Primary Hyperparathyroidism 2022: a comprehensive update with new guidelines for evaluation and management

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Director, Metabolic Bone Diseases Unit
College of Physicians and Surgeons
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New York, NY

Santa Fe Bone Symposium
August 5-6, 2022
Today (Friday): 12:15-1:15

During the 15-minute break (noon-12:15) get your lunch and bring it to the Zia Room.
You will be able to eat lunch during the symposium.
Disclosures:

Abiogen (Consultant)
Amgen (Consultant, Advisory Board)
Amolyt (Consultant, Advisory Board)
Ascendis (Consultant, Advisory Board)
Ipsen (Consultant)
NovoNordisk (Consultant)
Takeda Pharmaceuticals (Consultant, Advisory Board)
Radius Pharmaceuticals (Consultant)
Regeneron (DSMB)
Ultragenyx (Consultant)
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.
The 5th International Workshop on the Evaluation and Management of Primary Hyperparathyroidism

Rationale:

➢ Since 2013, major advances have been made in our understanding of the epidemiology, pathophysiology, diagnosis, genetics, clinical presentations, target organ involvement, non-classical aspects, natural history, evaluation, surgical and non-surgical approaches.

➢ Thus, it was timely to convene an international group of experts to review the evidence for these advances and to revise current guidelines for evaluation and management.
Steering Committee Members

- John T. Potts, Honorary Chair
- John P. Bilezikian and Aliya Khan, Co-Chairs
- Maria Luisa Brandi
- Bart L. Clarke
- Michael Mannstadt
Scope of the 2-year project: participants

• **17 countries represented**: United States, Canada, Australia, Brazil, China, Denmark, France, Germany, India, Italy, Israel, Lebanon, Singapore, Spain, Sweden, UK


• **Over 100 Participants**
Results of the Workshop:
Outreach to interested organizations, societies, and patient advocacy groups

**International Organizations (10)**
- ENDO
- ESE
- AACE
- ASBMR
- ISCD
- IOF
- Int’l Soc Endo
- WORLD MEN Int’l Conf Committee
- ECTS
- Int’l Assoc of Endocrine Surgeons
- EndoBridge

**Regional: Surgical Societies (9)**
- Am Assoc Endo Surg
- British Assoc of Endo and Thy Surg (BAETS)
- Eur Soc Endo Surg
- Austr/NZ Endo Surg
- Asian Assoc of Endo Surg Org
- FELAC and LA Assn of Thyroid Surg
- Assoc of Endo Surg of Russia
- Hellenic Soc of Endo Surg
- Japanese Soc of Endo Surg

**Patient Advocacy Groups (7)**
- European Rare Bone Forum
- Rare Bone Disease Alliance
- Hypoparathyroidism Association
- Parathyroid UK
- AMEND
- Network Rare Bone Dis German Soc
- Osteology
- Hypopara Support and Advocacy
Results of the Workshop: International Outreach

About 50 countries

- USA
- Canada
- Italy
- Australia
- New Zealand
- Brazil
- Singapore
- UK
- Lebanon
- Russia
- Germany
- China
- Afghanistan
- Nepal
- Tunisia
- Bangladesh

- India
- Armenia
- Tunisia
- Morocco
- Pakistan
- Qatar
- Saudi Arabia
- Kuwait
- Hungary
- Austria
- Iran
- Peru
- Sri Lanka
- Mauritius
- Greece
- Korea

- Argentina
- Georgia
- Romania
- Chile
- Japan
- Denmark
- France
- Israel
- Switzerland
- Sweden
- Mexico
- Colombia
- Costa Rica
- Turkey
- Cyprus
- Jordan
## Results of Workshop

Over 65 International and Regional Societies have already endorsed these guidelines

<table>
<thead>
<tr>
<th>Society Name</th>
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<tbody>
<tr>
<td>Can Soc Endo Metab</td>
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<tr>
<td>FIRMO</td>
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<td>Canadian Endo Update</td>
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<td>Societa Italian di Endocrinologia</td>
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<td>The Associazione Italian sulle MEN, AIMEN</td>
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<td>OrtoMedSociety</td>
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<td>Society for Endocrinology</td>
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<td>Bone Research Society</td>
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<td>Lebanese Soc Endo, Diabetes, Lipidology</td>
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<td>Aust/NZ Bone Mineral Soc</td>
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<td>ENDO Soc of Australia (ESA)</td>
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<td>Chapter Endo, College of Phys (Singapore)</td>
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<td>Endo and Metabolic Soc of Singapore</td>
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<td>Russian Assoc of Endo</td>
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<td>German Soc of ENDO</td>
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<td>Dachverban Osteologie</td>
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<td>Chinese Soc of OP, Bone, Min Res</td>
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<td>Chinese Soc Endo</td>
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<td>Indian Soc Bone Min Res</td>
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<td>Endo Soc of India</td>
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<td>Russian Assoc of Osteoporosis</td>
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<td>Armenian Assoc Osteoporosis</td>
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<td>Tunisian Soc of Endo, Diabetes, Metab</td>
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<td>Moroccan Soc of Endo</td>
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<td>Pakistan Endo Soc</td>
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<td>Perkumpulan Endo Indonesia (PERKENI)</td>
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<td>Saudi Soc Endo Metab</td>
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<td>Jordanian Soc of ENDO</td>
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<td>Soc Endo Metab Turkey</td>
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<td>Malaysian Endo Metab Soc (MEMS)</td>
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<td>Danish Bone Society</td>
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<td>Afghan Endo Soc</td>
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<td>Tunisia Endo Soc/Metab</td>
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<td>Bangladesh Endo Soc</td>
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<td>Japan Soc of Ped Endo</td>
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<td>Philippine Soc of Endo</td>
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<td>Jordan OP Prev Soc</td>
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<td>Italian Soc of OP, Min Metab and Bone Dis (SIOMM)</td>
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<td>Korean Endo Soc</td>
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<td>Korean Soc for Bone Min Res</td>
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METHODOLOGY

Systematic Reviews
GRADE methodology utilized for task force on Evaluation and Management
Principal Methodologists: Gordon Guyatt and Zhikang Ye

Narrative Reviews
Non-graded recommendations: all task forces
Source Materials

- Comprehensive reviews by each Task Force
- Search Engines included: Pubmed, Medline, Embase, and Cochrane
- Search types: systematic reviews, meta analyses, original publications
- Time periods:
  - 1940- for historical references
  - 1970- for all other aspects of PHPT
- The Summary and Guidelines paper supported by 7 other papers were simultaneously submitted to the J Bone Miner Res (Feb 2022). Currently in revision. Publications expected in Summer, 2022.
# Primary Hyperparathyroidism Task Forces:

## Epidemiology, Pathophysiology, and Genetics

**Salvatore Minisola and Raj Thakker,**  
Andrew Arnold, Zhanna Belaya, Maria Luisa Brandi, Bart Clarke, Fadil Hannan, Lorenz Hofbauer, Karl Insogna, Andre Lacroix, Uri Liberman, Andrea Palermo, Jessica Pepe, Rene Rizzoli, Robert Wermers

## Classical and Non-Classical Features

**Ghada El Hajj Fuleihan and Claudio Marcocci,**  
Marlene Chakhtoura, Cristiana Cipriani, Richard Eastell, Jian-Min Liu, Salvatore Minisola, ATatiana Karonovambrish Mithal, Carolina Moreira, Munro Peacock, Marian Schini, Barbara Silva, Marcella Walker, Ola El Zein

## Surgical Aspects

**Nancy Perrier and Antonio Sitges-Serra,**  
Brian Lang, Leonard Bandeira Farias, Leyre Lorente Poch, Mark Swayk, Martin Almquist, Menno Vriens, Michael Yeh, Omair Shariq, Quan-Yang Duh, Randy Yeh, Thinh Vu, Virginia LiVolsi

## Evaluation and Management

**John Bilezikian and Shonni Silverberg,**  
Francisco Bandeira, Filomena Cetani, Manju Chandran, Natalie Cusano, Peter Ebeling, Anna Maria Formenti, Morten Frost, Jessica Gosnell, Michael Lewiecki, Fred Singer, Neil Gittoes, Aliya Khan, Claudio Marcocci, Lars Rejnmark, Zhikang Ye, Gordon Guyatt, John Potts
An update on the evidence related to important features of PHPT

- Diagnosis and Differential Diagnosis
- Epidemiology
- Genetics
- Physiology and Pathophysiology
- Clinical presentations
- Biochemical Presentation
- Evaluation of classical manifestations
- Evaluation of non-classical manifestations
- Surgical Aspects
- Medical Management
- PHPT in Pregnancy

Noteworthy comments or conclusions
**PRIMARY HYPERPARATHYROIDISM**

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

- Pathological forms:
  - Single benign adenoma including atypical (85%)
  - Multiple gland involvement (15%)
  - Cancer (< 1%)

Bilezikian JP, JCEM, 2018; Cetani et al., Front Horm Res, 2019; Cetani et al, Endocr Relat Cancer, 2019
Hypoparathyroidism

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

Box defined by dotted lines represents normal

Total Serum Calcium (mg/dL)
Diagnosis of hypercalcemic PHPT

1. Hypercalcemic PHPT:

Elevated serum calcium, adjusted for albumin, in the presence of an elevated or inappropriately normal intact PTH (utilizing either a 2nd or 3rd generation assay) on two occasions at least two weeks apart.
Differential diagnosis of hypercalcemia and elevated levels of PTH

- Familial Hypocalciuric Hypercalcemia (FHH)
  - Becomes apparent usually in younger individuals (typically < 30)
  - Urinary calcium / creatinine clearance ratio < 0.01
  - Family history of hypercalcemia
- Thiazide diuretics and lithium
- Ectopic secretion of PTH (very rare)
An update on the evidence related to important features of PHPT

- **Epidemiology**

  - Biochemical screening leads to an increase in incidence, whenever screening is introduced in a country.

  - These individuals are discovered incidentally and called ‘asymptomatic.’

  - Current incidence figures in the USA 23/10,000 (women); 8.5/10,000 (men)

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Panel Conclusions

- **Genetics**
  - 10% will have a mutation in one of 10 genes that have been implicated
  - Testing can facilitate the diagnosis of syndromic or non-syndromic forms of PHPT
  - The diagnosis or confirmation of PHPT does not require genetic testing and is not recommended
  - Genetic testing can be helpful in:
    - Hyperparathyroidism jaw tumor syndrome
    - MEN 1 or MEN 2
    - If FHH is suspected

Minisola et al. JBMR, 2021; Marini et al, Clin Cases in Min and Bone, 2017; Cetani et al, Front Horm Res, 2019, Cetani et al, Endocr Relat Cancer, 2019
An update on the evidence related to important features of PHPT

- Physiology and Pathophysiology

  - Clonally dysregulated overgrowth of parathyroid tissue with excessive secretion of PTH

  - Reduced expression of the calcium sensing receptor

- Pathophysiologica consequences:
  - Set-point for calcium-induced inhibition of PTH is higher
  - Rate of bone resorption is accelerated
  - Renal tubular reabsorption of calcium is facilitated
  - Renal phosphate reabsorption is reduced
  - Intestinal calcium absorption is increased

Singh et al JCEM, 2020; Corbetta et al. Clin Endocrinol, 2000;
Brown, JCEM 2013; Arnold et al. Nat Rev Endocrinol, 2021; Rizzoli et al. JCI, 1977
An update on the evidence related to important features of PHPT

- Clinical presentations

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

The captain (1918-1926)
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>
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<tbody>
<tr>
<td>Calcium (mg/dl)</td>
<td>10.7±0.1</td>
<td>8.4-10.2</td>
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<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>
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</table>

Silverberg, Bilezikian et al. 1989
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 can present with persistently elevated PTH with normal adjusted and ionized calcium in the absence of any secondary causes
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

- **Asymptomatic PHPT**
  - Routine biochemical screening

- **Normocalcemic PHPT**
  - Medical centers where metabolic bone diseases are a specialty and PTH levels are routinely obtained even with normal albumin-adjusted and ionized serum calcium levels
The paradox:
How a disease can change but not change

Biochemical screening and advances in imaging technology have helped to define multiple phenotypes of a disease chronologically but in fact it has unmasked those phenotypes that have probably always been present.
Three Generational Phenotypes of Primary Hyperparathyroidism: Evolution Defined by Technology

The disease hasn’t changed: we have!
An update on the evidence related to important features of PHPT

- Further refinement of varying clinical presentations
Panel Conclusions
Further refinement of varying clinical presentations

Clinical presentations

Symptomatic PHPT: any of the following
- marked hypercalcemia
- osteitis fibrosa cystica
- fractures
- chronic kidney disease
- nephrolithiasis
- nephrocalcinosis
- neuromuscular (proximal myopathy)
Panel Conclusions
Further refinement of varying clinical presentations

Clinical presentations

Asymptomatic PHPT

2 forms now defined, both usually discovered in the context of routine biochemical screening without antecedent signs or symptoms

Defined *AFTER* the recommended evaluation:

- Asymptomatic *without* target organ involvement
- Asymptomatic *with* target organ involvement

El-Hajj Fuleihan, JBMR, 2022 (submitted)
Normocalcemic PHPT

- Normal adjusted total calcium and normal ionized calcium levels
- Elevated intact PTH (2nd or 3rd generation assay) on at least two occasions over 3-6 months
- Alternative causes for secondary hyperparathyroidism ruled out:
  - Vitamin D deficiency (25-OH D < 30 ng/mL)
  - Renal insufficiency (eGFR < 60 mL/min)
  - Medications (Thiazide diuretics, Lithium)
  - Hypercalciuria
  - Malabsorption
  - Other metabolic bone diseases that could be associated with elevated PTH (e.g., Paget’s disease)
Normocalcemic PHPT: noteworthy points

- Published studies have not always used consistent definitions nor a regular follow up at defined points
- Normocalcemic PHPT can be:
  - Symptomatic
  - Asymptomatic with or without target organ involvement

An update on the evidence related to important features of PHPT

- Biochemical Evaluation
How should patients be evaluated after the diagnosis has been established?

- 25-hydroxyvitamin D
- Estimate of renal function by creatinine clearance or eGFR
- 24-hour urine for calcium (preferred over a fasting sample)
- Phosphorus (not essential)
- Bone turnover (not generally recommended)
An update on the evidence related to important features of PHPT

- Evaluation of classical manifestations:

  Skeletal Assessment
An update on the evidence related to important features of PHPT: classical features

Skeletal Assessment

The densitometric signature of PHPT

Silverberg, Bilezikian et al. JBMR, 1989
Based upon BMD and bone biopsy data, expectations for fracture incidence in PHPT:

- Vertebral sites
- Non-vertebral sites
Fracture Risk in Primary Hyperparathyroidism is not restricted to the cortical skeleton

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

Vertebral

Distal Forearm

Rib

All

Fractured cases (%)

P=0.15
P<0.0001

Symptomatic (n=41)
Asymptomatic (n=109)
Controls (n=300)

Vignali et al, JCEM, 2009

Microstructural analyses of bone in PHPT by HRpQCT and TBS have elucidated involvement of both cortical and trabecular compartments of bone in PHPT

Hansen et al, JBMR, 2012
Stein E, Silva BC et al. JBMR, 2013
Silva et al. JCEM, 2013
Panel Recommendations

Skeletal Evaluation

- Three-site DXA: lumbar spine, hip (total and femoral neck), distal 1/3 radius
- Vertebral imaging
  - Vertebral fracture assessment (VFA) or Vertebral X-rays
  - TBS, if available
An update on the evidence related to important features of PHPT

- Evaluation of classical manifestations:
  - Renal Assessment
# Emergence of the Modern Clinical Profile of Primary Hyperparathyroidism

<table>
<thead>
<tr>
<th>Condition</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>
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</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>
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</table>
What we know:

- Stones and renal calcifications continue to be a common complication of PHPT
- Hypercalciuria is a risk factor
- Marked hypercalciuria is seen in 1/3 of PHPT stone formers
- Other risk factors (hyperuricosuria, hypomagnesuria, hyperoxaluria, hypocitraturia, cystinuria) may play a role

An update on the evidence related to important features of PHPT: classical features

What we think we know:

- A threshold of < 60cc/min is associated with stabilized renal function after PTX
- Without surgery, continued declines are seen
- Reduced eGFR < 60 ml/min is associated with greater declines in BMD and increased fracture risk

An update on the evidence related to important features of PHPT: classical features

What we don’t know:

- Whether reduced renal function in PHPT is due to the disease or to independent factors
Panel Recommendations

• Renal evaluation
  – Measure creatinine clearance (or eGFR)
  – 24-hour urine for calcium and for other stone risk factors
  – Imaging for nephrolithiasis, nephrocalcinosis (spiral CT, ultrasound, or convention X-rays)

Bilezikan JP et al. JBMR (submitted), 2022
Non-classical Manifestations of PHPT

Quality of life
Cardiovascular
Neurocognitive
Gastrointestinal
Metabolic
Inconsistent data from 4 randomized controlled trials of the effect of parathyroidectomy on psychiatric/cognitive symptoms and quality of life*

Ambrogini, Marcocci et al., JCEM 2007
Bollerslev et al. JCEM, 2007
Rao, Talpos et al., JCEM 2007
Walker, Silverberg et al. JCEM, 2009

*Silverberg et al. J Clin Endocrinol Metab, 2014
Cheng et al. 2015.
Pretorius M.........Bolleslev J. Effect of parathyroidectomy on Quality of Life: 10 Years of Data from a Prospective Randomized Controlled Trial on Primary Hyperparathyroidism. J Bone Miner Res, 2020

- 192 subjects with asymptomatic PHPT
- Randomized 1:1 to PTX or Observation (Obs)
- Two qOL scales (SF-36 and CPRS) tested at baseline, and years 2, 5 and 10

- 33% attrition, equal between groups
- 17 in the Obs group underwent PTX but were included in the Obs group re ITT analysis
PTX: biochemical cure: Obs: Calcium and PTH remained elevated without change
SF-36: Only 1 of 8 scales (vitality) improved
CPRS: both groups improved similarly

Conclusions over 10 years:
- PTX does not improve quality of life
- Observation does not worsen quality of life
Putative Cardiovascular manifestations of PHPT

**Cardiovascular Risk Factors:** Yu et al. Endocrinology, ’10, ’13


**Left Ventricular Function:** Oslo et al. Circulation ‘12

**Left Ventricular Mass:** Persson et al. Clin Endocrinol ‘11, McMahon D et al. JCEM ‘15

**CVD:** Walker et al. JCEM, ‘09, ’10, ’12

**CAD:** Shin et al. JCEM, ’11

**Carotid Intimal Thickness:** Farahnukel et al. Eur J Endo, ’10

**Coronary Flow Reserve:** Fallow et al, JCEM, ’03

**Valve calcifications:** Rubin et al. ’05, Sacco L et al. JCEM, ’12, Carveli et al. Clin Inter Aging, 2020

**Compliance and Stiffness:** Smith et al. JCEM, ’00

**Flow mediated vasodilation:** Schillaci et al. Atherosclerosis, ’11; Carrelli et al. JCEM, ’13, Bolleslev et al, JCEM, ’09

**Micro-microvasculature:** Pepe J et al. Sci Rep, ’18

**Epicardial Fat:** Kizilgul M et al. Turk J Med Sci ‘19

Very uncertain or subtle cardiovascular manifestations are seen in asymptomatic PHPT
An update on the evidence related to important features of PHPT: nonclassical features

Panel
Conclusions:

More research is needed!

After an extensive literature search was conducted, these non-classical features were not recommended for evaluation or to be used when making recommendations for parathyroid surgery.
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

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>
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<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)

![Bar chart showing mean PTH levels (pg/ml) for 25OHD<20 and 25OHD≥20 groups.](image)

*P<0.01

Mean ± SD
Panel Conclusions

Vitamin D sufficiency
25-OH D levels > 20 ng/mL (50 nmol/l) are recommended

Calcium intake should follow national guidelines
An update on the evidence related to important features of PHPT

Surgical Aspects

A 50-year Dilemma in the Management of Asymptomatic PHPT

• Who needs surgery?

• Who doesn’t need surgery?
  - (Who can be followed safely without surgery?)
An update on the evidence related to important features of PHPT

**Surgical Aspects:**

- Recommended for all symptomatic patients with PHPT unless there are medical contraindications.

- The dilemma (surgery or no surgery) applies to asymptomatic PHPT.
## Table 1. Trials Included in Systematic Review of Parathyroid Surgery (7)

<table>
<thead>
<tr>
<th>Categories of subjects</th>
<th>Calcium (mg/dL)</th>
<th>PTH (pg/mL)</th>
<th>Urinary Ca (mg/d)</th>
<th>Conclusions of all Systematic Reviews (both rows)</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>No Surgical Criteria</td>
<td>10.3 ± .46</td>
<td>105 ± 38</td>
<td>239 ± 104</td>
<td>Surgery results in biochemical cure; patients are not cured if they do not undergo surgery.</td>
<td>Ambrogini et al. (157); Morris et al. (162), Perrier et al. (163), Rao et al. (156)</td>
</tr>
<tr>
<td>Asymptomatic with or without surgical criteria</td>
<td>10.9 ± .38</td>
<td>92 ± 31</td>
<td>264 ± 121</td>
<td>Surgery increases BMD and by inference may reduce vertebral and nonvertebral fractures*</td>
<td>Almqvist et al. (159,160); Ejlsmark-Svensson et al. (161); Lundstam et al. (103); Pretorius et al. (149); Persson et al. (155); Ambrogini et al (157); Bollerslev et al. (227); Lundstam et al. (164).</td>
</tr>
</tbody>
</table>

*Using GRADE terminology: surgery “may” reduce these fractures due to low quality of evidence (inferred from BMD without fracture data)
Panel Conclusions, based upon the systematic and narrative reviews

What is the role of surgical management of PHPT?

Combine graded and ungraded statements:

- In the hands of experienced surgeons, surgery achieves a biochemical cure in 97.8% and is a safe procedure (high quality evidence).
- Surgery is associated with a significant increase in bone mineral density and, only by inference, may be associated with a reduction in relative risk of vertebral fracture at 10 years.
- Surgery has an uncertain effect on renal, neurocognitive, quality of life and cardiovascular indices.
Improvements in Bone Density after Parathyroid Surgery

Rubin, Bilezikian, Silverberg et al. JCE&M, 2008
Panel Conclusions: Guidelines for Surgery in Asymptomatic Primary Hyperparathyroidism
(Bilezikian et al. JBMR submitted, 2022) Ungraded recommendations

<table>
<thead>
<tr>
<th>Index</th>
<th>Guideline: any one of the following</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum calcium (above normal)</td>
<td>&gt; 1 mg/dL</td>
</tr>
<tr>
<td>Skeletal Involvement</td>
<td></td>
</tr>
<tr>
<td></td>
<td>A Fx by VFA or X-Ray; or DXA: T-Score ≤ -2.5 at any site</td>
</tr>
<tr>
<td>Renal</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Creatinine clearance or eGFR &lt; 60 ml/min; or Stone or nephrocalcinosis by X-ray, CT, or ultrasound; or Urinary calcium (mg/day) &gt;300 (men); &gt;250 (women)</td>
</tr>
<tr>
<td>Age</td>
<td></td>
</tr>
<tr>
<td></td>
<td>&lt; 50 years alone (without any aforementioned criteria)</td>
</tr>
</tbody>
</table>
Panel Conclusions: Guidelines for Surgery in Asymptomatic Primary Hyperparathyroidism
(Bilezikian et al. JBMR submitted, 2022) Ungraded recommendations

If no one of the aforementioned indices is met, parathyroidectomy is still an option with concurrence of the patient and the physician and if there are no contraindications.
Panel Conclusions: ungraded recommendations

Surgical Aspects: The role of preoperative imaging

- Preoperative imaging (e.g., high resolution neck ultrasound, technetium-99m-sestamibi subtraction scintigraphy, contrast-enhanced 4D-CT) is recommended for those who are going to have parathyroid surgery.

- Preoperative imaging is not recommended for diagnostic purposes.
Panel Conclusions: ungraded recommendations

Surgical Aspects: The role of preoperative imaging:

- With successful preoperative imaging, selective parathyroidectomy, combined or not with intraoperative PTH monitoring, achieves high cure rates in the hands of experienced surgeons (95-97%).

- Advantages of the selective approach include: shorter operative time, less tissue scarring, less risk to surrounding structures, and reduced hospital costs. No head-to-head comparisons are available.
Another guideline that should never be overruled

- SUCCESSFUL IDENTIFICATION OF THE PARATHYROID SURGEON

- Experienced – outstanding track record
- Experienced – outstanding track record
- Experienced – outstanding track record
Preoperative Localization

“The most important preoperative localization challenge in PHPT is to locate the parathyroid surgeon!”

Dr. John Doppman
1975
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*
An update on the evidence related to important features of PHPT

Medical Therapeutics:

• In those who are not going to have parathyroid surgery but in whom surgical guidelines are met, what are the data for effects of pharmacologic intervention on:
  - Reducing serum calcium
  - Increasing bone density (surrogate for reducing fracture risk)?
Medical Management of PHPT

- **Pharmacological approaches**
  - Estrogen/raloxifene*
  - Bisphosphonate* - if BMD is low
  - Cinacalcet - if hypercalcemia is symptomatic
  - Cinacalcet and Bisphosphonate* - if hypercalcemia is symptomatic 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>↓</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td>Bisphosphonate(^3)</td>
<td>←←</td>
<td>↑</td>
<td></td>
</tr>
<tr>
<td>Cinacalcet(^4)</td>
<td>↓↓</td>
<td>←←</td>
<td>↓</td>
</tr>
<tr>
<td>Cinacalcet and Bisphosphonate(^5)</td>
<td>↓↓</td>
<td>↑</td>
<td>↓</td>
</tr>
<tr>
<td>Denosumab(^6)</td>
<td>←←</td>
<td>↑</td>
<td></td>
</tr>
</tbody>
</table>


A 2-year study of PHPT vs OP postmenopausal women
## Systematic Review: Pharmacological Approaches
**(Bilezikian et al. JBMR, submitted, 2022)**

<table>
<thead>
<tr>
<th>Intervention</th>
<th>[Calcium] (mg/dL)</th>
<th>[PTH] (pg/mL)</th>
<th>Urinary Ca (mg/d)</th>
<th>Conclusions of Systematic Reviews (effect on fractures)*</th>
<th>Conclusions of Systematic Reviews (effect on serum calcium)</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alendronate</td>
<td>11.0 ± 0.5</td>
<td>170 ± 95</td>
<td>204 ± 109</td>
<td>Increases BMD</td>
<td>No effect</td>
<td>Chow et al. (200); Khan et al. (197); Rossini et al. (201)</td>
</tr>
<tr>
<td>Estrogen Raloxifene</td>
<td>10.6 ± 0.16</td>
<td>149 ± 32</td>
<td>240 ± 41</td>
<td>Increases BMD (E only)</td>
<td>Reduced</td>
<td>Grey et al. (204); Rubin et al. (205)</td>
</tr>
<tr>
<td>Cinacalcet</td>
<td>11.2 ± 0.45</td>
<td>138 ± 46</td>
<td>290.0 ± 120</td>
<td>No effect</td>
<td>Reduced</td>
<td>Khan et al. (210); Peacock et al. (208)</td>
</tr>
<tr>
<td>Denosumab</td>
<td>10.9 ± 0.1</td>
<td>115 ± 16</td>
<td>NR</td>
<td>Increases BMD</td>
<td>No effect</td>
<td>Leere et al. (212)</td>
</tr>
<tr>
<td>Vitamin D</td>
<td>11.0 ± 0.3</td>
<td>83 ± 15</td>
<td>376 (320-432)</td>
<td>Increases BMD</td>
<td>No effect</td>
<td>Lind et al. (191); Roglighed et al. (189,190)</td>
</tr>
</tbody>
</table>
Panel Conclusions, based upon the systematic and narrative reviews

What is the role of pharmacological intervention in PHPT in those who do not have surgery?

Combined Graded and Ungraded Panel Statements:

- Alendronate and denosumab increase bone density and only by inference may reduce vertebral and non-vertebral fractures (limited by quality of evidence from RCTs)
- Cinacalcet reduces serum calcium into the normal range and to a greater extent than it reduces PTH levels.
- Calcium intake/supplements should follow IOM guidelines
- Vitamin D supplementation: aim for 25-OHD > 30 ng/mL (70 nmol/l)
Panel Conclusions: Normocalcemic PHPT

- There is a higher prevalence of multi-gland disease than in hypercalcemic PHPT
- BMD increases after PTX, in some studies
- Limited data on benefits of PTX on renal, cardiovascular, and quality of life

How should normocalcemic PHPT be managed?

Ungraded panel recommendations

- Referral to an experienced endocrinologist is advised
- Limited data do not permit definitive guidelines for surgery
- Preoperative localization studies are less successful than in hypercalcemic disease but are necessary in those who are going to have parathyroid surgery
Panel Conclusions: What monitoring plan is recommended in patients who do not undergo PTX? (Bilezikian et al. JBMR submitted, 2022)

**Ungraded recommendations**

<table>
<thead>
<tr>
<th>Index</th>
<th>5th Int’l Workshop (Bilezikian et al, JBMR, submitted, 2022)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum Calcium and 25-OH D</td>
<td><strong>Annually</strong></td>
</tr>
<tr>
<td>Skeletal</td>
<td>3-Site DXA: every 1 or 2 years</td>
</tr>
<tr>
<td></td>
<td>Vertebral X-ray, VFA or TBS if clinically indicated</td>
</tr>
<tr>
<td>Renal</td>
<td>Creatinine clearance: annually</td>
</tr>
<tr>
<td></td>
<td>Abdominal imaging (X-ray, CT, or ultrasound) if clinically indicated</td>
</tr>
<tr>
<td></td>
<td>24-hour urine for calcium, if clinically indicated</td>
</tr>
</tbody>
</table>
Panel Conclusions:

When should parathyroid surgery be recommended in hypercalcemic or normocalcemic PHPT who are being monitored?

Ungraded Panel Statements:

- Serum calcium becomes consistently > 1 mg/dL (0.25 mmol/L) above the upper limit of normal.
- A low trauma fracture
- A kidney stone
- A significant reduction in BMD (as defined by a loss > the least significant change and a T-score < -2.5), at any site
- A significant reduction in creatinine clearance (averaging > 3 ml/min over a 1-2 years) if associated with other changes that indicate progressive involvement
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
Primary Hyperparathyroidism in Pregnancy

• A rare event but the true incidence is unknown. The data are confounded because some of these individuals probably had PHPT before the onset of the pregnancy. ¹,²

• In most, the disease is mild, with serum calcium values < 11 mg/dL. ²

• Outcomes (miscarriage, prematurity, low birth weight- conflicting data ¹,³) may be related to the maternal serum calcium when > 11.4 mg/dL ⁴

Panel Conclusions:

How should PHPT be managed during pregnancy?

Ungraded Panel Statements:

- Mild cases can be managed by maintaining good hydration and monitoring calcium levels
- Pharmacological agents
  - Calcitonin - doesn’t cross the placenta
  - Bisphosphonates: possible endochondral bone effects (do not use)
  - Denosumab: crosses the placenta; monkey toxicities in pregnancy (do not use)
  - Cinacalcet crosses the placenta (not recommended)

References:

Panel Conclusions:

How should PHPT be managed during pregnancy?

Ungraded Panel Statements:

- If the serum calcium is > 11.0 mg/dL, and there are no contraindications, consider surgery in the 2nd trimester

- Preoperative imaging should be limited to ultrasound

- If surgery is deferred, the neonate should be closely monitored for hypocalcemia

- If surgery is deferred, PTX should be done after delivery, and before a subsequent pregnancy

Panel Conclusions: Recommended Research Agenda

Presentations
- Global presentations and factors to account for differences
- Global differences in incidence and prevalence of the various forms of PHPT
- Long-term consequences/natural history of the various forms of PHPT with or without PTX.
- Definition of normocalcemic PHPT
- A global registry

Pathophysiology
- Differences among the hypercalcemic and normocalcemic variants
- Accounting for differences in predominant presentations of each form vis a vis single or multi-glandular disease
- Potential role of diet and the microbiome on clinical manifestations of PHPT.
- Potential role of CaSR signaling pathways in abnormal parathyroid tissue

Genetics
- CaSR mutations as they relate to PHPT vs FHH: similar or different?
- Potential role of GNA11 or AP2S1 on pathogenesis
- Role of genetic testing
- Utility of genetic testing modalities
- Identification of heretofore unidentified, causative genes

Serum calcium and vitamin D
- How/whether to adjust downward for a serum albumin of > 4 g/dL
- Is there a threshold at which PTX is indicated?
- Optimal levels of serum 25OHD
- What is the best way to replete vitamin D in PHPT?

Renal
- Stone Risk in PHPT.
- Can a predictive model be developed to document risk?
- Threshold values of renal function for recommending surgery
- Factors associated with worsening renal function
- Relationships between reduced creatinine clearance, PTH, calcium, phosphorus, 1,25(OH)2D
- Medical and surgical therapeutics

Skeletal
- TBS, HRpQCT and other measures of bone quality
- FRAX tool as a risk factor in PHPT
- Factors associated with reduced bone density and/or fractures
- Fracture risk before and after PTX

Non-classical manifestations
- Neurocognitive
- Cardiovascular
- Metabolic

Surgical Aspects
- Complications of combined thyroid and parathyroid procedures
- Risk factors for parathyromatosis and local recurrence
- Timing medical therapy for osteoporosis after PTX
- Review of complications
- Parathyroid cancer
- The role of genetics in decision-making for PTX
Key Points

• Primary Hyperparathyroidism is a common endocrine disorder

• ‘Asymptomatic’ PHPT is most often seen in developed countries

• Symptomatic PHPT and Normocalcemic PHPT co-exist with asymptomatic hypercalcemic disease throughout the world

• The relative proportion of these 3 phenotypes depends on common medical practices like screening)
Key Points

• 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

• Pharmacological intervention is generally reserved for those whose serum calcium is high and/or whose BMD is low and surgery is not an option

• Long-term conservative management, beyond 10 years, is advised with caution
Conclusions

• This evidence-based review is meant to aid clinicians and investigators in our collective quest to apply the best evidence available to understand, evaluate, and to manage primary hyperparathyroidism

• We hope that this information will be helpful clinically and in our never-ending search for new knowledge
Special event: Satellite Symposium

**Hypoparathyroidism 2022:** a comprehensive update with new guidelines for evaluation and management

Today (Friday): 12:15-1:15

During the 15-minute break (noon-12:15) get your lunch and bring it to the Zia Room.

You will be able to eat lunch during the symposium.
THANK YOU!