UPDATES ON PRIMARY HYPERPARATHYROIDISM

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New York, NY
Disclosures

- Speaker (Honorarium): Shire
- Off-label use of estrogen, raloxifene and alendronate
Outline

• Introduction
• Clinical presentation
• Guidelines
  • Diagnosis and indications for genetic testing
  • Screening and management guidelines
    • Bones
    • Kidney
    • Normocalcemic PHPT
    • Medical therapy
    • Surgery
History of the parathyroid glands
History of the parathyroid glands

- First discovered by Richard Owen in 1852 during an autopsy on the Great Indian Rhinoceros owned by the Zoological Society of London
  - He noted “a small compact yellow glandular body attached to the thyroid at the point where the vein emerged”
- Ivar Viktor Sandröm (1852-1889), a medical student at the University of Uppsala is credited with naming the “glandulae parathyroidae”
- William George MacCallum (1874-1944), a Canadian-American physician and pathologist, proposed their role in calcium metabolism

Primary hyperparathyroidism is relatively common

- Parathyroid hormone (PTH) is made by the (usually) four parathyroid glands that sit on top of the thyroid
- Primary hyperparathyroidism (PHPT) is a disorder traditionally characterized by hypercalcemia and elevated levels of PTH
- PHPT is one of the most common endocrine disorders
  - Estimated prevalence 0.1-1% in postmenopausal women
  - Prevalence is about 3 times greater in women than men
  - More common in African Americans
  - More common with increasing age

The prevalence of PHPT in the US has tripled

Phenotypes of PHPT

Before 1970:
A disease of bones, stones, groans, and moans
The early clinical picture of PHPT

1918

The early clinical picture of PHPT

1918

1926

Symptomatic PHPT

- Nephrolithiasis
  - Remains the most common complication of PHPT
- Osteitis fibrosa cystica
  - Manifest clinically by bone pain and radiographically by “salt and pepper” appearance of the skull (A), tapering of the distal clavicles (B), subperiosteal bone resorption of the phalanges (C), and cysts and brown tumors of the long bones (D)

https://clinicalgate.com/primary-hyperparathyroidism
Symptomatic PHPT remains common in certain regions

- Spivacow F, et al., Medicina (B Aires) 2010
- Bandeira F, et al., Curr Rhematol Rep 2015
- Lo CY, et al., Arch Surg 2004
- Zhao L, et al., J Clin Endocrinol Metab 2013
- Pradeep PV, et al., Int J Endocrinol 2011
- Bandeira F, et al., Curr Rhematol Rep 2015
Phenotypes of PHPT

Before 1970:
A disease of bones, stones, groans, and moans

After 1970:
A disease with primarily biochemical and densitometric signatures
The modern clinical profile of PHPT

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*More common if imaging performed for screening

# The modern clinical profile of PHPT

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- 96 patients without PHPT without known history of nephrolithiasis
- Occult urolithiasis was detected in 21% of patients

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- 96 patients without PHPT without known history of nephrolithiasis
- Occult urolithiasis was detected in 21% of patients
- Urinary calcium threshold of >211 mg/day had a sensitivity of 84.2% and specificity of 55.3%
- 1,25(OH)<sub>2</sub>D threshold of >91pg/mL had a sensitivity and specificity of 62.5% and 90.0%

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None of the patients in the prior cohort were taking vitamin D supplements compared to 64% in the new cohort (median 800 IU daily)

Walker MD et al. Osteoporos Int 2015; 26:2837-43
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Walker MD et al. Osteoporos Int 2015; 26:2837-43
The densitometric signature of PHPT in the modern era

The densitometric signature of PHPT in the modern era -2-

Walker MD et al. Osteoporos Int 2015; 26:2837-43
Management of asymptomatic PHPT

- Who needs surgery?
- Who doesn’t need surgery?

Even though patients may not meet any specific criteria for surgery, parathyroidectomy is not inappropriate, as long as there are no medical contraindications.
Management of asymptomatic PHPT

- Who needs surgery?
- Who doesn’t need surgery?

- First International Workshop, 1990
- Second International Workshop, 2002
- Third International Workshop, 2008
- Fourth International Workshop, 2013
- American Association of Endocrine Surgeons, 2016
Guidelines overview

- Biochemical presentation
- Diagnostics
- Clinical presentations
- Natural history
- Densitometric features
- Other skeletal features
- Non-traditional features
- Pharmacological approaches
- Localization and surgical approaches

Outline

- Introduction
- Clinical presentation
- **Guidelines**
  - Diagnosis and indications for genetic testing
  - New screening and management guidelines
    - Bones
    - Kidney
    - Normocalcemic PHPT
    - Medical therapy
Differential diagnosis

Patient with hypercalcemia and normal or high PTH; not taking drugs (i.e. thiazide, lithium, vitamin D preparations)

Eastell R et al, J Clin Endocrinol Metab 2014;99:3570-9
Differential diagnosis

Patient with hypercalcemia and normal or high PTH; not taking drugs (i.e. thiazide, lithium, vitamin D preparations)

If low PTH, exclude biotin supplements

Eastell R et al, J Clin Endocrinol Metab 2014;99:3570-9
Differential diagnosis

Patient with hypercalcemia and normal or high PTH; not taking drugs (i.e. thiazide, lithium, vitamin D preparations)

Assess for family history of PHPT and for syndromic forms of PHPT

YES

Proceed to genetic testing (next figure)
Differential diagnosis

Patient with hypercalcemia and normal or high PTH; not taking drugs (i.e. thiazide, lithium, vitamin D preparations)

Assess for family history of PHPT and for syndromic forms of PHPT

NO

Measure: Urinary calcium: creatinine
Serum 25-hydroxyvitamin D
Estimated GFR

\[ \text{UCCR} = \frac{\text{[24-hour urine Ca x serum Cr]}}{\text{[Serum Ca x 24-hour urine Cr]}} \]
Differential diagnosis

Patient with hypercalcemia and normal or high PTH; not taking drugs (i.e. thiazide, lithium, vitamin D preparations)

Assess for family history of PHPT and for syndromic forms of PHPT

Measure:
- Urinary calcium:creatinine
- Serum 25-hydroxyvitamin D
- Estimated GFR

UCCR >0.02
Sporadic PHPT >90% likelihood
Differential diagnosis

Patient with hypercalcemia and normal or high PTH; not taking drugs (i.e. thiazide, lithium, vitamin D preparations)

- Assess for family history of PHPT and for syndromic forms of PHPT

Measure:
- Urinary calcium:creatinine
- 25(OH)D >30 ng/mL
- eGFR >60 cc/min

- UCCR >0.02
  - Sporadic PHPT >90% likelihood

- UCCR = 0.01 to 0.02
  - Not able to distinguish PHPT and FHH

- Genetic testing for CASR, GNA11 and AP2S1 to confirm FHH1, FHH2 and FHH3, respectively
Differential diagnosis

Patient with hypercalcemia and normal or high PTH; not taking drugs (i.e. thiazide, lithium, vitamin D preparations)

Assess for family history of PHPT and for syndromic forms of PHPT

Measure: Urinary calcium:creatinine
25(OH)D >30 ng/mL
eGFR >60 cc/min

UCCR > 0.02
Sporadic PHPT >90% likelihood

UCCR = 0.01 to 0.02
Not able to distinguish PHPT and FHH

UCCR <0.01
FHH >95% likelihood

Consider genetic testing to facilitate screening of relatives
Approach to suspected genetic etiology

Patient with PHPT

- Young age, multigland disease, parathyroid carcinoma or atypical adenoma

Young age = Age < 45 years
Multigland disease = ≥2 glands
Atypical adenoma = Cysts, fibrous bands

Eastell R et al, J Clin Endocrinol Metab 2014;99:3570-9
Approach to suspected genetic etiology

Patient with PHPT

Young age, multigland disease, parathyroid carcinoma or atypical adenoma

Sporadic PHPT; no genetic testing

Family history in 1st degree relatives, clinical assessment for MEN, HPT-JT
Approach to suspected genetic etiology

Patient with PHPT

Young age, multigland disease, parathyroid carcinoma or atypical adenoma

YES

Mutational analysis (in order of likely frequency):
1. MEN1
2. CASR, AP2S1, GNA11
3. HRPT2 (CDC73)
4. CDKN-1A, -B, -2B, -2C
5. RET
6. PTH
   o PRAD1

Mutation detected.
1. Follow-up with regular screening for other tumors in MEN syndrome or HPT-JT
2. Screen 1st degree relatives

Mutation not detected.
Likelihood of MEN, HPT-JT or FHH low
Approach to suspected genetic etiology

Patient with PHPT

Young age, multigland disease, parathyroid carcinoma or atypical adenoma

Family history in 1st degree relatives, clinical assessment for MEN, HPT-JT

Mutational analysis (in order of likely frequency):
1. MEN1
2. CASR, AP2S1, GNA11
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5. RET
6. PTH
   - PRAD1

Family members affected; abnormalities consistent with MEN, HPT-JT or FHH
- Pursue appropriate genetic analysis
Approach to suspected genetic etiology

Patient with PHPT

Young age, multigland disease, parathyroid carcinoma or atypical adenoma

Family history in 1st degree relatives, clinical assessment for MEN, HPT-JT

Family members affected; no abnormalities of MEN, HPT-JT or FHH

Mutational analysis (in order of likely frequency):
1. MEN1
2. CASR, AP2S1, GNA11
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4. CDKN-1A, -B, -2B, -2C
5. RET
6. PTH
   o PRAD1
Approach to suspected genetic etiology

Recommendation 1-6: Genetic counseling should be performed for patients younger than 40 years with PHPT and multigland disease and considered for those with a family history or syndromic manifestations (strong recommendation; low-quality evidence)
Outline

• Introduction
• Clinical presentation

• Guidelines
  • Diagnosis and indications for genetic testing
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    • Bones
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    • Normocalcemic PHPT
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Surgical guidelines for asymptomatic PHPT

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<tr>
<td>Serum calcium</td>
<td>&gt;1.0 mg/dL above normal</td>
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Recommendation 3-2: Parathyroidectomy is indicated when the serum calcium level is greater than 1 mg/dL above normal, regardless of whether objective symptoms are present or absent (strong recommendation; low-quality evidence).

Recommendation 3-5: Parathyroidectomy is indicated when PHPT is diagnosed at 50 years or younger regardless of whether objective or subjective features are present or absent (strong recommendation; moderate-quality evidence).
Fracture risk in PHPT

- Bone density and bone biopsy data show decreased cortical bone but preservation of the trabecular skeleton\textsuperscript{1-3}
- Fracture risk may be expected to be
  - ▪ at vertebral sites
  - ▲ at nonvertebral sites

\textsuperscript{1}Silverberg SJ et al. J Bone Miner Res 1989;4:283-91
\textsuperscript{2}Parisien M, et al. J Clin Endocrinol Metab 1990;70:930-8
\textsuperscript{3}Dempster DW, et al. Bone 2007;41:19-24
Fracture risk in PHPT -2-

Khosla S et al, J Bone Miner Res 1999;14:1700-7
Fracture risk in PHPT -2-

Khosla S et al, J Bone Miner Res 1999;14:1700-7
Fracture risk in PHPT -3-

Fracture risk in PHPT -3-

Most studies of fracture risk in PHPT demonstrate an increase in both vertebral and nonvertebral fractures.
Trabecular bone is also affected in asymptomatic PHPT

- High-resolution peripheral quantitative computed tomography (HRpQCT) is a non-invasive methodology to determine bone quality
- Using HRpQCT, two groups have demonstrated abnormalities in both cortical and trabecular bone in women with PHPT


Normal

Osteoporotic

xtremeCT
Microstructure is abnormal in asymptomatic PHPT

Microstructure is abnormal in asymptomatic PHPT

Cortical and trabecular indices are reduced at the radius and tibia in asymptomatic PHPT

Changes in skeletal microstructure by HRpQCT 24 months after parathyroidectomy

Volumetric BMD, cortical parameters, trabecular BMD, stiffness and failure load improve after successful parathyroidectomy

Surgical guidelines for asymptomatic PHPT

<table>
<thead>
<tr>
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</tr>
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<tbody>
<tr>
<td>Age</td>
<td>&lt;50 years</td>
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<tr>
<td>Serum calcium</td>
<td>&gt;1.0 mg/dL above normal</td>
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<td>Skeletal</td>
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</tr>
<tr>
<td></td>
<td></td>
<td>➢ Vertebral fracture by vertebral fracture assessment (VFA), X-ray, CT or MRI</td>
</tr>
</tbody>
</table>

Recommendation 3-4: Parathyroidectomy is indicated in patients with PHPT and osteoporosis, fragility fracture, or evidence of vertebral compression fracture on spine imaging (strong recommendation; high-quality evidence)
Renal guidelines from the Third Workshop (2008)

- 24-hour urine was not recommended as a guideline for surgery (but recommended to rule out FHH)
  - No evidence that urinary calcium excretion alone (without other urinary biochemical indices of increased stone risk) is a risk factor for stones
- Creatinine clearance <60 cc/min recommended as a guideline for surgery
  - Speculation that the increase in PTH when clearance <60 cc/min is detrimental

More recent data and reinterpretation of old data

- Kidney stones are still the most common complication of PHPT
- Kidney stones can be detected by non-invasive imaging (e.g. X-ray, ultrasound, CT)

Prevalence of kidney stones in “asymptomatic” patients with PHPT

Prevalence of kidney stones in “asymptomatic” patients with PHPT

17 of 76 (22.4%) patients classified as “asymptomatic” at baseline without osteoporosis by DXA were found to have kidney stones or vertebral fractures on imaging.

More recent data and reinterpretation of old data

- Kidney stones are still the most common complication of PHPT
- Kidney stones can be detected by non-invasive imaging (e.g. X-ray, ultrasound, CT)
- A 24-hour urine for analysis of biochemical stone risk factors (Ca^{2+}, P, SO_{4}, uric acid, etc.) is predictive of stones in PHPT
- Following successful parathyroid surgery, the probability of developing new stones decreases markedly (although a small risk remains likely due to coexisting idiopathic hypercalciuria)
- Skeletal involvement more evident in PHPT when the eGFR<60 cc/min

# Surgical guidelines for asymptomatic PHPT

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| Skeletal | • T-score <-2.5 at any site  
• Clinical fragility fracture | • T-score <-2.5 at any site  
• Clinical fragility fracture  
➢ Vertebral fracture by VFA, X-ray, CT or MRI |
| Renal | Creatinine clearance <60 cc/min [24-hour urine not recommended] | eGFR <60 cc/min  
➢ Kidney stone by X-ray, CT, or US  
➢ Urinary calcium >400 mg + other urinary indices of increased stone risk |

**Recommendation 3-3:** Parathyroidectomy is indicated for objective evidence of renal involvement, including silent nephrolithiasis on renal imaging, nephrocalcinosis, hypercalciuria (24-hour urine calcium level >400 mg/dL) with increased stone risk, or impaired renal function (glomerular filtration rate <60 mL/min) (weak recommendation; low-quality evidence)
Other aspects of PHPT

• Neurocognitive
• Cardiovascular
• Calcium and vitamin D
Putative neurocognitive and constitutional manifestations of asymptomatic PHPT

Frequent complaints
- Weakness
- Easy fatigability
- Depression
- Intellectual weariness
- Increased sleep requirements

Issues in attribution
- Present in many chronic conditions
- Lack specificity
- Difficult to quantitate
- Adequately controlled studies are a challenge

Inconsistent data from 3 randomized trials of the effect of parathyroidectomy on psychiatric/cognitive symptoms and quality of life (QoL), despite similar design and assessment tools:
- One RCT suggested parathyroidectomy prevents worsening of quality of life and improves psychiatric symptoms
- Another demonstrated improvement in QoL
- The third RCT indicated no benefit

Putative cardiovascular manifestations of asymptomatic PHPT

- Subtle abnormalities have been noted in:
  - Vascular reactivity
  - Left ventricular function
  - Carotid intimal thickness
- The functional significance is unknown and uncertain
- Reversibility after successful parathyroid surgery is not clear

Recommendations: Neurocognitive and cardiovascular

Neurocognitive and Cardiovascular complications:
Still not enough data for decisions on surgical management

Recommendation 3-8: Parathyroidectomy is recommended for patients with neurocognitive and/or neuropsychiatric symptoms that are attributable to PHPT (strong recommendation; low-quality evidence)

Recommendation 3-9: Parathyroidectomy may be offered to surgical candidates with cardiovascular disease who might benefit from mitigation of potential cardiovascular sequelae other than hypertension (weak recommendation; low-quality evidence)
Recommendations: Neurocognitive and cardiovascular

Recommendation 3-10a: The nontraditional symptoms of muscle weakness, functional capacity, and abnormal sleep patterns should be considered in the decision for parathyroidectomy (weak recommendation; moderate-quality evidence)

Recommendation 3-10b: The nontraditional features of gastro-esophageal reflux and fibromyalgia symptoms may be considered in the decision for parathyroidectomy (insufficient evidence)
Calcium intake and PHPT

- No data to support dietary restriction of calcium in patients with PHPT
- Patients with PHPT are often erroneously advised to restrict calcium intake
- Low dietary calcium intake has been shown to stimulate PTH secretion
- In a longitudinal natural history study, daily calcium intake thresholds (<300 mg, 300-800 mg, >800 mg) were found to have no effect on serum calcium, PTH, or urinary calcium excretion
- In a prospective trial, asymptomatic PHPT patients with daily calcium intake <450 mg were supplemented with 500 mg daily
  - No significant increase in serum calcium level after 4 and 12 weeks
  - ↓ in serum PTH after 4 weeks
  - ↑ in femoral neck BMD after 52 weeks

Vitamin D deficiency in PHPT

- A meta-analysis and literature review of 10 studies (340 patients) showed preoperative vitamin D repletion in patients with PHPT and vitamin D deficiency produced no significant change in serum calcium levels despite a significant increase in 25-hydroxyvitamin D
  - 5 patients developed worsening hypercalcemia, requiring cessation of vitamin D
  - No patient developed hypercalcemic crisis
- A double-blind randomized control trial showed cholecalciferol 2800 IU daily vs. placebo significantly ↓PTH (↓17%), ↑BMD (↑2.5% at the lumbar spine) and decreased bone turnover markers
  - No difference in adverse events between groups
  - No difference in any time point in serum or urinary calcium levels between groups

1 Shah VN, et al. Clin Endocrinol (Oxf) 2014;80:797-803
Recommendations: Calcium and vitamin D intake

Nutritional elements
- Calcium intake should follow national guidelines
- 25-hydroxyvitamin D levels $>20$ ng/mL ($>50$ nmol/L) using initial doses of 600-1000 IU daily
- Monitor serum and urine calcium with vitamin D repletion

Recommendation 5-1: Most patients with PHPT should follow Institute of Medicine guidelines for calcium intake (strong recommendation; moderate quality evidence)

Recommendation 5-2: Prior to parathyroidectomy, patients with PHPT who are vitamin D deficient can safely begin vitamin D supplementation (weak recommendation; low quality evidence)
Phenotypes of PHPT

Before 1970:
A disease of bones, stones, groans, and moans

After 1970:
A disease with primarily biochemical and densitometric signatures

After 2000:
A disease that may present at first with a more subtle biochemical signature – elevated PTH levels with normal serum calcium
Normocalcemic PHPT

- Recognized at the time of the Third International Workshop
- No diagnostic criteria or management recommendations were made at that time
- There is still no evidence to guide physicians regarding management decisions
Diagnostic features of normocalcemic PHPT

- Elevated PTH
- Normal albumin-adjusted serum calcium
- Normal ionized calcium
- Corrected and ionized calcium *ALWAYS NORMAL*

Eastell R et al, J Clin Endocrinol Metab 2014;99:3570-9
Exclude secondary hyperparathyroidism

- Vitamin D deficiency
  - Minimal goal level should be 20 ng/mL (50 nmol/L) but desirable >30 ng/mL (>75 nmol/L)
- Renal insufficiency
  - eGFR <60 cc/min
- Medications
  - Thiazide or loop diuretics, lithium, bisphosphonates, denosumab
- Hypercalciuria
- Malabsorption

Eastell R et al, J Clin Endocrinol Metab 2014;99:3570-9
Management of asymptomatic normocalcemic PHPT

Calcium and PTH annually
DXA every 1-2 years

Progression to hypercalcemic PHPT

Follow guidelines

Management of asymptomatic normocalcemic PHPT

Calcium and PTH annually
DXA every 1-2 years

Progression to hypercalcemic PHPT
Follow guidelines

Progression of disease
- Worsening bone density or fracture
- Kidney stone or nephrocalcinosis

Surgery
Phenotypes of PHPT

Before 1970:
A disease of bones, stones, groans, and moans

After 1970:
A disease with primarily biochemical and densitometric signatures

After 2000:
A disease that may present at first with a more subtle biochemical signature – elevated PTH levels with normal serum calcium

The present:
The parathyroid incidentaloma
Parathyroid incidentaloma

- Incidental parathyroid nodules noted at the time of an imaging study or during neck surgery
- Less than 50 cases reported in the literature
- The majority of reported cases are biochemically silent
- Monitoring and other management?

Medical management of PHPT

• Observation
• Pharmacological approaches

## 15-year natural history without surgery

<table>
<thead>
<tr>
<th>Index</th>
<th>Baseline</th>
<th>5 years</th>
<th>10 years</th>
<th>13 years</th>
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<tbody>
<tr>
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<td>25-hydroxyvitamin D</td>
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<td>22 ± 3</td>
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<td>20 ± 4</td>
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<tr>
<td>1,25-dihydroxyvitamin D</td>
<td>50 ± 2</td>
<td>58 ± 3</td>
<td>54 ± 6</td>
<td>40 ± 5</td>
<td>48 ± 7</td>
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<tr>
<td>Urine calcium</td>
<td>238 ± 19</td>
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15-year natural history without surgery -2-
37% of patients developed one or more indications for surgery during 15 years of monitoring (nephrolithiasis, hypercalcemia, or reduced bone mineral density).

63% of patients did not develop an indication for surgery during 15 years of monitoring (nephrolithiasis, hypercalcemia, or reduced bone mineral density)
Pharmacologic approaches to PHPT

- **When?**
  - Surgery is indicated but medically contraindicated or patient declines

- **Which agent?**
  - The surgical indication can be ameliorated by the drug (e.g., severe hypercalcemia, reduced bone density)
  - Cinacalcet is the only approved agent for therapy of hypercalcemia in the US and EU
  - Other agents that have been studied include: estrogen, raloxifene, alendronate
# Pharmacologic approaches to PHPT

<table>
<thead>
<tr>
<th>Agent</th>
<th>Serum calcium</th>
<th>PTH</th>
<th>Bone density</th>
</tr>
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<tbody>
<tr>
<td>Estrogen&lt;sup&gt;1&lt;/sup&gt;</td>
<td>![arrow]</td>
<td>![arrow]</td>
<td>![arrow]</td>
</tr>
<tr>
<td>Raloxifene&lt;sup&gt;2&lt;/sup&gt;</td>
<td>![arrow]</td>
<td>![arrow]</td>
<td>![arrow]</td>
</tr>
<tr>
<td>Alendronate&lt;sup&gt;3&lt;/sup&gt;</td>
<td>![arrow]</td>
<td>![arrow]</td>
<td>![arrows]</td>
</tr>
<tr>
<td>Cinacalcet&lt;sup&gt;*&lt;/sup&gt;&lt;sup&gt;4&lt;/sup&gt;</td>
<td>![arrows]</td>
<td>![arrow]</td>
<td>![arrow]</td>
</tr>
<tr>
<td>Cinacalcet + Alendronate&lt;sup&gt;5&lt;/sup&gt;</td>
<td>![arrows]</td>
<td>![arrow]</td>
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*The only agent approved for PHPT in the US and EU

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*Grey et al., 1996; ²Rubin et al., 2005; ³Khan et al., 2004; ⁴Peacock et al., 2005, 2009; ⁵Faggiano et al., 2011*
Recommendations: Pharmacologic management

- For the control of hypercalcemia, cinacalcet is the treatment of choice
- To improve BMD, bisphosphonate therapy is recommended
  - The best evidence is for the use of alendronate
- To reduce the serum calcium and improve BMD, combination therapy with both agents is reasonable, but strong evidence for efficacy is lacking

Recommendation 3-12: Operative management is more effective and cost-effective than either long-term observation or pharmacologic therapy (strong recommendation; moderate quality evidence)
Surgical management of PHPT

- Surgical approaches include minimally invasive parathyroidectomy with intraoperative PTH and full exploration
  - In the modern era, MIP with iPTH has helped achieve cure rates of 97-99%
- Preoperative localization is necessary (ultrasound, $^{99m}$Tc sestamibi, MIBI SPECT/CT, $^{18}$F-fluorocholine PET/CT, MRI)
- The ideal localization study depends on local availability and expertise, the preference of the surgeon, need for reoperation

“The most important preoperative localization challenge in PHPT is to locate the parathyroid surgeon!” – John Doppman, 1975

Surgical management of PHPT

Recommendation 4-1: Patients who are candidates for parathyroidectomy should be referred to an expert clinician to decide which imaging studies to perform based on their knowledge of regional imaging capabilities (strong recommendation; low-quality evidence)

Recommendation 4-3: Cervical ultrasonography is recommended to localize parathyroid disease and assess for concomitant thyroid disease (strong recommendation; low-quality evidence)
Following successful parathyroid surgery…

- Serum calcium
- PTH
- 25-hydroxy- and 1,25-dihydroxyvitamin D
- Urine calcium
- Risk of nephrolithiasis
- Bone markers (resorption and formation)
- Bone density
- Bone microarchitecture

→ **Normalize or return towards normal**
Surgical guidelines for asymptomatic PHPT

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### Monitoring guidelines for asymptomatic PHPT

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<tbody>
<tr>
<td>Serum calcium</td>
<td>Annually</td>
<td>Annually</td>
</tr>
<tr>
<td>Skeletal</td>
<td>DXA: Every 1-2 years</td>
<td>• DXA: Every 1-2 years&lt;br&gt;• Imaging if clinically indicated</td>
</tr>
<tr>
<td>Renal</td>
<td>Annual monitoring of creatinine clearance</td>
<td>• Annual monitoring of eGFR&lt;br&gt;• Stone risk profile or abdominal imaging if clinically indicated</td>
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## Indications for surgery during monitoring

<table>
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<th>Fourth workshop (2013)</th>
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<tr>
<td>Serum calcium</td>
<td>&gt;1 mg/dL above the normal limit</td>
</tr>
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| Skeletal | • T-score <-2.5 at lumbar spine, total hip, femoral neck, or distal 1/3 radius; or a significant reduction in BMD*  
  • Vertebral fracture by X-ray, CT, MRI or VFA                                         |
| Renal  | • eGFR <60 cc/min  
  • Clinical development of a kidney stone or by imaging (X-ray, ultrasound, or CT) |

*A significant change is defined by a reduction that is greater than the least significant change (LSC) as defined by the International Society for Clinical Densitometry. If the reduction is > LSC of the measurement to a T-score that is <-2.5 then, surgery is recommended. If the patient demonstrates a progressive reduction in BMD that exceeds the LSC at any site and is between -2.0 and -2.5, the physician may opt to recommend surgery even though guidelines have not been strictly met.
Are the scales tipping toward surgery?

**Surgery**
- 15-year natural history
- Vitamin D deficiency
- Neurocognitive data?
- Cardiovascular data?
- Cortical and trabecular abnormalities and improvement following surgery
- Better imaging techniques
- Improvements in surgical technique
- Patient preference

**Medical management**
- 15-year natural history
- Use of vitamin D
- Medical alternatives
- Patient preference

Both options are important to consider in each patient.
Key Points

• Guidelines for parathyroid surgery have been revised consistent with the latest new information

• Non-surgical management may be appropriate for individuals who do not meet surgical criteria or if there are contraindications to surgery

• Surgery may also be appropriate for individuals who do not meet surgical criteria, if there are no medical contraindications
THANK YOU