Primary hyperparathyroidism and indications for surgery

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Mount Sinai Health System
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Overview

1. PHPT is **underdiagnosed**
2. **Evidence** for the guidelines
3. Are the guidelines **absolute**?
Diagnosis & initial evaluation
PHPT: blood test diagnosis

Excessive secretion of PTH inappropriate to the serum calcium concentration

10-20% of patients have normal serum calcium levels

Calcium & PTH levels fluctuate... repeat labs
Serum Ca/PTH relationship

Inverse relationship
PHPT epidemiology

3 : 1 female : male

2% post-menopausal women (Swedish study)

80-90% single adenoma

5% double adenoma

10-15% 4-gland hyperplasia

Action of PTH

Parathyroids

Adenoma

Intestine

Bone

ECF Ca²⁺

ECF Pi

Ca²⁺

Pi

Kidney

Urine Pi

1,25(OH)₂D₃

25(OH)D₃

1α(OH)ase

Hyperparathyroidism

Pi: Phosphate

Goltzman, Diseases of Bone and Mineral Metabolism 2008
CASE

A 51 year old woman with osteopenia has bloodwork done:
calcium of 9.8 (nl 8.6-10.2),
PTH 82 (nl 10-65)
creatinine 0.8.

Differential Diagnosis? Is this HPT?

PHPT (normocalcemic or classic) or secondary HPT

Workup?

Check another Ca (levels can fluctuate), vitamin D level, 24h urine calcium
Types of hyperparathyroidism

- **Primary** (normal creatinine)
- **Secondary** (hypocalcemic or normocalcemic)
  - ESRD $\rightarrow$ *low vitamin D*, elevated PO4
  - Vitamin D deficiency
  - Malabsorption, short gut syndrome, gastric bypass
- **Tertiary** (hypercalcemic)
  - Classically described after renal transplant
  - Progression of secondary to autonomously hyperfunctioning glands
What is “asymptomatic HPT”?

Lack of specific symptoms or signs traditionally associated with PHPT, such as:

– Renal stones
– Myopathies
– Osteofibrosis cystica
Incidental finding on “routine blood work”

- No longer the classic syndrome of “bones, stones, groans, and psychiatric overtones”
- Most patients are asymptomatic
- Use of multichannel blood autoanalyzer in 1970s

### Table 1 The changing clinical profile of primary hyperparathyroidism.

<table>
<thead>
<tr>
<th>Researchers (study period)</th>
<th>Symptoms observed (% of patients)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Nephrolithiasis</td>
</tr>
<tr>
<td>Cope (1930–1965)(^1)</td>
<td>57</td>
</tr>
<tr>
<td>Heath et al. (1965–1974)(^2)</td>
<td>51</td>
</tr>
<tr>
<td>Mallette et al. (1965–1974)(^3)</td>
<td>37</td>
</tr>
<tr>
<td>Silverberg, Bilezikian, and colleagues (1984–2006; various studies)</td>
<td>17</td>
</tr>
</tbody>
</table>

Abbreviation: NR, not reported.
Ask about...

- Nephrolithiasis
- T score, history of fractures
- Neurocognitive symptoms
“But doc, I feel fine...”

Incidental hypercalcemia on “routine blood work” performed by PCP

Workup reveals PHPT

Who benefits from surgery?
CASE

55F with Ca 10.9, PTH 72, normal creatinine.
24h urine 420 mg
T -2.1 lumbar spine
Asymptomatic

Diagnosis?

PHPT

Does she meet consensus guidelines for surgery?

NO  (but many would offer surgery)

What are the guidelines for surgery?
Rationale for guidelines

Majority of patients are asymptomatic

This led to the Consensus Development Conference on the Management of Asymptomatic Primary Hyperparathyroidism at the National Institutes of Health (1990)

Revised in 2002, 2008 & 2013 (Florence, Italy, manuscript in press)
Guidelines for the Management of Asymptomatic Primary Hyperparathyroidism: Summary Statement from the Third International Workshop

John P. Bilezikian, Aliya A. Khan, and John T. Potts, Jr. on behalf of the Third International Workshop on the Management of Asymptomatic Primary Hyperthyroidism*
Third international workshop on the management of asymptomatic hyperparathyroidism

Updated in 2013…
Renal ultrasound to screen for kidney stones
Additional skeletal testing
Algorithm for treatment of normocalcemic HPT
Evidence supporting the guidelines
Evidence supporting the guidelines

Exhibit A:
The natural history of primary hyperparathyroidism
The Natural History of Primary Hyperparathyroidism with or without Parathyroid Surgery after 15 Years

Mishaela R. Rubin, John P. Bilezikian, Donald J. McMahon, Thomas Jacobs, Elizabeth Shane, Ethel Siris, Julia Udesky and Shonni J. Silverberg
15 year observational study of patients with primary HPT

116 patients
99 with asymptomatic disease (85%)
17 with symptomatic disease (15%)

Surgery in 59 patients (51%)
50 with asymptomatic disease
9 with symptomatic disease

Normalization of biochemical values and increased bone mineral density in 59 patients
(100% of symptomatic and asymptomatic patients)

Disease progression in 22 patients
18 with asymptomatic disease
7 with surgical criteria; 11 without surgical criteria
(37% of asymptomatic patients)
8 with symptomatic disease
(100% of symptomatic patients)

No surgery in 57 patients (49%)
49 with asymptomatic disease
20 with surgical criteria; 29 without surgical criteria
8 with symptomatic disease

Stable disease in 31 patients
31 with asymptomatic disease
13 with surgical criteria; 18 without surgical criteria
(63% of asymptomatic patients)

Rubin, JCEM 2008
Observational study of patients with primary HPT

Calcium slowly increased over 15 years

<table>
<thead>
<tr>
<th>Variable</th>
<th>Baseline (n = 49)</th>
<th>Yr 5  (n = 25)</th>
<th>Yr 10 (n = 11)</th>
<th>Yr 13 (n = 9)</th>
<th>Yr 15 (n = 6)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum calcium (mg/dl)</td>
<td>10.5 ± 0.1</td>
<td>10.7 ± 0.1</td>
<td>10.8 ± 0.2</td>
<td>11.0 ± 0.2&lt;sup&gt;a&lt;/sup&gt;</td>
<td>11.1 ± 0.2&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>PTH (pg/ml)</td>
<td>122 ± 10</td>
<td>119 ± 12</td>
<td>123 ± 14</td>
<td>124 ± 16</td>
<td>121 ± 18</td>
</tr>
</tbody>
</table>

Rubin, JCEM 2008
Observational study of patients with primary HPT

<table>
<thead>
<tr>
<th>Observed</th>
<th>Surgery</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>57 (49%)</td>
<td>59 (51%)</td>
</tr>
<tr>
<td>Kidney stones</td>
<td>Recurrence in 100%</td>
<td>No recurrences</td>
</tr>
<tr>
<td>(of those with prior stones)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Femur/radius BMD</td>
<td>-10%/-35% (in 59%)</td>
<td>+10%/+7%</td>
</tr>
<tr>
<td></td>
<td>0.002</td>
<td></td>
</tr>
<tr>
<td>Lumbar spine BMD</td>
<td>Stable</td>
<td>+12%</td>
</tr>
<tr>
<td></td>
<td>0.02</td>
<td></td>
</tr>
</tbody>
</table>

At 15 years, surgical patients had increased BMD despite expected age-related bone loss

These data argue for early surgical intervention

Rubin, JCEM 2008
Observational study of patients with primary HPT

- **37%** of asymptomatic patients eventually satisfy criteria for surgery (*1990 criteria*)
- This number would likely be higher by the 2008 criteria
- 60% of observed patients continued to lose BMD
- 100% of the surgical group had increased BMD
PEAR study (Scotland)

The natural history of treated and untreated primary hyperparathyroidism: the Parathyroid Epidemiology and Audit Research Study

N. YU¹, G.P. LEESE², D. SMITH³ and P.T. DONNAN¹
PEAR study

1100 patients: mild primary hyperparathyroidism
Tayside, Scotland (1997-2006)

  904 observed (median calcium 10.5 mg/dl, PTH 61 pg/mL)
  200 had surgery

Followup: 4.7-5.8 years

15% with increasing calcium

  • Age at diagnosis and baseline PTH were predictors of hypercalcemia
Hyperparathyroidism

PEAR study

Rates per 100 person-years

<table>
<thead>
<tr>
<th>Other complications</th>
<th>Before surgery</th>
<th>After surgery</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiovascular disease</td>
<td>2.48</td>
<td>1.66</td>
<td>NS</td>
</tr>
<tr>
<td>Renal stones</td>
<td>3.10</td>
<td>0.38</td>
<td>0.01</td>
</tr>
<tr>
<td>Renal failure</td>
<td>4.96</td>
<td>0.90</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Osteoporosis fractures</td>
<td>1.56</td>
<td>0.76</td>
<td>NS</td>
</tr>
<tr>
<td>Cancer</td>
<td>1.86</td>
<td>2.30</td>
<td>NS</td>
</tr>
<tr>
<td>Psychiatric disease</td>
<td>0.32</td>
<td>0.12</td>
<td>NS</td>
</tr>
</tbody>
</table>

Surgery decreased the risk of:
Kidney stones (by 88%)
Fractures (by 50%, not significant, underpowered)

Yu, QJM 2011
Cohort study on effects of parathyroid surgery on multiple outcomes in primary hyperparathyroidism

Peter Vestergaard, Leif Mosekilde

- Danish cohort study (3213 patients; 1980-1999)
  - 1934 (60%) underwent surgery
  - 1279 (40%) were observed

- Lower risk of fractures, ulcers and death in the surgical group
Randomized controlled trials for asymptomatic primary HPT

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>Observation</th>
<th>Surgery</th>
</tr>
</thead>
<tbody>
<tr>
<td>Henry Ford Hospital.</td>
<td>53</td>
<td>BMD loss: 0.6% / year</td>
<td>Increase in BMD: 1.2% / year</td>
</tr>
<tr>
<td>Rao. JCEM. 2004.</td>
<td></td>
<td>BMD loss: 0.6% / year</td>
<td>Improved QOL (at 2 yrs)</td>
</tr>
<tr>
<td>Pisa. Ambrogini. JCEM. 2007</td>
<td>50 with mild disease (did not meet 1990 criteria)</td>
<td>BMD loss (hip) 23% met criteria for surgery at 1 year</td>
<td>Increased BMD (at 1 yr) Improved QOL (at 1 yr)</td>
</tr>
<tr>
<td>Sweden. Bollerslev. JCEM. 2009.</td>
<td>191</td>
<td>Decreased BMD Worse QOL</td>
<td>Increased BMD (at 2 yrs)</td>
</tr>
<tr>
<td>Meta-analysis. Sankaran. 2010. JCEM 2010.</td>
<td>34 publications</td>
<td>BMD loss: 0.6-1.0% / year</td>
<td>Increased BMD: 2% L-spine 7% femur</td>
</tr>
</tbody>
</table>

Benefits to surgery are observed relatively soon
These RCTs argue for early intervention
What about fracture risk?

- Degree of osteoporosis predicts fracture risk
- Primary HPT → increased fracture risk in all patients
- Postoperative data conflicting; many studies underpowered

### 10 Year Fracture Free Survival Rates

<table>
<thead>
<tr>
<th>T score</th>
<th>Surgical group (n=159)</th>
<th>Observed (n=374)</th>
<th>Absolute risk reduction</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt; -1.0</td>
<td>98%</td>
<td>89%</td>
<td>9%</td>
<td>NS</td>
</tr>
<tr>
<td>-1 to – 2.5</td>
<td>92%</td>
<td>80%</td>
<td>12%</td>
<td>NS</td>
</tr>
<tr>
<td>&lt;-2.5</td>
<td>82%</td>
<td>70%</td>
<td>12%</td>
<td>.02</td>
</tr>
<tr>
<td>All</td>
<td>94%</td>
<td>81%</td>
<td>13%</td>
<td>.006</td>
</tr>
</tbody>
</table>

Number needed to treat: 8

Vanderwalld, World J Surg 2009
GFR $< 60 \text{ ml / min}$

- PTH increases with decreased GFR
- This may worsen the primary hyperparathyroid state
- Recent data indicates that PTH increases at GFR $< 30 \text{ ml/min}$
- Increased surface erosion of bone with decreased GFR

Fajtova, Calcif Tissue Int 1995
Tassone, JCEM 2009
Walker, JCEM 2012
24 hour urine: no longer a criterion

- Hypercalciuria is not a risk factor for nephrolithiasis in PHPT (if the patient has never had a kidney stone)
- Still helpful in initial evaluation, to rule out familial hypocalciuric hypercalcemia
Age < 50

Increased lifetime in which sequelae will occur

Young age (<50) is associated with increased risk of progression
Are the guidelines absolute?
CASE

60 yo woman with calcium 10.9, PTH 65. Symptoms: depression, memory loss, and fatigue.

Operate or observe?

“Although it’s nothing serious, let’s keep an eye on it to make sure it doesn’t turn into a major lawsuit.”
Are 80% of patients really “asymptomatic”?  

• With standardized questioning, 80-98% of patients with “asymptomatic HPT” are symptomatic  
• Many of these “symptoms” are vague and non-specific  

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>Associated conditions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fatigue</td>
<td>Osteopenia</td>
</tr>
<tr>
<td>Weakness</td>
<td>Osteitis fibrosa cystica</td>
</tr>
<tr>
<td>Depression</td>
<td>Nephrolithiasis</td>
</tr>
<tr>
<td>Loss of recent memory</td>
<td>Nephrocalcinosis</td>
</tr>
<tr>
<td>Polydipsia</td>
<td>Peptic ulcer disease</td>
</tr>
<tr>
<td>Polyuria</td>
<td>Pancreatitis</td>
</tr>
<tr>
<td>Nocturia</td>
<td>Gout</td>
</tr>
<tr>
<td>Musculoskeletal aches and pains</td>
<td>Pseudogout</td>
</tr>
<tr>
<td>Constipation</td>
<td>Hypertension</td>
</tr>
<tr>
<td>Abdominal or flank pain</td>
<td></td>
</tr>
</tbody>
</table>

Clark, J of Bone and Min Res 1991  
Eigelberger, Annals Surgery 2004
Are 80% of patients really “asymptomatic”?

• Several studies suggest that surgery improves neurocognitive symptoms in up to 80% of patients

• Reduced mood and anxiety symptoms and improved visuospatial working memory in a prospective study

• May be placebo effect; follow-up time is short

• The data are not definitive, and are not part of the guidelines

Clark, J of Bone and Min Res 1991
Eigelberger, Annals Surgery 2004
Roman, Sosa, Surgery 2005
Roman, Sosa, Ann Surg 2011
Are the guidelines cost-effective?

Parathyroidectomy is more cost effective than observation...
if life expectancy greater than 5 years
Are guidelines being followed?

  - Of patients who *met* guidelines, < 50% had surgery
  - Of patients *not* meeting guidelines, 16% had surgery
  - Of patients with *nephrolithiasis*, only 50% had surgery

- *Parathyroidectomy is underutilized*
Why aren’t the guidelines being followed?

- Lack of knowledge of the guidelines
- Lack of consultation with a surgeon
- **Lack of localization** may incorrectly lead to continued observation

- Patients with biochemically-proven PHPT should be referred to a parathyroid surgeon for consultation
- A surgeon is the ideal individual to explain the risks, benefits and alternatives to operative intervention
Normocalcemic hyperparathyroidism
Normocalcemic PHPT

Rule out elevated PTH due to

- **25-OH vitamin D deficiency** (<20-30 ng/mL)
  - Treat with vitamin D, PTH will decrease
- **Primary renal calcium leak**
  - Treat with HCTZ, PTH will decrease
- **Impaired kidney function/ESRD**
- **Low calcium diet, malabsorption**
  - Treat with calcium, PTH will decrease
Do patients with normocalcemic HPT benefit from surgery?

Controversial, probably yes

Cured of recurrent nephrolithiasis

Expect that patients with nephrolithiasis & osteoporosis would benefit

Johansson, Surgery 1975
Maruani, JCEM 2003
Do *asymptomatic* patients with normocalcemic HPT benefit from surgery?

Can we apply the 2008 consensus guidelines for patients with asymptomatic HPT to patients with NHPT?

Unclear...perhaps in a young patient with osteopenia
With normocalcemic HPT...

*Is there an easy way to diagnose HPT?*
Regression model for PTH levels

• Model helps distinguish primary vs secondary HPT
• Based on age, calcium, PTH and Vitamin D levels
• **Expected PTH** (pg/ml) =
  \[ 120 - (6 \times \text{Ca mg/dl}) - (0.52 \times 25-\text{OH Vit D ng/ml}) + (0.26 \times \text{age}) \]
• Validated on an independent cohort, successfully identified
  – 100% hypercalcemic PHPT
  – 96% normocalcemic HPT

Harvey, Endocrine Practice 2011
Secondary HPT
ESRD/HPT Indications for surgery

- Patients with severe HPT who fail medical therapy (Sensipar, Vitamin D, Phosphate binders) or cannot perform surveillance
- Persistently hypercalcemic
- PTH > 800 pg/mL
- Calciphylaxis, fractures, bone pain or pruritis
- Ca * Po4 > 70

K/DOQI Clinical Practice Guidelines for Bone Metab and Disease in CKD. Am J Kidney Dis 2003
Dumasias, Oto Clinic N America 2010
Cinacalcet (Sensipar)

- Calcimimetic
- Increases the sensitivity of the calcium-sensing receptor to circulating serum calcium
- *Does not improve bone density*
- FDA approved for
  - HPT in patients with *chronic kidney disease*
  - severe hypercalcemia in patients with PHPT who cannot undergo surgery
  - Treatment of hypercalcemia in patients with parathyroid carcinoma

Hyperparathyroidism

Duntas, Endocrine 2011
www.fda.gov
ESRD/HPT operative management

• Subtotal vs total with autotransplantation
• Often require calcium gtt & high doses of Rocaltrol post-op, due to hungry bone syndrome
SUMMARY

1. 80% of patients with primary HPT are asymptomatic
2. Parathyroidectomy results in increased BMD and perhaps QOL
3. Many observed patients would benefit from surgery
4. Low morbidity surgery will benefit the majority of patients
5. Patients with normocalcemic HPT may benefit from surgery
Contact information

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Hyperparathyroidism