Primary Hyperparathyroidism: New Insights, Concepts and Guidelines

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Nashville, Tennessee
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John P. Bilezikian, M.D.

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Amgen (Consultant, Advisory Board, Research Grant)
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Merck (Consultant, Advisory Board)
NPS Pharmaceuticals (Consultant, Advisory Board, Research Grant)
GSK (Consultant, Advisory Board)
Radius Pharmaceuticals (Consultant)
PRIMARY HYPERPARATHYROIDISM

- A common endocrine disorder characterized by incompletely regulated, chronic, excessive secretion of parathyroid hormone from one or more parathyroid glands.

- Primary Hyperparathyroidism is associated with hypercalcemia and elevated levels of parathyroid hormone.

Before 1970:
A disease of bones, stones, and groans
PHPT IN THE EARLY YEARS, 1929-1970

The captain (1929-1933) and The lady (1970)

Before 1970:
A disease of bone, stones, and groans

After 1970:
A disease with primarily biochemical and densitometric signatures
### The biochemical signatures of primary hyperparathyroidism in the modern era

<table>
<thead>
<tr>
<th>Index</th>
<th>Patients</th>
<th>nl range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calcium (mg/dl)</td>
<td>10.7±0.1</td>
<td>8.4-10.2</td>
</tr>
<tr>
<td>Phosphorus (mg/dl)</td>
<td>2.9±0.1</td>
<td>2.5-4.5</td>
</tr>
<tr>
<td>Alk Phos (IU/l)</td>
<td>114±4</td>
<td>&lt;100</td>
</tr>
<tr>
<td>PTH (pg/ml)</td>
<td>121±7</td>
<td>10-65</td>
</tr>
<tr>
<td>25-OH Vit D (ng/ml)</td>
<td>21±1</td>
<td>30-100</td>
</tr>
<tr>
<td>1,25-OH₂ Vit D (pg/ml)</td>
<td>59±2</td>
<td>15-60</td>
</tr>
<tr>
<td>Urinary calcium (mg)</td>
<td>248 ± 12</td>
<td>100-300</td>
</tr>
</tbody>
</table>

Silverberg, Bilezikian et al.

### The densitometric signature of primary hyperparathyroidism in the modern era

- **Bone Mineral Density (% of Expected)**
  - Lumbar Spine
  - Femoral Neck
  - Radius

*Differs from radius, p<.05

Silverberg, Bilezikian et al.

JBMRI, 1989
A 45-year Dilemma in the Management of Asymptomatic PHPT

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

Genesis of the 45 year-old dilemma

The introduction and widespread use of biochemical screening tests that include a serum calcium determination
Addressing this and other questions related to the changing phenotype of PHPT, 4 International Workshops have been held

- 1991
- 2002
- 2008
- 2013
4th International Workshop on:
THE MANAGEMENT OF ASYMPTOMATIC PRIMARY HYPERPARATHYROIDISM
Florence (Italy), September 19th - 21st, 2013

Organized by
UNIVERSITÀ DEGLI STUDI DI FIRENZE, FLORENCE, ITALY
MASSACHUSETTS GENERAL HOSPITAL, HARVARD MEDICAL SCHOOL,
BOSTON, MASSACHUSETTS, USA
COLLEGE OF PHYSICIANS AND SURGEONS, COLUMBIA UNIVERSITY,
NEW YORK, NY, USA
and
FONDAZIONE INTERNAZIONALE MENARINI
Palazzo Ximènes Panciatichi
Maria Luisa Brandi John T. Potts, Jr. John P. Bilezikian
Università degli Studi di Firenze MGH College of Phys & Surg
Florence (Italy) Harvard Medical School Columbia University

Held in Florence, Italy,
19-21 September 2013
The 4th International Workshop on the Management of Asymptomatic Primary Hyperparathyroidism

4 Working Groups:

- **Diagnosis** (Richard Eastell, Maria Luisa Brandi, Aline G. Costa Pierre D’Amour, Dolores M. Shoback, Raj V Thakker)

- **Presentation** Shonni J. Silverberg, Bart Clarke, Munro Peacock, Francisco Bandeira, Stephanie Boutroy, Natalie Cusano, David Dempster, E. Michael Lewiecki, Liu Jian-Min, Salvatore Minisola, Lars Rejnmark, Barbara Silva, Marcella Walker, John Bilezikian)

- **Surgical Management** (Robert Udelsman, Göran Akerström Carlo Biagini, Quan-Yang Duh, Paolo Miccoli, Bruno Niederle, Francesco Tonelli).

- **Medical Management** (Claudio Marcocci, Jens Bollerslev, Aliya A. Khan, Dolores M. Shoback)
Workshop Methodology for all Working Groups

- Complete review of the peer-reviewed literature since 2008.
- Related to information available at the time of the last workshop in 2008
- Presentations at the Florence Meeting
- Manuscripts papers prepared within several months and submitted to JCEM
- All 5 papers published in JCEM, 2014

Since the 3rd International Workshop on the Management of Asymptomatic Primary Hyperparathyroidism

New information about asymptomatic patients:

- Biochemical Presentation
- Diagnostics
- Clinical presentations
- Natural history
- Densitometric features
- Other skeletal features
- Non-traditional features
- Localization and Surgical Approaches
- Pharmacological approaches
### The biochemical signatures of primary hyperparathyroidism 2010-2012

<table>
<thead>
<tr>
<th>Index</th>
<th>'84-'00</th>
<th>'10-'12</th>
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<tbody>
<tr>
<td>Calcium (mg/dl)</td>
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<td>10.6±0.1</td>
<td>8.4-10.2</td>
</tr>
<tr>
<td>Phosphorus (mg/dl)</td>
<td>2.9±0.1</td>
<td>3.2±0.1</td>
<td>2.5-4.5</td>
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<tr>
<td>Alk Phos (IU/l)</td>
<td>114±4</td>
<td>79±3</td>
<td>&lt;100</td>
</tr>
<tr>
<td>PTH (pg/ml)</td>
<td>121±7</td>
<td>75±7</td>
<td>10-65</td>
</tr>
<tr>
<td>25-OH Vit D (ng/ml)</td>
<td>21±1</td>
<td>36.7±1.6</td>
<td>30-100</td>
</tr>
<tr>
<td>1,25-OH$_2$ Vit D (pg/ml)</td>
<td>59±2</td>
<td>67.6±6.1</td>
<td>15-60</td>
</tr>
<tr>
<td>Urinary calcium (mg)</td>
<td>248</td>
<td>234±38</td>
<td>100-300</td>
</tr>
</tbody>
</table>

Silverberg et al, 1989  
Cusano et al. 2013

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**Serum Calcium**

<table>
<thead>
<tr>
<th>Year</th>
<th>Value (mg/dl)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1984-2000</td>
<td>10.7</td>
</tr>
<tr>
<td>2010-2012</td>
<td>10.6</td>
</tr>
</tbody>
</table>

**Phosphorus**

<table>
<thead>
<tr>
<th>Year</th>
<th>Value (mg/dl)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1984-2000</td>
<td>2.9</td>
</tr>
<tr>
<td>2010-2012</td>
<td>3.2</td>
</tr>
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</table>

**Alkaline Phosphatase**

<table>
<thead>
<tr>
<th>Year</th>
<th>Value (IU/l)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1984-2000</td>
<td>114</td>
</tr>
<tr>
<td>2010-2012</td>
<td>79</td>
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</table>

**PTH**

<table>
<thead>
<tr>
<th>Year</th>
<th>Value (pg/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1984-2000</td>
<td>121</td>
</tr>
<tr>
<td>2010-2012</td>
<td>74</td>
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</tbody>
</table>

Silverberg et al, 1989  
Cusano et al. 2013
Hypoparathyroidism

Silverberg et al, 1989
Cusano et al. 2013
Normocalcemic primary hyperparathyroidism: what must be ruled out?

- Vitamin D deficiency
  - 25-hydroxyvitamin D < 30 ng/mL
- Renal insufficiency
  - eGFR < 60 mL/min
- Medications
  - Thiazide diuretics
  - Lithium
- Hypercalciuria
- Gastrointestinal malabsorption
- Other metabolic bone diseases that could be associated with elevated PTH (e.g., Paget’s disease)
How should we define “normal”?  

- The “normal range” for PTH excludes 2.5% of normal individuals above 2 SD from the mean

Definition of “normal” -2-  

- While “normal” serum calcium varies widely across the population, serum calcium within a given individual is remarkably constant over time, with a more narrow range than that for the population

Farquhason RF and Tibbetts DM, 1931
Normocalcemic PHPT: The Columbia Experience

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N= 37</td>
</tr>
<tr>
<td>Age (y)</td>
<td>58 ± 12</td>
</tr>
<tr>
<td>Women</td>
<td>35 (95%)</td>
</tr>
<tr>
<td>Postmenopausal</td>
<td>29 (78%)</td>
</tr>
<tr>
<td>Premenopausal</td>
<td>6 (16%)</td>
</tr>
<tr>
<td>Men</td>
<td>2 (5%)</td>
</tr>
</tbody>
</table>

Lowe H, et al. 2007
Lowe, McMahon, Rubin, Bilezikian
Silverberg, J Clin Endocrinol Metab, 2007

Reasons for PTH Measurement

- Low bone mass: 73%
- Kidney stone: 6%
- Fracture: 11%
- Other: 10%

Lowe, McMahon, Rubin, Bilezikian
Silverberg, J Clin Endocrinol Metab, 2007
### Biochemical Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Mean ± SE</th>
<th>Range</th>
<th>NL Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum Calcium (mg/dL)*</td>
<td>9.4 ± 0.1</td>
<td>8.5-10.2</td>
<td>8.5-10.4</td>
</tr>
<tr>
<td>PTH (pg/mL)</td>
<td>93 ± 5</td>
<td>65-182</td>
<td>10-65</td>
</tr>
<tr>
<td>Serum Phosphorus (mg/dL)</td>
<td>3.3 ± 0.1</td>
<td>2.4-4.8</td>
<td>2.1-4.3</td>
</tr>
<tr>
<td>Alkaline Phosphatase (U/L)</td>
<td>72 ± 5</td>
<td>39-134</td>
<td>20-125</td>
</tr>
<tr>
<td>Urinary Calcium (mg/24h)</td>
<td>193 ± 12</td>
<td>71-350</td>
<td>50-300</td>
</tr>
<tr>
<td>Urinary NTX (nM BCE/mM Cr)</td>
<td>38 ± 5</td>
<td>7-69</td>
<td>10-110</td>
</tr>
<tr>
<td>25-hydroxyvitamin D (ng/mL)**</td>
<td>33 ± 1</td>
<td>20-54</td>
<td>30-100</td>
</tr>
<tr>
<td>1,25-dihydroxyvitamin D (pg/mL)</td>
<td>62 ± 4</td>
<td>31-109</td>
<td>19-67</td>
</tr>
</tbody>
</table>

*Corrected for serum albumin

**By definition, 25-hydroxyvitamin D was >20 pg/mL

Lowe H, et al. 2007

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### Baseline Densitometric Features

**T-score**

- Lumbar Spine
- Femoral Neck
- Radius

**Percentage with Osteoporosis**

- Spine
- Hip
- Radius
- Any Site

Lowe, McMahon, Rubin, Bilezikian
Silverberg, J Clin Endocrinol Metab, 2007
Densitometric Comparison of Normocalcemic and Hypercalcemic PHPT Cohorts

Percentage with Osteoporosis

- Normocalcemic (n=37)
- Hypercalcemic (n=139)

Lumbar spine Femoral neck Radius

Hypothesis:

- **A paradox:** Patients with normocalcemic PHPT present with more symptoms than typical cohorts of hypercalcemic subjects with mild PHPT

- **An explanation:** Patients were identified after referral to a Metabolic Bone Diseases Unit for evaluation of a skeletal problem (selection bias)
Normocalcemic PHPT

• Key Point:

They are not being discovered “incidentally”

Lowe, McMahon, Rubin, Bilezikian
Silverberg, J Clin Endocrinol Metab, 2007

The Development of Primary Hyperparathyroidism: An Evolving View

OLD:

<table>
<thead>
<tr>
<th>SUBCLINICAL</th>
<th>CLINICAL</th>
</tr>
</thead>
<tbody>
<tr>
<td>PHASE 1</td>
<td>PHASE 2</td>
</tr>
</tbody>
</table>

NEW:

<table>
<thead>
<tr>
<th>SUBCLINICAL</th>
<th>CLINICAL</th>
</tr>
</thead>
<tbody>
<tr>
<td>PHASE 1 –symptomatic* -asymptomatic**</td>
<td>PHASE 2</td>
</tr>
</tbody>
</table>

*Lowe et al, 2007; **Cusano et al. JCEM, 2013
Conclusion

Screening a wider population of unselected, community-dwelling individuals* without skeletal complaints will be required to identify and to characterize the forerunner of mild, asymptomatic primary hyperparathyroidism

*MrOS (ASBMR, 2011), Dallas Heart Study (ASBMR, 2012)
*Cusano N et al. J Clin Endocrinol Metab, 2013

Three generational phenotypes of Primary Hyperparathyroidism

Before 1970:
A disease of bone, stones, and groans

After 1970:
A disease with primarily biochemical and densitometric signatures

After 2000:
A disease that may present with a more subtle biochemical signature, namely only with PTH levels elevated, at first.
Normocalcemic PHPT is a clinical presentation of PHPT: management approach is recommended.

Management of Asymptomatic NPHPT: A Proposal for Discussion

- Calcium and PTH annually
- DXA every 1-2 years

Progression to hypercalcemic PHPT

- Follow guidelines

Progression of disease

- Worsening BMD or fracture
- Kidney stone or nephrocalcinosis

Surgery

Three generational phenotypes of Primary Hyperparathyroidism

The extent to which a country or region will demonstrate a preponderance of:

- Symptomatic PHPT
- Asymptomatic PHPT
- Normocalcemic PHPT

will depend, at least in part, upon the presence and use of multichannel screening, more routine measurements of PTH, and nutritional elements such as vitamin D adequacy.

Traditional Aspects of Primary Hyperparathyroidism

- Skeletal Assessment
- Renal Assessment
Based upon BMD and bone biopsy data, expectations for fracture incidence in PHPT:

- Vertebral sites
- Non-vertebral sites

But......
Fracture Risk in Primary Hyperparathyroidism

Khosla et al, J Bone Min Res 14:1700-1707, 1999

Mosekilde L. Clin Endocrinology, 2008
Fracture risk in PHPT

- 9 references: 1988-2006 (5 from Northern Europe)
- Mostly cross-sectional
- Relative risk of non-spine and spine fractures increased generally but not in all studies

HRpQCT (Xtreme CT)

- 3-D stack of 110 high resolution slices
- ~3 min scan time
- <4 µSv radiation
- Reproducibility:
  - Density: 0.7-1.8%
  - Structure: 1.2-5.2%

Bouyay et al. JCEM 2005. 90(12): 6508-15
Hansen S et al. Parathyroidectomy and changes by HRpQCT. J Bone Miner Res 2012;27:1150-1158

- 27 subjects with PHPT vs 31 controls
- Well matched
- Mostly postmenopausal: 14 and 18 years
- Hx of fractures 9/27 (PHPT) and 6/31 (C)
- HRpQCT performed at baseline and 1 year after PTX or for controls 1 year thereafter

Baseline data: PHPT vs Controls (p<0.05)

<table>
<thead>
<tr>
<th>Index</th>
<th>RADIUS</th>
<th>TIBIA</th>
</tr>
</thead>
<tbody>
<tr>
<td>TV BMD</td>
<td></td>
<td>↓</td>
</tr>
<tr>
<td>Cort BMD</td>
<td>↓</td>
<td></td>
</tr>
<tr>
<td>Trab BMD</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td>Trab BV/TV</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td>Tb.N</td>
<td>↓</td>
<td></td>
</tr>
<tr>
<td>Tb. Th</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tb. Sp</td>
<td>↑</td>
<td></td>
</tr>
<tr>
<td>Strength</td>
<td>↓</td>
<td></td>
</tr>
<tr>
<td>Failure Load</td>
<td>↓</td>
<td></td>
</tr>
</tbody>
</table>
HRpQCT in PHPT
(Stein E, Silva BC et al. J Bone Miner Res, 2013)

**Matched Control**

**PHPT**

Trabecular and cortical indices are reduced at radius and tibia in Asymptomatic PHPT

Stein E, Silva BC et al. HRpQCT in PHPT, J Bone Miner Res, 2013
Microstructure as analyzed by Individual Trabecula Segmentation (ITS)- Guo and Liu, 2010

• ITS can differentiate between plate- and rod-like trabeculae type
  – More plates are associated with greater strength

ITS in Primary Hyperparathyroidism
Stein E, Silva BC J Bone Miner Res, 2013

Matched Control       Primary Hyperparathyroidism

Green: horizontal plates (more competent)
Red: vertical plates (less competent)
The Conundrum in Primary Hyperparathyroidism

- Lumbar spine BMD in PHPT is discordant with fracture data
- HRpQCT indices in PHPT are concordant with fracture data
- DXA is readily available
- HRpQCT is not

Needed: A readily accessible method that can give information about skeletal microstructure

TRABECULAR BONE SCORE (TBS)

The general idea!
Romagnoli E, Cipriani C, Nofrani I, et al. TBS in postmenopausal women with PHPT. Bone 2012:154-159

Adapted from Table 2

<table>
<thead>
<tr>
<th>Index</th>
<th>VF+ (n=29)*</th>
<th>VF- (n=44)</th>
<th>P value</th>
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</thead>
<tbody>
<tr>
<td>Age (yrs)</td>
<td>67.6 ± 8.2</td>
<td>61.0 ± 8.9</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>YSM (yrs)</td>
<td>19.2 ± 10.3</td>
<td>11.5 ± 8.3</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>BMI</td>
<td>27.4 ± 6.2</td>
<td>24.8 ± 3.6</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>TBS</td>
<td>1.14 ± 0.10</td>
<td>1.22 ± 0.10</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>LS BMD</td>
<td>-2.29 ± 1.2</td>
<td>-1.78 ± 1.3</td>
<td>NS</td>
</tr>
<tr>
<td>FN BMD</td>
<td>-1.85 ± 1.01</td>
<td>-1.88 ± 0.8</td>
<td>NS</td>
</tr>
<tr>
<td>1/3 RAD</td>
<td>-2.34 ± 1.2</td>
<td>-1.73 ± 1.2</td>
<td>&lt;0.05</td>
</tr>
</tbody>
</table>

*24/29 Grade 1 Fx
Densitometric and TBS data in 22 PHPT postmenopausal women
(Silva et al, J Clin Endo Metab, 2013)

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>PHPT (n=22)</th>
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<tbody>
<tr>
<td><strong>TBS</strong></td>
<td>1.24 ± 0.02</td>
</tr>
<tr>
<td>L1-L4 T-Score</td>
<td>-1.0 ± 0.4</td>
</tr>
<tr>
<td>Total hip T-Score</td>
<td>-1.1 ± 0.3</td>
</tr>
<tr>
<td>Femoral neck T-Score</td>
<td>-1.4 ± 0.3</td>
</tr>
<tr>
<td>1/3 radius T-Score</td>
<td>-1.3 ± 0.4</td>
</tr>
<tr>
<td>Osteoporosis at any site</td>
<td>11 (50%)</td>
</tr>
</tbody>
</table>

Microarchitecture partially degraded

<1.2 = degraded
1.2 – 1.35 = partially degraded
>1.35 = normal

<table>
<thead>
<tr>
<th>L1-L4 T-score classification</th>
<th>n (%)</th>
</tr>
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<tbody>
<tr>
<td>Osteoporosis</td>
<td>3 (14)</td>
</tr>
<tr>
<td>Osteopenia</td>
<td>7 (32)</td>
</tr>
<tr>
<td>Normal</td>
<td>12 (53)</td>
</tr>
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</table>

<table>
<thead>
<tr>
<th>L1-L4 TBS classification</th>
<th>n (%)</th>
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<tbody>
<tr>
<td>Degraded</td>
<td>8 (36)</td>
</tr>
<tr>
<td>Partially degraded</td>
<td>8 (36)</td>
</tr>
<tr>
<td>Normal</td>
<td>6 (27)</td>
</tr>
</tbody>
</table>

Moving the field forward with a “new” hypothesis

Primary hyperparathyroidism, even when presenting as an asymptomatic disorder, is characterized by compromised cortical and trabecular compartments and increased fracture risk.
Skeletal evaluation, in addition to DXA is recommended in the evaluation of PHPT: VFA, TBS or vertebral X-rays

Traditional Aspects of Primary Hyperparathyroidism
Emergence of the Modern Clinical Profile of Primary Hyperparathyroidism

<table>
<thead>
<tr>
<th></th>
<th>Cope et al. '30-'65</th>
<th>Mallette et al. '65-'74</th>
<th>Silverberg et al. '84-'00</th>
<th>Cusano et al. '10-'12</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nephrolithiasis</td>
<td>57%</td>
<td>37%</td>
<td>17%</td>
<td>14.3%</td>
</tr>
<tr>
<td>Hypercalciuria</td>
<td>Not reported</td>
<td>40%</td>
<td>39%</td>
<td>29%</td>
</tr>
<tr>
<td>Overt Skeletal Disease</td>
<td>23%</td>
<td>14%</td>
<td>1.4%</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>Asymptomatic</td>
<td>0.6%</td>
<td>22%</td>
<td>80%</td>
<td>&gt;80%</td>
</tr>
</tbody>
</table>


- 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 increase stone risk) is a risk factor for stones
- Clcr <60 cc/min recommended as a guideline for surgery
  - Speculation that the increase in PTH when the Clcr < 60 cc/min is detrimental
Eroded Surface

Eroded surface 45% greater and remained significant controlling for age

Walker et al. JCEM (2012)

Activation Frequency

Activation frequency 45% lower

Walker et al. JCEM (2012)
New data and reinterpretation of old data

• Skeletal involvement more evident in PHPT when the eGFR < 60 cc/min (Walker et al, 2012)
• A 24-hour urine for analysis of biochemical stone risk factors (Ca, P, SO4, uric acid etc) is predictive of stones in PHPT (Peacock, 2013)
• Kidney stones can be detected by non-invasive imaging (e.g. X-ray, ultrasound, CT)
• Kidney stones are still the most common complication of PHPT
Other Aspects of Primary Hyperparathyroidism

Neuro-cognitive

Cardio-vascular

Gastro-intestinal

Vitamin D

Putative Neuropsychological and Constitutional Manifestations of Primary Hyperparathyroidism

Frequent Complaints
- Weakness
- Easy fatigability
- Depression
- Intellectual weariness
- Increased sleep requirement

Issues in Attribution
- Present in many chronic conditions
- Lack specificity
- Difficult to quantitate
- Adequately controlled studies are a challenge
Neuropsychiatric Studies: Randomized Controlled Trial Data

- Inconsistent data from 4 randomized controlled trials of the effect of parathyroidectomy on psychiatric/cognitive symptoms and quality of life*
  
  *Rao, Talpos et al., JCEM 2007
  Ambrogini, Marcocci et al., JCEM 2007
  Bollerslev et al. JCEM, 2007
  Walker, Silverberg et al. JCEM, 2009


Cardiovascular manifestations of PHPT

<table>
<thead>
<tr>
<th>Literature</th>
<th>Indices measured</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yu et al. Endocrinology ‘10,’13</td>
<td>CV risk factors (BP, etc)</td>
</tr>
<tr>
<td>Oslo et al. Circulation ‘12</td>
<td>LVF</td>
</tr>
<tr>
<td>Persson et al. Clin Endocrinol ‘11</td>
<td>LVM</td>
</tr>
<tr>
<td>Walker et al. JCEM ‘09, ‘10, ‘12</td>
<td>CVD- fatal and non fatal</td>
</tr>
<tr>
<td>Shin et al. JCEM, ‘11</td>
<td>CAD</td>
</tr>
<tr>
<td>Farahnukan et al. Eur J Endo ‘10</td>
<td>Carotid Intimal Thickness</td>
</tr>
<tr>
<td>Fallow et al. JCEM ‘03</td>
<td>Coronary Flow Reserve</td>
</tr>
<tr>
<td>Rubin et al. JCEM ‘05</td>
<td>Aortic calcifications/area</td>
</tr>
<tr>
<td>Smith et al. JCEM ‘00</td>
<td>Compliance and Stiffness</td>
</tr>
<tr>
<td>Schillaci et al. Atherosclerosis ‘11</td>
<td>Flow-mediated vasolilation</td>
</tr>
<tr>
<td>Carrelli et al. JCEM, ‘13</td>
<td></td>
</tr>
</tbody>
</table>
Putative Cardiovascular Manifestations of Asymptomatic PHPT*

*Silverberg et al. Clinical Presentations of Primary Hyperparathyroidism J Clin Endo Metab, 2014

- Subtle abnormalities in:
  - vascular reactivity
  - left ventricular function
  - carotid intimal thickness

- Functional significance unknown and uncertain
- Reversibility after successful parathyroid surgery not clear

Cardiovascular Manifestations of PHPT

- General Results
  - Heterogeneous populations:
  - More active disease associated with greater abnormalities
  - When relationship exists, it is with PTH, not calcium
  - Improvement after surgery is uncertain, but usually restricted to those who have preoperative abnormalities in that index
Neurocognitive and CV systems: Data are not secure enough for decisions on the surgical management of PHPT

Other Aspects of Primary Hyperparathyroidism

- Neuro-cognitive
- Cardio-vascular
- Gastro-intestinal
- Vitamin D
The Hypothesis of Double Trouble

The clinical manifestations of Primary Hyperparathyroidism may be more severe in the presence of Vitamin D deficiency.

PHPT: The Global View

NEW YORK                              BEIJING
Bone Disease/Fractures Common

Asymptomatic                             Symptomatic
Bone Disease/Fractures Common

Bilezikian, Meng, Shi, Silverberg. 2000
Primary Hyperparathyroidism:

<table>
<thead>
<tr>
<th></th>
<th>New York</th>
<th>Beijing</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Calcium (mg/dl)</strong></td>
<td>10.7 ± 0.1</td>
<td>12.4 ± 1.1</td>
</tr>
<tr>
<td><strong>Alk Phos (% &gt; nl)</strong></td>
<td>40%</td>
<td>80%</td>
</tr>
<tr>
<td><strong>PTH (x nl)</strong></td>
<td>1.86</td>
<td>21.4</td>
</tr>
<tr>
<td><strong>Uca (% &gt; nl)</strong></td>
<td>38%</td>
<td>51%</td>
</tr>
<tr>
<td><strong>Phos (% &lt; nl)</strong></td>
<td>25%</td>
<td>60%</td>
</tr>
<tr>
<td><strong>25-OH D (ng/ml)</strong></td>
<td>21.1 ± 1</td>
<td>8.8 ± 7.2</td>
</tr>
</tbody>
</table>

Bilezikian, Meng, Shi, Silverberg. 2000

**PTH Levels as function of Vitamin D status**
(Stein et al. JCEM, 2011)

![Graph showing PTH levels and Vitamin D status](image)

Mean ± SD

P<0.01
Nutritional elements:
Vitamin D sufficiency
(25-OH D levels > 20 are recommended)*
Calcium intake should follow national guidelines

Some experts recommend > 30 ng/mL

Surgical Management of Primary Hyperparathyroidism

- Preoperative localization- mandatory adjunct to parathyroid surgery (CT, Ultrasound, Sestamibi)
- The parathyroid surgeon
  - “The most important preoperative localization challenge in PHPT is to locate the parathyroid surgeon!” – John Doppman, 1975
- Surgical approaches (MIP with intraoperative PTH; full exploration)
Biochemical Indices After Successful Parathyroid Surgery

- Calcium
- PTH*
- 25-OH and 1,25-OH D
- Urinary Calcium
- Bone Markers
  - Bone Resorption
  - Bone Formation

All return to normal*

Improvements in Bone Density after Parathyroid Surgery

Rubin, Bilezikian, Silverberg et al. JCE&M, 2008
Improvement in microarchitecture after parathyroid surgery

BY HIGH RESOLUTION pQCT

Silverberg, Shane, Bilezikian, 2006

Medical Management of PHPT

- Observation
- Pharmacological approaches
Without Parathyroid Surgery
15-Year Natural History of PHPT
Biochemical Indices

<table>
<thead>
<tr>
<th>Index</th>
<th>Baseline</th>
<th>5</th>
<th>10</th>
<th>13</th>
<th>15</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ca</td>
<td>10.5 ± 1</td>
<td>10.7 ± 1</td>
<td>10.8 ± 1</td>
<td>11.0 ± 1</td>
<td>11.1 ± 1</td>
</tr>
<tr>
<td>PTH</td>
<td>122 ± 10</td>
<td>119 ± 12</td>
<td>123 ± 14</td>
<td>124 ± 16</td>
<td>121 ± 18</td>
</tr>
<tr>
<td>Uca</td>
<td>238 ± 19</td>
<td>215 ± 23</td>
<td>185 ± 32</td>
<td>247 ± 36</td>
<td>202 ± 36</td>
</tr>
<tr>
<td>25-OHD</td>
<td>21 ± 1</td>
<td>22 ± 2</td>
<td>22 ± 3</td>
<td>21 ± 3</td>
<td>20 ± 4</td>
</tr>
<tr>
<td>1,25-OH$_2$D</td>
<td>50 ± 2</td>
<td>58 ± 3</td>
<td>54 ± 6</td>
<td>40 ± 5</td>
<td>48 ± 7</td>
</tr>
</tbody>
</table>

Rubin, Bilezikian, Silverberg et al. JCE&M, 2008

Without Parathyroid Surgery: 15-year course of BMD

Rubin, Bilezikian, Silverberg et al., JCE&M, 2008
Without Parathyroid Surgery:
15-year Course in
in Asymptomatic Patients

• 37% developed one or more indications for surgery during 15 years of monitoring
  (hypercalcemia, hypercalciuria, or reduced BMD)

Rubin, Bilezikian, Silverberg et al.,
JCE&M, 2008

Relative youth as a risk factor for progressive
disease in asymptomatic primary
hyperparathyroidism

Silverberg & Bilezikian
Medical Management of PHPT

- Observation
- Pharmacological approaches
  - When?
    - Surgery indicated but is not going to be carried out
    - The surgical indication can be ameliorated by the drug (e.g. reduced bone density, severe hypercalcemia)
  - What agent?
    - Estrogen/raloxifene- (not FDA-approved)
    - Bisphosphonate (not FDA-approved)- if BMD is low
    - Cinacalcet (FDA-approved)- if hypercalcemia is severe
    - Cinacalcet and Bisphosphonate- if hypercalcemia is severe and bone density is low.
    - Denosumab (not FDA-approved): ongoing study by Bilezikian et al.

Pharmacological Approaches to PHPT

<table>
<thead>
<tr>
<th>Agent</th>
<th>Serum calcium</th>
<th>Bone Mineral Density</th>
<th>PTH</th>
</tr>
</thead>
<tbody>
<tr>
<td>Estrogen&lt;sup&gt;1&lt;/sup&gt;</td>
<td>↓</td>
<td>←</td>
<td>←</td>
</tr>
<tr>
<td>Raloxifene&lt;sup&gt;2&lt;/sup&gt;</td>
<td>↓</td>
<td>←</td>
<td>←</td>
</tr>
<tr>
<td>Bisphosphonate&lt;sup&gt;3&lt;/sup&gt;</td>
<td>←</td>
<td>↑</td>
<td>←</td>
</tr>
<tr>
<td>Cinacalcet&lt;sup&gt;4&lt;/sup&gt;</td>
<td>↑</td>
<td>←</td>
<td>↓</td>
</tr>
<tr>
<td>Cinacalcet and Bisphosphonate&lt;sup&gt;5&lt;/sup&gt;</td>
<td>↑</td>
<td>↑</td>
<td>↓</td>
</tr>
</tbody>
</table>

### 2014 Guidelines for Surgery in Asymptomatic Primary Hyperparathyroidism (Bilezikian et al., JCEM, 2014)

<table>
<thead>
<tr>
<th>Recommended Index</th>
<th>3rd Int’l Workshop (Bilezikian et al., JCEM 2009)</th>
<th>4th Int’l Workshop (Bilezikian et al., 2014)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum calcium (above normal)</td>
<td>&gt;1.0 mg/dL</td>
<td>&gt; 1 mg/dL</td>
</tr>
<tr>
<td>Skeletal</td>
<td>DXA: T-Score &lt; -2.5 at any site; any fragility fracture</td>
<td>DXA: T-Score &lt; -2.5 at any site; Vert Fx by X-ray or VFA</td>
</tr>
<tr>
<td>Renal</td>
<td>Clcr &lt; 60 cc/min 24 hr urine: Not recommended</td>
<td>Clcr &lt; 60 cc/min  Stone by X-ray, CT, or ultrasound  Urinary calcium: &gt;400 mg/d plus other urinary biochemical indices of increased stone risk</td>
</tr>
<tr>
<td>Age</td>
<td>&lt;50</td>
<td>&lt; 50</td>
</tr>
</tbody>
</table>

### Surgery in Primary Hyperparathyroidism: another view of the Int’l Workshop (Bilezikian et al, JCEM, 2009)

Even though patients may not meet any specific criteria for surgery, parathyroidectomy is not an inappropriate course of action, as long as there are no medical contraindications.
2014 Guidelines for Monitoring in Asymptomatic Primary Hyperparathyroidism
(Bilezikian et al. JCEM, 2014)

<table>
<thead>
<tr>
<th>Index</th>
<th>3rd Int’l Workshop (Bilezikian et al. JCEM, 2009)</th>
<th>4th Int’l Workshop (Bilezikian et al., JCEM, 2014)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum Calcium</td>
<td>Annually</td>
<td>Annually</td>
</tr>
<tr>
<td>Skeletal</td>
<td>DXA: Every 1 or 2 years</td>
<td>DXA: Every 1 or 2 years; CT or VFA if clinically indicated</td>
</tr>
<tr>
<td>Renal</td>
<td>Clcr-Annually</td>
<td>Clcr-Annually; stone risk profile if clinically indicated Abdominal imaging (X-ray, CT, or ultrasound) if clinically indicated</td>
</tr>
</tbody>
</table>

Surgery vs No Surgery in Asymptomatic PHPT
Is The Pendulum Swinging in the Direction of Surgery?

Both options, however, are still important to consider in every patient

Threshold Level
Key Points

- Primary Hyperparathyroidism is a common endocrine disorder
- Asymptomatic PHPT is the most common presentation in developed countries
- In 2014, guidelines for surgery were revised consistent with the latest 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
Primary Hyperparathyroidism Project at Columbia, 1984-

- John Bilezikian
- Shonni Silverberg
- Ethel Siris
- Thomas Jacobs
- Mishaela Rubin
- David Dempster
- Marcella Walker
- Natalie Cusano
- James Lee
- Don McMahon
- Amy Zhang
- Ronald Staron
- Wendy Fan
- Farnoosh Mahdavi
- Aline Costa
- Barbara Silva
- Cristiano Cipriani
- Alice Abraham

Thank You!