AGGIORNAMENTI SU IPERPARATIROIDISMO

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A.S.O. S. Croce e Carle, Cuneo

Cuneesi al rhum …

AME Position Statement: Primary hyperparathyroidism in clinical practice

Michele Zini[1], Roberto Attanasio[2], Roberto Cesareo[3], Ignazio Emmolo[4], Andrea Frasoldati[1], Laura Gianotti[5], Rinaldo Guglielmi[6], Alessandro Piovesan[7], Massimo Procopio[8], Alfredo Scillitani[9], Annibale Versari[10], Jens Bollerslev[11], Dhanwada Sudhaker Rao[12], Claudio Marcocci[13], and Giorgio Borretta[5]

J. Endocrinol. Invest. 35 (Suppl. to no. 7): 2-21, 2012

Diagnostic, therapeutic and healthcare management protocols in parathyroid surgery: II Consensus Conference of the Italian Association of Endocrine Surgery Units (U.E.C. CLUB)

L. Rosato · M. Raffaelli · R. Bellantone · A. Pontecorvi · N. Avenia · M. Boniardi · M. L. Brandi · F. Cetani · M. G. Chiofalo · G. Conzo · M. De Palma · G. Gasparri · A. Giordano · N. Innaro · E. Leopaldi · G. Mariani · C. Marcocci · P. Marini · P. Miccoli · P. Nasi · F. Pacini · R. Paragliola · M. R. Pelizzo · M. Testini · G. De Toma

J Endocrinol Invest (2014) 37:149–165

Diagnosi e Inquadramento clinico

We recommend the concomitant determination of total serum calcium and PTH to confirm the diagnosis of PHPT. Correction for serum albumin is recommended.

We suggest using ionized calcium determination when a reliable assay is available

Qualcosa di nuovo?

Vitamin D status in primary hyperparathyroidism: a Southern European perspective

Francesco Tassone*, Laura Gianotti*, Claudia Baffoni*, Gianluca Viscontit, Micaela Pellegrino*, Sara Cassibba*, Chiara Giulia Croce*, Giampaolo Magro*, Flora Cesario*, Roberto Attanasio‡ and Giorgio Borretta*

	Plasma 25OHD		
	<20 ng/ml (n = 75)	≥ 20 ng/ml (n = 131)	P
25OHD (ng/ml)	12·2 ± 4·4	41·0 ± 20·4	<0·00000001
Bone disease (%)	20 (26·7%)	17 (13%)	0·0226
Stone disease (%)	37 (49·3%)	55 (42%)	NS
Age (years)	60·8 ± 14·1	59·4 ± 13·4	NS
BMI (kg/m^2)	25·5 ± 6·1	25·2 ± 4·6	NS
PTH (ng/l)	280·5 ± 249·4	175·9 ± 154·4	<0·0004
S-Calcium (mM)	2·82 ± 0·37	2·75 ± 0·25	0·046
Ionized calcium (mM)	1·49 ± 0·19	1·42 ± 0·15	0·023
S-Phosphate (mM)	0·80 ± 0·16	0·87 ± 0·18	0·009
S-Creatinine (μM)	70·7 ± 16·8	77·8 ± 23·9	<0·04
Alkaline phosphatase (U/l)	124·1 ± 72·7	94·3 ± 36·4	<0·0003
Bone alkaline phosphatase (U/l)	29·4 ± 23·9	19·9 ± 13·7	<0·0006
Osteocalcin (ng/ml)	67·2 ± 69·2	45·8 ± 29·2	<0·003
Urinary cross-links (nMmcr/ml)	15·9 ± 17·5	9·6 ± 5·9	<0·022
Femoral BMD (g/cm^2)	0·69 ± 0·14	0·76 ± 0·19	<0·017
Femoral T-score	−2·28 ± 1·2	−1·85 ± 1·26	<0·025
Lumbar BMD (g/cm^2)	0·77 ± 0·17	0·84 ± 0·17	<0·005
Lumbar T-score	−2·79 ± 1·36	−2·36 ± 1·42	<0·045
Forearm BMD (g/cm^2)	0·38 ± 0·11	0·44 ± 0·13	<0·001
Forearm T-score	−2·85 ± 1·68	−1·94 ± 1·58	<0·00045

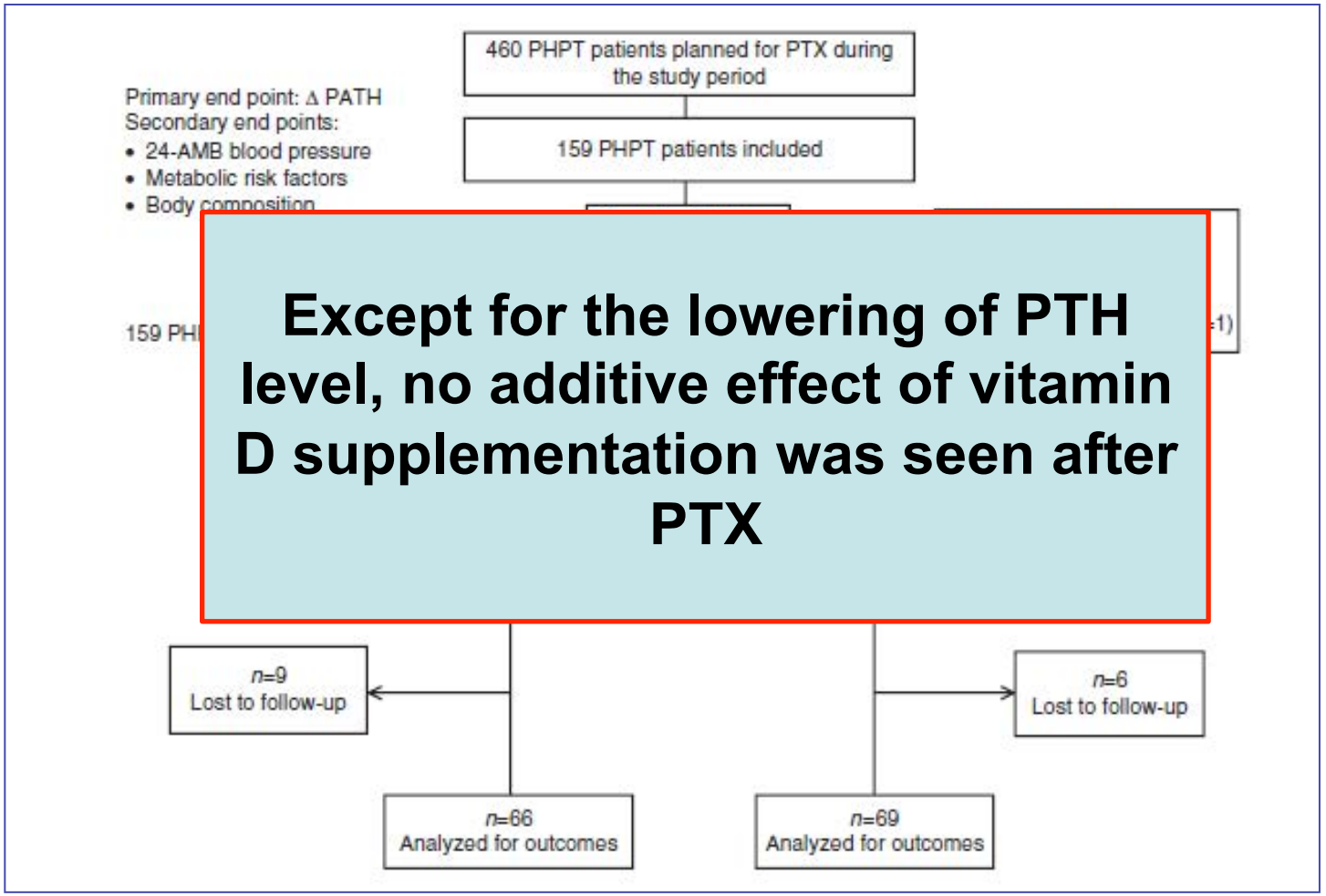
206 consecutive PHPT patients
VDD = 36.4%; severe VDD = 11,7%

	pHPT (n = 113)	Controls (n = 113)	P
Age (years)	52·9 ± 8·5	51·7 ± 7·7	NS†
Sex (M/F)	35/78	35/78	NS†
BMI (kg/m^2)	25·59 ± 4·90	25·05 ± 3·50	NS
S-Calcium (mM)	2·78 ± 0·33	2·36 ± 0·87	<0·00001
Ionized calcium (mM)	1·45 ± 0·18	1·21 ± 0·046	<0·00001
PTH (ng/l)*	141 (105–234)	39·1 (29·5–50·2)	<0·00001
25OHD (ng/ml)	29·8 ± 19·1	42·5 ± 21·9	<0·00001
(nM)	74·4 ± 47·7	106·8 ± 54·7	<0·00001
VDD (%)	38 (33·6%)	12 (10·6%)	<0·0001
Severe VDD (%)	10 (8·8%)	2 (1·8%)	<0·034

Clinical Endocrinology (2013) **79**, 784–790

Primary hyperparathyroidism and metabolic risk factors, impact of parathyroidectomy and vitamin D supplementation, and results of a randomized double-blind study

Sophie Norenstedt[1,2], Ylva Pernow[1,3], Kerstin Brismar[1,3], Maria Sääf[1,3], Ayla Ekip[1], Fredrik Granath[4], Jan Zedenius[1,2] and Inga-Lena Nilsson[1,2]



Except for the lowering of PTH level, no additive effect of vitamin D supplementation was seen after PTX

European Journal of Endocrinology (2013) 169 795–804

Vitamin D Treatment in Primary Hyperparathyroidism: a Randomized Placebo Controlled Trial

Lars Rolighed[1], Lars Rejnmark[2], Tanja Sikjaer[2], Lene Heickendorff[3], Peter Vestergaard[2,4], Leif Mosekilde[2], and Peer Christiansen[1]

2800 UI/die di colecalciferolo per 26 settimane (prima di PTX):

- riduzione di PTH del17% (p=0.01)
- riduzione di CTX del 22% (p<0.005)
- **incremento d BMD colonna lombare del 2.5% (p=0.01)**

JCEM 2014

Presentazione clinica

- **Symptomatic**
- **Asymptomatic/Mild**
- **Normocalcemic**
- *Hypercalcemic crisis*
- *PHPT inPregnancy*
- *Neonatal*

Presentazione clinica

AME Position Statement: Primary hyperparathyroidism in clinical practice

Michele [illegible]lo[4], Andrea [illegible]Piovesan[7], Massimo [illegible]rslev[11], Dhanwac[illegible]a[5]

Symptoma[illegible]phrocalcino-sis, overt b[illegible]a)

Asymptom[illegible]

Aortic Valve Calcification in Mild Primary Hyperparathyroidism

Shinichi Iwata, Marcella Donovan Walker, Marco R. Di Tullio, Eiichi Hyodo, Zhezhen Jin, Rui Liu, Ralph L. Sacco, Shunichi Homma, and Shonni J. Silverberg

(calcium >10.2 but <12.0 mg/dl

JCEM 2012

Presentazione clinica

Current evidence for recommendation of surgery, medical treatment and vitamin D repletion in mild primary hyperparathyroidism

Jens Bollerslev[1,2], Claudio Marcocci[3], Manuel Sosa[4], Jörgen Nordenström[5], Roger Bouillon[6] and Leif Mosekilde[7]

As no specific definition is provided, we suggest that……. The main characteristics of mild PHPT are that the patient is asymptomatic, has no hypercalcaemic symptoms, and there is no clinical evidence of bone, renal or stone disease

European Journal of Endocrinology (2011) **165** 851–864

Normocalcemic Primary Hyperparathyroidism

Cusano NE

J Clin Densit 16-1. 2013

Summary of Cohorts With Normocalcemic Primary Hyperparathyroidism Described in the Literature

Study	Cohort size	Age (yr)	Female (%)	Osteoporosis (%)	Nephrolithiasis (%)	Comments
Symptomatic cohorts						
Lowe et al *(25)*	37	58 ± 12	95	57[a]	14	Ionized calcium not available for all
Tordjman et al *(26)*	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 *(27)*	33	64 ± 14	79	15[b]	18	Ionized calcium not measured
Cakir et al *(28)*	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 *(29)*	8	60	63	25[c]	25	Surgical cohort: Five subjects had single gland disease and 3 multiple glands
Asymptomatic cohort						
Garcia-Martin et al *(31)*	6	56 ± 3	100[d]	0	0	Ionized calcium not measured Population-based cohort

Prevalence of Normocalcemic Primary Hyperparathyroidism in Various Populations

Study	Population	Prevalence (%)	Comments
Lundgren et al *(32)*	Postmenopausal women aged 55–75 yr, Sweden	0.5	Secondary etiologies of hyperparathyroidism not excluded
Misra et al *(33)*	Men and women older than 45 yr, United States (NHANES)	1	Excluding renal failure (GFR lower than 60 mL/min) and vitamin D deficiency (25-hydroxyvitamin D level lower than 30 ng/dL)
Berger et al *(34)*	Men and women aged 19–97 yr, Canada (CaMos)	16.7	Excluding vitamin D deficiency (25-hydroxyvitamin D level lower than 20 ng/dL)
Garcia-Martin et al *(31)*	Postmenopausal women, Spain	6	Excluding renal disease, vitamin D deficiency (25-hydroxyvitamin D level lower than 30 ng/dL), and malnutrition

ORIGINAL ARTICLE

Endocrine Care

Normocalcemic Hyperparathyroidism and Hypoparathyroidism in Two Community-Based Nonreferral Populations

Natalie E. Cusano, Naim M. Maalouf, Patty Y. Wang, Chiyuan Zhang, Serge C. Cremers, Elizabeth M. Haney, Douglas C. Bauer, Eric S. Orwoll, and John P. Bilezikian

The Osteoporotic Fractures in Men [MrOS] =2364 Dallas Heart Study [DHS] =3450 M W

Prevalence (95% CI) of Normocalcemic Primary Hyperparathyroidism

Cohort	Normocalcemic Primary Hyperparathyroidism
MrOS study, %	0.4 (0.2–0.7)
DHS, %	
Baseline	3.1 (2.5–3.7)
Follow-up	0.6 (0.4–1.0)

J Clin Endocrinol Metab 98: 2734–2741, 2013

Normocalcemic versus Hypercalcemic Primary Hyperparathyroidism: More Stone than Bone?

Amaral ML et al. *J Osteop Volume 2012*

70 patients with PHPT, 33 normocalcemic and 37 mild hypercalcemic retrospectively

Variable	Normocalcemic		Hypercalcemic		Group total		*P* value
	N	%	N	%	N	%	
Total	33	100,0	37	100,0	70	100,0	
(i) Fracture							
Yes	5 1M/4F	15.2	4 0M/4F	10.8	9	12.9	$P^{(1)} = 0.726$
(ii) Kidney Stones							
Yes	6 0M/6F	18.2	7 3M/4F	18.9	13	18.6	$P^{(2)} = 0.937$

High prevalence of urolithiasis in normocalcemic primary hyperparathyroidism, but with the preservation of cortical bone.

This finding supports the hypothesis that this disease is not an idle condition and needs treatment.

Bone Mineral Density Evolution After Successful Parathyroidectomy in Patients With Normocalcemic Primary Hyperparathyroidism

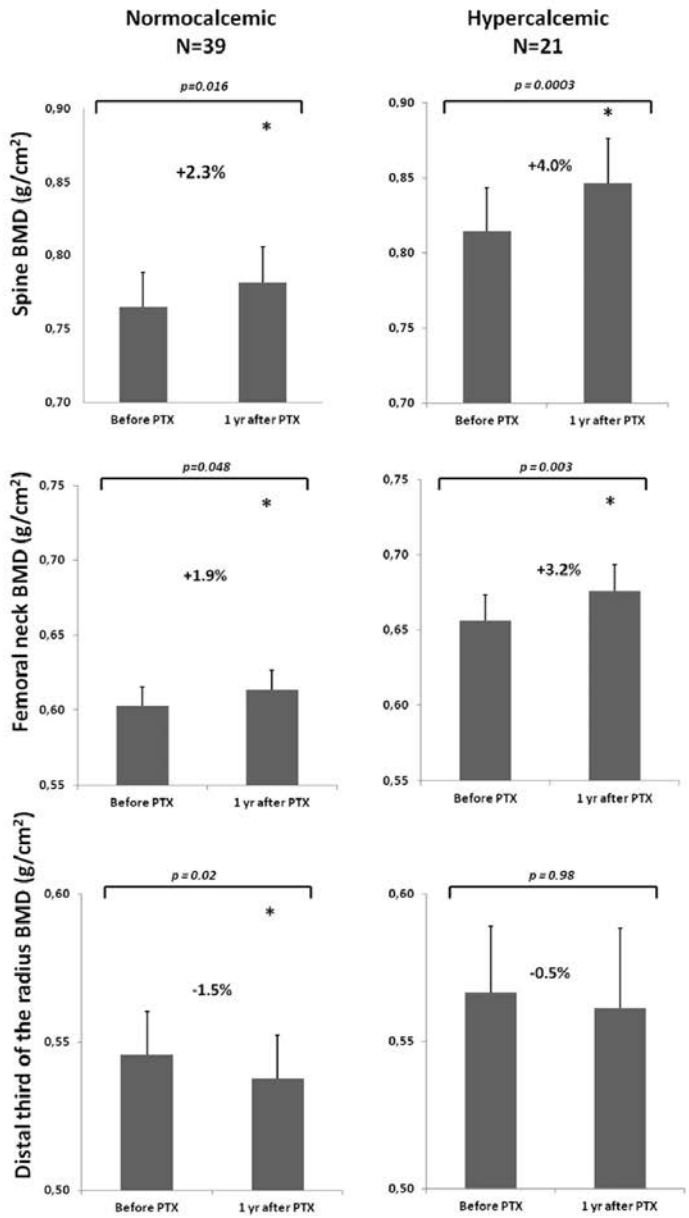
Koumakis et al., *JCEM, Aug 2013, 98(8)*

Table 1. Baseline Clinical, Biochemical, and Bone Densitometric Parameters of the 60 Patients Enrolled in the Study and Comparison of Baseline Parameters Between Normocalcemic and Hypercalcemic Individuals

Baseline Characteristics	Total PHPT Cohort (n = 60)	Normocalcemic (n = 39)	Hypercalcemic (n = 21)	*P* Value
Clinical				
Age, y	64.0 ± 10.1	66.1 ± 9.1	61.4 ± 11.3	.1
Women, n, %	57/60 (95.0)	36/39 (92.3)	21/21 (100)	.5
VAS fatigue	6.2 ± 2.0	6.2 ± 2.1	6.4 ± 1.9	.8
History of nephrolithiasis, n, %	8/60 (13.3)	7/39 (17.9)	1/21 (4.8)	.2
Chondrocalcinosis, n, %	2/60 (3.3)	1/39 (2.6)	1/21 (4.8)	1.0
Biochemical				
Serum total calcium, 2.20–2.60 mmol/L	2.53 ± 0.13	2.51 ± 0.08	2.69 ± 0.10	<.0001
Ionized calcium, 1.17–1.30 mmol/L	1.35 ± 0.07	1.32 ± 0.05	1.41 ± 0.06	<.0001
PTH, 10–46 pg/mL	68.9 ± 27.8	63.2 ± 20.9	79.6 ± 35.7	.08
Serum phosphorus, 0.80–1.40 mmol/L	0.89 ± 0.16	0.93 ± 0.16	0.82 ± 0.13	.01
24-Hour urinary calcium, n < 4 mg/k g ·d	4.62 ± 2.55	4.20 ± 2.31	5.39 ± 2.83	.07
eGFR, mL/min per 1.73 m^2	77.2 ± 17.0	80.7 ± 17.9	70.6 ± 13.3	.03
Alkaline phosphatase activity, 30–120 IU/L	72.7 ± 27.0	75.7 ± 29.7	66.7 ± 20.1	.4
Osteocalcin, ng/mL	32.6 ± 13.2	31.8 ± 13.0	34.0 ± 13.8	.4
Serum CTX, pmol/mL	5363 ± 2985	4651 ± 1997	6868 ± 4075	.02
25OHD, 30–60 ng/mL	33.0 ± 8.4	34.3 ± 7.2	30.4 ± 10.1	.1
Bone assessment				
History of fracture, n, %	21/60 (35)	15/38 (39.5)	6/21 (28.6)	.6
Osteoporosis, n, %[a]	52/60 (86.7)	36/39 (92.3)	16/21 (76.2)	.2
T-score ≤ −2.5 in at least 1 site, n, %	48/60 (80)	35/39 (89.7)	13/21 (61.9)	.02
T-score between −1 and −2.5 in at least 1 site, n, %	12/60 (20)	4/39 (10.3)	8/21 (38.1)	.02
Lumbar spine T-score (SD)	−2.4 ± 1.3	−2.5 ± 1.3	−2.1 ± 1.2	.1
Femoral neck T-score (SD)	−2.3 ± 0.7	−2.5 ± 0.6	−2.0 ± 0.7	.01
Distal third of the radius T-score (SD)	−2.5 ± 1.6	−2.6 ± 1.6	−2.1 ± 1.7	.3

Bone Mineral Density Evolution After Successful Parathyroidectomy in Patients With Normocalcemic Primary Hyperparathyroidism

Koumakis et al., *JCEM, Aug 2013, 98(8)*



parathyroid hyperplasia or of multiple adenomas was more frequent in the normocalcemic group (11 of 39, 28.2%) than in hypercalcemic patients (1 of 21, 4.8%) (*P* .04).

CONCLUSION

successful PTX in normocalcemic PHPT patients with osteoporosis is followed with mild but significant BMD improvement at the spine and hip at 1 year, comparable with that observed in hypercalcemic PHPT, suggesting that PTX may be beneficial in normocalcemic PHPT.

Normocalcemic Primary Hyperparathyroidism IS "ON THE MAP"

WAITING FOR ..
NEW GUIDELINES
IV international workshop
Firenze , 19-21 settembre 2013

Valutazione di Danno d'organo

Renal disease

We recommend serum creatinine and estimated GFR evaluation.

We suggest routine use of kidney US in patients with PHPT.

Cardiovascular (CV) involvement

We suggest evaluating for CV involvement by measuring arterial blood pressure, stratifying the CV risk factors at diagnosis and after curative surgery for PHPT. Other measurements cannot be recommended for routine use.

Bone disease

We recommend against skeletal X-ray as routine examination in PHPT.

We recommend BMD measurement at diagnosis and at 1-2-yr intervals in individuals with PHPT who do not undergo surgery (for follow-up after PTX see below).

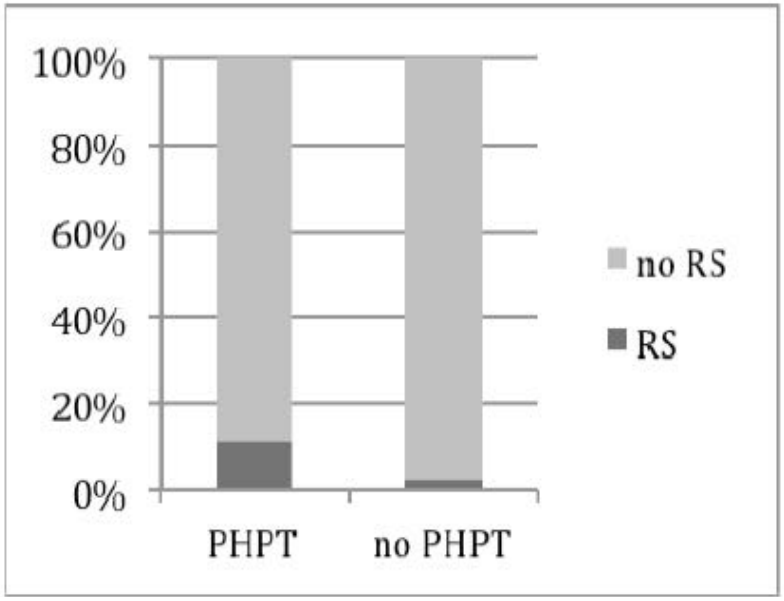
We suggest looking for vertebral fractures by vertebral morphometry in PHPT patients with osteoporosis or related symptoms.

Neuro-psychiatric manifestations

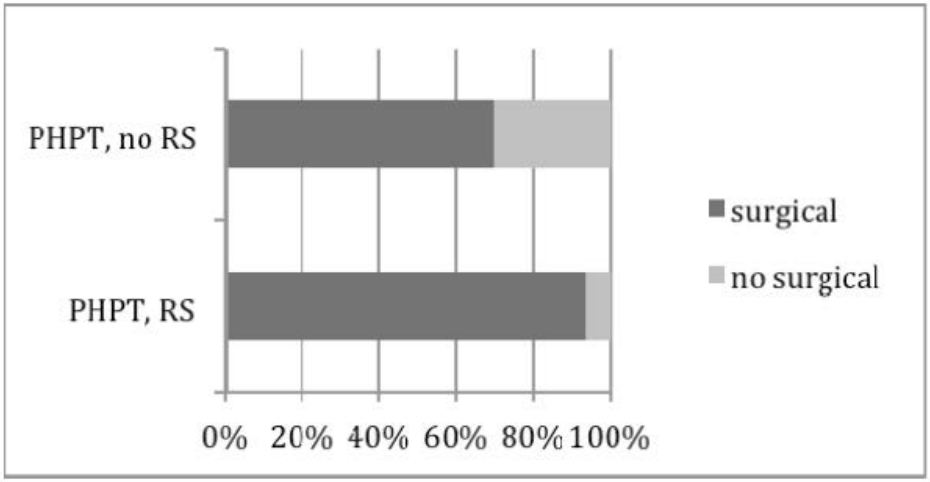
We suggest against routine formal testing for neurological, psychiatric, and cognitive symptoms, but it might be useful in some selected cases.

SILENT RENAL STONES IN PRIMARY HYPERPARATHYROIDISM: PREVALENCE AND CLINICAL FEATURES

Sara Cassibba[1], MD; Micaela Pellegrino[1], MD; Laura Gianotti[1], MD, PhD; Claudia Baffoni, MD, PhD; Enrico Baralis[2], MD; Roberto Attanasio[3], MD, PhD*; Andrea Guarnieri[4], MD; Giorgio Borretta[1], MD, and Francesco Tassone[1] MD, PhD.



% of renal stones in PHPT and controls
P<0.003



Surgical indication regardless renal stones

Submitted to Endocrine Practice

Surgery for 'asymptomatic' mild primary hyperparathyroidism improves some clinical symptoms postoperatively

Claire Blanchard, Muriel Mathonnet[1], Frédéric Sebag[2], Cécile Caillard, Antoine Hamy[3], Christelle Volteau[4], Marie-Françoise Heymann[5], Vincent Wyart, Delphine Drui[6], Malanie Roy, Bertrand Cariou[6], Françoise Archambeaud[7], Patrice Rodien[8], Jean-François Henry[2], Rasa Zarnegar[9], Jean-Benoît Hardouin[4,10] and Eric Mirallié

Table 3 Nonspecific symptoms in all patients at preoperative period, 3, 6, and 12 months.

Symptoms	**Preoperative** (%)	**3 months** (%)	**6 months** (%)	**12 months** (%)
Appetite loss	22	6*	11*	6*
Weight loss	24	11*	15	13*
Thirst	29	12*	8*	5*
Polyuria	26	18*	15	12*
		14		
		10		
		28*		
		38		
		20		
		27*		
		17		
		2*		
		17		
		33		
		17*		
		15		
		31*		
Depression	27	18*		
Mood swings	27	17*	15*	16*
Irritability	27	21	24	18*
Anxiety	50	34*	44	34*
Forgetfulness	25	21	28	25

Nonspecific symptoms significantly improved at 1 year

<70 years	≥70 years
Appetite loss	Appetite loss
Thirst	Thirst
Headaches	Headaches
Bone pain	Fatigue
Muscular weakness	
Constipation	
Fatigue	
Mood swings	
Anxiety	

Nonspecific symptoms significantly improved at 1 year

≥2.6 mmol/l	<2.6 mmol/l
Appetite loss	Thirst
Thirst	Fatigue
Polyuria	
Headaches	
Bone pain	
Constipation	
Fatigue	
Depression	
Mood swings	
Irritability	
Anxiety	

European Journal of Endocrinology (2013) **169** 665–672

Nontraditional Manifestations of Primary Hyperparathyroidism

Marcella Donovan Walker, Mishaela Rubin, and Shonni J. Silverberg*

More data from rigorously designed studies are needed to better inform the clinical management of asymptomatic PHPT patients

Journal of Clinical Densitometry: Assessment of Skeletal Health, vol. 16, no. 1, 40–47, 2013

Forme Familiari di Iperparatiroidismo Primario

Table 1 - *Familial forms of primary hyperparathyroidism.*

Disease	Mutated gene
MEN 1	*MEN1* (85)
MEN 2a	*RET* (86)
HPT-JT	*HPRT2* (87)

We suggest referral of patients with familial forms to tertiary level centers.
We recommend searching for mutation in *MEN 1* to confirm clinical diagnosis (even in atypical cases) and to identify carriers (in the first decade).
We suggest searching for mutation in *HPRT2* in familial forms of PHPT not due to *MEN 1* mutations or in presence of parathyroid carcinoma.
We suggest searching for mutations of *CaSR* gene in patients with biochemical findings suggestive for FHH or when screening of the familial forms of PHPT is inconclusive and also in newborns with severe hypercalcemia.

Mutations in *AP2S1* cause familial hypocalciuric hypercalcemia type 3

M. Andrew Nesbit[1], Fadil M. Hannan[1], Sarah A. Howles[1], Anita A.C. Reed[1], Treena Cranston[2], Clare E. Thakker[1], Lorna Gregory[3], Andrew J. Rimmer[3], Nigel Rust[4], Una Graham[5], Patrick J. Morrison[6], Steven J. Hunter[5], Michael P. Whyte[7], Gil McVean[3], David Buck[3], and Rajesh V. Thakker[1]

affecting parathyroids, kidneys and bone[5-7] These *AP2S1* mutations occurred in >20% of FHH patients without calcium-sensing GPCR (CaSR) mutations which cause FHH1[8-12]. *AP2S1* mutations decreased the sensitivity of CaSR-expressing cells to extracellular-calcium and reduced CaSR endocytosis, likely through a loss of interaction with a C-terminus CaSR dileucine-based motif whose disruption also decreased intracellular signalling. Thus, our results reveal a new role for AP2 in extracellular-calcium homeostasis.

Nat Genet. 2013 January ; 45(1): 93–97.

La diagnostica di immagine : studi di localizzazione

Taking into account that imaging procedures are not to be used for diagnostic purposes, **we recommend** performing imaging in all biochemically confirmed PHPT, with the combined use of US and scintigraphy (possibly completed by SPECT) as first line.

We recommend that all patients referred to parathyroid surgery undergo neck US because a detailed evaluation of thyroid gland as well as of cervical lymph nodes is required.

We recommend MRI and/or CT when an ectopic parathyroid adenoma is suspected.

We recommend MRI and/or CT when both US and scintigraphy are not conclusive in patients undergoing second surgery.

We recommend parathyroid FNAB with intralesional PTH measurement as a second-line technique in case of ambiguous and/or discrepant US and scintigraphy findings.

Diagnostic, therapeutic and healthcare management protocols in parathyroid surgery: II Consensus Conference of the Italian Association of Endocrine Surgery Units (U.E.C. CLUB)

TC sestamibi scintigraphy

roid disease (toxic adenoma or neoplasm). Furthermore, to perform the examination correctly, it may be useful to consider a wash-out period from potentially interfering medications or substances such as iodinated contrast medium, iodine-containing drugs, thyroxine, vitamin D, calcium mimetics and calcium antagonists (*Procedural Recommendations of the Italian Association of Nuclear Medicine and Molecular Imaging—Parathyroid Scintigraphy—V. 02/2012, p. 1/5*).

Associazione Italiana di Medicina Nucleare
ed Imaging Molecolare

RACCOMANDAZIONI PROCEDURALI

per la scintigrafia delle

PARATIROIDI

Classe Farmacologica	Commento
Mezzi di contrasto radiologici contenenti iodio, amiodarone, farmaci contenenti iodio	Meccanismo di saturazione da iodio "freddo". Eseguire scintigrafia con tecnica di sottrazione non prima di 4-6 settimane da indagini con mezzo di contrasto e 2-6 mesi da assunzione di amiodarone; in alternativa eseguire scintigrafia con tecnica "dual phase".
Terapia tiroidea sostitutiva	Può ridurre l'uptake del ^{123}I-Ioduro e del ^{99m}Tc-pertecnetato. Sospendere terapia sostitutiva per 2-3 settimane.
Vitamina D3	Può ridurre l'uptake paratiroideo del ^{99m}Tc-sestaMIBI Sospendere assunzione di Vitamina D3 per almeno 2 settimane.
Calciomimetici	Possono ridurre l'uptake paratiroideo del ^{99m}Tc-sestaMIBI. Sospendere calciomimetici per almeno 10 giorni.
Calcio-antagonisti	Potenzialmente modificano l'uptake del ^{99m}Tc-sestaMIBI.

Tab. 1. Farmaci che possono interferire con l'uptake dei traccianti per scintigrafia paratiroidea

2012

Diagnostic, therapeutic and healthcare management protocols in parathyroid surgery: II Consensus Conference of the Italian Association of Endocrine Surgery Units (U.E.C. CLUB)

FNAB with PTH measurement

Only when a diagnostic doubt cannot be resolved with other techniques.

It should be avoided when a carcinoma is supected

J Endocrinol Invest (2014) 37:149–165

La terapia chirurgica

We recommend surgery in:

- patients with symptomatic PHPT;
- patients with asymptomatic disease addressing one or more of the criteria indicated by the 2008 Workshop on asymptomatic PHPT.

We suggest surgery also in patients with asymptomatic disease addressing none of the criteria indicated by the 2008 Workshop on asymptomatic PHPT, if pre-operative parathyroid adenoma localization is positive by first-line imaging studies and if a skilled surgeon is available.

We suggest conservative treatment in patients with asymptomatic disease addressing none of the criteria indicated by the 2008 Workshop on asymptomatic PHPT, if pre-operative parathyroid adenoma localization is negative by first-line imaging studies.

Comparison of new and old guidelines for parathyroid surgery in asymptomatic PHPT*

Measurement	1990	2002	2008
Serum calcium (above upper limit of normal)	1-1.6 mg/dl	1.0 mg/dl	1.0 mg/dl
24-hr urinary calcium	>400 mg/day	>400 mg/day	Not indicated**
Creatinine clearance (calculated)	Reduced by >30%	Reduced by >30%	Reduced to <60 ml/min
Bone mineral density	Z score < -2.0 in forearm	T score < -2.5 at any site	T score < -2.5 at any site and/or previous fx ***
Age	<50	<50	<50

*Surgery is also indicated in patients for whom medical surveillance is neither desired nor possible

** some physicians still regard urinary calcium >400 mg as an indication for surgery

***Lumbar spine,total hip, femoral neck or 1/3 distal radius; the use of Z-score instead of T-score is recommended in evaluating BMD in premenopausal women and men < 50 yrs.

La terapia chirurgica

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We suggest conservative treatment in patients with asymptomatic disease addressing none of the criteria indicated by the 2008 Workshop on asymptomatic PHPT, if pre-operative parathyroid adenoma localization is negative by first-line imaging studies.

Diagnostic, therapeutic and healthcare management protocols in parathyroid surgery: II Consensus Conference of the Italian Association of Endocrine Surgery Units (U.E.C. CLUB)

- Indications for parathyroidectomy (PTx):
  - symptomatic primary hyperparathyroidism;
  - asymptomatic primary hyperparathyroidism [13, 19]
    with at least one of the following conditions:
    - serum calcium levels: 1.0 mg/dL above the upper limit of normal;
    - creatinine clearance <60 cc/min;
    - bone mineral density: T score < -2.5 at the 3 measurement sites (lumbar spine, femur, and 1/3 distal radius)/prior fragility fracture;
    - age <50 years.

In selected cases of asymptomatic HPT I (with difficult follow-up, when the patient appears to be willing to solve the problem even though the criteria are not met), PTx may be considered even in the absence of at least one of the aforementioned criteria, if only one parathyroid gland is suspected to be affected based on preoperative localization studies (ultrasound or scintigraphy) [16].

Diagnostic, therapeutic and healthcare management protocols in parathyroid surgery: II Consensus Conference of the Italian Association of Endocrine Surgery Units (U.E.C. CLUB)

Waiting time for surgery

- Within **1 month**: malignancy or severe hypercalcemia(>12 mg/dl)
- Withing **3 months**: CKD, severe osteoporosis, requiring surgery/ lithotripsy for renal stones, moderate/severe hypercalcemia, especially in advanced age and during summer
- Within **6 months**: other cases

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Before admission

•ENT consultation for assessment of vocal cord mobility (advisable in all, strongly recommendable in case of re-interventions)
•Discontinuation of antiplatelet therapy (wich may be substituted with low molecular weight heparins at least 1 week prior to surgery)
•Antibiotic therapy is not indicated (except particular cases)
•Autologous predeposit blood donation is not justified
•Informed consent

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La terapia chirurgica (2)

Since ioPTH would be an useful tool to confirm successful surgery in all patients submitted to PTX, **we recommend** performing ioPTH during MIP/UNE:

- when pre-operative localization by scintiscan and US is doubtful or discordant
- when pre-operative localization is based on a single study
- during repetitive surgery.

If a single gland is pre-operatively identified, **we recommend**:

- MIP or UNE if scintigraphy and US are concordant;
- BNE or MIP/UNE with ioPTH if scintigraphy and US are discordant or only one is positive.

If more than one gland is pre-operatively identified or both scintigraphy and US are negative, **we recommend** BNE.

We recommend referral of patients to a skilled surgeon.

La terapia chirurgica (3)

According to the different involvement of parathyroid glands in the different diseases, **we suggest** performing:

- in MEN 1 subtotal PTX or, as second option, total PTX + auto-transplantation;
- in MEN 2A and other non-MEN familial forms (HPT-JT syndrome, FIHPT, autosomal dominant mild PHPT) removal of enlarged glands only.

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Further recommendations

• **Robotic-assisted PTX**: proposed in recent years for transthoracic (ectopic mediastinal glands) and transaxillary approaches. High costs.

• **Carcinoma**: removal of the tumour and the sorrounding structures: thyroid lobe, ipsilateral parathyroid gland and ipsilateral central compartment lymph node dissection

• **MEN 1**: regardless of the techinique used, the thyreothymic ligament and the thymic horns must be removed (supernumerary glands)

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La terapia chirurgica (4)

Condizioni particolari:

Gravidanza

Gozzo

Le linee guida UEC non prendono in considerazione la chirurgia paratiroidea in gravidanza o combinata con la chirurgia tiroidea

La terapia medica

MIRATA A DANNO OSSEO

We recommend considering treatment with alendronate in non-operated patients with PHPT with high-risk profile for fractures.
If the recovery of good bone health status is unsatisfactory after successful PTX, **we suggest** that alendronate treatment should be advised as well.

We suggest vitamin D supplementation in vitamin D-deficient patients with PHPT, as currently done for non-PHPT patients.

MIRATA A DANNO RENALE

We suggest following the guidelines released by scientific societies of Nephrology for the clinical management of kidney stones and renal failure, keeping in mind that they do not specifically address PHPT patients.

CONTROLLO IPERCALCEMIA

In severe hypercalcemia **we recommend** adequate hydration and a stepwise approach with furosemide and iv bisphosphonates according to hypercalcemia degree.
We suggest considering cinacalcet treatment (starting with 30 mg/day and escalating along labeling indications according to blood calcium levels and tolerability) in PHPT patients with calcemia more than 1 mg/dl above the upper normal limit and one of the following:

- contraindications to surgery
- unwilling to have surgery
- previously unsuccessful PTX with persisting PHPT
- relapsing PHPT
- long time interval before surgery.

Iperparatiroidismo primario: Terapia medica di protezione ossea

Estrogeni

Qualcosa di nuovo?

Calcimimetici

Medical Management of Primary Hyperparathyroidism

*Aliya A. Khan**

A short trial with cinacalcet can also be of value in assessing the potential benefits of PTX in elderly individuals with cognitive impairment.
The improvements in cognition may lead to consideration of PTX in these patients

Journal of Clinical Densitometry: Assessment of Skeletal Health, vol. 16, no. 1, 60–63, 2013

J Clin Endocrinol Metab 99: 387–390, 2014

Denosumab for Management of Parathyroid Carcinoma-Mediated Hypercalcemia

Priyathama Vellanki, Karoline Lange, Dina Elaraj, Peter A. Kopp, and Malek El Muayed

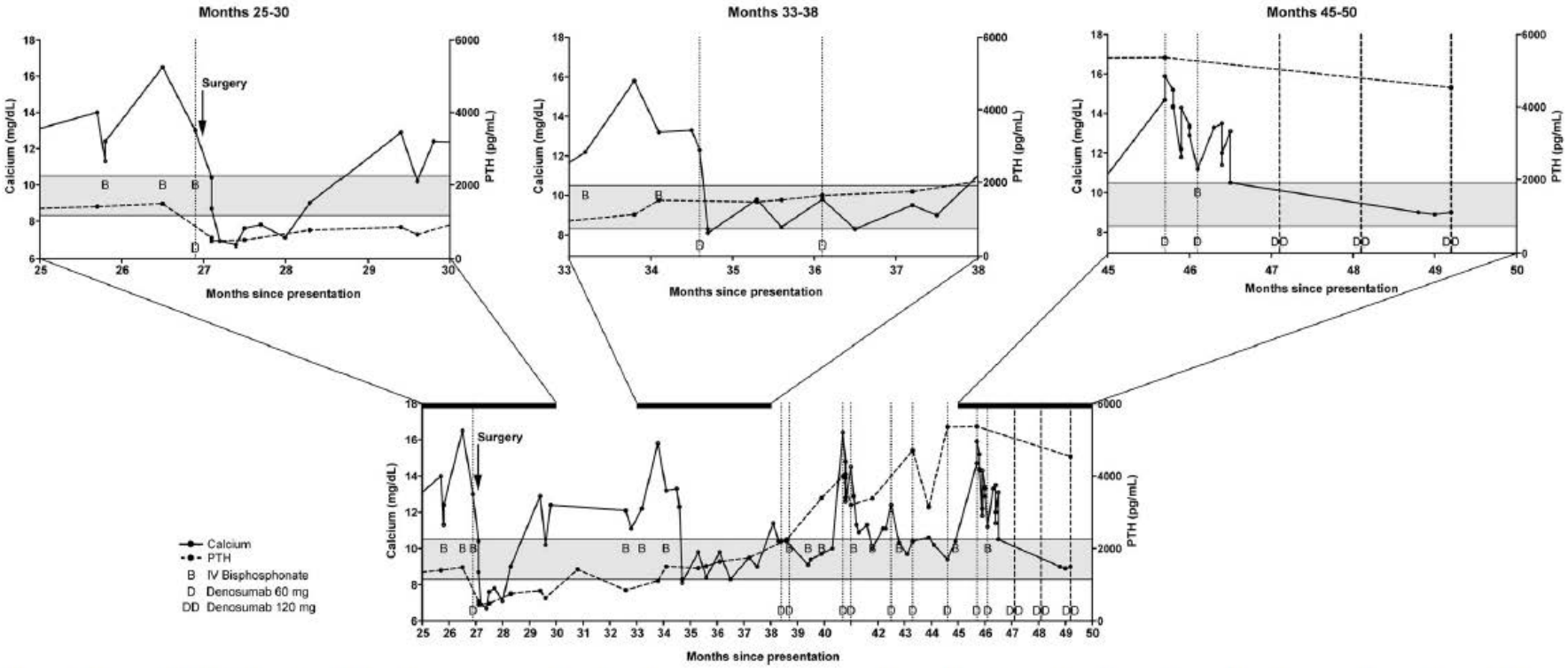

Figure 1. Graphic illustration of the time course of Ca levels (continuous line, scale on the left axis), PTH levels (dotted line, scale on the right axis) in relation to the administration of denosumab (illustrated by the letter D for 60 mg and DD for 120 mg), and iv bisphosphonates (zoledronic acid or pamidronate) (illustrated by the letter B).

Il Follow up dopo la chirurgia

We recommend close calcium monitoring before early discharge of patients operated on for severe PHPT or after bilateral PTX.

We suggest against long-term surveillance for sporadic PHPT recurrence in patients who are persistently normocalcemic after PTX.

We recommend assessing BMD at 1-2 yr after surgery to establish the effects of PTX.

Il Follow up dei pazienti non operati

In non-operated patients:

- **we recommend** a long-term follow-up based on yearly biochemical assessment and BMD evaluation every 2 yr;
- **we recommend** the adoption of pharmacological treatment aimed to calcium level control and prevention of fractures (see above) whenever needed.

CLINICAL MONITORING

TABLE 2. Comparison of new and old management guidelines for patients with asymptomatic primary hyperparathyroidism who do not undergo parathyroid surgery

Measurement	1990	2002	2008
Serum calcium	Biannually	Biannually	Annually
24-h urinary calcium	Annually	Not recommended	Not recommended
Creatinine clearance (24-h urine collections)	Annually	Not recommended	Not recommended
Serum creatinine	Annually	Annually	Annually
Bone density	Annually (forearm)	Annually (3 sites)	Every 1–2 yr (3 sites)[a]
Abdominal x-ray (±ultrasound)	Annually	Not recommended	Not recommended

[a] This recommendation acknowledges country-specific advisories as well as the need for more frequent monitoring if the clinical situation is appropriate.

3rd CONSENSUS, May 13 2008

Ringrazio

Elena & Roberto