Management of Asymptomatic Hyperparathyroidism
Faculty

Robert A. Wermers, M.D.
Division of Endocrinology, Diabetes, Metabolism and Nutrition and Department of Internal Medicine
Mayo Clinic Rochester, MN U.S.A.

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, tracheoesaphageal 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-dihydroxyvitamin 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**
  - \( \frac{U_{Ca} \times S_{Cr}}{S_{Ca} \times U_{Cr}} \) < 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

<table>
<thead>
<tr>
<th>Mid-High Normal or Elevated PTH</th>
<th>Medications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary hyperparathyroidism</td>
<td></td>
</tr>
<tr>
<td>• Sporadic</td>
<td></td>
</tr>
<tr>
<td>- Adenoma (80-85%)</td>
<td>• Thiazide diuretics</td>
</tr>
<tr>
<td>- Hyperplasia/multiple glands (15-20%)</td>
<td>• Lithium</td>
</tr>
<tr>
<td>- Carcinoma (&lt; 1%)</td>
<td>Chronic renal failure</td>
</tr>
<tr>
<td>Familial</td>
<td>Aluminum</td>
</tr>
<tr>
<td>• Isolated</td>
<td>Tertiary hyperparathyroidism</td>
</tr>
<tr>
<td>• MEN 1</td>
<td>Autoimmune hypocalciuric hypercalcemia</td>
</tr>
<tr>
<td>• MEN 2A</td>
<td></td>
</tr>
<tr>
<td>• MEN4</td>
<td></td>
</tr>
<tr>
<td>• Jaw Tumor Syndrome (CDC73)</td>
<td></td>
</tr>
<tr>
<td>Familial benign hypocalciuric hypercalcemia</td>
<td></td>
</tr>
</tbody>
</table>
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
<table>
<thead>
<tr>
<th>Disorder</th>
<th>Responsible gene</th>
<th>Pathogenic mechanism</th>
<th>Associated clinical features</th>
</tr>
</thead>
<tbody>
<tr>
<td>MEN type 1*</td>
<td>MEN1, CDKN1B</td>
<td>Loss-of-function mutation</td>
<td>Pituitary and gastroenteropancreatic tumors; less frequently, adrenal tumor, facial angiofibroma, collagenoma and lipoma</td>
</tr>
<tr>
<td>MEN type 2A</td>
<td>RET</td>
<td>Gain-of-function mutation</td>
<td>Medullary thyroid cancer, pheochromocytoma, cutaneous lichen amyloidosis</td>
</tr>
<tr>
<td>Hyperparathyroidism – jaw tumor syndrome</td>
<td>CDC73</td>
<td>Loss-of-function mutation</td>
<td>Fibromas in mandible or maxilla, renal and uterine tumors, ↑ rate of parathyroid carcinomas (15-20%)</td>
</tr>
<tr>
<td>Familial hypocalciuric hypercalcemia</td>
<td>CASR</td>
<td>Loss-of-function mutation</td>
<td>Rare pancreatitis, relative hypocalciuria (24-hr urinary calcium:creatinine ratio &lt;0.01)</td>
</tr>
<tr>
<td>Neonatal severe primary hyperparathyroidism</td>
<td>CASR</td>
<td>Loss-of-function mutation</td>
<td>Life-threatening condition with marked hypercalcemia, hypotonia and respiratory distress</td>
</tr>
<tr>
<td>Familial isolated hyperparathyroidism</td>
<td>MEN1, CDC73, CASR, CDKN1B</td>
<td>Loss-of-function mutation</td>
<td>Lack of specific features of other syndromic forms</td>
</tr>
</tbody>
</table>

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

MEN-1* PHPT
Clinical Expression vs. Sporadic

- Younger age (present 2\textsuperscript{nd} to 4\textsuperscript{th} 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

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

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
“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%)

Thiazide-Associated Hypercalcemia

221 patients

Thiazide continued

138 patients

72 patients continued hypercalcemia

66 patients normalization of calcium

5 patients

53 patients diagnosed with primary hyperparathyroidism

Multi-gland disease in 30% of those undergoing surgery

83 patients

Thiazide discontinued

24 patients normalization of calcium

59 patients continued hypercalcemia

48 patients

Other Unique PHPT Patients

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


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

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
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
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

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

AAES Indications for Parathyroidectomy

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

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

## Meta-Analysis: Surgery vs. Observation Asymptomatic PHPT

<table>
<thead>
<tr>
<th>Outcome*</th>
<th>Randomized clinical trials</th>
<th>Observational studies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fracture risk</td>
<td>No difference</td>
<td>Unknown (108 pts followed with no reported fractures)</td>
</tr>
<tr>
<td>Kidney stones risk</td>
<td>No difference</td>
<td>Unknown (108 pts followed without symptomatic stones)</td>
</tr>
<tr>
<td>Hypercalcemic crisis</td>
<td>NA</td>
<td>Unknown (108 pts followed without crisis)</td>
</tr>
<tr>
<td>QOL/NPS</td>
<td>Clinical significance not clear (statistically significant treatment advantage for surgery in specific subdomains)</td>
<td>NA</td>
</tr>
<tr>
<td>Cardiovascular events</td>
<td>No difference</td>
<td>NA</td>
</tr>
<tr>
<td>Mortality</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>BMD changes</td>
<td>Clinical significance not clear (statistically significant treatment advantage for surgery)</td>
<td>No clear effect</td>
</tr>
</tbody>
</table>

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).

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%

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

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)$_2$

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

## Non-Surgical Treatment of PHPT

<table>
<thead>
<tr>
<th>Treatment</th>
<th>BMD</th>
<th>Serum calcium</th>
<th>PTH</th>
<th>Turnover markers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alendronate</td>
<td>↑</td>
<td>0</td>
<td>0</td>
<td>↓</td>
</tr>
<tr>
<td>Estrogen</td>
<td>↑</td>
<td>↓</td>
<td>0</td>
<td>↓</td>
</tr>
<tr>
<td>Raloxifene</td>
<td>No data</td>
<td>↓</td>
<td>0</td>
<td>↓</td>
</tr>
<tr>
<td>Cinacalcet</td>
<td>0</td>
<td>↓</td>
<td>↓/0</td>
<td>↑/0</td>
</tr>
<tr>
<td>Cinacalcet + Alendronate</td>
<td>↑</td>
<td>↓</td>
<td>↓/0</td>
<td>↓</td>
</tr>
</tbody>
</table>
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

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

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

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

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

References


References


References


References


References


