Iperparatiroidismo primitivo normocalcemico

Laura Gianotti

SC Endocrinologia, Diabetologia, Metabolismo

A.O. S.Croce e Carle Cuneo

8th AME National Meeting and
4th Joint Meeting with AACE

Turin, October 10-12, 2008
HYPERPARATHYROIDISM IN THE 3rd MILLENIUM

NORMOCALCEMIC PRIMARY HYPERPARATHYROIDISM: *MYTH OR REALITY ?*

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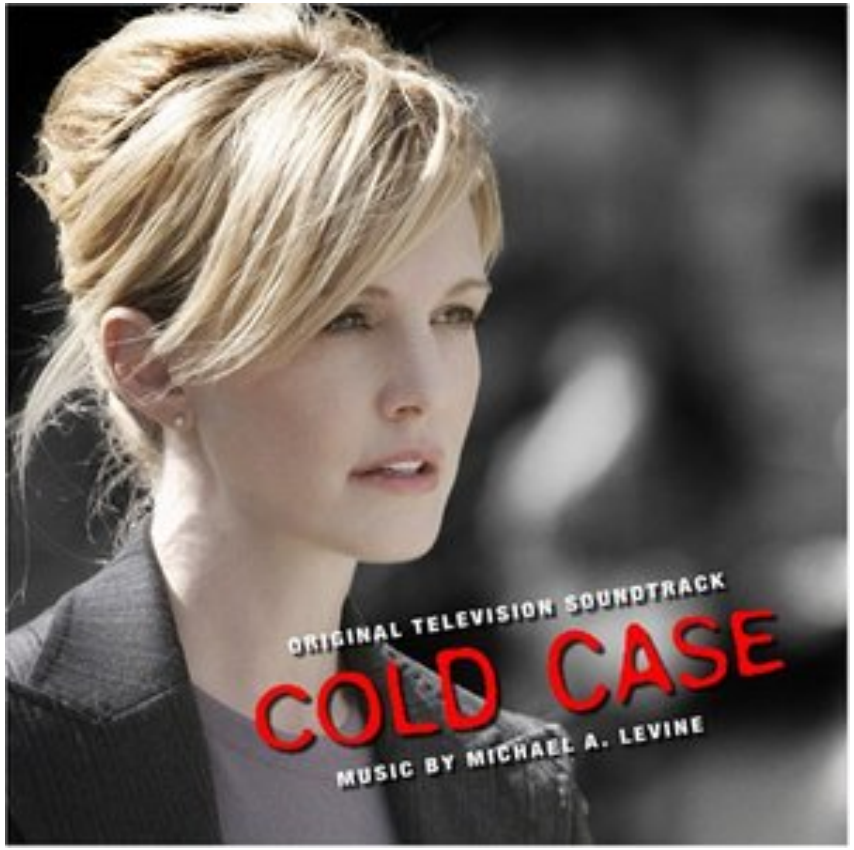
Normocalcemic Primary Hyperparathyroidism in 2008

ILLNESS IN EVOLUTION OR NEW ILLNESS?

WAITING FOR
…. NEW GUIDELINES …..

NORMOCALCEMIC PHPT in 2017



DEFINITION

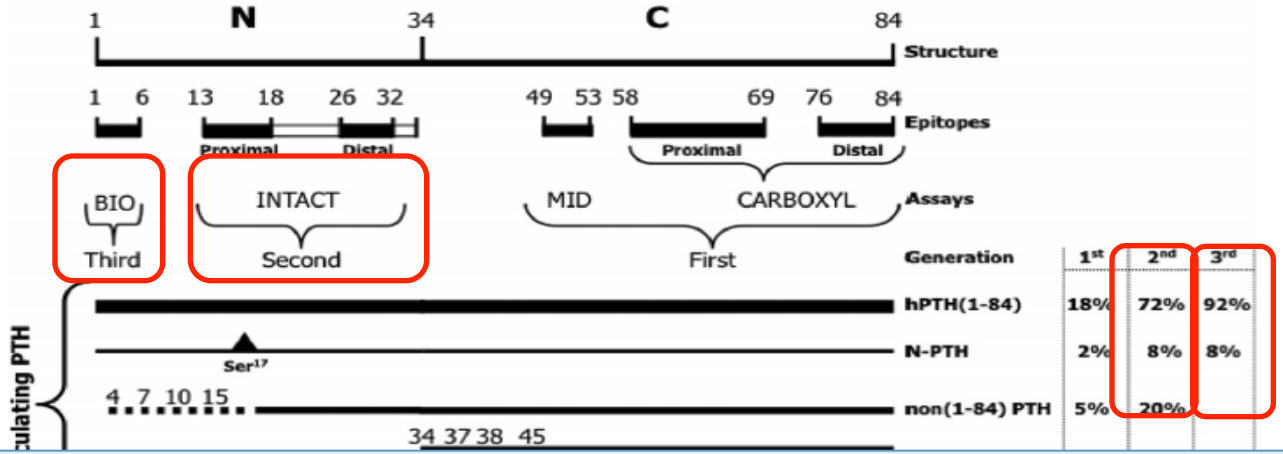
Condition characterized by
normal total and ionized serum **calcium**
and
consistently elevated PTH levels

Consistently ↑ PTH ?

an isolated level of PTH above the upper limit of the normal range should be **confirmed on at least two furher occasions** over a period of 3-6 months

IV international workshop 2013 (JCEM 2014)

PTH measurement



The diagnostic sensitivity for PHPT is similar between second- and third-generation PTH assays.
It is important to have the **adequate reference range** for each assay to determine whether PTH concentrations are elevated.

Eastell R et al JCEM 2014

Hyperparathyroidism

✓**Consideration of the normal distribution range for any analyte is important.**

✓The so-called **normal range of PTH** spans two standard deviations about the mean (eg, 10–65 ng/L), and some patients with NC PHPT might be healthy, but are just on the fringe of the normal distribution curve for parathyroid hormone. Patients could be three standard deviations away from the mean and still be healthy, which is improbable but possible.

✓Another point is the **normal serum calcium concentration distribution** .. and change / increase within a normal range for the population..but not for the patient

Lancet Sept 2017

Calcium measurement

- Serum **total calcium should be corrected** with serum albumin

Formula for corrected calcium = (4-serum albumin) * 0.8 + serum calcium

It's reasonable to measure in 3 consecutive days concomitant ionized and total calcium and an intact parathyroid hormone on 1 of these days.

Ionized calcium : is better?

“ **The era has come for** elimination of total serum calcium and albumin – corrected calcium **in favor of ionized calcium** in investigation of suspected calcium disturbance”

Larsso
J Bone

The Importance of Measuring Ionized Calcium in Characterizing Calcium Status and Diagnosing Primary Hyperparathyroidism

Gregory S. Y. Ong, John P. Walsh, Bronwyn G. A. Stuckey, Suzanne J. Brown, Enrico Rossi, Jennifer L. Ng, Hieu H. Nguyen, G. Neil Kent, and Ee Mun Lim

rinol Metab 97: 3138–3145, 2012)

✓Analytical variability (EGA)

✓Normal Range

nosis and
yroidism:

May C. Tee, M.D., M.P.H.[a], Daniel T. Holmes, M.D.[b], Sam M. Wiseman, M.D.[a,*]

The American Journal of Surgery (2013) 205, 591-596

DEFINITION

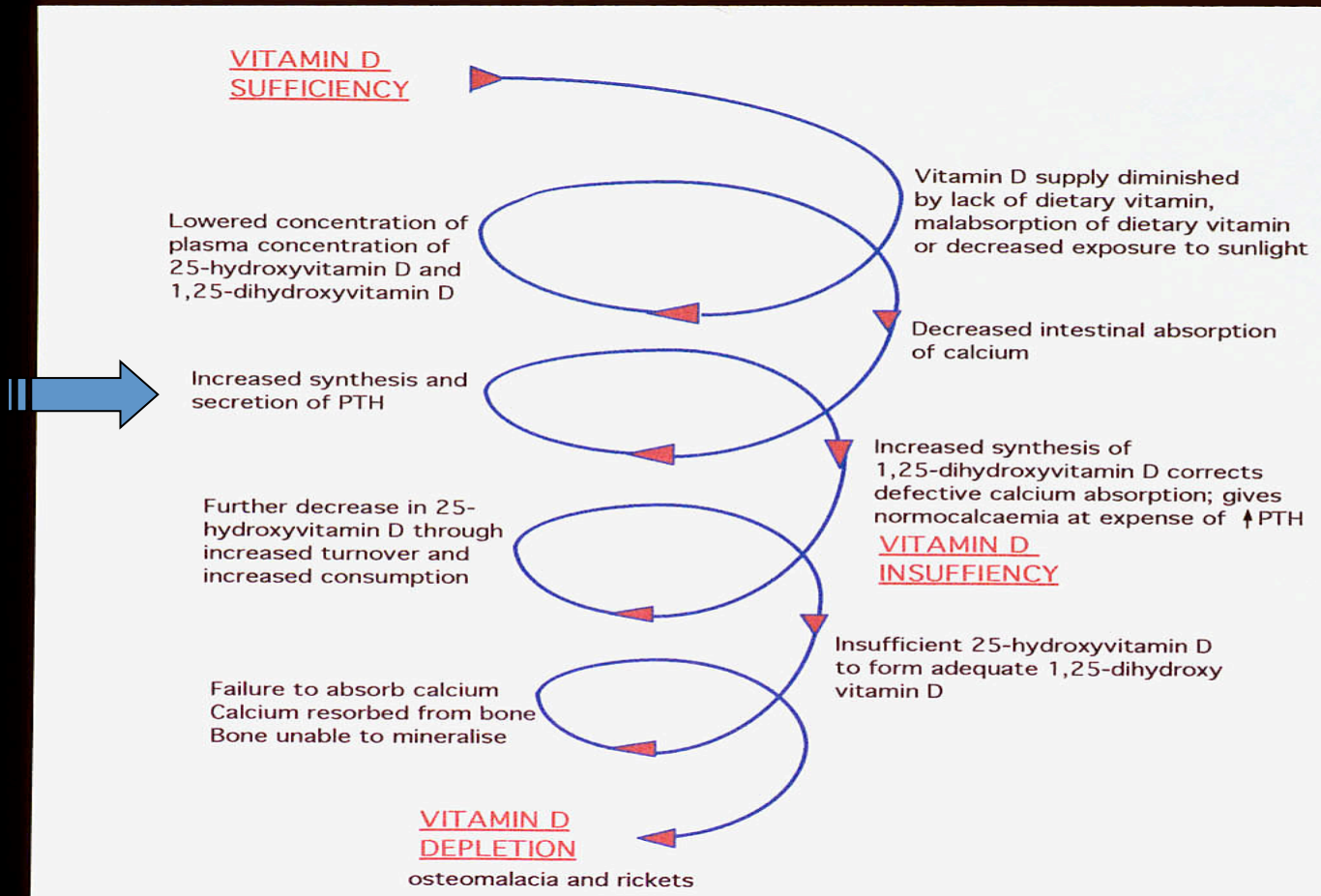
Condition characterized by normal total and ionized serum calcium concentrations and consistently elevated PTH levels

SECONDARIO

PRIMITIVO

Diagnosis … by exclusion

- **Vitamin D insufficiency** (< 30 ng/ml or 80 nmol/L)
- **Renal failure** (GFR below 60/ml/min)
- **Drugs** (furosemide, bisphosphonates, anti-convulsants, lithium)
- **Idiopathic hypercalciuria** (fasting hypercalciuria and mildly elevated PTH but normocalcemia have been diagnosed with “renal leak”)
- Very low calcium or protein intake
- Chronic disease associated with malabsorption


VITAMIN D SUFFICIENCY
Vitamin D supply diminished by lack of dietary vitamin, malabsorption of dietary vitamin or decreased exposure to sunlight
Decreased intestinal absorption of calcium
Increased synthesis of 1,25-dihydroxyvitamin D corrects defective calcium absorption; gives normocalcaemia at expense of ↑PTH
VITAMIN D INSUFFIENCY
Insufficient 25-hydroxyvitamin D to form adequate 1,25-dihydroxy vitamin D
Failure to absorb calcium
Calcium resorbed from bone
Bone unable to mineralise
VITAMIN D DEPLETION
osteomalacia and rickets
Lowered concentration of plasma concentration of 25-hydroxyvitamin D and 1,25-dihydroxyvitamin D
Increased synthesis and secretion of PTH
Further decrease in 25-hydroxyvitamin D through increased turnover and increased consumption

Prevalence of Vitamin D Insufficiency in an Adult Normal Population

M.-C. Chapuy[1], P. Preziosi[2], M. Maamer[3], S. Arnaud[1], P. Galan[2], S. Hercberg[2] and P. J. Meunier[1]
[1]INSERM U. 403, Hôpital Edouard Herriot, Lyon; [2]ISTNA/CNAM, Paris; and [3]Laboratoire Innothéra, Arcueil, France

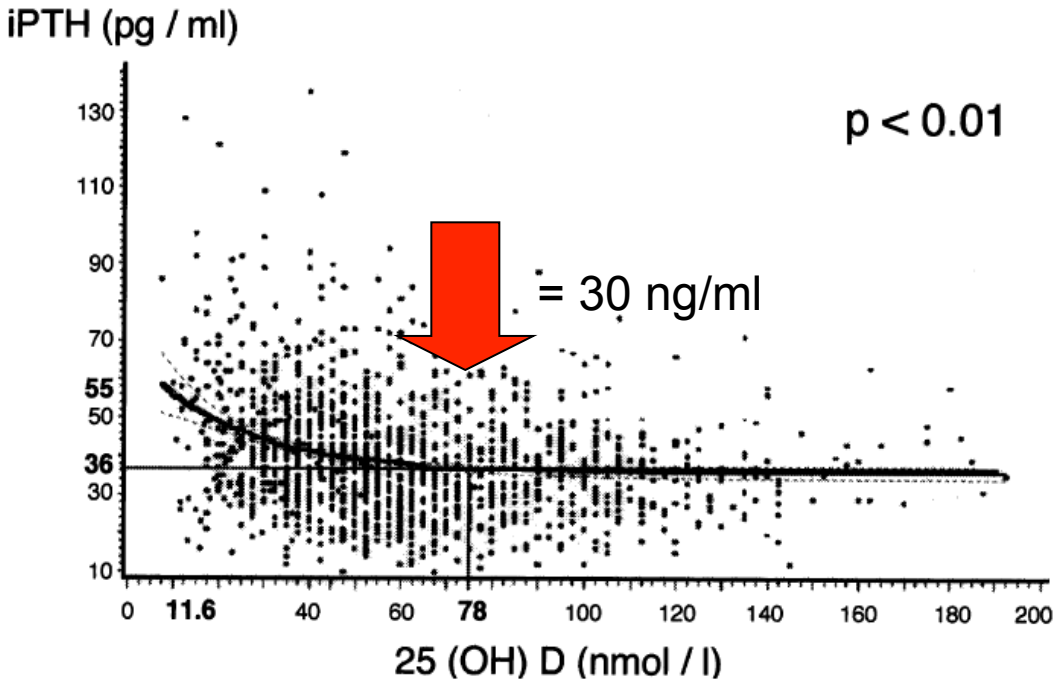


Fig. 1. Relationship between serum intact parathyroid hormone (iPTH) and 25-hydroxyvitamin D (25(OH)D) values in the whole population studied. For a 25(OH)D concentration higher than 78 nmol/l (31 ng/ml), there is a plateau level at 36 pg/ml for iPTH. When 25(OH)D values are lower than 78 nmol/l (31 ng/ml), the serum iPTH values begin to increase.

Osteoporos Int 1997

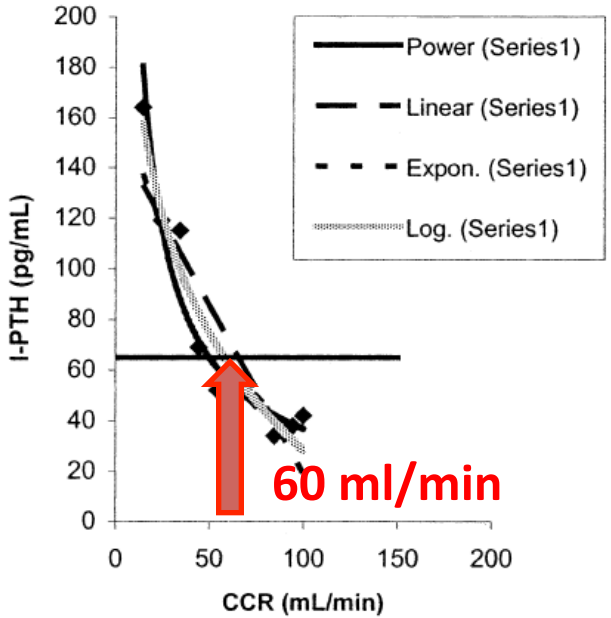
- …. It is important to **exclude disorders** that are associated with secondary or compensatory elevated PTH with normal calcium concentrations, **such as vitamin D insufficiency**
- **25(OH)D minimal goal level = 50 nmol/L (20 ng/ml) but > 75 nmol/L (30 ng/ml) is desirable**

EXCLUDE VITAMIN D INSUFFICIENCY AND REPLENISH IT

(minimum > 20; desirable > 30 ng/ml)

PTH LEVELS AND RENAL FUNCTION

K/DOQI Clinical Practice Guidelines for Bone Metabolism and Disease in Chronic Kidney Disease *(Am J Kidney Dis, 42, 4, S3, 2003)*



Graph showing relationship between serum I-PTH levels and CCR based on data extracted from Martinez et al (1997).

PTH LEVELS AND DRUGS

- Diuretici
- Denosumab
- Bisfosfonati
- Litio
- Farmaci interferenti con il metabolismo calcico (steroidi)
- Farmaci interferenti con il metabolismo della vitamina D (anticomiziali)

JAMA Intern Med. 2015 January ; 175(1): 137–138. doi:10.1001/jamainternmed.2014.5857.

ITALIAN CHAPTER

Association of Loop Diuretic Use With Higher Parathyroid Hormone Levels in Patients With Normal Renal Function

Kristin M. Corapi, MD, MMSc, Gearoid M. McMahon, MBBCh, Julia B. Wenger, MPH, Julian L. Seifter, MD, and Ishir Bhan, MD

loop diuretics induce natriuresis by inhibiting the Na-K-2Cl transporter in the thick ascending limb of the loop of Henle

Increased urinary calcium losses and increased PTH

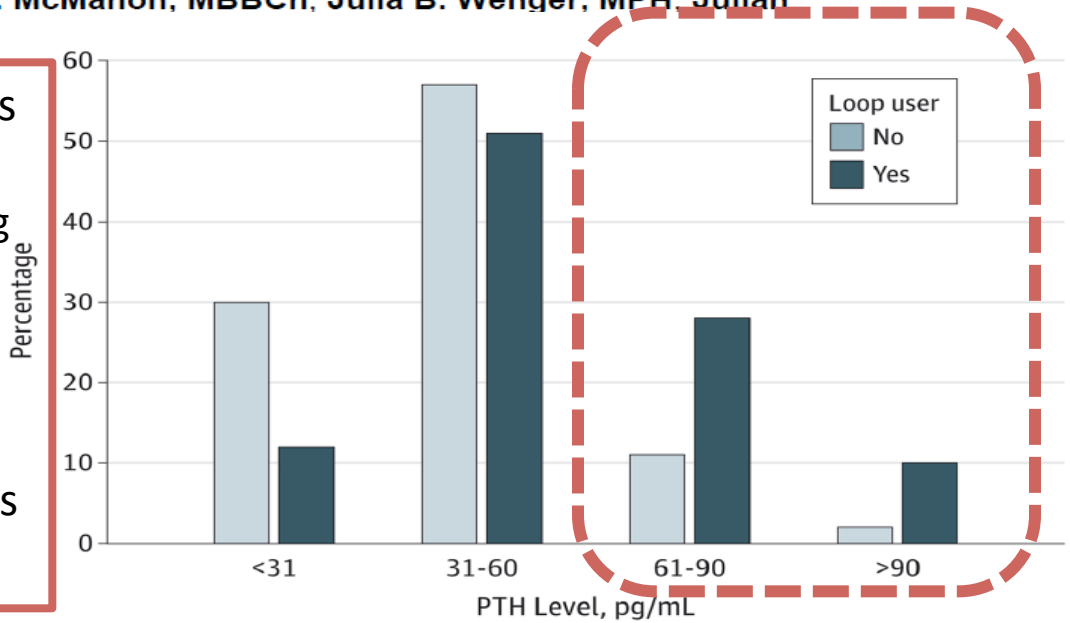


Figure. The Range of Parathyroid Hormone (PTH) Levels Among Loop Users and Nonusers
Levels are depicted in increments of 30 pg/mL. More loop users have PTH values above the upper limit of normal.

Hypertension, Antihypertensive Medications, and Risk of Incident Primary Hyperparathyroidism

Anand Vaidya, Gary C. Curhan, Julie M. Paik, Henry Kronenberg, and Eric N. Taylor

J Clin Endocrinol Metab 100: 2396–2404, 2015

Table 3. Relative Risks For Incident Primary Hyperparathyroidism among Those with a History of Hypertension According to Classes of Antihypertensive Medication Use

	Thiazide Diuretic	Furosemide	Calcium Channel Blocker	β-Adrenergic Receptor Antagonist	ACE Inhibitor
No. of incident P-HPTH cases	55	22	42	72	50
Person-years of follow-up	120 932	29 986	97 142	149 811	109 333
Age-adjusted RR (95% CI)	1.25 (0.91–1.72)	1.79 (1.15–2.79)	1.15 (0.82–1.62)	1.31 (0.99–1.74)	1.02 (0.74–1.41)
Multivariate-adjusted RR (95% CI)[a]	1.20 (0.88–1.66)	1.77 (1.12–2.78)	1.10 (0.78–1.55)	1.26 (0.95–1.67)	1.01 (0.73–1.39)
Multivariate + antihypertensive medication–adjusted RR (95% CI)[b]	1.21 (0.88–1.67)	1.71 (1.08–2.71)	1.10 (0.78–1.55)	1.26 (0.95–1.68)	1.05 (0.76–1.46)

Conclusions: In a large longitudinal prospective cohort study of mostly older white women, a history of hypertension and use of furosemide were associated with a significantly higher risk of developing P-HPTH. (*J Clin Endocrinol Metab* 100: 2396–2404, 2015)

Thiazide-Associated Hypercalcemia: Incidence and Association With Primary Hyperparathyroidism Over Two Decades

Table 2. Clinical and Laboratory Spectrum of Thiazide-Associated Hypercalcemia Among Olmsted County, Minnesota, Residents 1992–2010, Overall and in a Subset Later Found to Have PHPT

Characteristic	All Patients	PHPT Subset
Years from thiazide start to hypercalcemia	5.2 ± 5.0	5.8 ± 7.2

THIAZIDE CHALLENGE

may be a useful way to distinguish resorptive hypercalciuria (ie, PHPT) from a renal calcium leak causing secondary hyperparathyroidism in patients with normal renal function (21).

Marcio L. Griebeler, Ann E. Kearns, Euijung Ryu, Prabin Thapa, Matthew A. Hathcock, L. Joseph Melton III, and Robert A. Wermers

J Clin End Met 2016

Idiopathic hypercalciuria and PTH

Hypercalciuria : daily calcium excretion over 250 mg/day in women or 300 mg/24 h in men or 4 mg/kg body weight in either

Formation of insoluble calcium salts, calcium oxalate or calcium phosphate

Pathogenetic mechanisms :

interplay between genetic background and environment

1) '**absorptive**' hypercalciuria in which a primary increase in intestinal calcium absorption may result in increased urine calcium (PTH ↓);

2) '**resorptive**' hypercalciuria, caused by an increase in bone turnover, leading to loss of bone calcium in the urine (PTH may be ↑ ; Primary hyperparathyroidism);

3) '**renal leak**' hypercalciuria **PTH ↑ (secondary hyperparathyroidism)**

Worcester EM & Coe FL Semin Nephrol. 2008

Other conditions

Age-related increase in PTH levels due to:

- decreased renal clearance
- secondary hyperparathyroidism due to hypovitaminosis D
- low dietary calcium intake
- gut resistance to vitamin D action

whether ageing per se contributes to the age-related increase in iPTH, independent of these other comorbid factors, remains unclear

Susan T. Haden, Edward M. Brown, Shelley Hurwitz, Jennifer Scott and Ghada El-Hajj Fuleihan
The effects of age and gender on parathyroid hormone dynamics Clinical Endocrinology (2000) 52, 329±338

DIAGNOSIS

Condition characterized by normal total and ionized serum calcium concentrations and (consistently) elevated PTH levels

~~SECONDARIO~~

PRIMITIVO

Diagnosis of Asymptomatic Primary Hyperparathyroidism: Proceedings of the Fourth International Workshop

2014

(*J Clin Endocrinol Metab* 99: 3570–3579, 2014)

Richard Eastell, Maria Luisa Brandi, Aline G. Costa, Pierre D'Amour, Dolores M. Shoback, and Rajesh V. Thakker

The diagnosis of NPHPT must include normal serum total calcium and ionized calcium on several occasions. Although there are not enough data to determine the timing or frequency of sampling to establish the diagnosis of NPHPT, this panel suggests that an isolated level of PTH

Thus, NPHPT is part of the diagnostic spectrum of PHPT, and we need to ensure a correct diagnosis and to follow up by serum calcium measurement because these patients may develop hypercalcemia.

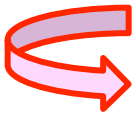
pathogenetic mechanisms

- Early phase of the disease
- PTH-resistance in target tissues
- Coexistence of vit D deficiency

Normocalcemia (pseudo) and vitamin D deficiency

Ensure that the 25-hydroxyvitamin D level is greater than 30 ng/ml

Normocalcemic pts with high PTH levels will become hypercalcemic when 25-hydroxyvitamin D levels are raised to higher than 30 ng/ml

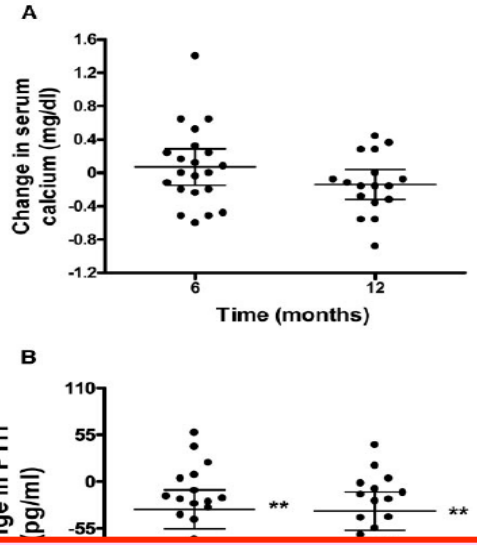


The correct diagnosis is **traditional hypercalcemic pHPT** that is **masked by the vitamin D deficiency**

Natalie Cusano, J Clin Densitometry 2013

Vitamin D Repletion

by Grey et al 2005



…judicious replacement of vitamin D may be **safe in patients with PHPT and coexistent vitamin D insufficiency**…

Some pts with high PTH levels and normocalcemia will become hypercalcemic when 25- hydroxyvitamin D levels are raised to higher than 30 ng/ml (**masked by vit D deficit**)

values to millimoles per liter, divide by 4. To convert PTH values to picomoles per liter, divide by 11.1

Clinical presentation

0021-972X/07/$15.00/0
Printed in U.S.A.

The Journal of Clinical Endocrinology & Metabolism 92(8):3001–3005

doi: 10.1210/jc.2006-2802

Normocalcemic Primary Hyperparathyroidism: Further Characterization of a New Clinical Phenotype

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

Department of Medicine, College of Physicians and Surgeons, Columbia University, New York, New York 10032

JCEM 2007,92:3001-3005

Patients seen in a referral center with normocalcemic hyperparathyroidism (n=37)

Osteoporosis (57%)
Kidney stones (14%)

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

Clinical presentation

by Cusano NE et al , J Clin Densitom 2013

Table 1

Summary of cohorts with normocalcemic primary hyperparathyroidism described in the literature.

Study	Cohort Size	Age (years)	Female (%)	Osteoporosis (%)	Nephrolithiasis (%)	Comments
Symptomatic cohorts						
Lowe et al. [23]	37	58 ± 12	95	57[a]	14	Ionized calcium not available for all
Tordjman et al. [24]	32	61 ± 11	84	36	9	Six with hypercalciuria not responding to hydrochlorothiazide, 3 with vitamin D deficiency although hyperparathyroidism persisted despite vitamin D repletion
Amaral et al. [25]	33	64 ± 14	79	15[b]	18	Ionized calcium not measured
Cakir et al. [26]	18	50 ± 10	47	47	11	Ionized calcium not measured Aim of investigating glucose and lipid metabolism; no differences between patients and age-, sex-, and BMI-matched controls with respect to indicators of insulin resistance
Wade et al. [27]	8	60	63	25[c]	25	Surgical cohort: Five subjects had single gland disease and 3 multiple glands
Asymptomatic cohort						
Garcia-Martin et al. [29]	6	56 ± 3	100[d]	0	0	Ionized calcium not measured Population-based cohort

Mean ± SD

Body Mass Index, BMI

[a] 11% with fragility fracture

[b] Only fracture history available

[c] 13% with fragility fracture

[d] Study design

Natural history
by Lowe et al., JCEM 2007

TABLE 2. Comparison of baseline parameters between individuals who remained normocalcemic and those who became hypercalcemic

Baseline parameter	Patients who became hypercalcemic (n = 7)	Persistently normocalcemic patients (n = 30)	*P* value
Age (yr)	64 (2)	57 (2)	0.028
Years of follow-up	3.1 (0.6)	3.0 (0.3)	NS
Baseline serum Ca (mg/dl)[a]	9.7 (0.2)	9.3 (0.09)	0.003
PTH IRMA (pg/ml)	96 (15)	93 (5)	NS
Serum phosphorus (mg/dl)[b]	3.4 (0.2)	3.3 (0.1)	NS
Urinary calcium (mg per 24 h)[a]	230 (13)	183 (15)	0.024
25-Hydroxyvitamin D (ng/ml)[c]	29 (3)	33 (2)	0.037
1,25-Dihydroxyvitamin (pg/ml)[d]	62 (11)	62 (4)	NS
Urinary NTX (nM BCE per mM creatinine)	41 (11)	38 (5)	NS
Lumbar spine T-score	−1.47 (0.59)	−2.17 (0.28)	NS
Femoral neck T-score	−1.78 (0.29)	−1.85 (0.22)	NS
Distal one third radius T-score	−1.81 (0.45)	−1.71 (0.25)	NS

Longitudinal follow-up

37 patients were followed up for 3 yrs (maximum 8; median 3 yr)

TABLE 3. Patients developing new manifestations of primary hyperparathyroidism over time

Any	15
Hypercalcemia	7
Kidney stone	1
Fracture	1
New osteoporosis	4
Urinary calcium greater than 400 mg per 24 h	2
Greater than 10% decline in BMD	6

Management

Table 1. Guidelines for Surgery in Asymptomatic PHPT: A Comparison of Current Recommendations With Previous Ones[a]

	1990	2002	2008	2013
Measurement[b]				
Serum calcium (>upper limit of normal)	1–1.6 mg/dL (0.25–0.4 mmol/L)	1.0 mg/dL (0.25 mmol/L)	1.0 mg/dL (0.25 mmol/L)	1.0 mg/dL (0.25 mmol/L)
Skeletal	BMD by DXA: Z-score <−2.0 (site unspecified)	BMD by DXA: T-sc…	…T-score …y site[b]	A. BMD by DXA: T-score < −2.5 at lumbar spine, total hip, femoral neck, or distal 1/3 radius[b] B. Vertebral fracture by x-ray, CT, MRI, or VFA
Renal			…y …c/min …r …d	A. Creatinine clearance < 60 cc/min B. 24-h urine for calcium >400 mg/d (>10 mmol/d) and increased stone risk by biochemical stone risk analysis[d] C. Presence of nephrolithiasis or nephrocalcinosis by x-ray, ultrasound, or CT
Age, y	<50	<50	<50	<50

In 2008

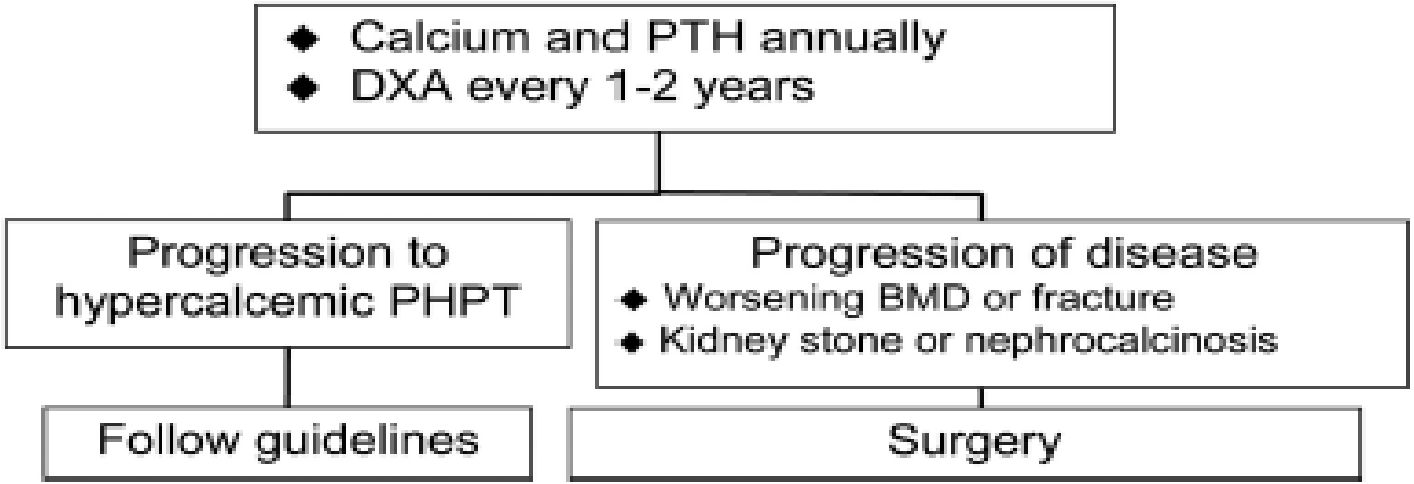
The guidelines for the management of asymptomatic PHPT can not be applied with confidence in NCPHPT

Management in 2013 .. some criteria

- Monitor subjects with NC PHPT in the same way we monitor those with asymptomatic PHPT.
- If the disease evolves into the hypercalcemic form, then follow the guidelines from the Third International Workshop (would be reasonable).
- Progression of the disease, such as worsening bone density, a fracture, or a kidney stone would signal a more proactive surgical approach to the disease, even if patients continue to be normocalcemic

Cusano et al J Clin Densitom **2013**

Management in 2014



Algorithm for monitoring patients with normocalcemic PHPT

Surgical & A-P features of NC PHPT
by LIM et al al 2017

Normocalcemic PHPT is associated with a high incidence of multigland disease.

Normocalcemic disease seems [illegible] predictor

normocalcemic patients will require
bilateral neck operations
>8 times more frequently than
patients with a classic biochemical profile

Table III. Logistic regression model to predict multigland disease including biochemical profiles of primary hyperparathyroidism; Nagelkerke $R^2 = 0.244$

Predictor variable	*OR*	*95% CI*	P *value*
Age	0.99	0.98–1.02	.914
Women	1.43	0.66–3.09	.370
Race			.751
White	Ref	Ref	Ref
Black	1.71	0.65–4.51	.282
Asian	0.00	0.00	.999
Unknown/other	0.95	0.31–2.89	.924
Family history	4.51	1.75–11.64	.002
Neck irradiation	0.54	0.16–1.85	.326
GFR <60	2.38	1.01–5.59	.046
Lithium use	0.76	0.06–9.37	.829
Osteoporosis	0.98	0.52–1.84	.942
Kidney stones	0.90	0.47–1.73	.755
Biochemical profiles			<.001
Classic	Ref	Ref	Ref
Normocalcemic	8.17	4.49–14.83	<.001
Normohormonal	0.94	0.34–2.58	.902

CI, Confidence interval; *OR*, odds ratio.

(Surgery 2017;161:70-7.)

Summary & THM

- NC PHPT does exist
- Low prevalence /increases in some population
- Exclusion diagnosis
- Symptomatic rather than asymptomatic
- Management and treatment according to guidelines and clinical experience …

Some open questions

- Prevalence/Incidence
- **Pathogenesis**
- Clinical manifestations
- **Clinical outcome**
- **Therapeutical management**
- **Screening** (reasonable **in at risk population**)
- Define the normal distribution range for any analyte

NC PHPT is still a cold case that needs more definitive characterization