



CONVEGNO MACROREGIONALE  
**AME DAY**



20/21  
MAGGIO 2016



# Iperparatiroidismo Primitivo.

## Quale Terapia ?

## Quale Iperparatiroidismo

## Primitivo Richiede Terapia ?

*Giuseppe Murabolo*

*Struttura Complessa di Medicina,*

*Ospedale di Assisi*



# The Face/Off of Primary Hyperparathyroidism (PHPT)

---



A CASE OF OSTEITIS FIBROSA CYSTICA (OSTEOMALACIA?)  
WITH EVIDENCE OF HYPERACTIVITY OF THE PARA-  
THYROID BODIES. METABOLIC STUDY I<sup>1</sup>

By R. R. HANNON, E. SHORR, W. S. McCLELLAN AND E. F. DuBOIS

*(From the Russell Sage Institute of Pathology in affiliation with the Second Medical (Cornell)  
Division of Bellevue Hospital, New York)*

(Received for publication July 15, 1929) THE JOURNAL OF CLINICAL INVESTIGATION.



Dr. Eugene DuBois

A CASE OF OSTEITIS FIBROSA CYSTICA (OSTEOMALACIA?)  
WITH EVIDENCE OF HYPERACTIVITY OF THE PARA-  
THYROID BODIES. METABOLIC STUDY II<sup>1</sup>

By WALTER BAUER,<sup>2</sup> FULLER ALBRIGHT<sup>3</sup> AND JOSEPH C. AUB

*(From the Medical Clinic of the Massachusetts General Hospital, Boston)*

(Received for publication February 5, 1929)

THE JOURNAL OF CLINICAL INVESTIGATION, VOL. VIII, NO. 2



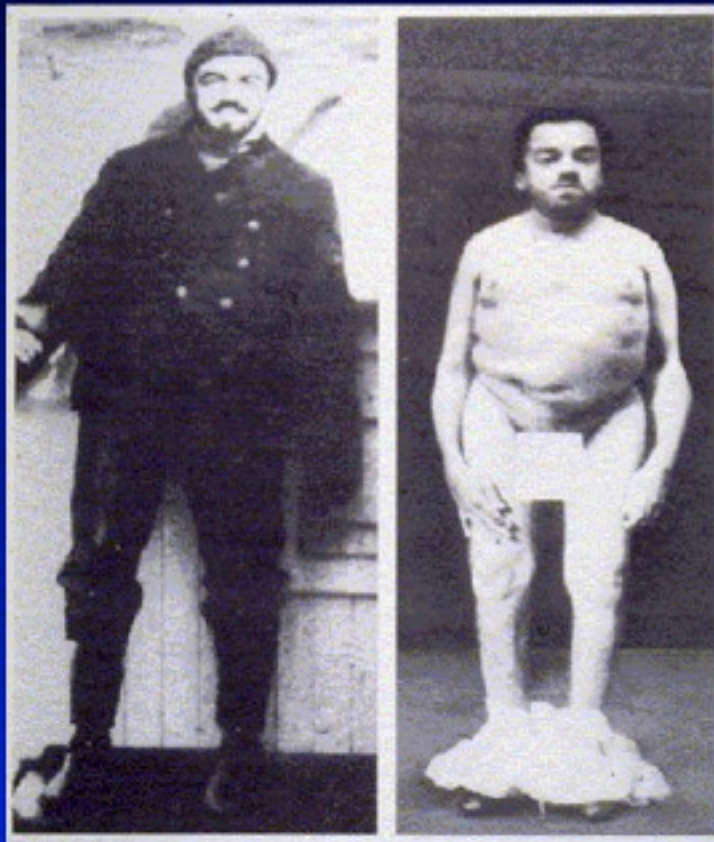
Dr. Fuller Albright

# The changing of clinical profile in PHPT: 1929 -1970

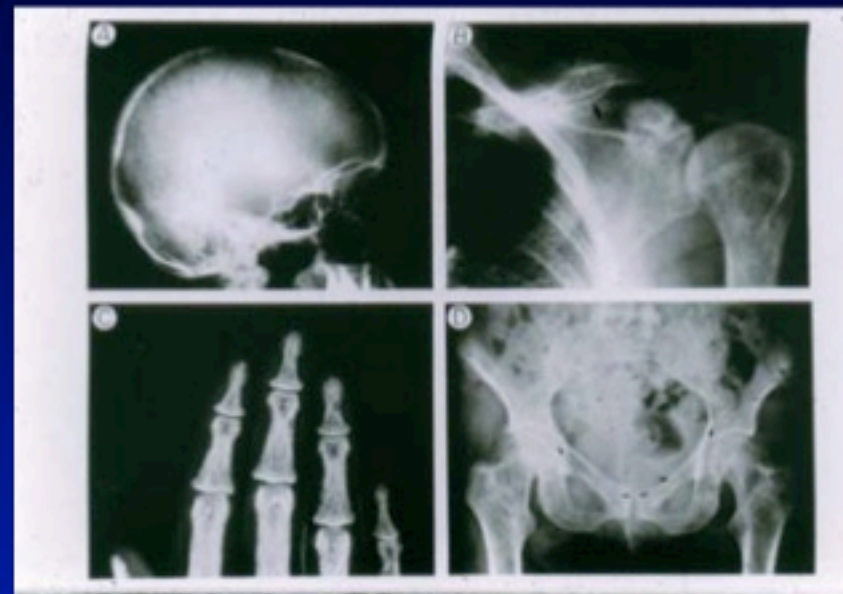
Captain Charles E. Martell

30 y

50 y



The Lady  
1970



After 1970:  
A disease with **primarily biochemical and densitometric signatures**

Before 1970 syndrome of "ones"  
**"bones, stones, groans, and psychiatric overtones"**

# Biochemical and Densitometric Signatures of PHPT in modern era

Changing proportion of asymptomatic pts with clinical manifestations of PHPT at 6 y intervals

| Researchers (study period)  | Symptoms observed (% of patients) |                |                        |                   |
|---|-----------------------------------|----------------|------------------------|-------------------|
|   | Nephrolithiasis                   | Hypercalciuria | Overt skeletal disease | No overt symptoms |
| Cope (1930–1965) <sup>81</sup>                                      | 57                                | NR             | 23                     | 0.6               |
| Heath <i>et al.</i> (1965–1974) <sup>2</sup>                        | 51                                | 36             | 10                     | 18                |
| Mallette <i>et al.</i> (1965–1974) <sup>82</sup>                    | 37                                | 40             | 14                     | 22                |
| Silverberg, Bilezikian, and colleagues (1984–2006; various studies) | 17                                | 39             | 1.4                    | 80                |

Abbreviation: NR, not reported.

1951-1956

1957-1962

1963-1968

1969-1974

1975-1980

1981-1986

1987-1992

Years

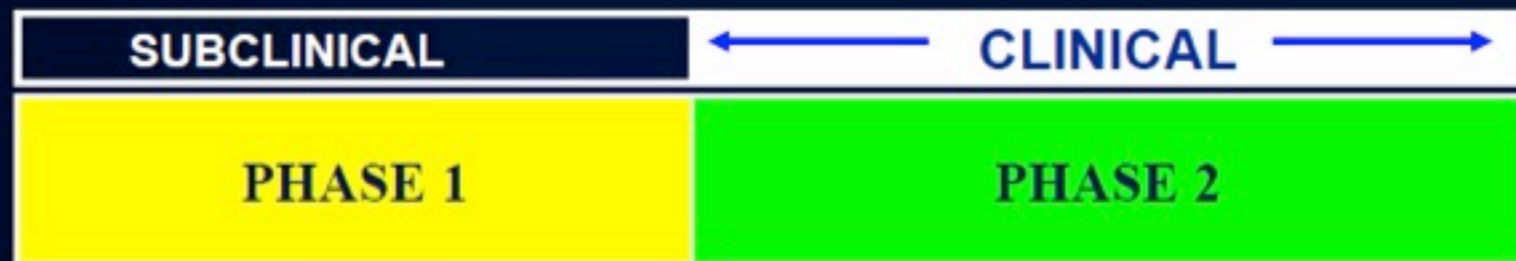
# Generational phenotypes of Primary Hyperparathyroidism

🏠 Before 1970:  
a disease of bones, stones, and groans;

**"Symptomatic" PHPT**

🏠 After 1970:  
a disease with primarily biochemical and densitometric signatures;

**"Asymptomatic" PHPT**



# The natural history of Subclinical “Asymptomatic” PHPT

---

## **The Natural History of Primary Hyperparathyroidism with or without Parathyroid Surgery after 15 Years**

Mishaela R. Rubin, John P. Bilezikian, Donald J. McMahon, Thomas Jacobs, Elizabeth Shane,  
Ethel Siris, Julia Udesky, and Shonni J. Silverberg

*(J Clin Endocrinol Metab 93: 3462–3470, 2008)*

Ethel Siris, Julia Udesky, and Shonni J. Silverberg

---

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

N. YU<sup>1</sup>, G.P. LEESE<sup>2</sup>, D. SMITH<sup>3</sup> and P.T. DONNAN<sup>1</sup>

*Q J Med 2011; 104:513–521*

N. YU<sup>1</sup>, G.P. LEESE<sup>2</sup>, D. SMITH<sup>3</sup>, and P.T. DONNAN<sup>1</sup>

# Observational study of pts with PHPT:

Prospective Columbia University Natural Study (15 y follow-up)

---

## ■ **37% of asymptomatic pts eventually satisfy criteria for surgery (1990 criteria):**

- This number would likely be higher by the 2008-2014 criteria;
- 60% of observed patients continued to lose BMD;
- 100% of the surgical group had increased BMD;

## ■ Kidney stones:

- recurrence in 100% in pts with stones who declined surgery;
- no recurrence in pts with stones who had surgery

## ■ Predictors of disease "progression" at baseline ?

(100% of symptomatic patients)



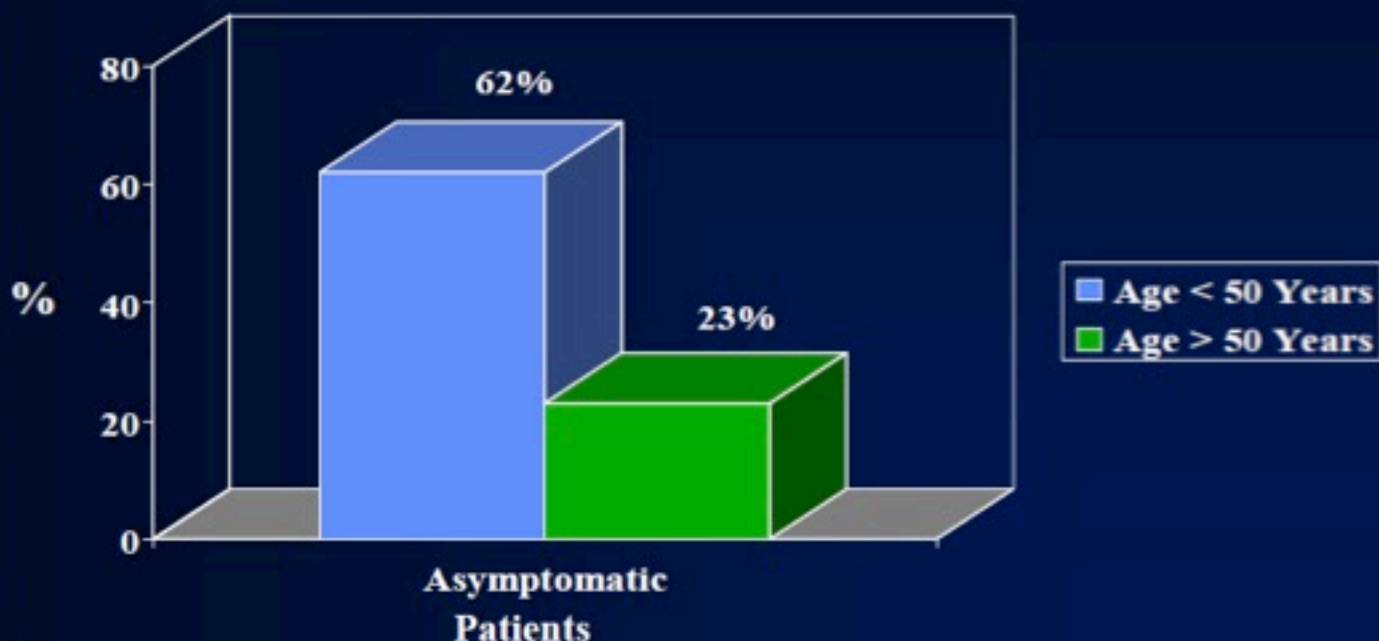
# Relative youth as a risk factor for progressive disease in "asymptomatic" PHPT

## BRIEF OBSERVATION

### Age As a Criterion for Surgery in Primary Hyperparathyroidism

Shonni J. Silverberg, MD, Ijeoma Brown, John P. Bilezikian, MD

Serum and urinary biochemistry values and calciotropic indices were monitored every 4 months, whereas urinary calcium excretion and bone mineral densitometry were measured annually (14). Statistical analyses included unpaired (surgical vs. nonsurgical patients) and paired (baseline vs. postoperative measurements) *t* tests and chi-squared tests (development of new surgical criteria in younger vs. older patients). This study was per-



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

N. YU<sup>1</sup>, G.P. LEESE<sup>2</sup>, D. SMITH<sup>3</sup> and P.T. DONNAN<sup>1</sup>

*Q J Med* 2011; 104:513–521

## Comparison of baseline characteristics between progressed and un-progressed mild untreated PHPT patients

| Variables                                 | No progression   | Progression      | P-value |
|---|------------------|------------------|---------|
| Number, <i>n</i> (%)                      | 783 (86.6)       | 121 (13.4)       | –       |
| Age, mean (SD), years                     | 66.9 (13.4)      | 69.7 (13.7)      | 0.032   |
| Female, <i>n</i> (%)                      | 587 (75)         | 87 (71.9)        | NS      |
| Follow-up time, median months (range)     | 55 (6.2–151.9)   | 64 (7.4–152.1)   | 0.018   |
| Progression time, median months (range)   | –                | 39 (6.8–114.0)   | –       |
| Baseline biochemical indices <sup>a</sup> |                  |                  |         |
| Serum calcium (mmol/l)                    | 2.61 (2.55–2.88) | 2.63 (2.55–2.89) | 0.036   |
| PTH (pmol/l)                              | 6.4 (3.0–29.9)   | 8.5 (3.0–25.6)   | 0.006   |
| Alkaline phosphatase (μ/l)                | 93 (28–1187)     | 94 (36–258)      | NS      |
| Serum creatinine (μmol/l)                 | 96 (56–150)      | 96 (60–150)      | NS      |
| Cholesterol (mmol/l)                      | 5.1 (1.7–14.1)   | 5.4 (2.2–8.7)    | NS      |

The risk of progression increased by:

- 📊 35% for each 5 pmol/L (47 pg/mL) increase in the baseline PTH level (P=0.017);
- 📊 18% for each 5 years increase in age at diagnosis (P=0.020)

# The Scandinavian Investigation of PHPT (SIPH): Quality of Life and Cardio-Metabolic Outcomes

---

## **Medical Observation, Compared with Parathyroidectomy, for Asymptomatic Primary Hyperparathyroidism: A Prospective, Randomized Trial**

*J Clin Endocrinol Metab*, May 2007, 92(5):1687-1692

Jens Bollerslev, Svante Jansson, Charlotte L. Mollerup, Jörgen Nordenström, Eva Lundgren, Ove Tørring, Jan-Erik Varhaug, Marek Baranowski, Sylvi Aanderud, Celina Franco, Bo Freyschuss, Gunhild A. Isaksen, Thor Ueland, and Thord Rosen, on behalf on the SIPH Study Group\*

*Gunhild A. Isaksen, Thor Ueland, and Thord Rosen, on behalf on the SIPH Study Group, Jan-Erik Varhaug, Marek Baranowski, Sylvi Aanderud, Celina Franco, Bo Freyschuss.*

## **Effect of Surgery on Cardiovascular Risk Factors in Mild Primary Hyperparathyroidism**

Jens Bollerslev, Thord Rosen, Charlotte L. Mollerup, Jörgen Nordenström, Marek Baranowski, Celina Franco, Ylva Pernow, Gunhild A. Isaksen, Kristin Godang, Thor Ueland, and Svante Jansson on behalf of the SIPH Study Group

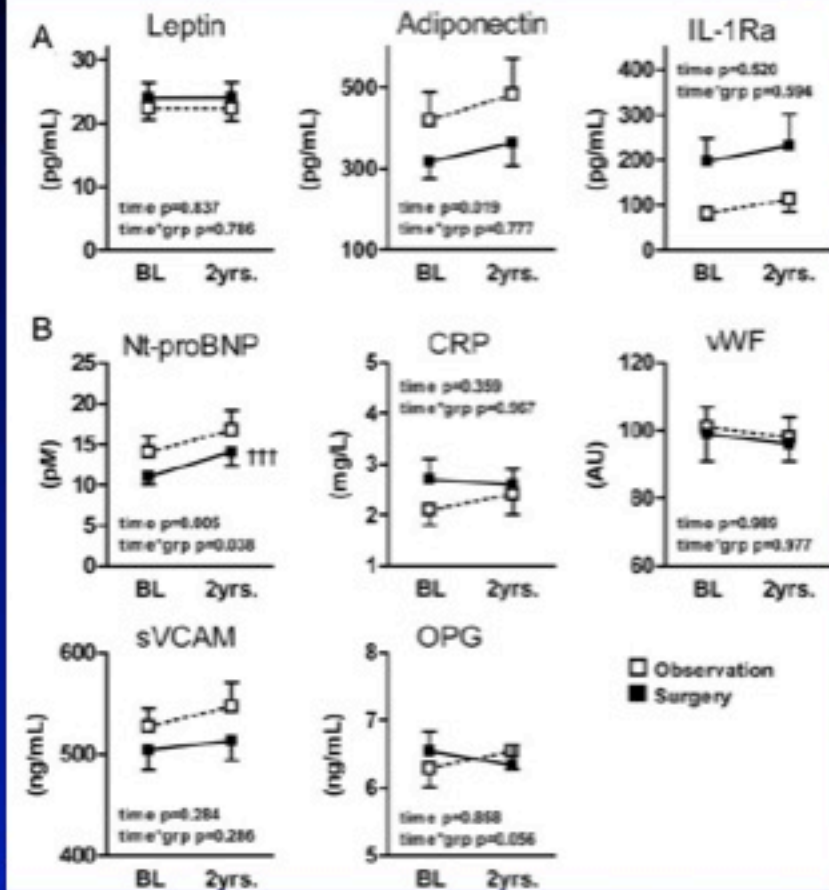
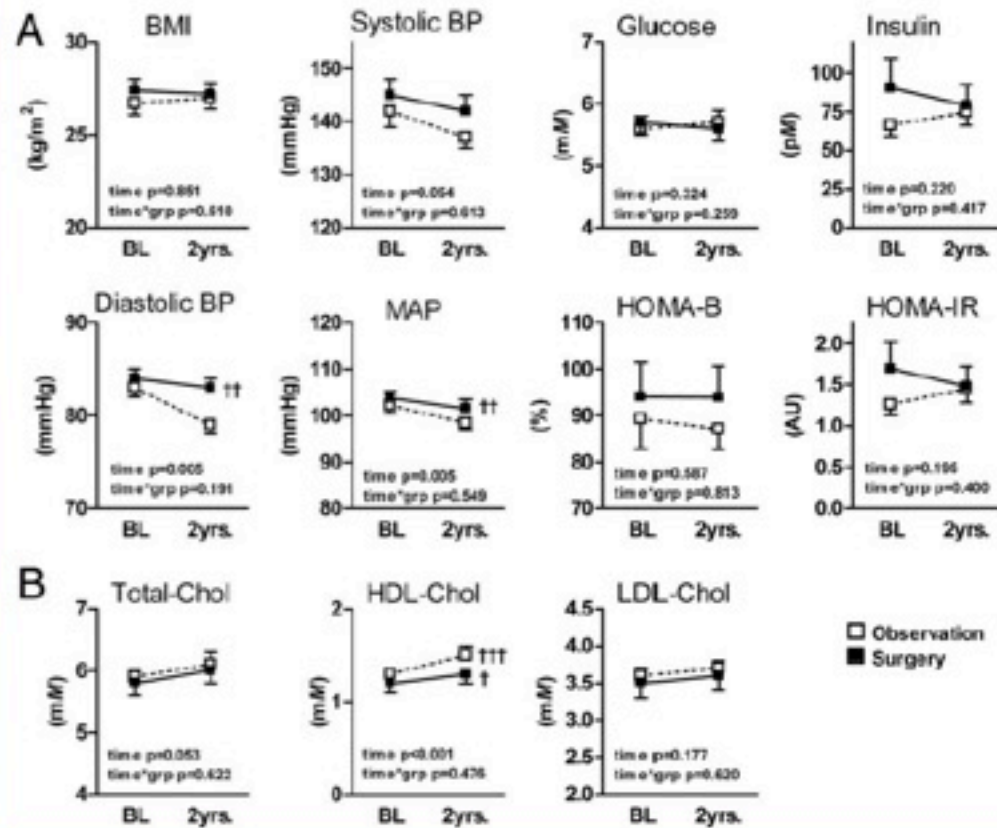
*Thor Ueland, and Svante Jansson on behalf of the SIPH Study Group, Marek Baranowski, Celina Franco, Ylva Pernow, Gunhild A. Isaksen, Kristin Godang.*

# The Scandinavian Investigation on PHPT (SIPH): Health-related QoL Outcomes

- 🇺🇸 **Randomized** 96 pts to surgery vs 95 pts to med follow-up (multicenter Denmark, Norway, Sweden);
- 🇺🇸 **Baseline Quality of Life (SF-36) LOWER** in PHPT pts and more psychological symptoms than general population (of Sweden);
- 🇺🇸 **Longitudinal QoL:** no significant changes of surgery vs medical observation

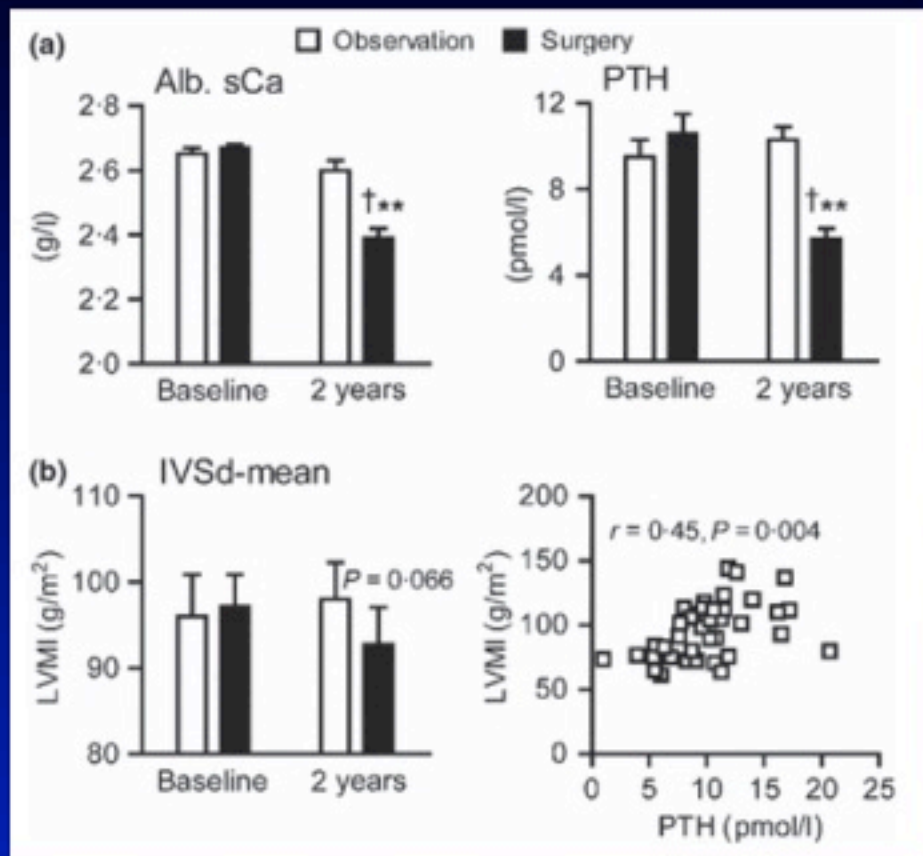
| Description                | Patients                 | Normal values |
|----------------------------|--------------------------|---------------|
| SF-36 standardized scores  |                          |               |
| Physiological functioning  | 74.9 ± 22.1              | 75.1 ± 26.1   |
| Role physical              | 66.3 ± 40.5              | 72.5 ± 38.6   |
| Bodily pain                | 66.8 ± 29.0              | 68.0 ± 28.7   |
| General health             | 66.4 ± 22.2              | 68.9 ± 23.7   |
| Vitality                   | 57.5 ± 26.4 <sup>a</sup> | 67.7 ± 25.4   |
| Social functioning         | 83.2 ± 23.3 <sup>b</sup> | 86.7 ± 22.0   |
| Role emotional             | 67.8 ± 41.1 <sup>a</sup> | 80.9 ± 33.6   |
| Mental health              | 74.6 ± 21.1 <sup>a</sup> | 80.9 ± 33.6   |
| Physical component summary | 44.6 ± 11.0              | 45.2 ± 11.6   |
| Mental component summary   | 46.3 ± 12.4 <sup>a</sup> | 51.0 ± 10.4   |
| CPRS                       | 9.63 ± 7.63 <sup>a</sup> | 6.22 ± 4.10   |

# The Scandinavian Study of PHPT: Cardio-Metabolic Outcomes



- No differences between surgical vs medical groups at baseline;
- No changes in indices of Met. Syndrome, CV risk, adipokines with surgery;
- No negative effects of conservative management

# Scandinavian Study in PHPT: ECHO Findings



- 49 pts echo's at baseline and 2 yrs (N=23 observation vs N=26 surgery);
- Well-comparable at baseline (biochemical and CV parameters);
- Borderline significant drop in LV mass index (-6%; p=0.06);**
- Correlation w/LVMI and PTH levels

# Natural History of subclinical “asymptomatic” PHPT: SUM-UP

---

## 🏢 Columbia University series--15 y follow-up study:

- 🏢 Confirmed long-term benefits of PTX on BMD and on stone-formation;
- 🏢 Risk of progression 37% (very small number of subjects at the end);
- 🏢 BMD deteriorated after 10 yrs (med F/U);

## 🏢 The Parathyroid Epidemiology and Audit Research Study (PEARS) -- retrospective population-based ~6 y f/u study:

- 🏢 Risk of progression 13.4% (mean time 3 y);
- 🏢 Predictors of progression:
  - 🏢 Baseline PTH (serum calcium) concentrations;
  - 🏢 Age at diagnosis;

## 🏢 Scandinavian RCT -- 2 y follow-up study:

- 🏢 QoL, psychological functioning: no clear benefits;
- 🏢 Cardio-metabolic outcomes (surrogates): no significant improvement w/ surgery, including ECHO parameters;
- 🏢 Reinforced bone benefits of surgical cure in mildly affected pts

# Subclinical PHPT After 2000'





# Normocalcemic Primary Hyperparathyroidism: Further Characterization of a New Clinical Phenotype

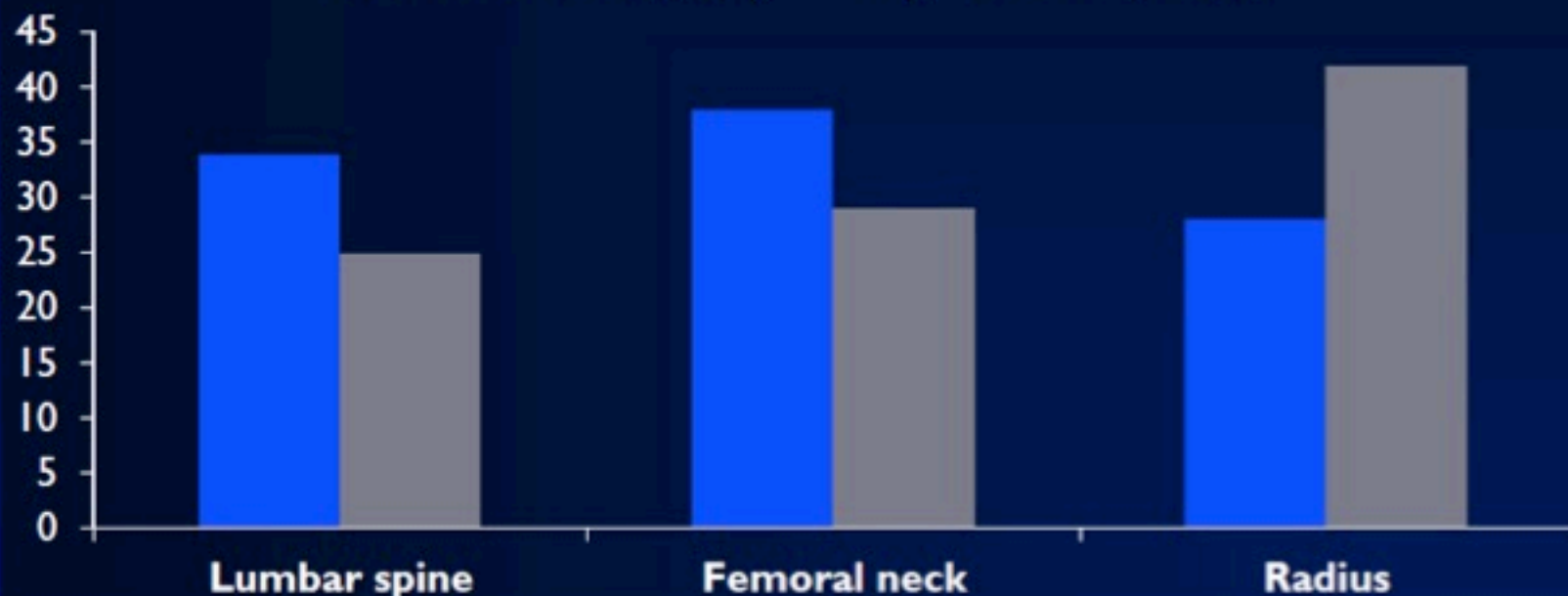
J Clin Endocrinol Metab, August 2007, 92(8):3001-3005

H. Lowe, D. J. McMahon, M. R. Rubin, J. P. Bilezikian, and S. J. Silverberg

## Densitometric Comparison of Normocalcemic and Hypercalcemic PHPT Cohorts

### Percentage with Osteoporosis

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



These patients may represent the earliest form of "symptomatic", rather than "asymptomatic", subclinical PHPT

# Natural history of Normocalcemic PHPT

---

- 👤 Data on the clinical presentation and natural history of this phenotype are limited;
- 👤 In the cohort of Tordjman (20 pts; mean follow-up 4.1 y) and Garcia-Martin et al. (6 pts, follow-up 1 y), no occurrence of hypercalcemia, nephrolithiasis, or fracture was reported;
- 👤 In the **Columbia cohort**, a symptomatic population at diagnosis:
  - 👤 **40%** of the 37 individuals **developed further signs of PHPT** during the mean follow-up period of 3.1 y;
  - 👤 **hypercalcemia developed in 19%** of these individuals;
  - 👤 The subjects who became hypercalcemic ("progressors") tended
    - 👤 to be **older**;
    - 👤 to have higher baseline **serum calcium levels**;
    - 👤 to exhibit higher baseline **urinary calcium excretion**

# Three generational phenotypes of Primary Hyperparathyroidism

---

Before 1970:

A disease of bone, stones, and groans;

**"Symptomatic" PHPT**

After 1970:

A disease with primarily biochemical and densitometric signatures;

**"Asymptomatic" PHPT;**

After 2000:

A disease that may present with a more subtle biochemical signature, namely only with PTH levels elevated, at first;

**"Normocalcemic" PHPT**

# The Development of PHPT: An Evolving View

---

**OLD:**



**NEW:**



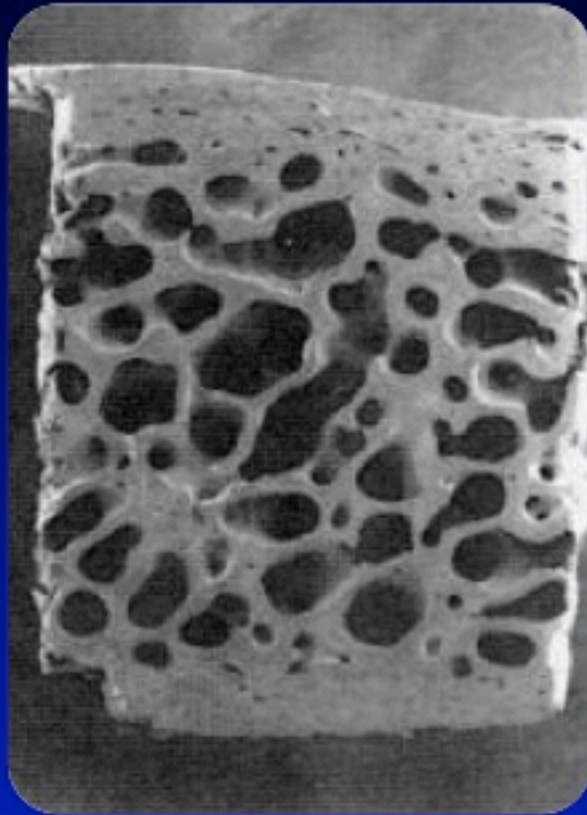
Which Face belongs  
to the "Bad" ?

---

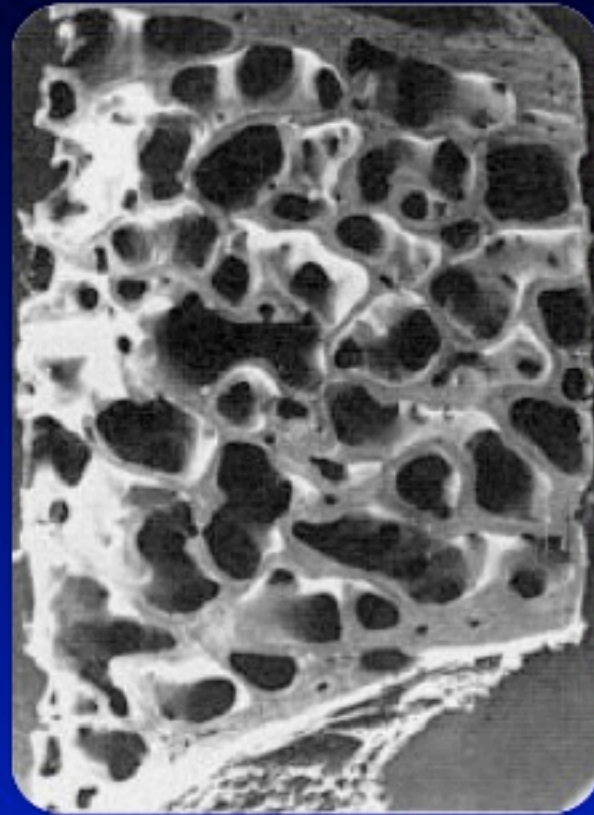


# Maintenance of trabecular bone and involvement of cortices in PHPT

---



**Normal bone**



**PHPT**

Iliac crest biopsy specimens viewed by scanning electron microscopy

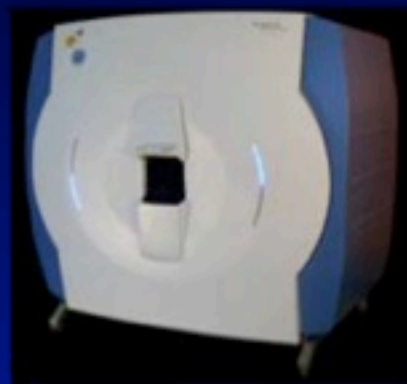
# Fracture Risk in "Mild" or "Asymptomatic" PHPT

## Densitometric Vertebral Fracture Assessment (VFA)



— Patients —

# Assessment of Trabecular Bone Microarchitecture by High-Resolution Peripheral Quantitative Computed Tomography HRpQCT (Xtreme CT)



Non dominant distal radius and tibia



Radius

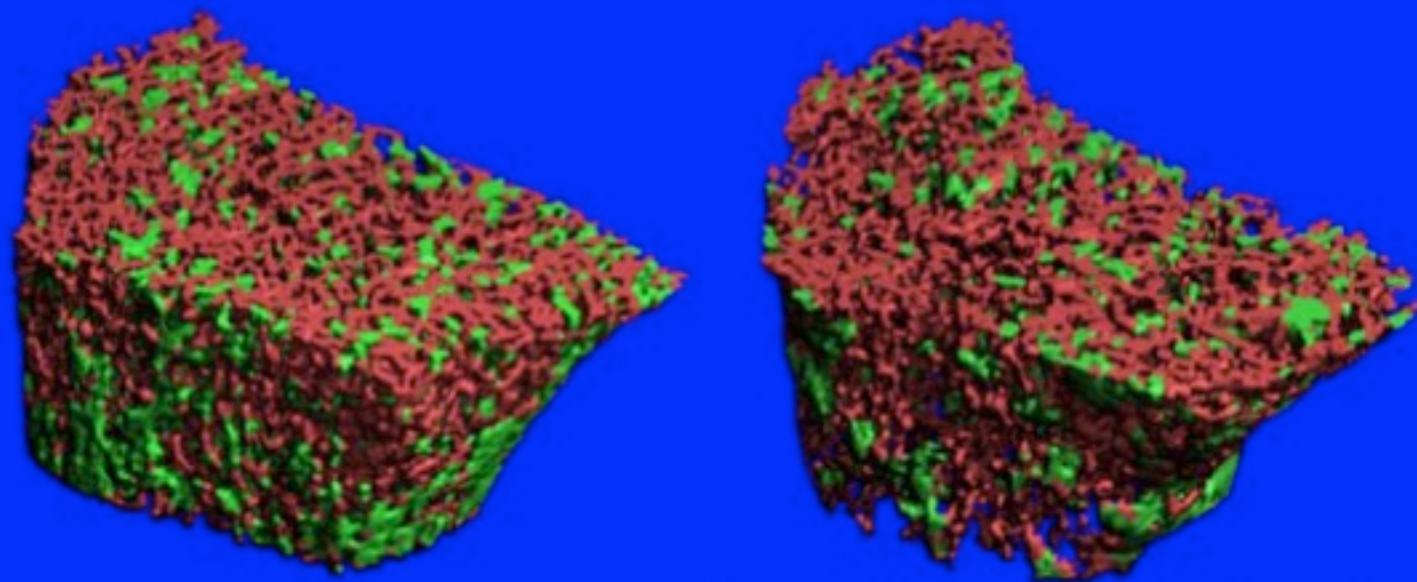
Tibia

- 3-D stack of 110 high resolution slices (82- $\mu$ m isotropic voxel size)
  - ~ 3 min scan time;
  - <4  $\mu$ Sv radiation;
- Reproducibility:
  - Density: 0.7-1.8%;
  - Structure: 1.2-5.2%;



# Individual Trabecula Segmentation (ITS) by HR-pQCT Discriminates Fragility Fractures Independently of DXA

## Individual Trabecula Segmentation (ITS)



Control

Primary Hyperparathyroidism

Green: horizontal plates (more competent)

Red: vertical plates (less competent)

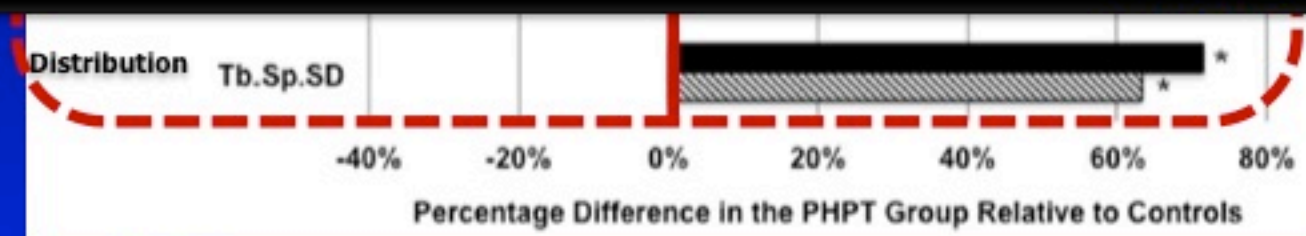
# Abnormal Cortical and Trabecular Microstructure in "mild" PHPT by HRpQCT



## A novel paradigm:

*“Primary hyperparathyroidism, even when presenting as an “asymptomatic” disorder, is characterized by compromised cortical and trabecular compartments and increased fracture risk”.*

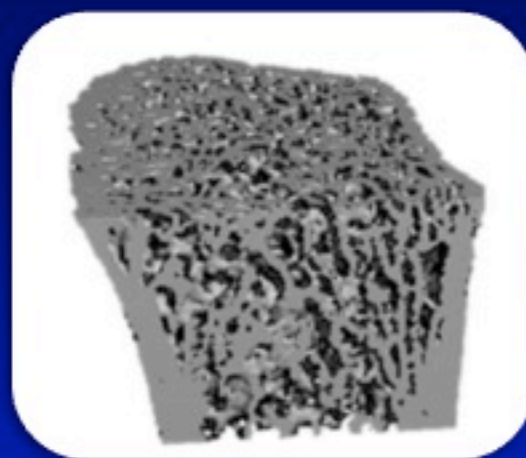
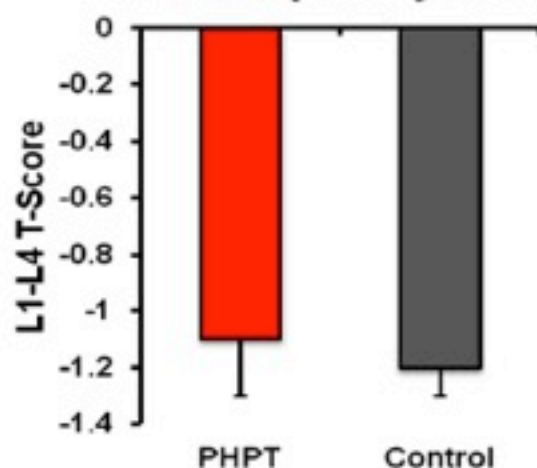
*JP Bilezikian*



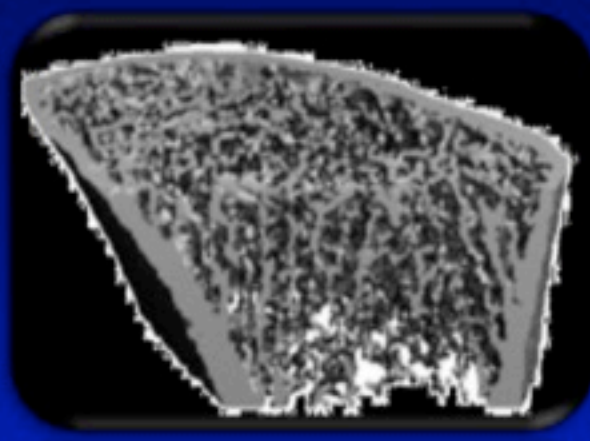
# The Conundrum in Primary Hyperparathyroidism

- 🏠 Lumbar spine BMD by DEXA in PHPT is discordant with fracture data (DEXA does not directly measure trabecular bone);
- 🏠 HRpQCT indices in PHPT are concordant with fracture data;
- 🏠 DEXA is readily available, while HRpQCT is not yet widely available

Lumbar Spine by DEXA



Control



PHPT

A readily accessible method that can give information about skeletal microstructure is needed

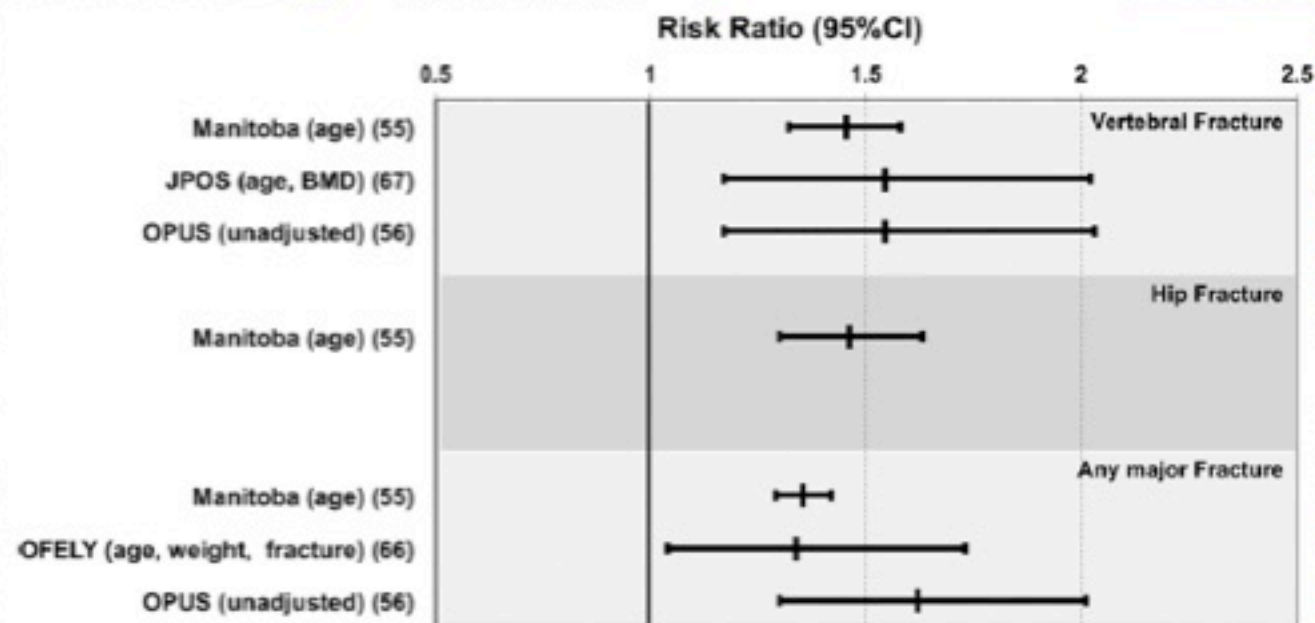
# Trabecular Bone Score:

A Noninvasive Analytical Method Based Upon the DXA Image

BMD= 0.972

Illustration of  
Well-structured  
trabecular bone

TBS= 1.459



243

TBS RRs for different types of osteoporotic fractures in prospective studies of postmenopausal women.

# Management of "sub-clinical" PHPT: A 45-years Dilemma

---

- 👤 Observation ("watchful waiting");
- 👤 Pharmacological approaches: when?
- 👤 Surgery indicated but is not going to be carried out ?
- 👤 The surgical indication can be ameliorated by the drug?  
(e.g. reduced bone density, severe hypercalcemia)?
- 👤 What agent?
  - 👤 Estrogen/SERMs (raloxifene) (not FDA-approved);
  - 👤 Bisphosphonate (not FDA-approved) - if BMD is low;
  - 👤 Cinacalcet (FDA-approved) - if hypercalcemia is severe;
  - 👤 Cinacalcet and Bisphosphonate- hypercalcemia severe and low BMD;
  - 👤 Denosumab (not FDA-approved): ongoing study;
- 👤 Role of Vitamin D and Calcium Supplementation

## **Guidelines for the Management of Asymptomatic Primary Hyperparathyroidism: Summary Statement from the Third International Workshop**

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

Columbia University College of Physicians & Surgeons (J.P.B.), New York, New York 10032; McMaster University (A.A.K.), Hamilton, Canada L8S 4L8; and Massachusetts General Hospital (J.T.P.), Boston, Massachusetts 02114

## **Guidelines for the Management of Asymptomatic Primary Hyperparathyroidism: Summary Statement from the Fourth International Workshop**

John P. Bilezikian, Maria Luisa Brandi, Richard Eastell, Shonni J. Silverberg, Robert Udelsman, Claudio Marcocci, and John T. Potts Jr

# Management of Subclinical Asymptomatic and Normocalcemic PHPT

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

**Table 2.** Guidelines for Monitoring Patients with Asymptomatic PHPT Who Do Not Undergo Parathyroid Surgery: A Comparison of Current Recommendations With Previous Ones<sup>a</sup>

| Measurement   | 1990                                       | 2002  | 2008  | 2013   |
|---------------|--|---|---|--|
| Serum calcium | Biannually                                 | Biannually  | Annually  | Annually   |
| Skeletal      | DXA, annually (forearm)                    | DXA, annually (3 sites)                           | DXA, every 1–2y (3 sites)                         | Every 1–2 y (3 sites), <sup>a</sup> x-ray or VFA of spine if clinically indicated (eg, height loss, back pain)                                   |
| Renal         | eGFR, annually; serum creatinine, annually | eGFR, not recommended; serum creatinine, annually | eGFR, not recommended; serum creatinine, annually | eGFR, annually; serum creatinine, annually. If renal stones suspected, 24-h biochemical stone profile, renal imaging by x-ray, ultrasound, or CT |

# Guidelines for Surgery in Asymptomatic PHPT

|  | 1990                             | 2002                       | 2008                       | 2013  |
|--|----------------------------------|----------------------------|----------------------------|---|
| Measurement <sup>b</sup>                     |                                  |                            |                            |   |
| Serum calcium<br>(>upper limit of<br>normal) | 1–1.6 mg/dL (0.25–0.4<br>mmol/L) | 1.0 mg/dL (0.25<br>mmol/L) | 1.0 mg/dL (0.25<br>mmol/L) | 1.0 mg/dL (0.25 mmol/L)   |
| Skeletal                                     | BMD by DXA; Z-score              | BMD by DXA; T-score        | BMD by DXA; T-score        | A. BMD by DXA; T-score<br>B. nephrocalcinosis by<br>x-ray, ultrasound, or<br>CT |
| Age, y                                       | <50                              | <50                        | <50                        | <50   |

*“Even though patients may not meet any specific criteria for surgery, parathyroidectomy is not an inappropriate course of action, as long as there are no medical contraindications.”*

*Bilezikian JP et al, JCEM, 2009*



# Safety of Observation vs Surgery in "Asymptomatic" PHPT ?

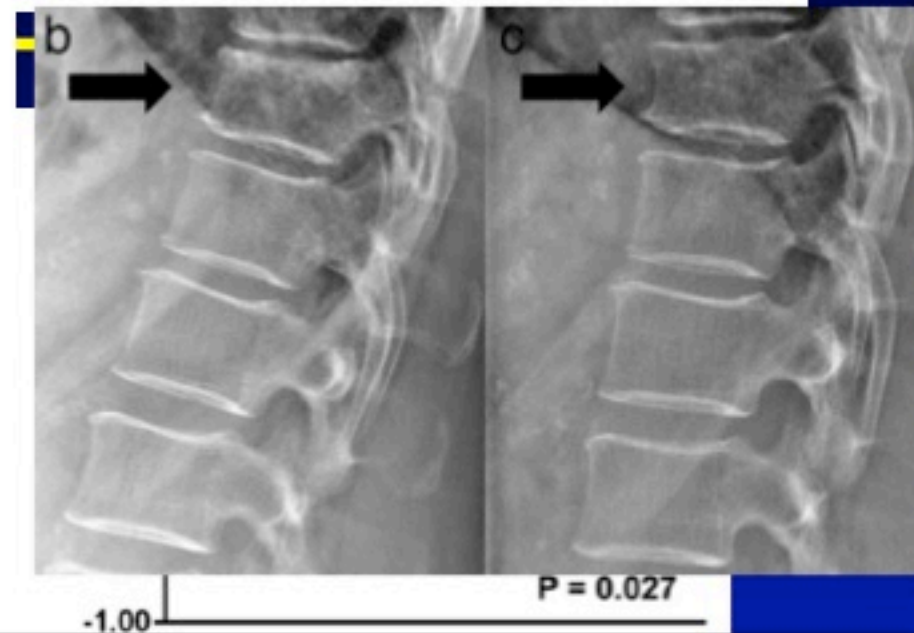
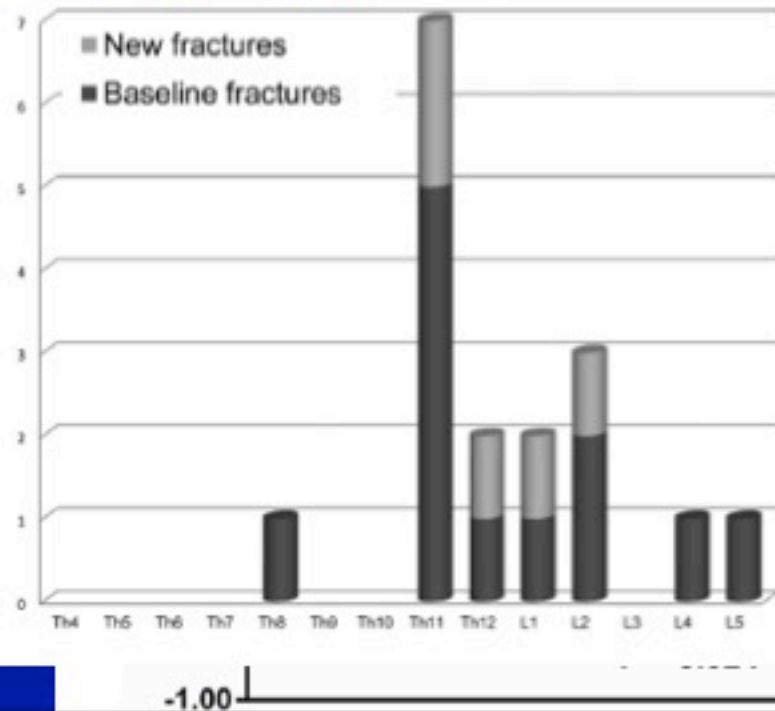
No prospective or randomized controlled trials have firmly demonstrated the benefits of surgery on risk of fracture



## Effects of Parathyroidectomy Versus Observation on the Development of Vertebral Fractures in Mild Primary Hyperparathyroidism

### Vertebral fractures distribution in the thoraco-lumbar spine

Marek Baranowski, Ylva Pernow, Jan Erik Varnhaug, Ola Hessman, Thorodd Rosen, On, Mikael Hellström,\* and Jens Bollerslev\*  
PT (J Clin Endocrinol Metab 100: 1359–1367, 2015)



- 9.1% of the pts in the OBS group (5 new VF in 5 female pts) developed a new vertebral fracture vs none in the PTX group (P=0.058);
- No difference in baseline age, biochemistry, T-score or Z-score between the pts with new fractures vs other patients included in the vertebral fracture assessment;
- Longer follow-up is needed to better clarify long-term safety of observation vs surgery

# Has medical treatment a role for patients with asymptomatic PHPT ?

J Clin Endocrinol Metab, October 2014, 99(10):3607–3618

SPECIAL FEATURE

Consensus Statement

## **Medical Management of Primary Hyperparathyroidism: Proceedings of the Fourth International Workshop on the Management of Asymptomatic Primary Hyperparathyroidism**

Claudio Marcocci, Jens Bollerslev, Aliya Aziz Khan, and Dolores Marie Shoback

Claudio Marcocci, Jens Bollerslev, Aliya Aziz Khan, and Dolores Marie Shoback

# Current issues in medical management of “asymptomatic” PHPT

---

- Medical management with pharmacological agents is an option for
  - patients who have contraindications to surgery;
  - patients who refuse parathyroidectomy;
  - patients who have not been cured by surgery;
- Pharmacological approaches are available, although most have not been approved by the Food and Drug Administration or other regulatory agencies;
- For most drugs, long-term data are insufficient regarding benefit and safety

# Bisphosphonates in “asymptomatic” PHPT: The Alendronate Experience

---

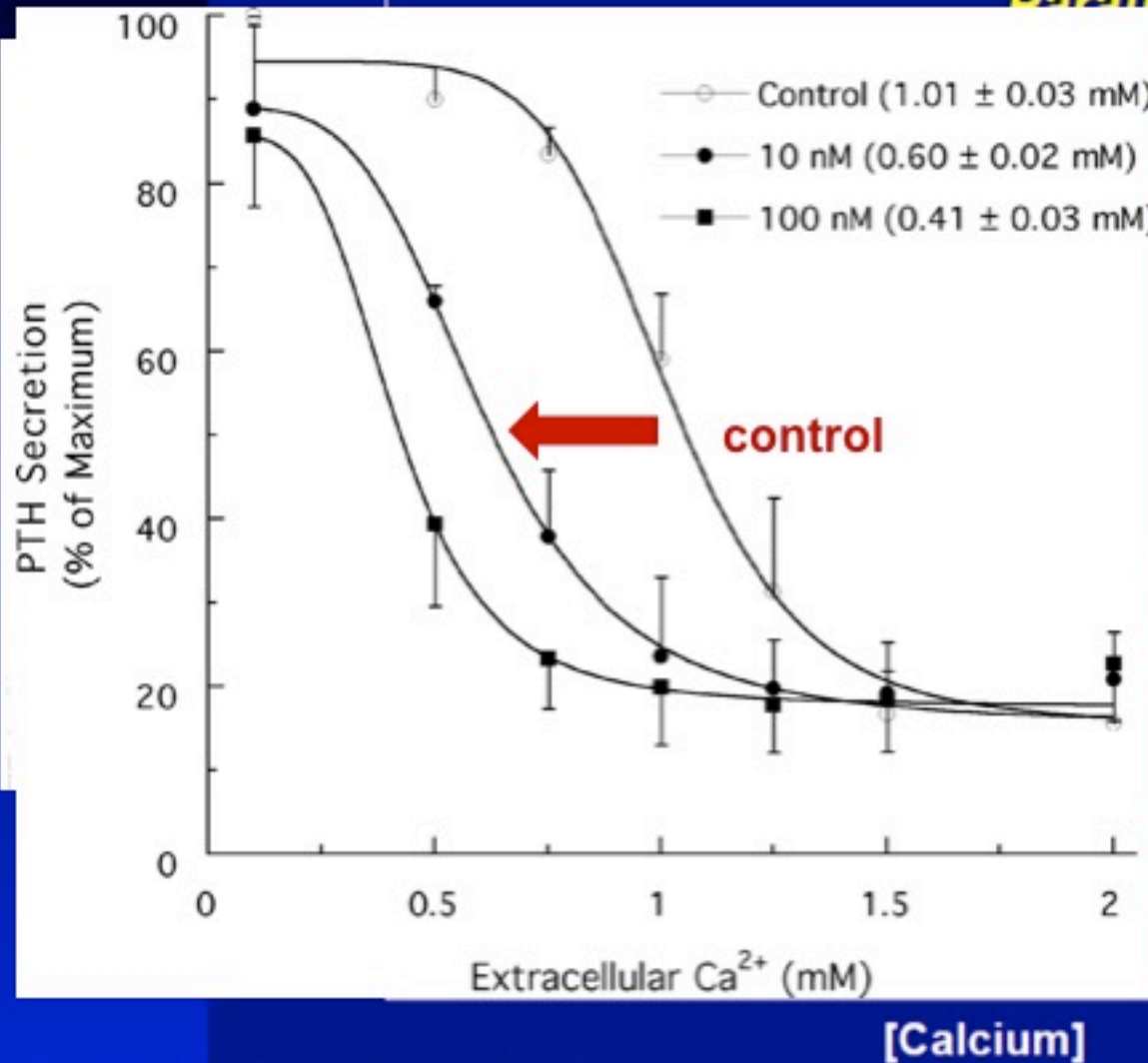
## Summary and recommendations

- 👤 The RCTs data have shown:
  - 👤 a positive effect on BMD at the lumbar spine and hip;
  - 👤 bone turnover markers ↓;
  - 👤 serum calcium remains stable;
- 👤 In subjects whose BMD is low and who are not candidates for parathyroid surgery, alendronate provides skeletal protection and is a medical option;
- 👤 There are currently **no fracture data** with bisphosphonate therapy in asymptomatic PHPT

Marcocci C et al, JCEM 2014

# Calcimimetics: Cinacalcet

Parathyroid cells from patients with primary HPT shift to the RIGHT in the point for PTH secretion

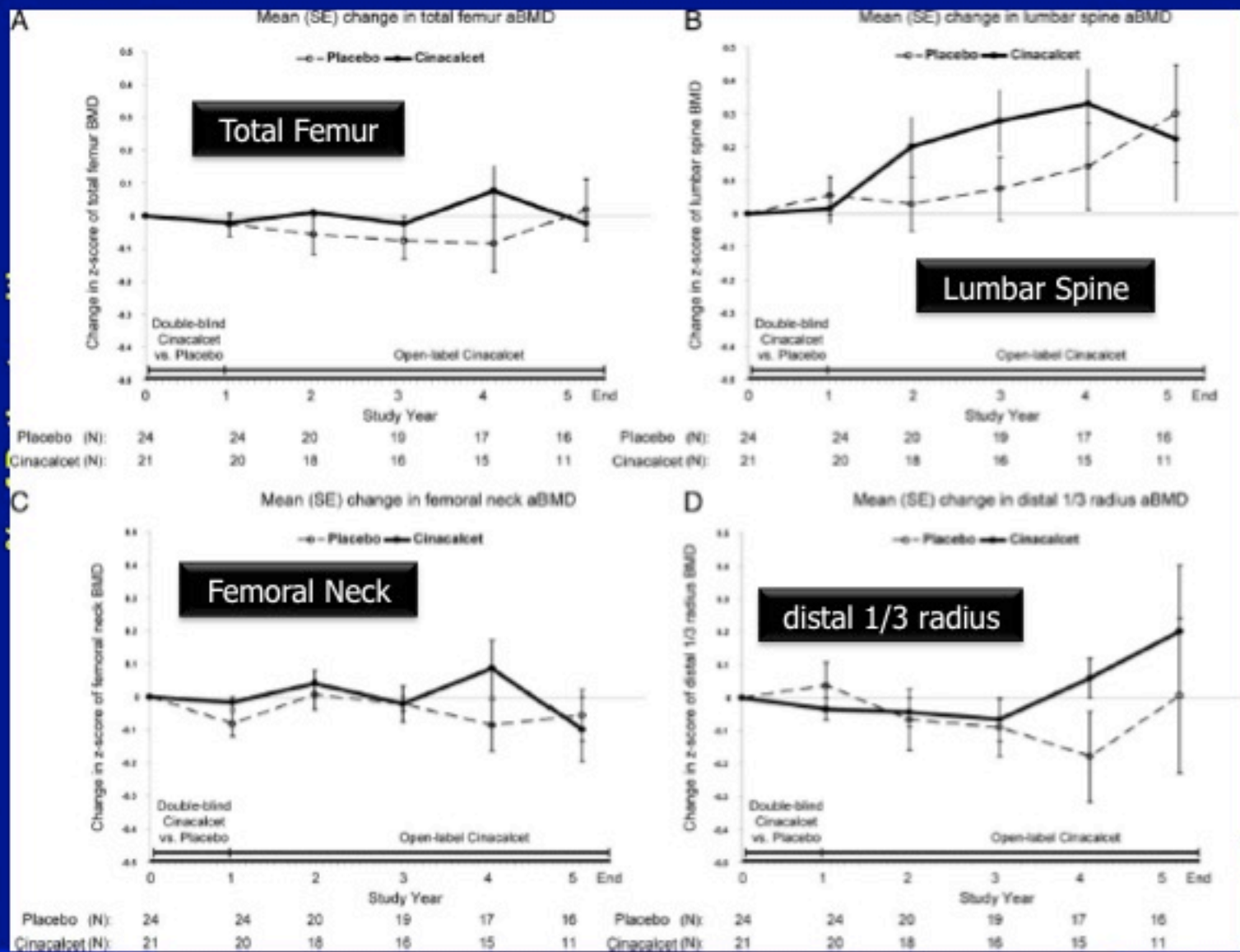


- Cinacalcet shifts PTH curve to left;
- Cells become more sensitive to the inhibitory effects of extracellular Ca on PTH secretion

(and 2°)

[Calcium]

# Cinacalcet in PHPT



# Cinacalcet HCl Reduces Hypercalcemia in Primary Hyperparathyroidism across a Wide Spectrum of Disease Severity

J Clin Endocrinol Metab, January 2011, 96(1):E9–E18

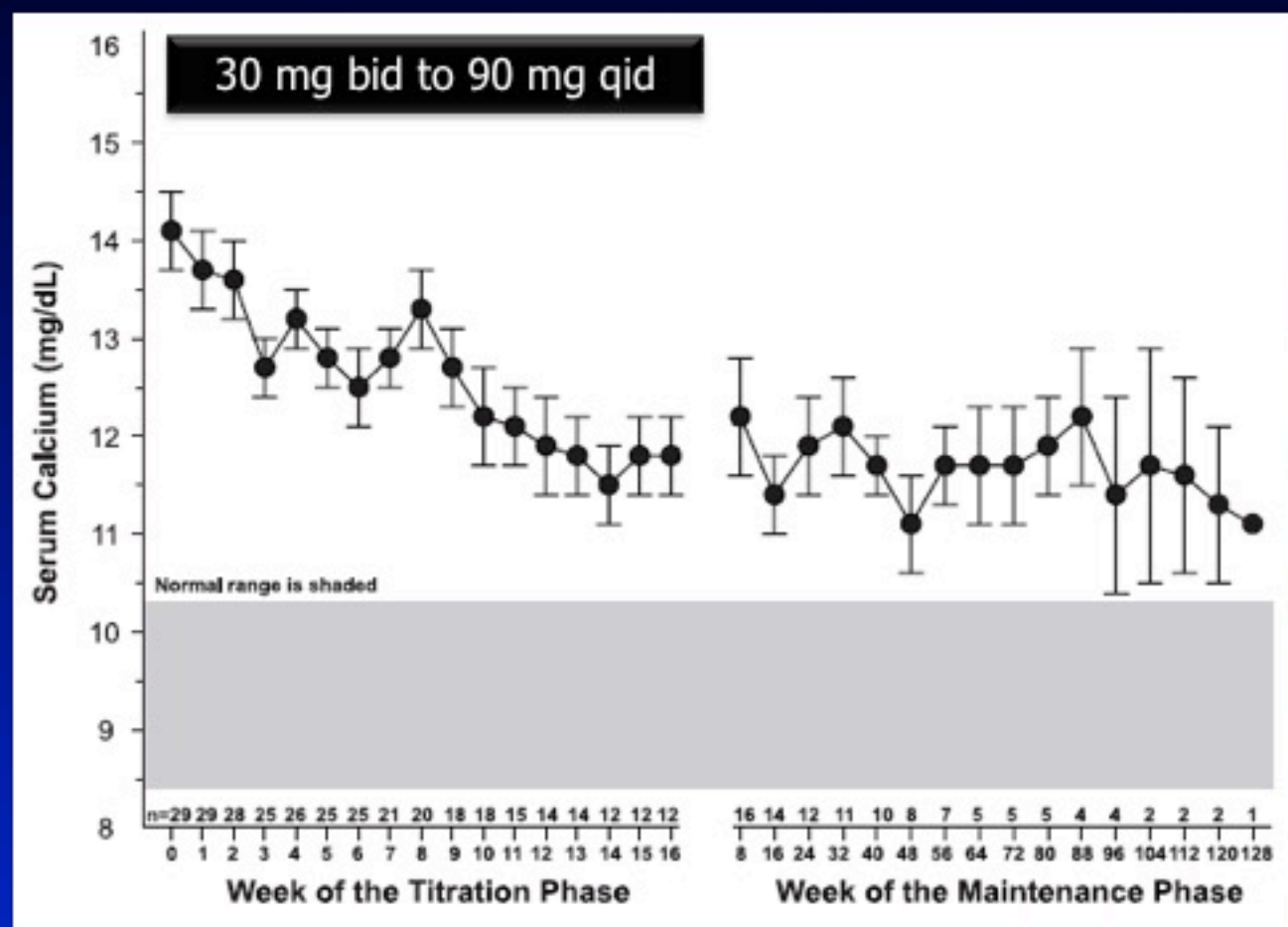
Munro Peacock, J. P. Bilezikian, M. A. Bolognese, Michael Borofsky, Simona Scumpia, L. R. Sterling, Sunfa Cheng, and Dolores Shoback

- 👤 Pooled Analysis (3 Trials)
- 👤 Patients grouped into 3 disease categories:
  - 👤 History of FAILED parathyroidectomy (N=29);
  - 👤 Meeting (2002) NIH criteria for surgery but NO surgery (N=37)
  - 👤 Mild asymptomatic disease (N=15);
- 👤 Treatment effects for up to 4.5 years

BL 0.5 1 2 3 4 Study Year      BL 0.5 1 2 3 4 Study Year

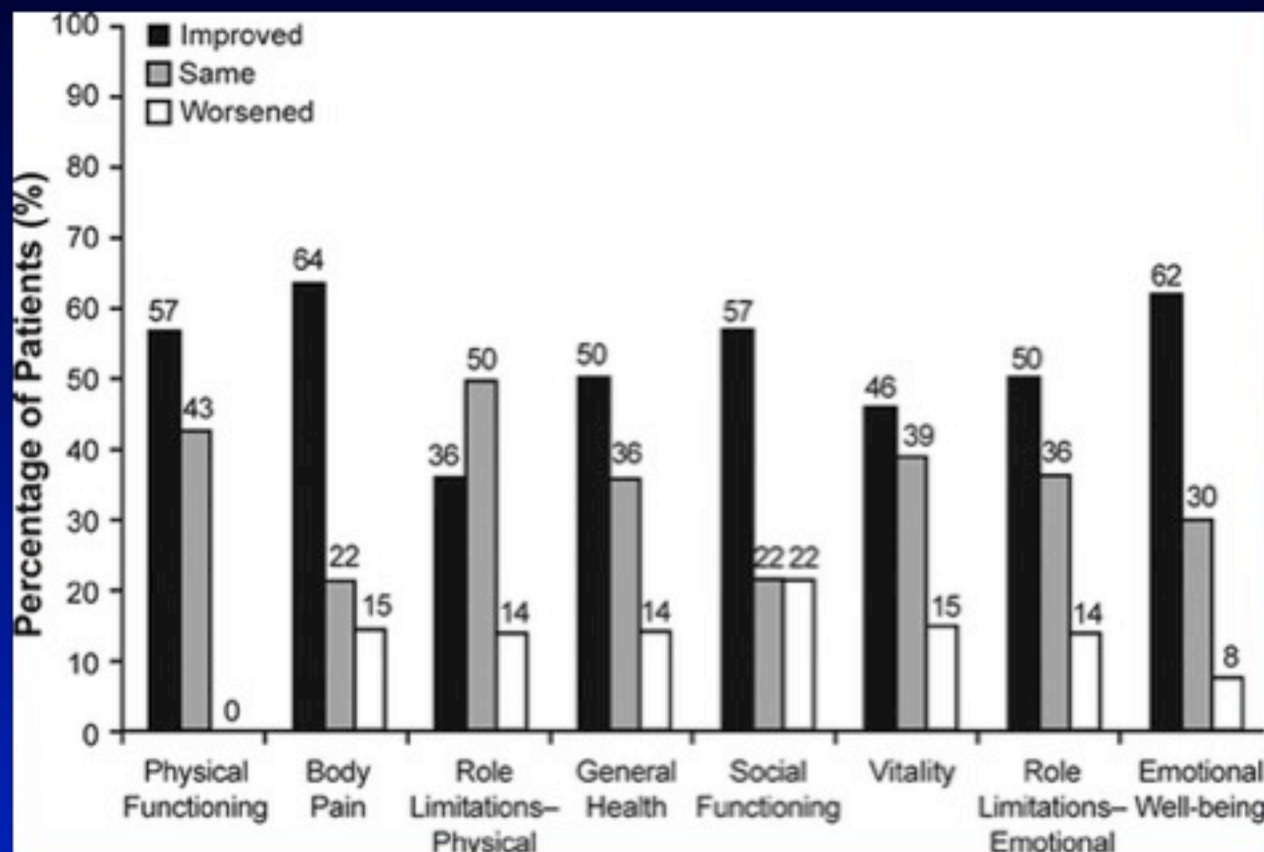


# Cinacalcet Reduces Serum Calcium in Inoperable Parathyroid Carcinoma



By the end of the titration phase, serum calcium fell by at least 1 mg/dl in **62% of patients**

# Cinacalcet in Pts with Intractable PHPT: Changes in Health-Related QoL Scores



Medical Outcomes Study (MOS) Short Form 36 (SF-36)  
Improvement (3-5 points=deemed significant)  
7/8 domains improved

# Cinacalcet in PHPT:

## Summary and recommendations

---

- 👤 Efficacy in lowering, and often normalizing, serum calcium in a wide spectrum of patients with PHPT;
- 👤 Effects on iPTH concentrations less pronounced, and actions on bone turnover markers and BMD inconsistent;
- 👤 Cinacalcet should be considered for PHPT pts in whom
  - 👤 parathyroidectomy is indicated, on the basis of serum calcium, but surgery "is not clinically appropriate or is contraindicated" (EMA);
  - 👤 presence of severe hypercalcemia in pts unable to undergo parathyroidectomy (FDA);
  - 👤 persistent or recurrent hypercalcemia after parathyroidectomy;
- 👤 Expensive (30 mg bid:~\$7000 per year; cost-effective vs surgery if cost would be < \$221 per year)

# Combined Therapy with

## Cinacalcet and Bisphosphonate in PHPT ?

---

- 👤 Lack of prospective or rigorously controlled study of combination therapy with cinacalcet and bisphosphonate in PHPT;
- 👤 Combination therapy appears to achieve both calcium-lowering effects of cinacalcet and stabilization of BMD by bisphosphonate treatment;
- 👤 In subjects with **low BMD** and **serum calcium levels** in the range that is appropriate for cinacalcet use, combined therapy could be beneficial but **strong evidence for efficacy is still lacking**

# Denosumab in PHPT: Work in Progress.....

## An Open-Label, Prospective Pilot Clinical Study of

*ClinicalTrials.gov*

A service of the U.S. National Institutes of Health

Example: "Heart attack" AND "Los Ang

Search for studies:

[Advanced Search](#) | [Help](#) | [Studies](#)

[Find Studies](#) ▾

[About Clinical Studies](#) ▾

[Submit Studies](#) ▾

[Resources](#) ▾

[About This Site](#) ▾

[Home](#) > [Find Studies](#) > [Study Record Detail](#)

### Denosumab in Primary Hyperparathyroidism

**This study has been completed.**

Sponsor:

John P. Bilezikian

ClinicalTrials.gov Identifier:

NCT01558115

First received: March 16, 2012

Last updated: April 7, 2015

*Hidetoshi Kamada, MD<sup>2</sup>; Akemi Ikota, MD<sup>1</sup>; Takeshi Usui, MD, PhD<sup>3</sup>;*

*Akira Shimatsu, MD, DMS<sup>3</sup>; Shigeki Koizumi, MD, PhD<sup>1</sup>*

# Vitamin D and Calcium in PHTP: The Hypothesis of "Double Trouble"

---

## Summary and recommendations

- 🏠 **Vitamin D sufficiency** is recommended:
  - 🏠 >20 ng/dL (50 nmol/L);
  - 🏠 >30 ng/dL (75 nmol/L) (according to some experts);
- 🏠 Prudent dosage regimens (eg, 600-1000 IU cholecalciferol);
- 🏠 There is **no rationale for dietary calcium restriction** in patients with asymptomatic PHPT;
- 🏠 Calcium intake should follow national guidelines

*Marcocci C et al, JCEM 2014*

PHTP LEVELS AS FUNCTION OF VITAMIN D STATUS

# Conclusions

---

- PHPT is a heterogeneous disorder with multiple phenotypes;
- Treatment of subclinical (symptomatic or asymptomatic) PHPT is still a matter for discussion (observation vs surgery vs drugs ?);
- Surgery, while constituting the only definitive treatment, appears to deliver fewer benefits on skeletal, cardiovascular and QoL outcomes;
- When surgery is rejected or contraindicated, medical treatment with bisphosphonates (ie, alendronate), may bring skeletal benefits similar to those observed with surgery;
- Cinacalcet significantly reduces calcemia and maintains BMD along a wide spectrum of disease severity (not cost-effective);
- Vitamin D supplements are required in case of "insufficiency";
- The role of denosumab is still awaited.