Primary Hyperparathyroidism, 2018: A Comprehensive Update

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Disclosures:

Amgen (Consultant, Advisory Board)
Shire Pharmaceuticals (Consultant)
Radius Pharmaceuticals (Advisory Board)
Ultradynyx (Consultant)
Regeneron (DSMB)
PRIMARY HYPERPARATHYROIDISM

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

- Primary Hyperparathyroidism, classically, is associated with hypercalcemia and elevated levels of parathyroid hormone.
PRIMARY HYPERPARATHYROIDISM

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

The captain (1918-1926) and The lady (1970)
PRIMARY HYPERPARATHYROIDISM

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. 1989
The densitometric signature of primary hyperparathyroidism in the modern era

Bone Mineral Density: % of Expected

* Differs from radius, p<.05

Silverberg, Bilezikian et al. JBMR, 1989
Genesis of a 45 year-old dilemma

The introduction and widespread use of biochemical screening tests that include a serum calcium determination
Figure 2: Changing proportion of asymptomatic patients with clinical manifestations of HPT at 6 year intervals.
Changing Profiles of PHPT

In countries where serum calcium is not a routine screening test, PHPT tends to present more as a symptomatic disease.
Symptomatic PHPT remains common in certain regions (denoted in blue)

- Lo CY, et al., Arch Surg 2004
- Zhao L, et al., J Clin Endocrinol Metab 2013
- Pradeep PV, et al., Int J Endocrinol 2011
- Spivacow F, et al., Medicina (B Aires) 2010
Changing Profiles of PHPT

In countries where serum calcium becomes a routine screening test, PHPT tends to present more as an asymptomatic disease.
The changing phenotype of PHPT in Brazil

The changing phenotype of PHPT in China

Beijing 1958-1993

Shanghai 2001-2010

Even with routine screening, prevalence of PHPT in the USA has tripled.
A 45-year Dilemma in the Management of Asymptomatic PHPT

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

Held in Florence, Italy,
19-21 September 2013

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Http://www.fondazione-menarini.it
Since the 3\textsuperscript{rd} 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
## Changes in The Biochemical Signature of PHPT in the Modern Era

<table>
<thead>
<tr>
<th>Index</th>
<th>1984-1991 N=103</th>
<th>2000-2014 N=100</th>
<th>p value</th>
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</thead>
<tbody>
<tr>
<td>Calcium (mg/dL)</td>
<td>10.6 ± 0.6</td>
<td>10.7 ± 0.6</td>
<td>0.14</td>
</tr>
<tr>
<td>PTH (pg/mL)</td>
<td>127 ± 69</td>
<td>85 ± 48</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>25-hydroxyvitamin D (ng/mL)</td>
<td>23 ± 10</td>
<td>29 ± 10</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>1,25-dihydroxyvitamin D (pg/mL)</td>
<td>57 ± 20</td>
<td>69 ± 24</td>
<td>0.002</td>
</tr>
<tr>
<td>Urinary calcium excretion (mg)</td>
<td>229 ± 119</td>
<td>250 ± 144</td>
<td>0.28</td>
</tr>
</tbody>
</table>

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
Hypoparathyroidism

P = Primary Hyperparathyroidism
T = Hypercalcemia of Malignancy
H = Hypoparathyroidism

Box defined by dotted lines represents normal

Total Serum Calcium (mg/dL)
Hypoparathyroidism
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
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.

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

<table>
<thead>
<tr>
<th>Category</th>
<th>Count (Percentage)</th>
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<tbody>
<tr>
<td>N</td>
<td>37</td>
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<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, 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>NI 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, McMahon, Rubin, Bilezikian Silverberg, J Clin Endocrinol Metab, 2007
Baseline Densitometric Features

Percentage with Osteoporosis

Lowe, McMahon, Rubin, Bilezikian, Silverberg, J Clin Endocrinol Metab, 2007
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
Screening a wider population of unselected, community-dwelling individuals without skeletal complaints has identified another cohort of patients with normocalcemic primary hyperparathyroidism who are asymptomatic. (Cusano N et al. J Clin Endocrinol Metab, 2013)
The Development of Primary Hyperparathyroidism: An Evolving View

OLD:

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

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

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

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.
Three phenotypes of Primary Hyperparathyroidism, while discovered over several generations, are concurrent throughout the world at this time.

- **Symptomatic PHPT**
  - Little or no biochemical screening; endogenous vitamin D deficiency

- **Asymptomatic PHPT**
  - Routine biochemical screening; vitamin D levels not too low

- **Normocalcemic PHPT**
  - Medical centers where metabolic bone diseases are a specialty and PTH levels are routinely obtained even with normal albumin-corrected and ionized serum calcium levels
Three Generational Phenotypes of Primary Hyperparathyroidism: Evolution Defined by Technology

These three variants of primary hyperparathyroidism have probably always co-existed.

Their recognition, however, has followed a time course that can be understood in terms of technical advances that permitted:

- Earlier recognition
- Definitive diagnosis (PTH assay)
- Skeletal involvement by non-invasive high resolution technology
- A proactive approach to the evaluation of suspected metabolic bone diseases
Three Generational Phenotypes of Primary Hyperparathyroidism:
Evolution Defined by Technology

The disease hasn’t changed: we have!
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

Fractured cases (%)

- Symptomatic (n=41)
  - $P=0.15$

- Asymptomatic (n=109)
  - $P<0.0001$

- Controls (n=300)
  - $P=0.03$

Surg. Criteria Met (n=64)
Surg. Criteria Not Met (n=45)
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%

Non-dominant distal radius and tibia

Radius
Tibia

Boutroy 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>
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<tbody>
<tr>
<td>TV BMD</td>
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<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>
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<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>
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</tr>
</tbody>
</table>
HRpQCT in PHPT
(Stein E, Silva BC et al. J Bone Miner Res, 2013)
Stein E, Silva BC et al. HRpQCT in PHPT, J Bone Miner Res, 2013

Trabecular and cortical indices are reduced at radius and tibia in asymptomatic PHPT.
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

Needed: A readily accessible method that can give information about skeletal microstructure.
TRABECULAR BONE SCORE (TBS)
The general idea!

1. Identify each single Tree?
   - Not possible

2. What about identifying all clearings?
   - Much easier
TBS Simplified Principle

TBS A > TBS B
<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><strong>TBS</strong></td>
<td><strong>1.14 ± 0.10</strong></td>
<td><strong>1.22 ± 0.10</strong></td>
<td><strong>&lt;0.01</strong></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><strong>1.24 ± 0.02</strong></td>
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<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>
</tbody>
</table>

Osteoporosis at any site 11 (50%)

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>
</thead>
<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>
</tbody>
</table>

<table>
<thead>
<tr>
<th>L1-L4 TBS classification</th>
<th>n (%)</th>
</tr>
</thead>
<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

- Skeletal Assessment
- Renal Assessment
## 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>
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 or nephrocalcinosis can be detected often (over 50%) by non-invasive imaging such as X-ray, ultrasound, CT (Cipriani et al, 2015)
- Kidney stones are still the most common complication of PHPT (Marcocci, 2013)
Renal system:
24-hour urine for calcium and other stone risk factors
Abdominal imaging
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

*Silverberg et al. Clinical Presentations of Primary Hyperparathyroidism J Clin Endocrinol Metab, 2014
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>
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<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>
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<tr>
<td>Shin et al. JCEM, ‘11</td>
<td>CAD</td>
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<tr>
<td>Farahnukel et al. Eur J Endo ‘10</td>
<td>Carotid Intimal Thickness</td>
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<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>
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<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 vasolitation</td>
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<tr>
<td>Carrelli et al. JCEM, ’13</td>
<td></td>
</tr>
<tr>
<td>Bolleslev et al. JCEM ‘09</td>
<td></td>
</tr>
</tbody>
</table>
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 clinical manifestations of Primary Hyperparathyroidism may be more severe in the presence of Vitamin D deficiency.
PHPT: The Global View

NEW YORK

Asymptomatic

BEIJING

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

Bilezikian, Meng, Shi, Silverberg. 2000
PTH Levels as function of Vitamin D status
(Stein et al. JCEM, 2011)

Mean ± SD

PTH (pg/ml)

25OHD<20
25OHD≥20

* P<0.01
Vitamin D Deficiency and Insufficiency in PHPT Associated with lower BMD at radius

In PHPT, the data favor a goal of 25-hydroxyvitamin D > 30 ng/mL

- Inverse relationship between 25OHD and PTH in PHPT

Walker, Silverberg et al. JCEM 2015
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, 4-D 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 Years of monitoring</th>
<th>10 Years of monitoring</th>
<th>13 Years of monitoring</th>
<th>15 Years of monitoring</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ca</td>
<td>10.5 ± 1</td>
<td>10.7 ± 1</td>
<td>10.8 ± 0.2</td>
<td>11.0 ± 0.2</td>
<td>11.1 ± 0.2</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-OH₂ 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
Medical Management of PHPT

- **Observation**
- **Pharmacological approaches**
  - **When?**
    - Surgery indicated but is not going to be carried out AND
    - 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 for PHPT):
## 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(^1)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Raloxifene(^2)</td>
<td>(\downarrow)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bisphosphonate(^3) (Alendronate)</td>
<td>(\leftrightarrow)</td>
<td>(\uparrow)</td>
<td></td>
</tr>
<tr>
<td>Cinacalcet(^4)</td>
<td>(\downarrow)</td>
<td></td>
<td>(\downarrow)</td>
</tr>
<tr>
<td>Cinacalcet and Bisphosphonate(^5)</td>
<td>(\downarrow)</td>
<td>(\uparrow)</td>
<td>(\downarrow)</td>
</tr>
<tr>
<td>Denosumab(^6)</td>
<td>(\leftrightarrow)</td>
<td></td>
<td>(\uparrow)</td>
</tr>
</tbody>
</table>


A 2-year study of PHPT vs OP postmenopausal women
Current Guidelines for Surgery in Asymptomatic Primary Hyperparathyroidism (Bilezikian et al. JCEM, 2014)

<table>
<thead>
<tr>
<th>Recommended Index</th>
<th>4&lt;sup&gt;th&lt;/sup&gt; Int’l Workshop (Bilezikian et al., 2014)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum calcium (above normal)</td>
<td>&gt; 1 mg/dL</td>
</tr>
<tr>
<td>Skeletal</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 Stone by X-ray, CT, or ultrasound</td>
</tr>
<tr>
<td></td>
<td>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>
</tr>
</tbody>
</table>
### 2014 Guidelines for Monitoring in Asymptomatic Primary Hyperparathyroidism

<table>
<thead>
<tr>
<th>Index</th>
<th>4th Int’l Workshop (Bilezikian et al, JCEM, 2014)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum Calcium</td>
<td>Annually</td>
</tr>
<tr>
<td>Skeletal</td>
<td>DXA: Every 1 or 2 years; CT or VFA if clinically indicated</td>
</tr>
<tr>
<td>Renal</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
Key Points

- Primary Hyperparathyroidism is a common endocrine disorder
- Asymptomatic PHPT is the most common presentation in developed countries
- Surgery can be recommended even for patients who do not meet guidelines, if there are no medical contraindications
- For patients who are not going to have surgery, conservative medical management is appropriate
- Long-term conservative management, beyond 10 years should be pursued with caution
- Occasionally, pharmacological agents are used to increase bone mineral density or to reduce the serum calcium level.
Primary Hyperparathyroidism Project at Columbia, 1984-
Research Team, 2018

- John Bilezikian
- Shonni Silverberg
- Mishaela Rubin
- David Dempster
- Marcella Walker
- Natalie Cusano
- James Lee
- John Williams

- Beatriz Omeragic
- Rukshana Majeed
- Aline Costa
- Barbara Silva
- Cristiano Cipriani
- Leonardo Bandeira
- Donovan Tschang
- Gaia Tobacco
- Sanchita Agarwal
Thank You!