twice daily with titration depending on serum calcium response every 2-4 weeks:
  - 60 mg twice daily
  - 90 mg twice daily
  - 90 mg three-four times daily
- 62% of patients' serum calcium dropped at least 1 mg/dL
- Mean serum calcium decreased from 14.21 mg/dL to 12.4 mg/dL
- PTH decreased but not significantly
- Nausea (66%), vomiting (52%), dehydration (24%), and headaches (21%) most common adverse events

Silverberg SJ et al. J Clin Endocrinol Metab 2007;92:3803-3808.

Cinacalcet in Primary Hyperparathyroidism

- Consider in patients with persistent or recurrent PHPT who are not surgical candidates or in patients who have contraindications to or decline parathyroidectomy with significant hypercalcemia
- Start 30 mg once to twice daily and titrate to serum calcium up to 90 mg four times daily if needed

Marcocci C et al. J Clin Endocrinol Metab 2009;94:2766-2772.
Peacock M et al. J Clin Endocrinol Metab 2005;90:135-141.
Peacock M et al J Clin Endocrinol Metab 2009;94:4860-4867.

Cinacalcet in Primary Hyperparathyroidism

- 88% of patients achieved at least 1 mg/dL drop in serum calcium
- PTH does not change significantly in short term with slight long-term decrease
- Treatment up to 5.5 years has demonstrated durable decrease in serum calcium, increased phosphorus with no effect on DEXA BMD, $1,25(D)_2$, or 24-hour urine calcium

Marcocci C et al. J Clin Endocrinol Metab 2009;94:2766-2772.
Peacock M et al. J Clin Endocrinol Metab 2005;90:135-141.
Peacock M et al J Clin Endocrinol Metab 2009;94:4860-4867.

Monitoring Observed Asymptomatic PHPT

- Annual serum calcium
- Annual creatinine and eGFR
- If stones suspected, obtain 24-hour Urine, biochemical stone profile or renal imaging
- Every one-two years BMD (three site)
  - If T-score falls to -2.5 or progress decrease in BMD beyond LSC and T-score -2.0 or less consider surgery
- Thoracic and lumbar spine images as indicated

Bilezikian JP et al: J Clin Endo Metab, 2014.

27% of observed PHPT patients at 10 years and 37% of patients at 15 years will show evidence of significant progression of their disease.

Silverberg S et al. N Engl J Med, 1999.
Rubin MR et al: J Clin Endocrinol Metab, 2008.

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