Primary Hyperparathyroidism 2023:
Key Management Issues After The Diagnosis

John P. Bilezikian, MD, PhD (hon)
Silberberg Professor of Medicine
Vice-Chair for International Education and Research
Chief, Division of Endocrinology, Emeritus
Director, Metabolic Bone Diseases Unit, Emeritus
Vagelos College of Physicians and Surgeons
Columbia University, New York, NY

"Elevated Parathyroid Hormone: Diagnostic Dilemmas and Therapeutic Considerations in Hyperparathyroidism"

Third Annual UT Southwestern Multidisciplinary Endocrine Tumor Symposium
A Virtual Meeting, September 8, 2023

John P. Bilezikian, MD, PhD (hon)

Disclosures:

Abiogen (Consultant)
Amgen (Consultant, Advisory Board)
Amolyt (Consultant, Advisory Board)
Ascendis (Consultant, Advisory Board)
NovoNordisk (Consultant)
Takeda Pharmaceuticals (Consultant, Advisory Board)
Radius Pharmaceuticals (Consultant)
Rani Therapeutics (Consultant)
Regeneron (DSMB)

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 (2020-2022): participants

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

- **45 Institutions represented**: Columbia, McMaster, Mayo Clinic, U Indiana, Ohio State U, Harvard, UCSF, Penn, U Chicago, Yale, NIH, MD Anderson, MSKCC, Hofstra, U New Mexico, John Wayne CC, U Birmingham, FIRMO, U Rome, U Rome Sapienza, U Conn, U Florence, All India Inst, U Pisa, AUB, Oxford, Sheffield U, U Singapore, Monash, Fed U Belo Horizonte, Fed U of Parana, U Paris, Aarhus U, Geneva U, U Gottingen, Sackler, Tech U Med Center, Shanghai Jiao-Tong U, Alberta Health, Karolinska, Western U, U Toronto, U Pernambuco, U Barcelona, U S Denmark, U Milan

- **Over 100 Participants**

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
- Mauritus
- 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

Can Soc Endo Metab
FIRMO
Canadian Endo Update
Brazilian Soc of Endo/Metab
Endocrine Metabolic Soc of Singapore
Chapter of Endo Acad of Med (Singapore)
Societa Italian di Endocrinologia
The Associazione Italian sulle MEN, AIMEN
OrtoMedSociety
Society for Endocrinology
Bone Research Society
Lebanese Soc Endo, Diabetes, Lipidology
Aust/NZ Bone Mineral Soc
ENDO Soc of Australia (ESA)
Chapter Endo, College of Phys (Singapore)
Endo and Metabolic Soc of Singapore
Russian Assoc of Endo
German Soc of ENDO
Dachverban Osteologie
Chinese Soci of OP, Bone, Min Res
Chinese Soc Endo
Indian Soc Bone Min Res
Endo Soc of India
Russian Assoc of Osteoporosis
Armenian Assoc Osteoporosis
Tunisian Soc of Endo, Diabetes, Metab
Moroccan Soc of Endo

Pakistan Endo Soc
Perkumpulan Endo Indonesia (PERKENI)
Saudi Soc Endo Metab
Jordanian Soc of ENDO
Soc Endo Metab Turkey
Malaysian Endo Metab Soc (MEMS)
Egyptian Assoc Endor
Libyan Assoc Diabetes Endo
Soc Alger of Endo/Metab
Qatar Diabet Assoc
Qatar Osteoporosis Assoc
The Saudi OP Soc
The Kawait Endo Soc
Hungarian Soc of Endo/Metab
Austrian Rheum
Iran Endo/Metab Res Inst (EMRI)
Peruvian Endo and Diab Assoc
Hong Kong Endo
Georgian Assoc Skeletal Metab
Romanian Soc of Endo
Chilean Soc Osteo Min Metab
Chilean Soc Endo/Metab
The Swiss Assoc Against OP
Swiss Diab & Endo Soc
Danish Bone Society
Danish Endo Society
Japan Endo Soc
Japan Soc Bone and Miner Res
ABRASSO
Endocrine Society of Sweden

Argentine Assoc Osteo/Min Metab
Arggentine Soc of Osteoprosis
Argentine Soc of Endo
Hong Kong Soc Endo/Metab/Repr
French Endo Soc
Georgian Assoc Skel Metab Dis
Israel Endo Soc
Mexico Nat'l Acad Med
Mexican Soc Nutr/Endo

Mexican Pediatric Endocrine Society
Colombia Assoc Osteo/Min Metab
Turkey Soc Endo/Metab (SEMT)
Italian Soc Endo
Irish Endo Soc
Afghan Endo Soc
Nepal Diab/Endo Assoc
Sri Lankan Endo soc
Mauritius Endo Soc
Tunisia Soc Endo/Metab
South Asian Fed Endo Soc
Hellenic Endo Soc (Bone group)
Cypriot Endo Soc
Bangladesh Endo Soc
Japan Soc of Ped Endo
Philippine Soc of Endo
Jordan OP Prev Soc
Italian Soc of OP, Min Metab and Bone Dis (SIOMM)
Korean Endo Soc
Korean Soc for Bone Min Res

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 have been published J Bone Miner Res (Nov, 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, Tatiana Karonov, Ambrish Mithal, Carolina Moreira, Munro Peacock, Marian Schini, Barbara Silva, Marcella Walker, Ola El Zein

Surgical Aspects

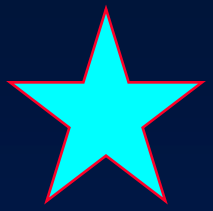
Nancy Perrier and Antonio Sitges-Serra,
Brian Lang, Leonard Bandeira Farias, Leyre Lorente Poch, Mark Swayk, Martin Almquist, Menno Vriens, Michael Yeh, Omair Shariq, Quan-Yang Duh, Randy Yeh, Thinh Vu, Virginia LiVolsi

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
- Nutritional and Pharmacological Management
- PHPT in Pregnancy



Noteworthy comments or conclusions

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!

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 et al, JBMR, 2022

Panel Conclusions

Further refinement of varying clinical presentations

Clinical presentations

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)*

Bilezikian et al, JBMR, 2022;
El-Hajj Fuleihan et al. JBMR, 2022

Panel Conclusions

Further refinement of varying clinical presentations

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

El-Hajj Fuleihan et al. JBMR 2022; Schini et al. JCEM, 2020,
Siprova et al, Endocr Pract 2016; Gomez-Ramirez et al. Am J Surg 2020;
Trinh et al. Otolaryngol Head Neck Surg 2018; Koumakis et al. JCEM 2013;
Koumakis et al, Osteoporoos Int, 2014

An update on the evidence related to important features of PHPT

- **Biochemical Evaluation**

Panel Conclusions

- **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)

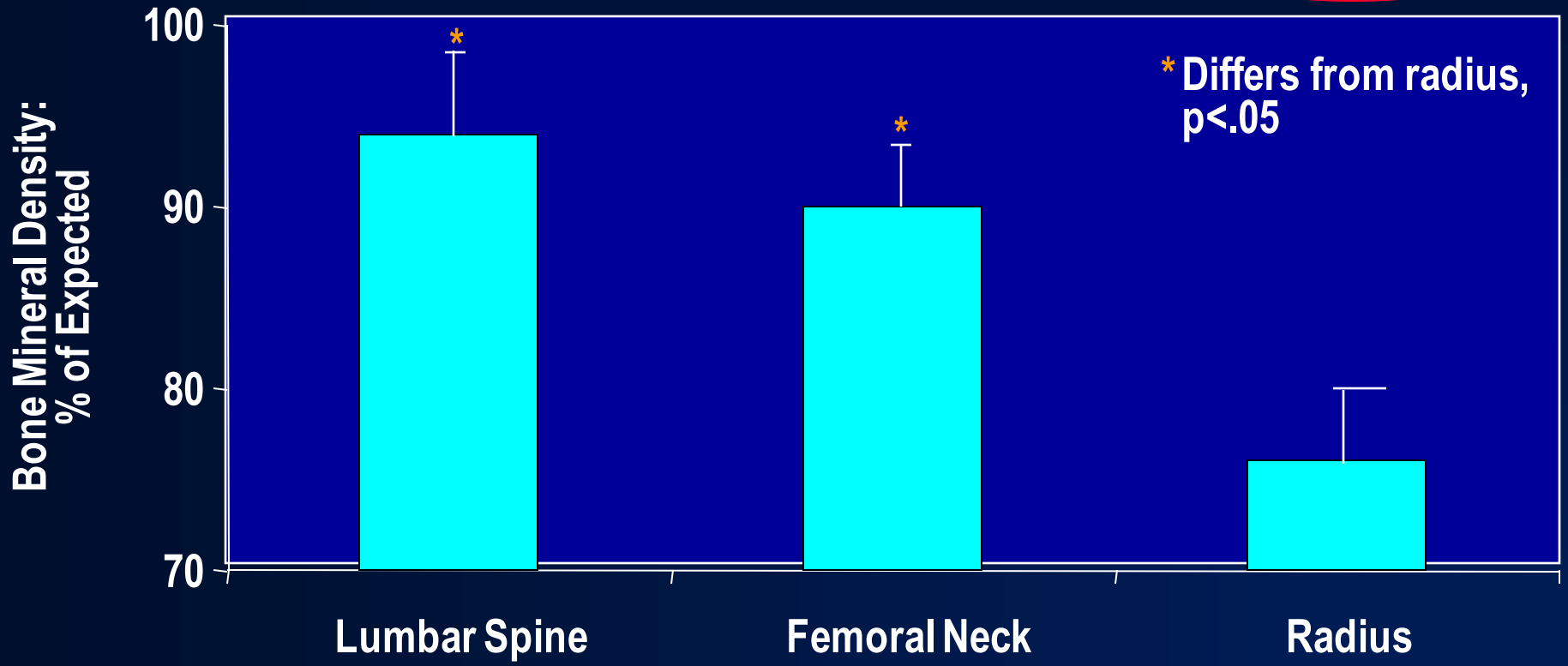
An update on the evidence related to important features of PHPT

- **Evaluation of classical manifestations:**

Skeletal Assessment

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

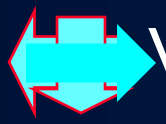
Skeletal Assessment

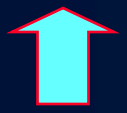


Silverberg, Bilezikian et al.
JBMR, 1989

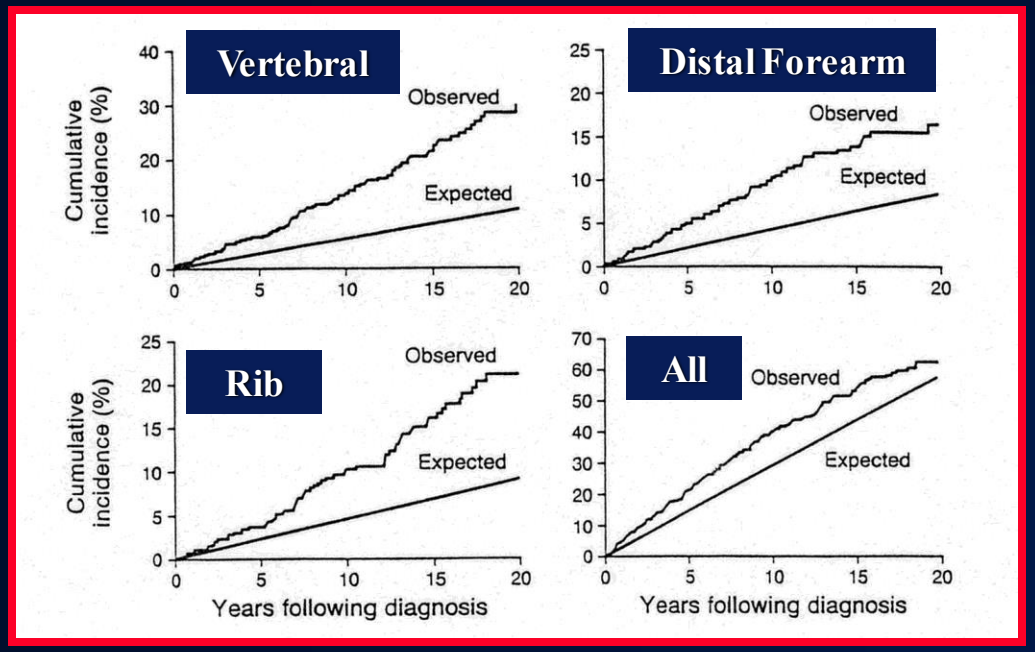
The densitometric signature of PHPT

Based upon BMD and bone biopsy data, expectations for fracture incidence in PHPT:

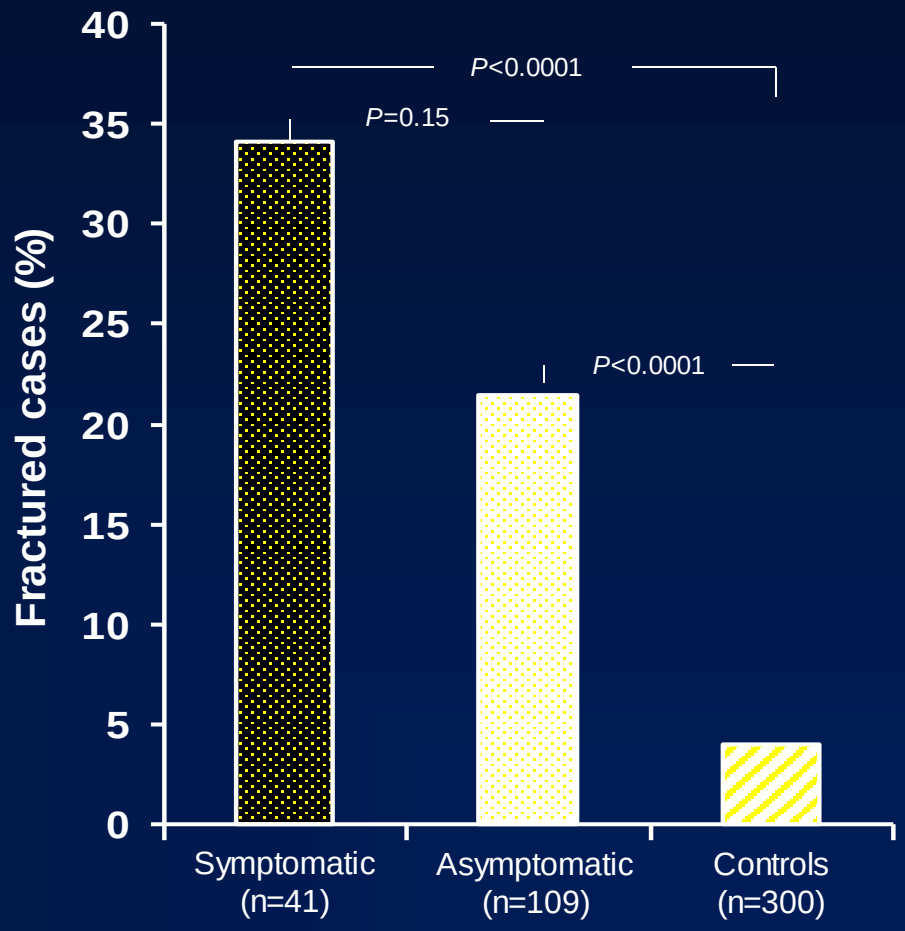
 Vertebral sites

 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

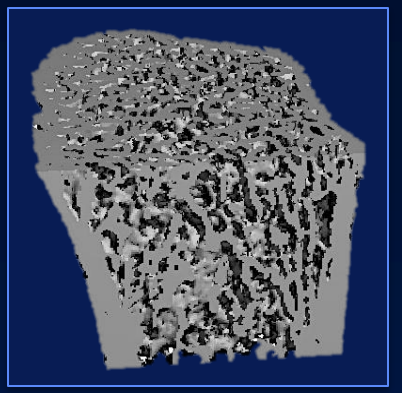


Vignali et al, JCEM, 2009

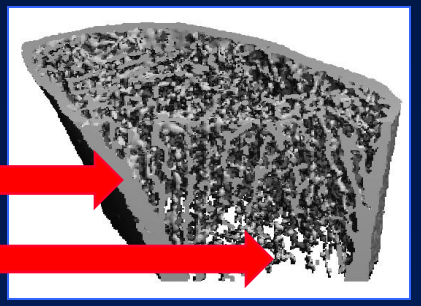
El-Hajj Fuleihan et al, JBMR 2022
Eller-Vainicher et al. Eur J Endocrinol, 2014;
Larsson et al. J intern Med, 1993; Ejlsmark-Svensson et al. Osteoporos Int 2021; DeGeronimo S et al. Eur J Endocrinol, 2006;
Ejlsmark-Svensson et al. JBMR, 2018

Skeletal Assessment

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



Matched Control



PHPT

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

Panel Recommendations

Skeletal Assessment

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

	Cope et al.'30-'65	Mallette et al. '65-'74	Silverberg et al. '84-'00	Cusano et al. '10-'12
Nephrolithiasis	57%	37%	17%	14.3%
Hypercalciuria	Not reported	40%	39%	29%
Overt Skeletal Disease	23%	14%	1.4%	<1%
Asymptomatic	0.6%	22%	80%	>80%

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

Kidney Stones

What we know:

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

Rejnmark et al. JCEM 2011; Eyre et al. BJU Int 2020; Ejlsmark-Svensson et al. JCEM 2018; Moe et al. Lancet 2006; Saponaro et al. JCEM 2020; Odvina et al. Urol Res 2007; Castellano et al Endocr Pract 2017; Tay et al. Endocr Res 2018; Saponaro et al. J Endocrinol Investig 2020; Curhan et al. Kidney Int 2008; Cassibba et al. Endo Pract, 2014.

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

Renal Function

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

Tassone et al, JCEM 2015; Tay et al. Indian J Endo Metab, 2016;
Agrawal et al. Clin Endocrinol 2020; Gianotti et al. JCEM, 2006;
Dukas et al. Osteoporosis Int, 2005;
Ensrud et al. Arch Int Med, 200; Fried et al. J Am Soc Nephrol, 2007;
Nickolas et al. J Am Soc Nephrol, 2013

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

Renal Function

What we don't know:

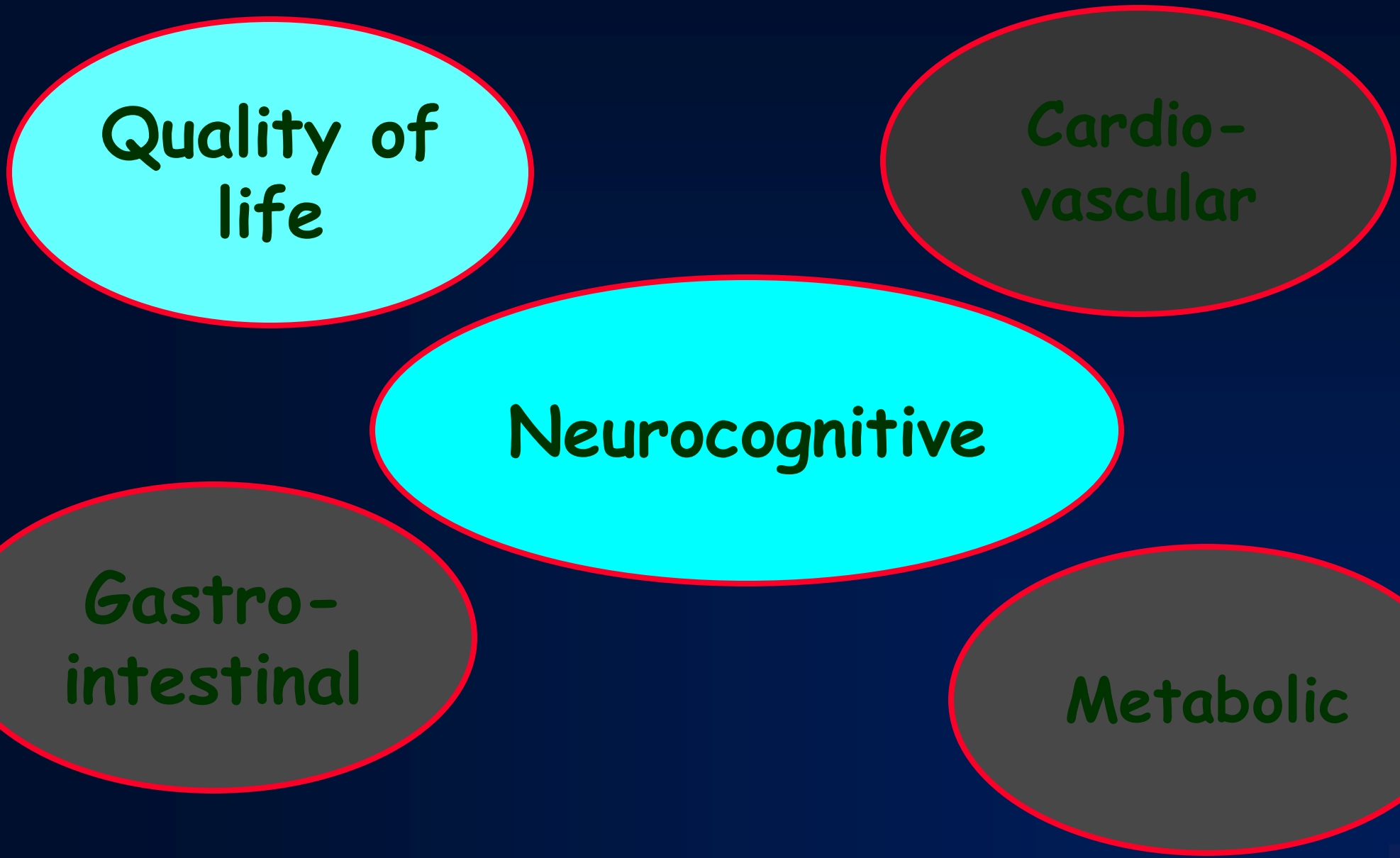
- Whether reduced renal function in PHPT is due to the disease or to independent factors

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 conventional X-rays)

Bilezikan JP et al. JBMR , 2022

Non-classical Manifestations of PHPT



Quality of Life: Randomized Controlled Trial Data

- Inconsistent data from 5 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
Pretorius et al. J Bone Mineral Res, 2020

**Silverberg et al. J Clin Endocrinol Metab, 2014*

Cheng et al. 2015.

Putative Cardiovascular manifestations of PHPT

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

Blood Pressure: Fisher et al. Gland Surg, 2020; Nelson et al. Gland Surg, 2020, Petramala L et al. Int J Endo, '12

Left Ventricular Function: Oslo et al. Circulation '12

Left Ventricu

CVD: Walker e

CAD: Shin et a

Carotid Intim

Coronary Fl

Valve calcifi

Compliance

Flow mediat 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

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.

Panel Conclusions:

More research is needed!

Other Aspects of Primary Hyperparathyroidism

Neuro-cognitive

Cardio-vascular

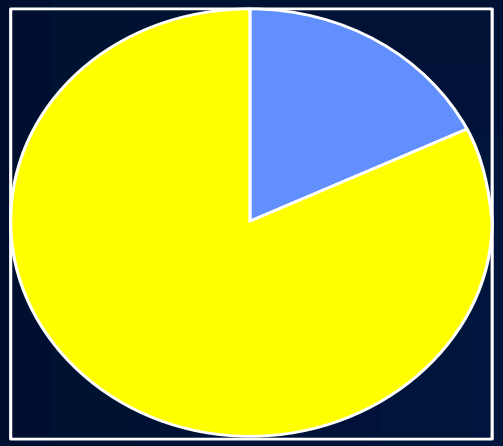
Gastro-intestinal

Vitamin D

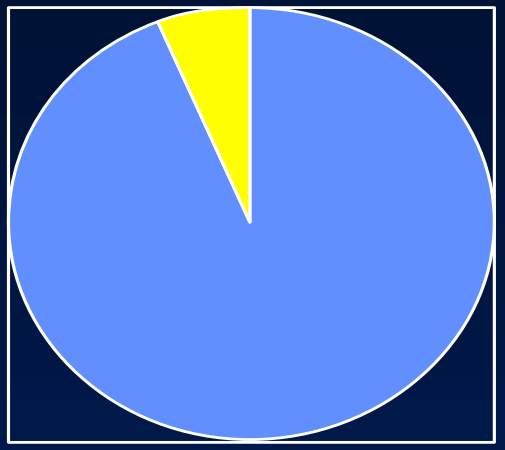
The Hypothesis of Double Trouble

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

PHPT: The Global View



NEW YORK



BEIJING

Asymptomatic

Symptomatic
Bone Disease/Fractures Common

Bilezikian, Meng, Shi, Silverberg. 2000

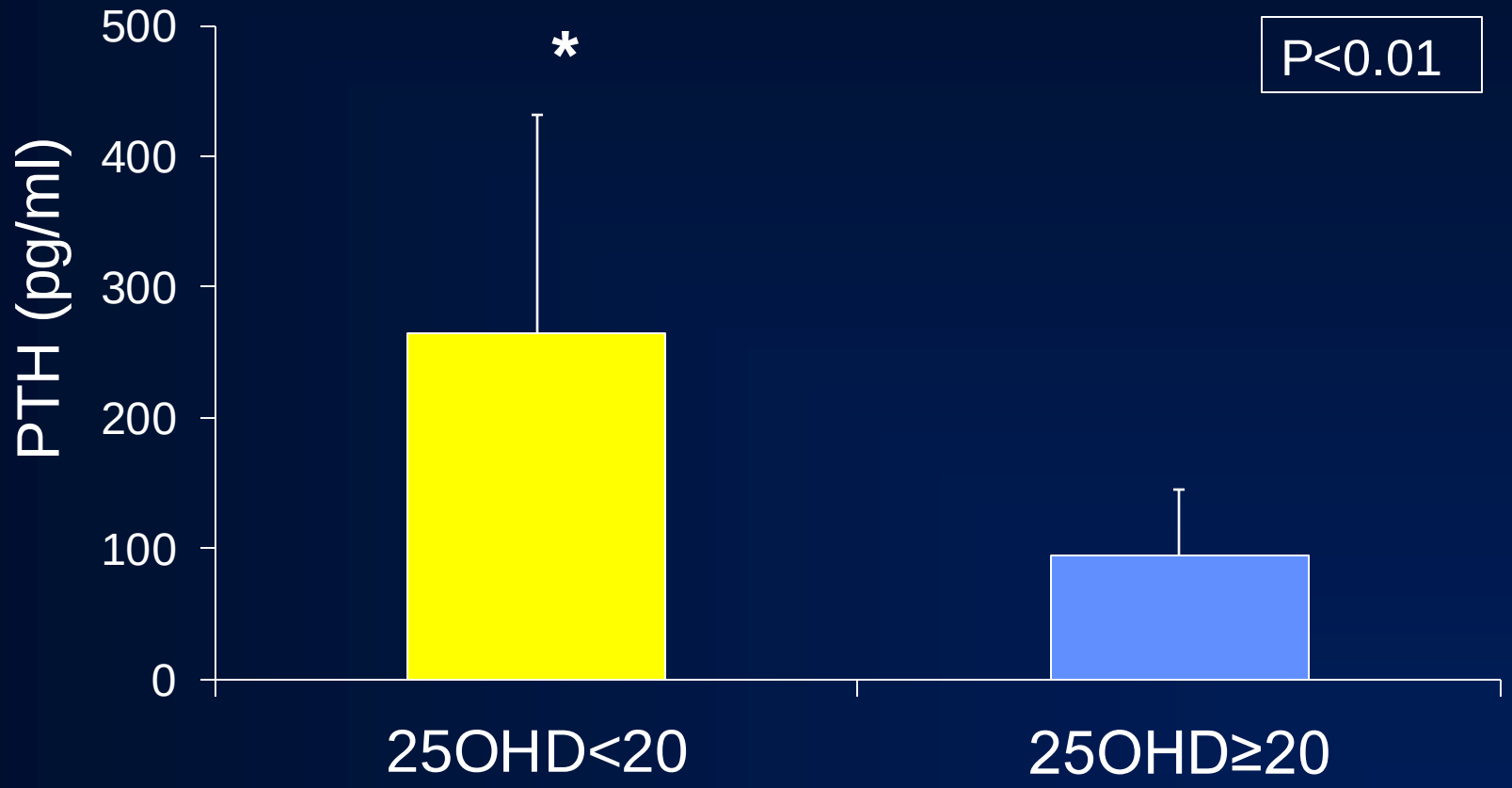
Primary Hyperparathyroidism:

	New York	Beijing
Calcium (mg/dl)	10.7 ± 0.1	12.4 ± 1.1
Alk Phos (% > nl)	40%	80%
PTH (x nl)	1.86	21.4
Uca (% > nl)	38%	51%
Phos (% < nl)	25%	60%
25-OH D (ng/ml)	**21.1 ± 1**	**8.8 ± 7.2**

Bilezikian, Meng, Shi, Silverberg. 2000

PTH Levels as function of Vitamin D status

(Stein et al. JCEM, 2011)



Mean ±SD

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

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

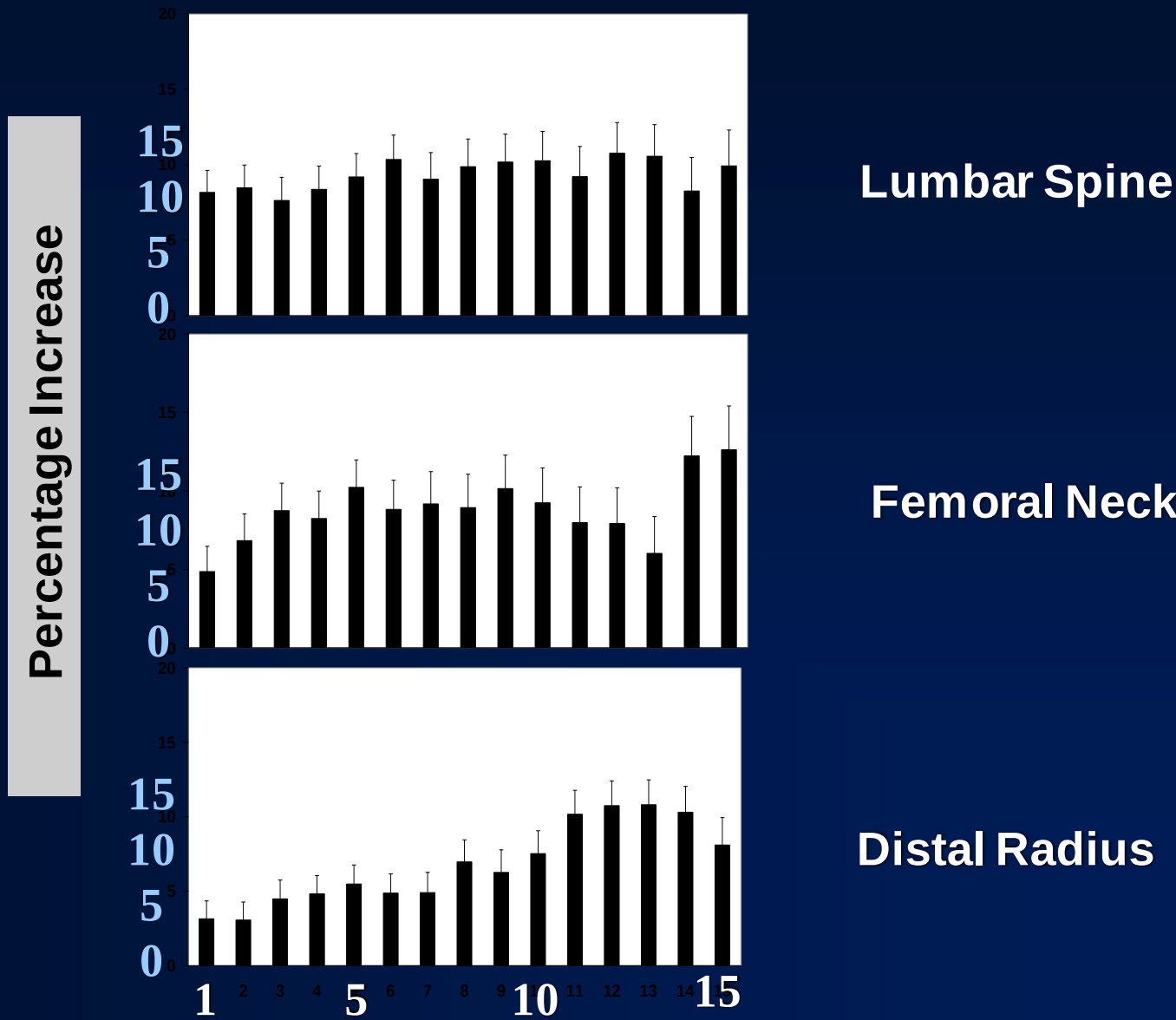
Panel Conclusions, based upon the systematic and narrative reviews

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*

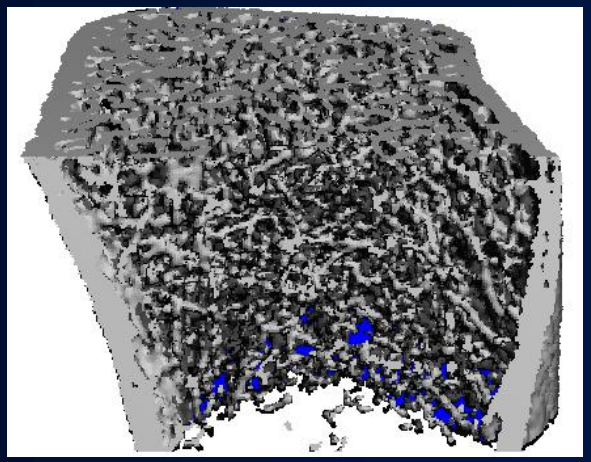
****See also: Pretorius et al. Annals Int Med, 2022 re prospective study: no difference in mortality, fractures, cancer, cardiovascular, cerebrovascular or renal outcomes***

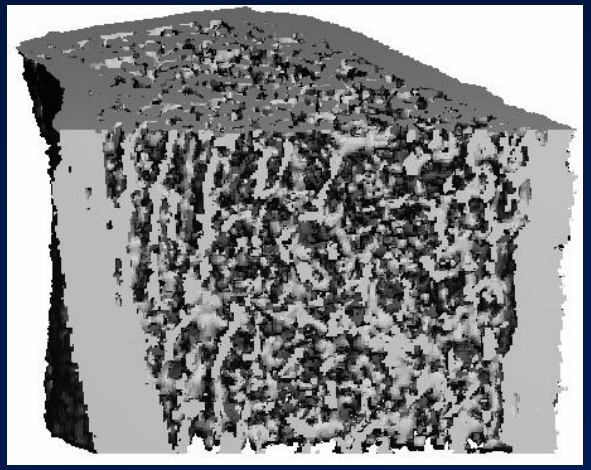
Improvements in Bone Density after Parathyroid Surgery



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

Improvement in microarchitecture after parathyroid surgery





BY HIGH RESOLUTION pQCT

Silverberg, Shane, Bilezikian, 2006

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*

Panel Conclusions: Guidelines for Surgery in Asymptomatic Primary Hyperparathyroidism

(Bilezikian et al. JBMR, 2022) Ungraded recommendations

Index	Guideline: any one of the following
Serum calcium (above normal)	> 1 mg/dL
Skeletal Involvement	A Fx by VFA or X-Ray; or DXA: T-Score ≤ -2.5 at any site
Renal	Creatinine clearance or eGFR < 60 ml/min; or Stone or nephrocalcinosis by X-ray, CT, or ultrasound; or Urinary calcium (mg/day) >300 (men); >250 (women)
Age	< 50 years alone (without any aforementioned criteria)

Panel Conclusions: Guidelines for Surgery in Asymptomatic Primary Hyperparathyroidism

(Bilezikian et al. JBMR, 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: Guidelines for Surgery in Normocalcemic Primary Hyperparathyroidism

(Bilezikian et al. JBMR, 2022) Ungraded recommendations

Index	Guideline:	NO CONCLUSIONS ABOUT GUIDELINES FOR SURGERY WERE REACHED IN NORMOCALCEMIC PHPT
Serum calcium (above normal)	N/A	
Skeletal Involvement	?	
Renal	?	
Age	?	

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

El-Hajj Fuleihan et al. JBMR, 2022
Bilezikian et al. JBMR, 2022

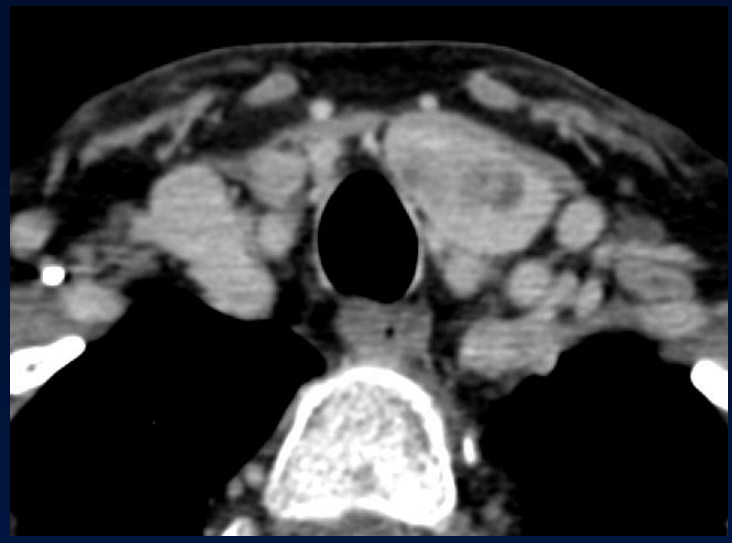
Panel Conclusions: ungraded recommendations

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.

Parathyroid Imaging



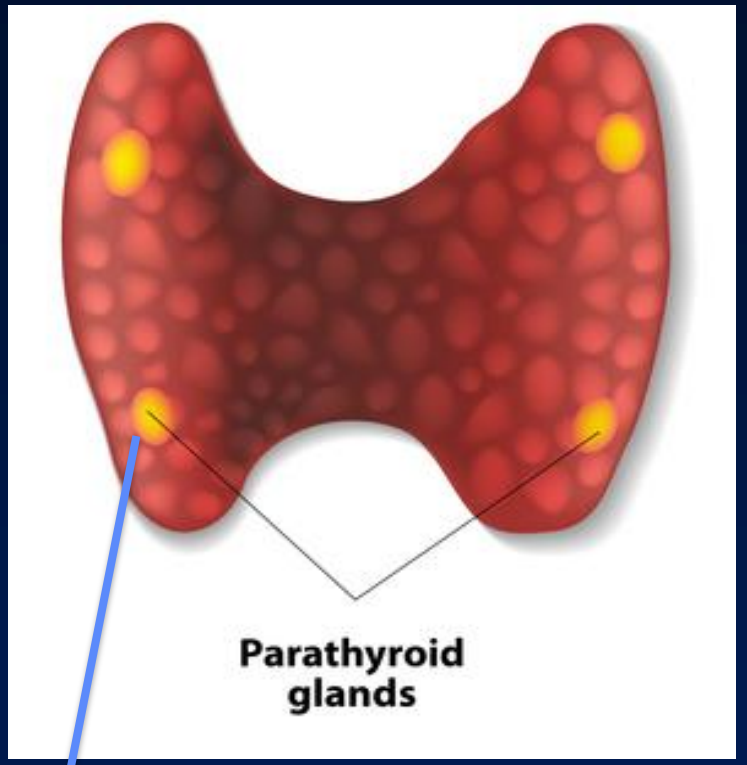
Prof. James Lee: Columbia Department of Surgery

https://eockingdommin.files.wordpress.com/2011/07/confused-doctor1.jpg

Why Do Radiologists Fear Parathyroid Imaging?

Parathyroids are Pesky!

- Small size: difficult to image (a normal gland is the size of a small pea)
- Variable location due to embryological development
- Variable characteristics: diseased glands (adenomas, hyperplasia) do not always follow the rules
  - Some enhance, others don't
  - Some take up sestamibi, others don't



Average weight: 29.5 mg ±17.8 mg, with upper limit 65 mg

Preoperative Imaging Modalities

- Available modalities:
  - Ultrasound
  - Nuclear Medicine: $Tc99^{m}$-Sestamibi (MIBI) scintigraphy including SPECT/CT
  - Parathyroid 4D CT
  - MRI
  - PET/CT with ^{11}C-Choline and Methionine (still considered to be a research technology)

Accuracy of Imaging Modalities

Diagnostic accuracy of imaging modalities for preoperative parathyroid localization

Imaging modality	Sensitivity (percent)	Positive predictive value (percent)
Sestamibi	71-79	72-95
Sestamibi-SPECT	70-81	91-95
Ultrasound	64-91	83-96
4D-CT	83-95	88-99
MRI	40-85	N/A
MET-PET-CT scan	79-90	93-94

SPECT: sestamibi-single photon emission computed tomography; CT: computed tomography; MRI: magnetic resonance imaging; N/A: not applicable; MET-PET-CT scan: 11C-methionine positron emission tomography and computed tomography.

Data from:

1. *Cheung K, Wang TS, Farrokhyar F, et al. A meta-analysis of preoperative localization techniques for patients with primary hyperparathyroidism. Ann Surg Oncol 2012; 19:577.*
2. *Mihai R, Simon D, Hellman P. Imaging for primary hyperparathyroidism--an evidence-based analysis. Langenbecks Arch Surg 2009; 394:765.*
3. *Weber T, Maier-Funk C, Ohlhauser D, et al. Accurate Preoperative Localization of Parathyroid Adenomas With C-11 Methionine PET/CT. Ann Surg 2013; 257:1124.*

UpToDate®

Yip, L, Silverberg, SJ, Fuleihan GE, Preoperative localization for parathyroid surgery in patients with primary hyperparathyroidism. In: UpToDate, Chen, W (Ed), UpToDate, Waltham, MA, 2016.

Yeh R, Tay YD, Tabacco G, Dercle L, Kuo JH, Bandeira L, McManus C, Leung DK, Lee JA, Bilezikian JP. Diagnostic Performance of 4D CT and Sestamibi SPECT/CT in Localizing Parathyroid Adenomas in Primary Hyperparathyroidism Radiology 291:469-476, 2019

Preoperative Imaging Modalities

- **No consensus on best imaging protocol**
  - Institutional availability
  - Local radiologist's expertise
  - Preference of the surgeon
  - Cost

- **For all modalities, localization is less accurate for multiglandular disease**

Not to minimize the value of preoperative localization, what is even more important?

- 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

The Natural History of PHPT

- With successful surgery: Cure
- Without surgery….

When parathyroid surgery is not necessarily an option

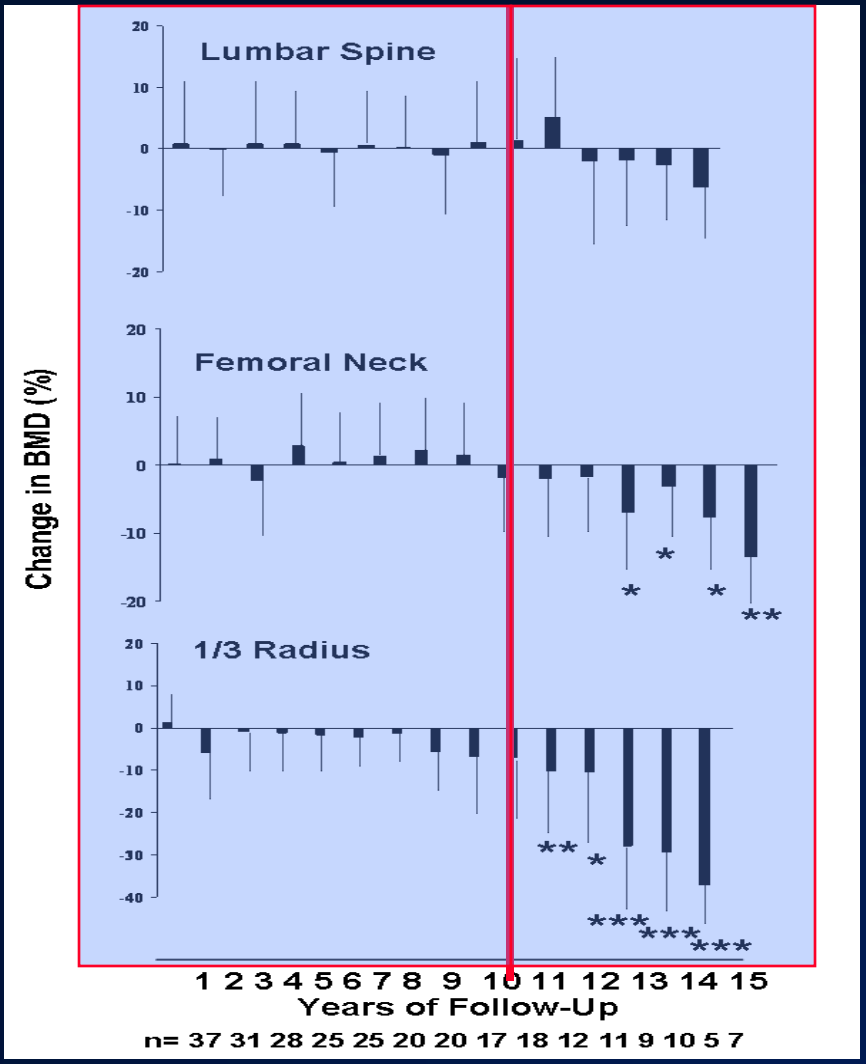
- Guidelines are not met and patient opts for non-surgical management
- Patient declines
- Previous neck surgery (usual multiple) making further surgery problematical
- Co-existing medical issues

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

Index	Baseline	5	10	13	15
		Years of monitoring			
Ca	10.5 ±.1	10.7±.1	10.8± .2	11.0 ±.2	11.1± .2
PTH	122± 10	119± 12	123± 14	124± 16	121± 18
Uca	238± 19	215± 23	185± 32	247± 36	202± 36
25-OHD	21± 1	22± 2	22± 3	21± 3	20± 4
1,25-OH_2 D	50± 2	58± 3	54± 6	40± 5	48± 7

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

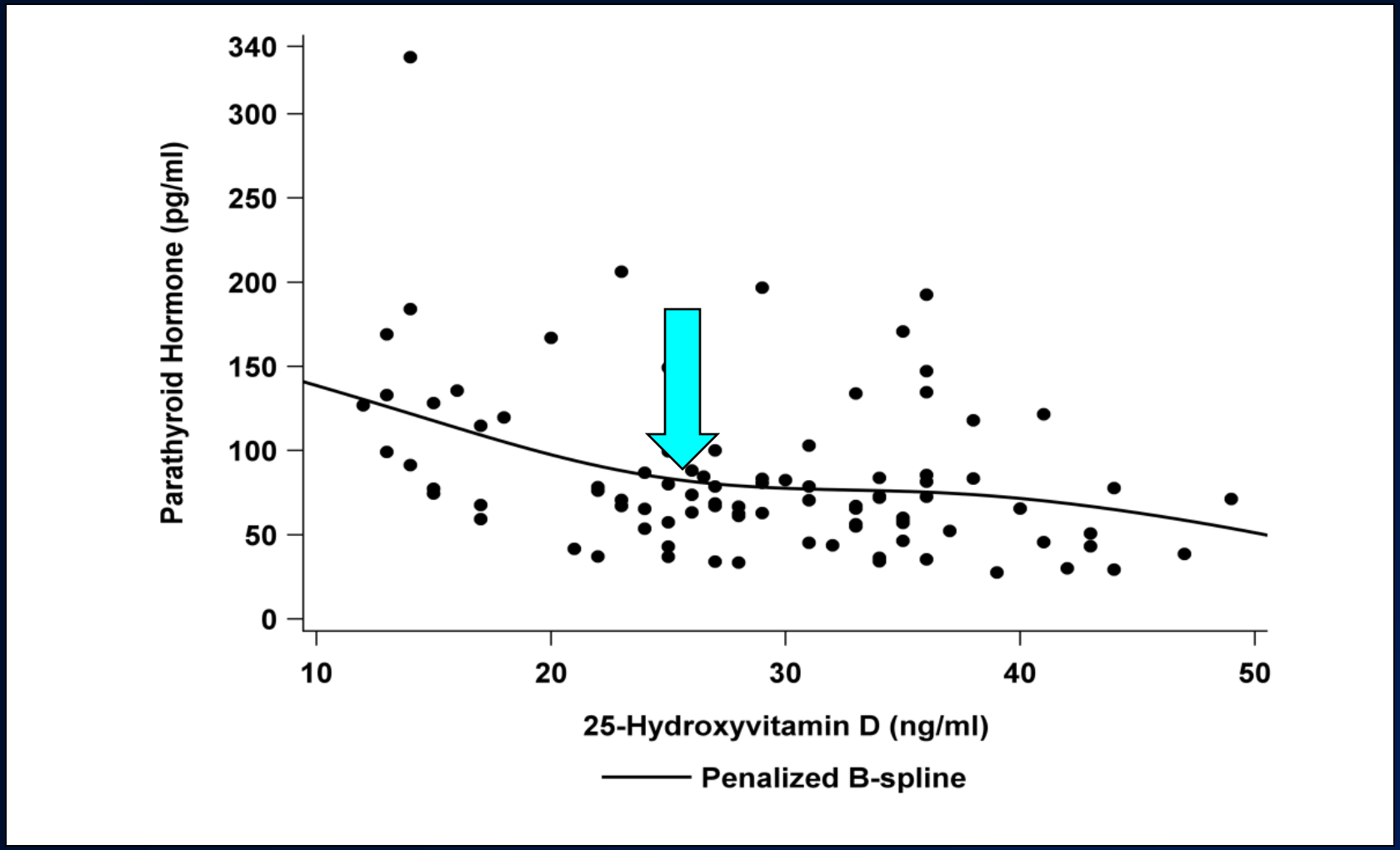
- **37% developed one or more indications for surgery during 15 years of monitoring**
  (hypercalcemia, hypercalciuria, or reduced BMD)

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

Options for Medical Management of PHPT

- *Nutritional*
- *Pharmacological*

In PHPT, PTH levels begin to rise further when 25OHD levels fall below about 25 ng/mL



Walker, Silverberg et al. JCEM 2015

Panel Conclusions

Vitamin D sufficiency

25-OH D levels > 30 ng/mL (75 nmol/l) are recommended

In Normocalcemic PHPT, some experts recommend 25-OH D levels > 40 ng/mL (100 nmol/l)

Bilezikian et al, JBMR, 2022;
El-Hajj Fuleihan et al. JBMR, 2022

Calcium Intake in PHPT*

- Advice should be no different from the normal population and national guidelines (IOM):
  - 1000-1200 mg/day
  - Preferably from foods
  - Supplements should be used to supplement

**It is almost never a good idea to restrict calcium intake in PHPT*

Pharmacological Management of PHPT

Medical Therapeutics:

- In those who are not going to have parathyroid surgery but in whom surgical guidelines are met, pharmacologic options can be considered to:
  - Reduce serum calcium
  - Increase bone density (surrogate for reducing fracture risk)?

Pharmacological Management of PHPT

- ***To reduce the serum calcium***, chronically, when
  - the hypercalcemia is usually well above the guidelines for surgery
  - surgery will not be performed
- Intervention
  - Estrogen: high doses needed; not used often (Grey et al)
  - Raloxifene: very limited data: small effect (Rubin et al)
  - Cinacalcet: the treatment of choice (Peacock et al)

Cinacalcet in Primary Hyperparathyroidism

- Calcium concentration generally normalizes and can be maintained in the vast majority of subjects
- PTH is modestly reduced but does not become normal
- Phosphorus concentration increases but is usually maintained within normal limits
- BMD does not change significantly
- Well tolerated

Peacock, Shoback, Bilezikian et al, JCEM, 2005; 2009: Khan, Bilezikian et al. 2015

Indications for Cinacalcet in Hyperparathyroidism (FDA)

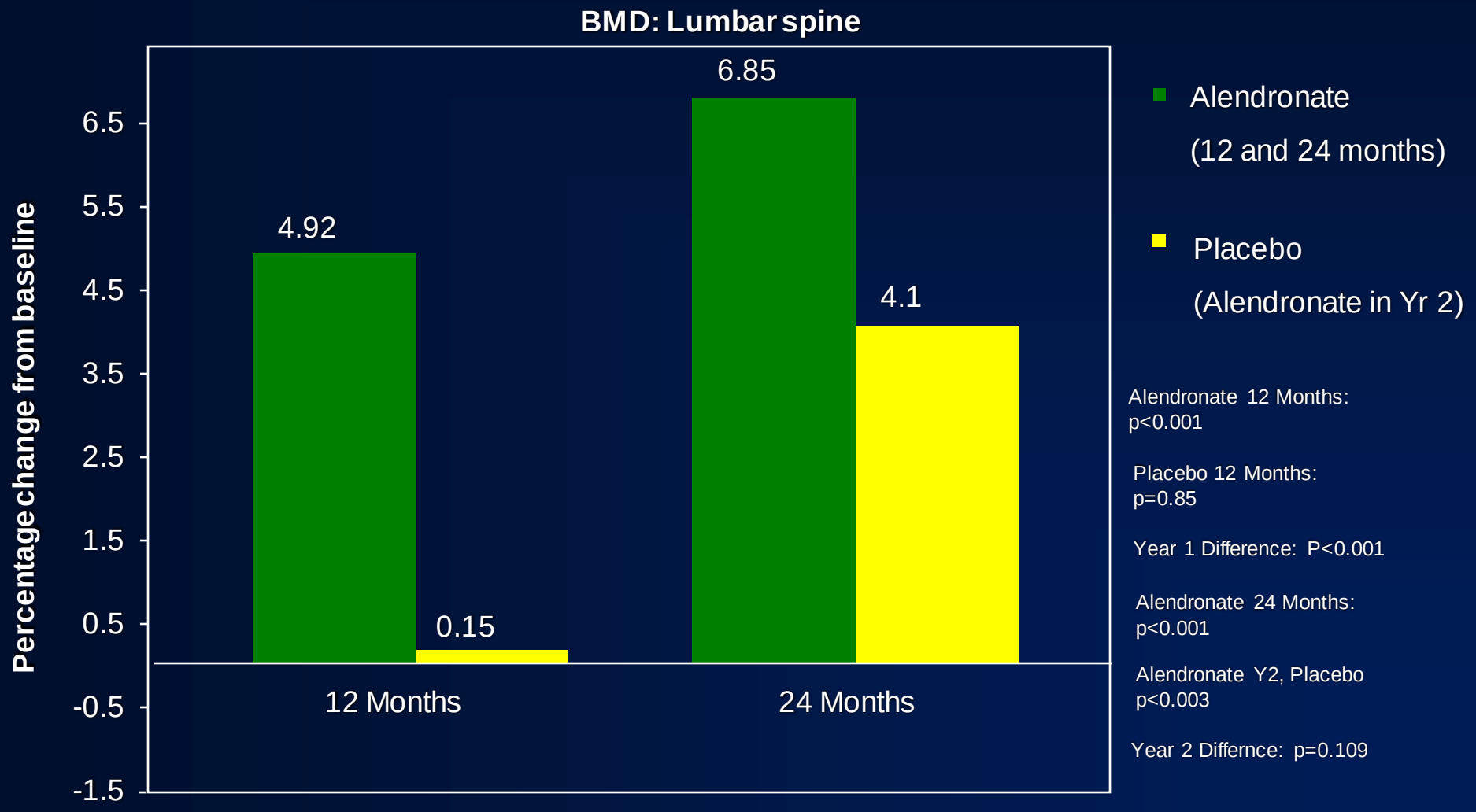
- Hyperparathyroidism associated with dialysis
- Parathyroid cancer
- Primary Hyperparathyroidism….for control of “advanced disease” (calcium > 1mg/dl above nl) in whom parathyroidectomy is medically not indicated or refused

Pharmacological Management of PHPT

- ***To increase bone mineral density*** when
  - Bone density is low
  - Surgery will not be performed
- Intervention
  - Estrogen: high doses needed; not used often (Grey et al)
  - Bisphosphonates
  - Denosumab

Alendronate in Primary Hyperparathyroidism

Khan, Bilezikian, Kung et al.
J Clin Endocrinol & Metab, 2004

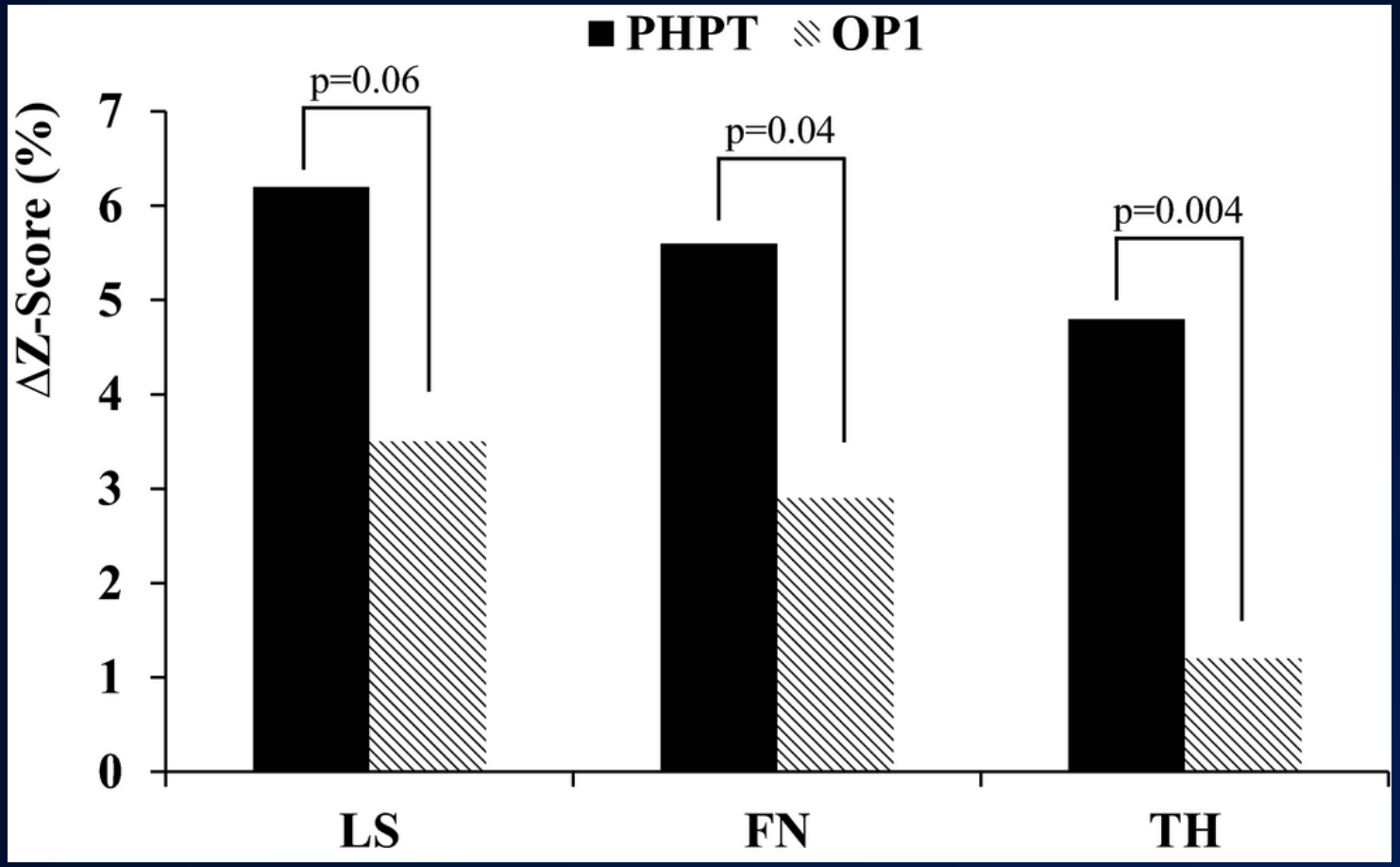


Alendronate in Primary Hyperparathyroidism

- Significant increase in lumbar spine BMD
- Bone density at total hip and 1/3 radial sites is stable
- Significant decline in bone markers
- Calcium, PTH stable
- Well tolerated

Khan, Bilezikian, Kung et al
J Clin Endocrinol & Metab, 2004

Protective Effect of Denosumab on Bone in Older Women with Primary Hyperparathyroidism. Eller-Vainicher et al. J Am Geriatr Soc, 2018*



A 2-year study of PHPT vs OP postmenopausal women

*see also: Gronskaya S, Belaya Z et al. Endocrine, 2023; Miyaoka D et al. Endocrine, 2020

Pharmacological Approaches to PHPT

Agent	Serum calcium	Bone Mineral Density	PTH
Estrogen[1]	↓	↔	↔
Raloxifene[2]	↓	↔	↔
Cinacalcet[3]	↓↓	↔	↓
Bisphosphonate [4] (Alendronate)	↔	↑	↔
Cinacalcet and Bisphosphonate[5]	↓↓	↑	↓
Denosumab [6]	↔	↑ vs PO women	↔

[1]Marcus et al, 1991; [2]Rubin et al, 2005, [3]Peacock et al, 2005, 2009, [4]Khan et al.2004, , [5]Faggiano et al, 2011, [6]Eller-Vainicher et al, 2018

Panel Conclusions, based upon the systematic and narrative reviews

A summary of nutritional and pharmacological approaches in those who do not have surgery

Combined Graded and Ungraded Panel Statements:

- **Calcium intake/supplements should follow IOM guidelines (1000-1200 mg/day)**
- **Vitamin D supplementation: aim for 25-OHD > 30 ng/mL (75 nmol/l)**
- **To reduce the serum calcium, cinacalcet is useful.**
- **To increase bone mineral density, effective options are alendronate or denosumab.**
- **To reduce the serum calcium and to increase bone density, options include a bisphosphonate or denosumab along with cinacalcet**

Bilezikian et al, JBMR, 2022

Panel Conclusions: What monitoring plan is recommended in patients who do not undergo PTX?

Ungraded recommendations

Index	5th Int'l Workshop (Bilezikian et al, JBMR, 2022)
Serum Calcium and 25-OH D	**Annually**
Skeletal	**3-Site DXA: every 1 or 2 years** **Vertebral X-ray, VFA or TBS if clinically indicated**
Renal	**Creatinine clearance: annually** **Abdominal imaging (X-ray, CT, or ultrasound) if clinically indicated** **24-hour urine for calcium, if clinically indicated**

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

Bilezikian et al, JBMR, 2022

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 beween 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

Bilezikian et al, JBMR, 2022

Key Points

- New guidelines have been published on the evaluation and management of Primary Hyperparathyroidism
- In those who will have parathyroid surgery, advanced preoperative localization techniques are usually successful
- The parathyroid surgeon is a key factor in the successful outcome of parathyroid surgery

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

THANK YOU!