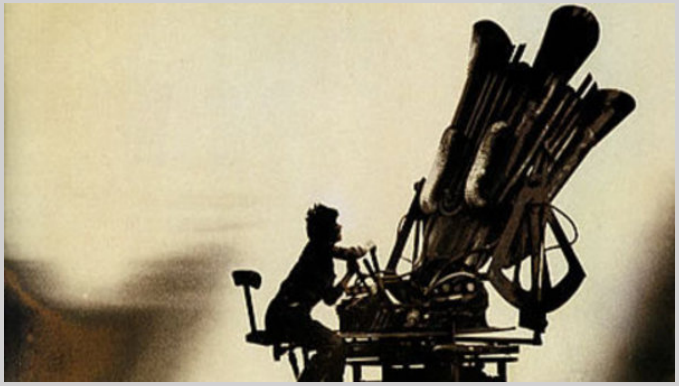
Iperparatiroidismo normocalcemico: vero o falso?

Bari,
7-10 novembre 2013



TERAPIA E FOLLOW-UP

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Occasional Survey

NORMOCALCÆMIC PRIMARY HYPERPARATHYROIDISM

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THE diagnosis of primary hyperparathyroidism is classically based upon the demonstration of a high plasma-calcium with a low plasma-phosphate concentration. According to the clinical presentation, patients with primary hyperparathyroidism may be classified into three main groups: (1) those with bone disease, (2) those with kidney stones, and (3) those with neither bone disease nor kidney stones. This third group consists of those patients in whom hypercalcæmia either is found in association with disturbances in other systems or is an accidental discovery. It is generally agreed that the finding of hypercalcæmia is the best index in the diagnosis of primary hyperparathyroidism,[1-7] and that changes in plasma-phosphate concentration are variable, even in the presence of normal renal function. Keating [3] defined an increase in plasma-calcium concentration as "borderline hypercalcæmia" if it fell within the 99 percentile limits of normals (mean+3 S.D.) and "significant hypercalcæmia" if it exceeded that limit. In recent years an increasing number of cases of proven primary hyperparathyroidism have been reported in patients who either were normocalcæmic, or had borderline hypercalcæmia, or had evidence of intermittent activity of the parathyroid adenoma as shown by episodes of normocalcæmia alternating with hypercalcæmic episodes.

OSTEITIS FIBROSA

The majority of reports of normocalcæmic primary hyperparathyroidism have been in patients presenting with renal stones, and normocalcæmia in hyperparathyroid patients with osteitis fibrosa is extremely rare. Mather [8] reported details of a patient with primary hyperparathyroidism who was normocalcæmic from the time of initial observation and during the ensuing three-month period until neck exploration and removal of the adenoma.

The patient was a 39-year-old woman who had developed diffuse aching pains in the lower limbs and back six months before admission to hospital, and had developed a "waddling" gait. Four values for serum-calcium concentration during the three-month period before operation were all within the normal range. Skeletal X-rays and sternal bone biopsy showed evidence of osteitis fibrosa. At operation the patient was found to have a *Wasserhelle-zelle* adenoma. After operation the bone pains vanished and by three months the gait was normal, with evidence of bone recalcification on radiological examination.

Eisenberg and Gotch [9] reported details of a 68-year-old man who had developed muscle weakness, polyuria, polydipsia, and mild constipation after an attack of gout.

In August, 1961, his serum-calcium was reported as 12·6 mg. per 100 ml., with a phosphate concentration of 5·3 mg. per 100 ml., blood-urea-nitrogen 54 mg. per 100 ml. (≡blood-urea 112 mg. per 100 ml.), and serum-creatinine of 5·8 mg. per 100 ml. These biochemical changes were associated with a generalised decrease in bone density on radiological survey, subperiosteal resorption of the phalanges and distal ends of the clavicles, and cysts in the first metacarpal bone and in the semilunar bone of the right hand. The radiological bone changes were considered to be consistent with hyperparathyroidism, although the bone cysts were similar to the bone lesions of gout. All subsequent estimations of serum calcium and phosphate concentration at that time and over the ensuing two years were found to be normal. In September, 1963, the serum-calcium concentration was slightly elevated on two occasions and surgical exploration of the neck was undertaken; a normal parathyroid gland was removed. The patient again remained normocalcæmic until January, 1965, when hypercalcæmia recurred. The hypercalcæmia persisted until September of that year, when his condition rapidly deteriorated over three days and he went into hypercalcæmic coma (serum-calcium 18·0 mg. per 100 ml.), which was treated by hæmodialysis. Subsequently a large retro-œsophageal parathyroid adenoma was removed.

This patient is of considerable interest because of the findings of bone changes consistent with hyperparathyroidism and the long duration of normocalcæmia after initial observation to the subsequent parathyroidectomy. Throughout the period of observation there was evidence of persistent, but not apparently progressive, renal damage, but no evidence of phosphate retention to account for suppression of hypercalcæmia. After parathyroidectomy radiological studies showed that subperiostal bone resorption of the hands was filled in, and the cystic lesions, which were presumably attributable to gout, had persisted.

RENAL STONES

It is particularly those patients with renal stones and hypercalciuria due to primary hyperparathyroidism who may present with serum-calcium concentrations that are within the normal range. Among this group of patients are many who have been reported with either fluctuations in the plasma-calcium concentration or a past history of a hypercalcæmic episode. In one of the five patients with primary hyperparathyroidism reported by Fanconi and Rose [10] the total plasma-calcium concentration was within the normal range on two occasions in the two-week period before operation. Although the total calcium in this patient was normal, the concentration of the ionised fraction was increased. McGeown and Morrison [11] reviewed a series of 53 patients with proven hyperparathyroidism and noted that serum-calcium values "well within the normal range are often observed in patients who are subsequently proved to have hyperparathyroidism". In their series the serum-calcium concentration had never exceeded 11·0 mg. per 100 ml. in 1 patient, and in 12 patients the highest value was below 12·0 mg. per 100 ml. McGeown and Morrison also noted fluctuations in the serum-calcium concentration in patients observed over long periods, and in one of their figures they showed data for 3 patients in whom the values fluctuated by 2 mg. per 100 ml. or more

THE THIRD INTERNATIONAL WORKSHOP ON THE MANAGEMENT OF ASYMPTOMATIC PRIMARY HYPERPARATHYROIDISM

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

2008

NORMOCALCEMIC PRIMARY HYPERPARATHYROIDISM

The expert panel stated that because so little is known about this form of the disease, the guidelines for the hypercalcemic form of primary hyperparathyroidism could not be applied with confidence.

Prevalence of Secondary Causes of Bone Loss Among Breast Cancer Patients With Osteopenia and Osteoporosis

Camacho et al. *JCO 26:5380-5385. 2008*

Table 2. Prevalence of Any Secondary Cause of Bone Loss in Both Groups

Category	Non–Breast Cancer Population (n = 174), %	Breast Cancer Population (n = 64), %	Pearson χ^2 test
Celiac disease	2.9	1.6	.567
Chronic renal failure	1.1	1.6	.8
Congestive heart failure	5.2	4.7	.88
Crohn disease	2.3	1.6	.725
Glucocorticoid excess*	8.6	3.1	.144
Idiopathic hypercalciuria†	8.0	15.6	.085
Hypocalciuria	1.7	0	.290
Hypogonadism, surgical and early menopause	1.1	6.3	.026
Primary hyperparathyroidism	1.7	4.7	.196
Normocalcemic hyperparathyroidism‡	5.7	3.1	.412
Hyperthyroidism	2.9	6.3	.226
Immobilization	1.7	0.00	.290
Irritable bowel syndrome	4.6	0.00	.081
Liver disease	2.3	3.1	.718
GnRH usage	0.60	6.3	.007
Malabsorptive syndromes other than the diseases above	17.2	4.7	.013
Organ transplantation	3.4	0.00	.132
Phenytoin use	0.6	0.00	.543
Rheumatic/immune disease	6.3	4.7	.635
Iatrogenic thyrotoxicosis§	1.1	0	.389
Vitamin D deficiency‖	51.1	37.5	.062
With elevated PTH	18.4	21.9	.546
Without elevated PTH	32.8	15.6	.009
Chemotherapy	2.9	35.9	< .001
Aromatase inhibitor usage	0	42.2	< .001
Lymphoma	1.7	3.1	.504
Warfarin usage	1.1	4.7	.091

Secondary Causes of Low Bone Mass in Patients With Breast Cancer: A Need for Greater Vigilance

G. Bruce Mann

JCO 27:3605-3610. 2009

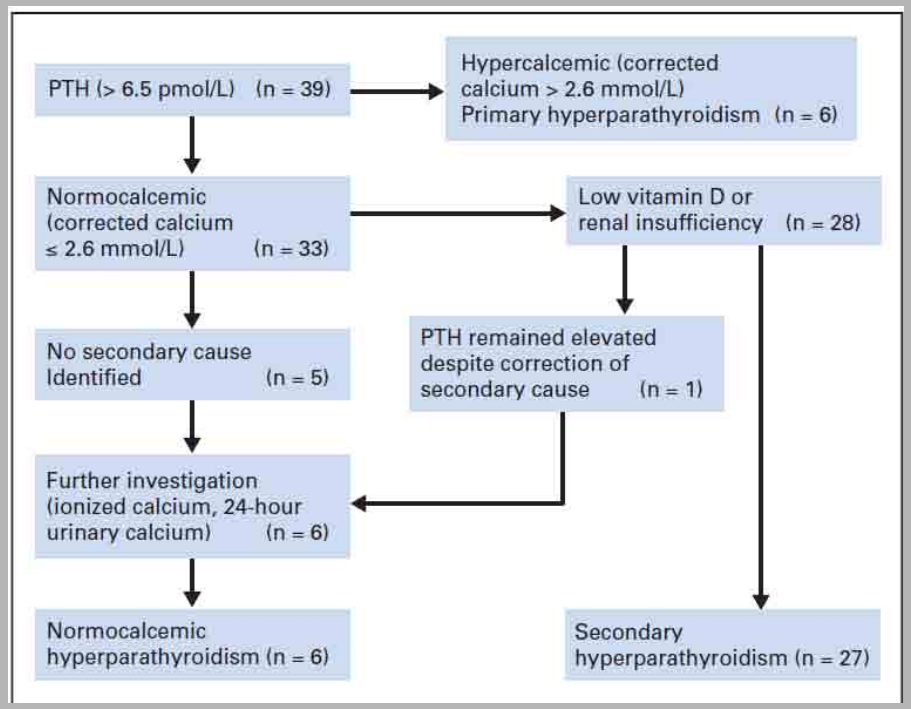


Table 3. Summary of Endocrine Diagnoses

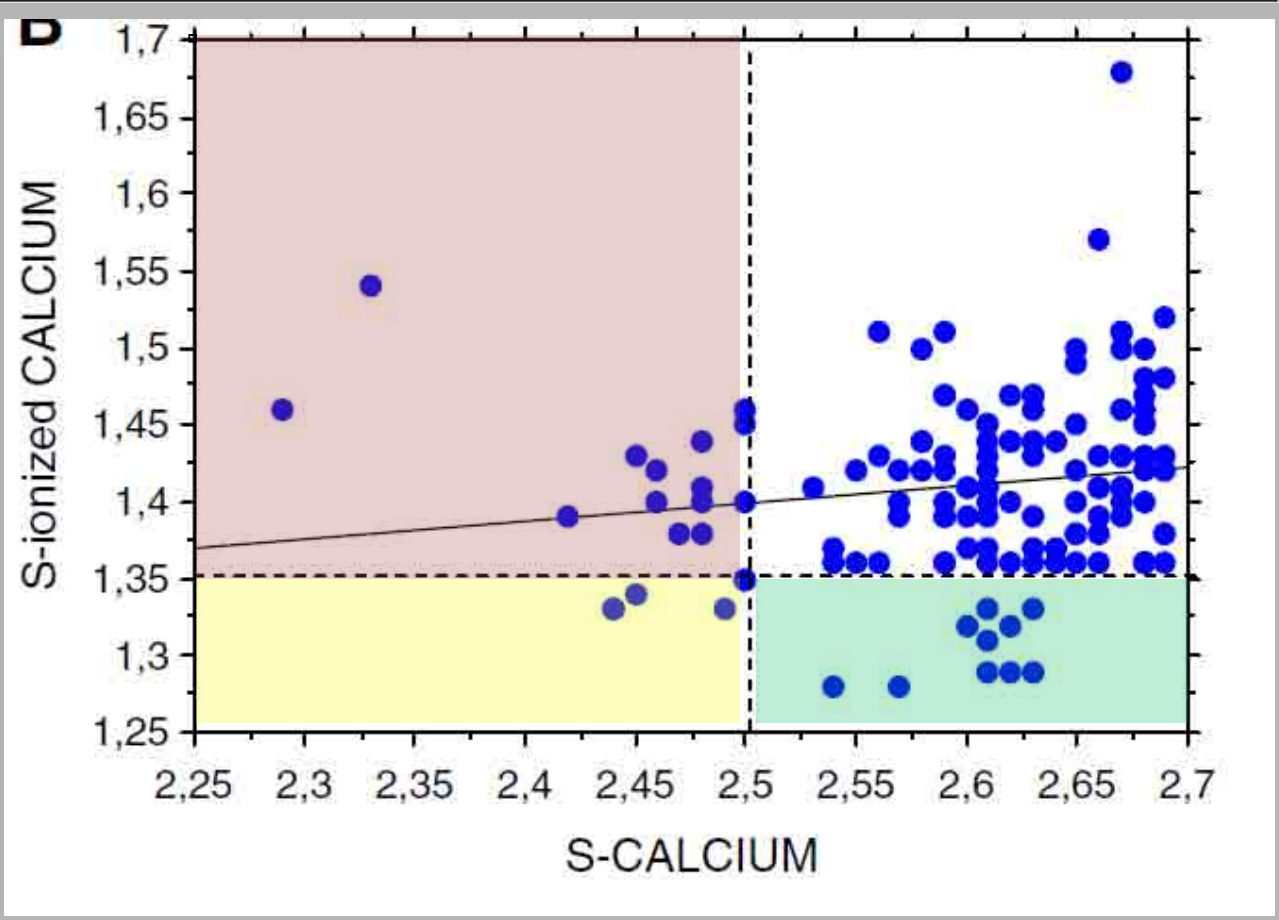
Endocrine Diagnosis	Patient Group by HR Status						*P*
	Total		Positive		Negative		
Parathyroid status							
Normal	156*	80	129*	78	27	90	
All hyperparathyroidism	41	21	38	22	3	10	.10
Primary	8*	4	8*	5	0	0	
Secondary	27	13	25	15	2	7	
Normocalcemic	6	3	5	3	1	3	

Biochemical diagnosis of primary hyperparathyroidism: Analysis of the sensitivity of total and ionized calcium in combination with PTH

Nordenström E et al. *Clin Biochem 44 –2011*

Lab test result preoperatively and diagnostic sensitivity in 436 patients operated on for pHPT.

Lab test result	Calcium[a]	Ionized calcium[b]	Calcium and ionized calcium[c]
Elevated test (n)	417	418	430
Normal test (n)	19	18	6



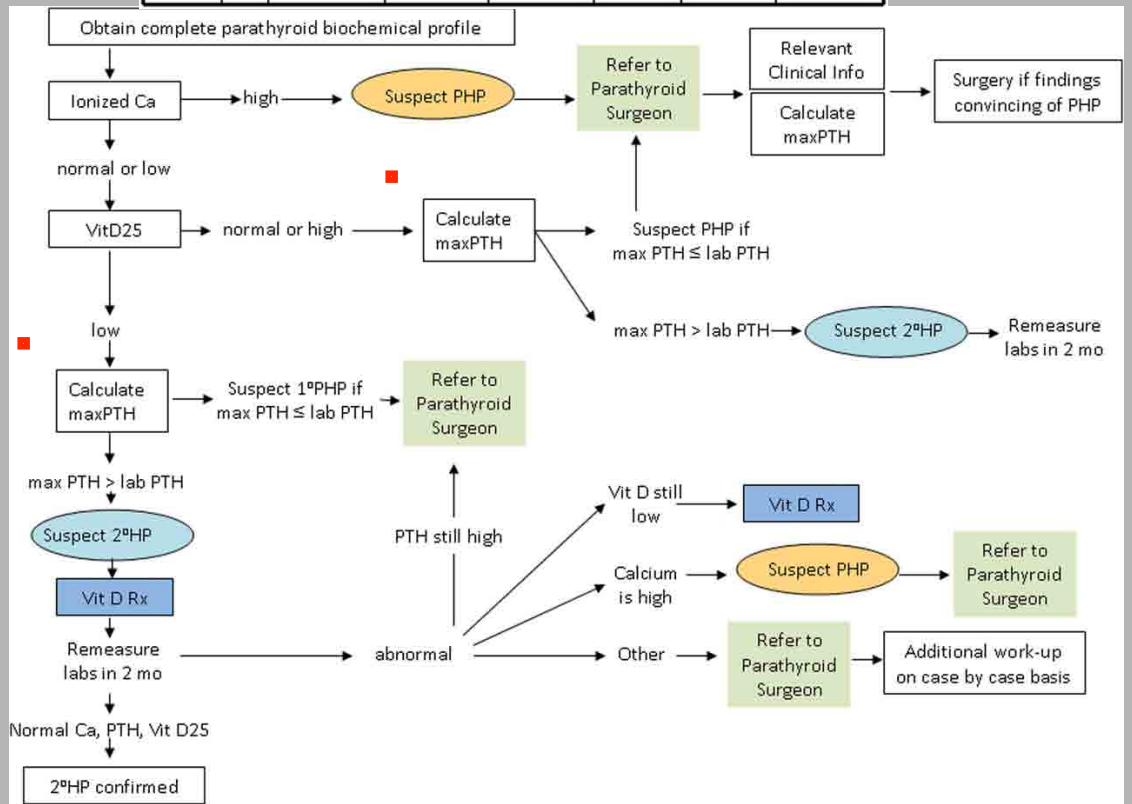
Calculating an individual maxPTH to aid diagnosis of normocalemic primary hyperparathyroidism

Jin J et al.

Surgery 2012;152:1184-92

$$\text{maxPTH} = 120 - (6 \times \text{calcium}) - (\tfrac{1}{2} \times \text{vitD25}) + (\tfrac{1}{4} \times \text{age})$$

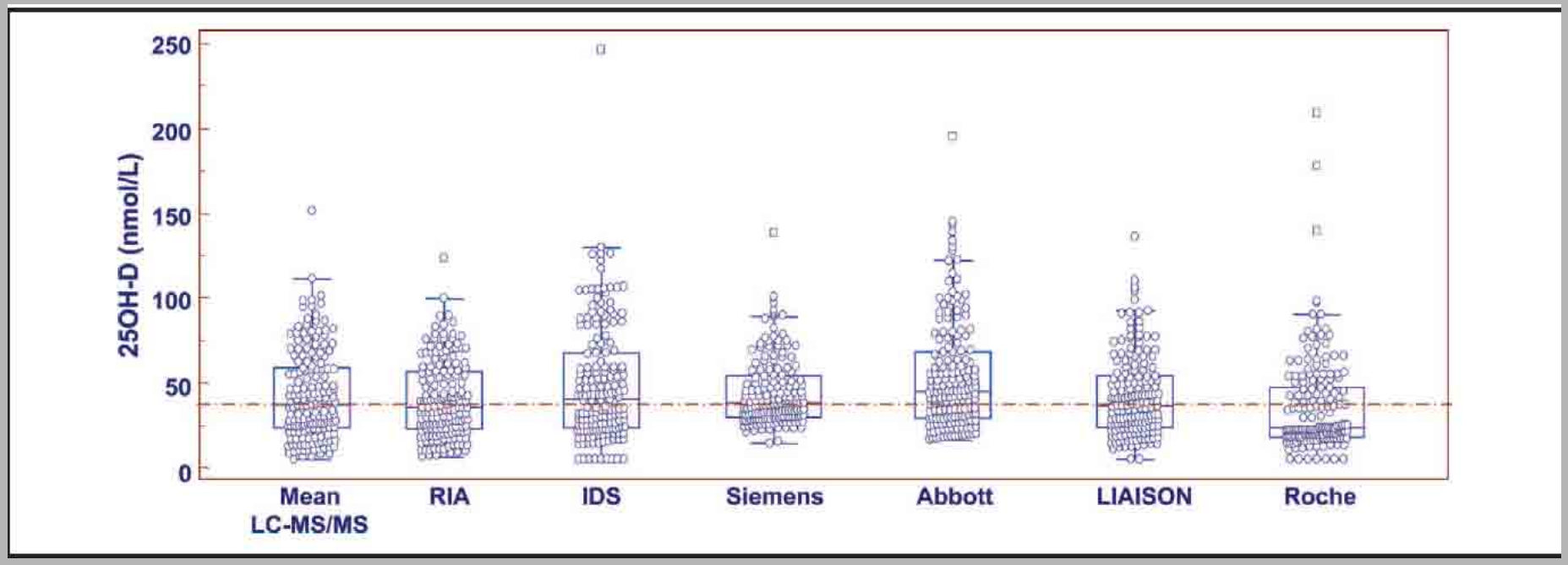
Patient #	Age	Calcium (8.5-10.5 mg/dl)	VitD25 (31-80 ng/ml)	PTH (10-60 pg/ml)	maxPTH	PTH> maxPTH?	Diagnosis
A	57	12.8	40	202	37	Yes	Classic PHP
B	54	10.5	20	89	59	Yes	Classic PHP or borderline NCPHP
C	69	9.9	11	139	72	Yes	NCPHP
D	55	9.7	8	68	72	No	2° HP from VitD25 deficiency
E	76	9.0	16	92	77	Yes	2° HP vs NHPHP



State-of-the-Art Vitamin D Assays: A Comparison of Automated Immunoassays with Liquid Chromatography–Tandem Mass Spectrometry Methods

Farrell CLJ

Clin Chem 58:3 2012)



Automated immunoassays demonstrated variable performance and not all tests met our minimum performance goals. It is important that laboratories be aware of the limitations of their assay.

Normocalcemic Primary Hyperparathyroidism—Characteristics and Clinical Significance of an Emerging Entity

Shlapack,et al. *Am J Med Sci 34; 2, Feb 2012*

TABLE 1. Suggested clinical approach in patients with NPH

Step 1: Laboratory Data: Elevated PTH *and* normal calcium levels

Step 2: Evaluate for possible secondary cause for hyperparathyroidism (renal insufficiency, osteomalacia, vitamin D deficiency, etc.)

Step 3: *Normocalcemic Primary Hyperparathyroidism* confirmed. Evaluate for:

- Low Bone Mass (bone mineral density measurement)
- Nephrolithiasis
- Urinary calcium excretion
- Fractures
- Temporal changes in calcium level over time
- Management interventions, if indicated (see text)

Patients are generally not advised parathyroidectomy unless they have clinical features that have a high probability of being attributable to HPT and not explained by other causes. Calcium and iPTH levels are rechecked 6 months after initial presentation and then annually thereafter

Normocalcemic primary hyperparathyroidism: A newly emerging disease needing therapeutic intervention

Díaz-Soto G et al. *HORMONES 2012, 11(4):390-396*

TABLE 1. Clinical presentation and evolution over time of patients with normocalcemic hyperparathyroidism

Author	Year	Total patients	Median follow-up (years)	25-OHvitD measurement	Patients characteristics at diagnosis	Disease progression at follow-up
Silverberg[1]	2003	22	1	Yes	10 (45.5%) osteoporosis, 1 (4.5%) fragility fracture, 3 (14%) kidney stone	3 (14%) developed hypercalcemia. Others features were not evaluated
Tordjam[17]	2004	32	4	Yes	12 (46%) osteoporosis at lumbar spine and 9 (36%) at hip, 3 (9%) nephrolitiasis	12 underwent surgery. 20 who did not undergo surgery did not develop hypercalcemia/hypercalciuria. Other features were not evaluated
Lowe[18]	2007	37	3	Yes	27 (73%) low BMD, 21 (57%) osteoporosis, 4 (11%) fragility fracture, 5 (14%) nephrolitiasis	7 (19%) developed hypercalcemia, 1 (3%) kidney stone, 1 (3%) fracture, 2 (5%) marked hypercalciuria, 4 (11%) new osteoporosis, 6 (16%) had >10% BMD loss

there are as yet no guidelines for the management of NCHPT and it is unknown if therapeutic intervention aimed to normalize PTH may have any true benefits in the short and long term in these patients.

Normocalcemic primary hyperparathyroidism in clinical practice: an indolent condition or a silent threat?

Fontenele Marques T et al. *Arq Bras Endocrinol Metab. 2011;55/5*

14/156 pts with NHPT (8.9%)

Table 1. Baseline characteristics and biochemical data of patients with and without NPHPT

	HPTN	Without HPTN	p
Age (years)	60.6 ± 14.8	62.4 ± 10.5	0.664
Time since menopause (years)	13.8 ± 13.6	14.6 ± 10.4	0.777
BMI (kg/m^2)	25.0 ± 3.1	25.6 ± 3.6	0.559
PTH (pg/mL)	109.5 ± 45.2	39.1 ± 14.3	< 0.001
Serum calcium (mg/dL)	9.4 ± 0.4	9.5 ± 0.4	0.765
CTX (pg/mL)	328.7 ± 142.2	342.0 ± 230.0	0.759
25 (OH) vitamin D (pg/mL)	41.5 ± 10.3	29.5 ± 16.0	< 0.001
BMD lumbar spine (g/cm^2)	0.97 ± 0.2	1.0 ± 0.1	0.511
BMD femoral neck (g/cm^2)	0.74 ± 0.1	0.78 ± 0.1	0.236

5/14 (35.7%).OP at DEXA
4/14 % (28.6%) Stone Disease

NPHPT has a diverse phenotypic presentation, implying that this may not be an “indolent” disease

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

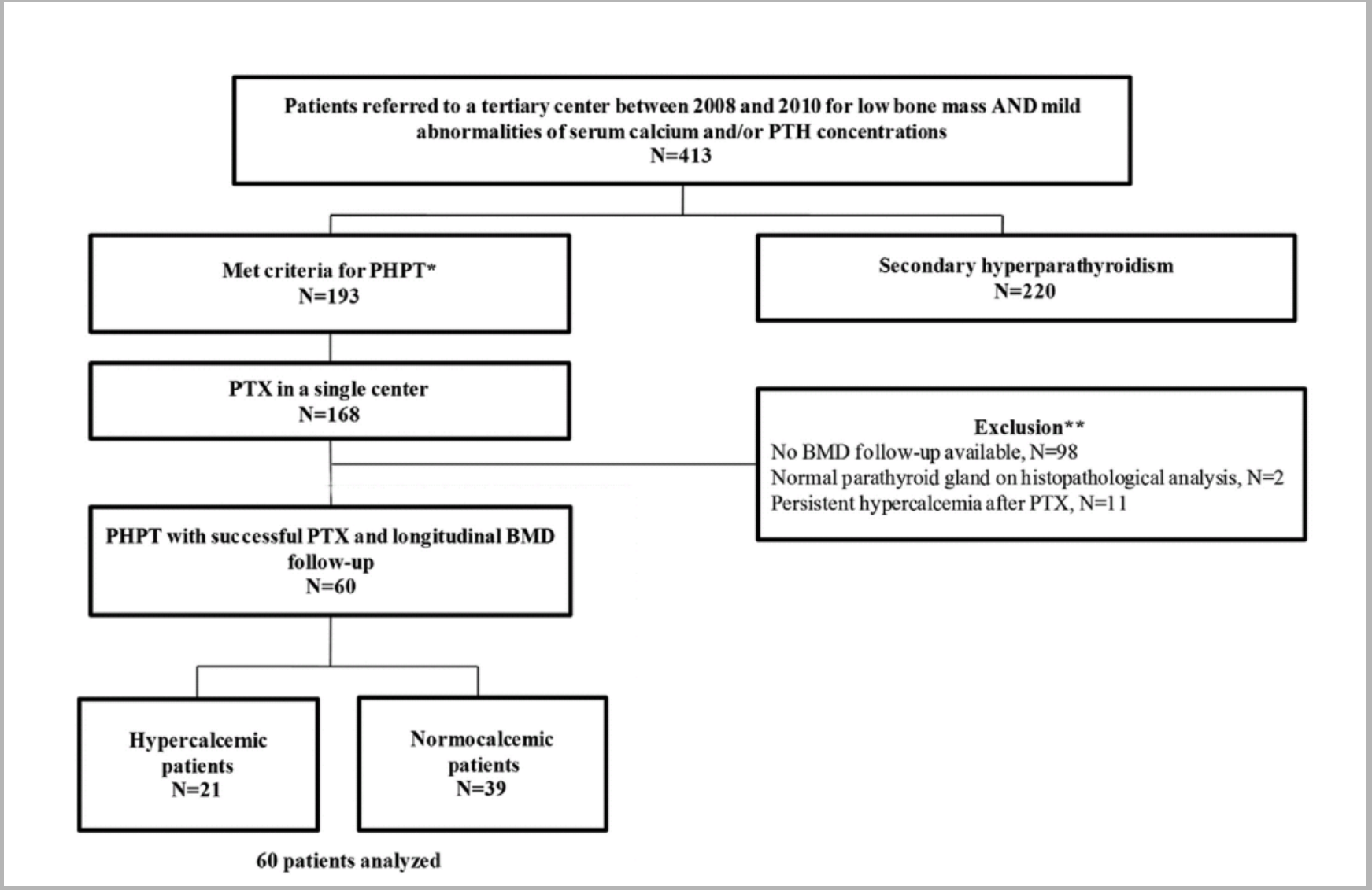
Variable	Normocalcemic		Hypercalcemic		Group total		*P* value
	N	%	N	%	N	%	
Total	33	100,0	37	100,0	70	100,0	
(i) Fracture							
Yes	5 1M/4F	15.2	4 0M/4F	10.8	9	12.9	$P^{(1)} = 0.726$
(ii) Kidney Stones							
Yes	6 0M/6F	18.2	7 3M/4F	18.9	13	18.6	$P^{(2)} = 0.937$

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)*



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

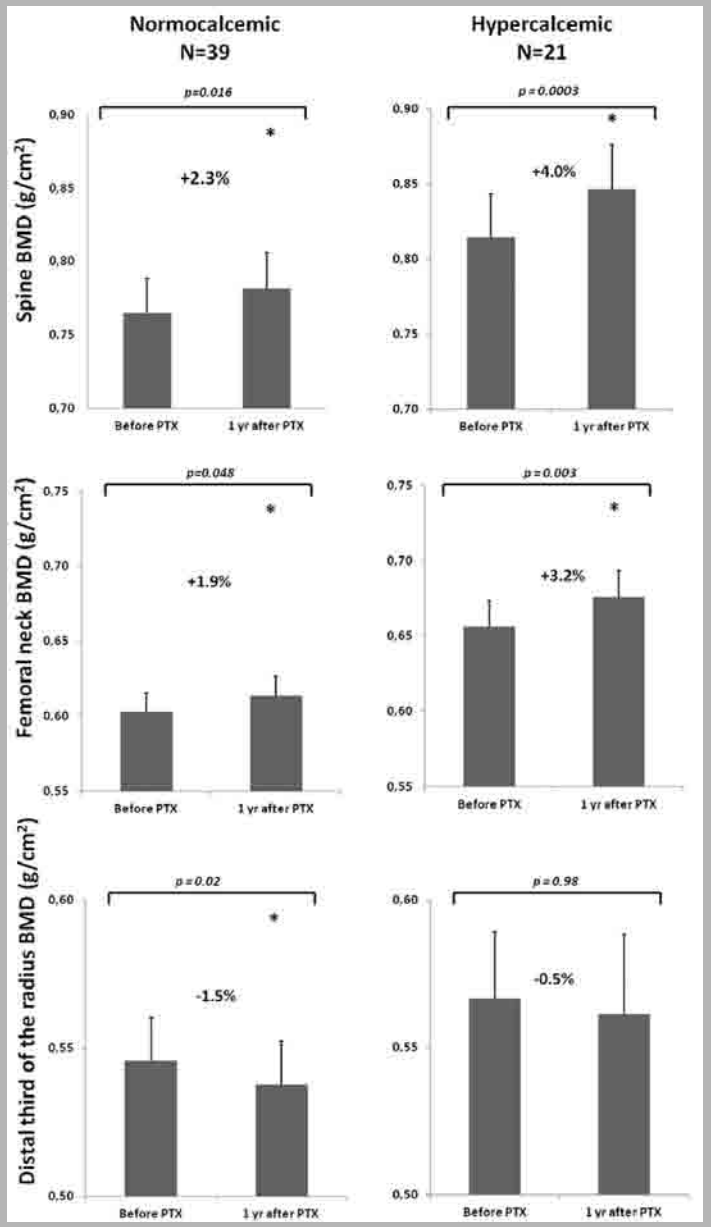
Koumakis et al., *JCEM, Aug 2013, 98(8)*

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.

Primary Hyperparathyroidism Revisited in Menopausal Women with Serum Calcium in the Upper Normal Range at Population-based Screening 8 Years Ago

Lundgren et al.

World J. Surg. (2002) 26

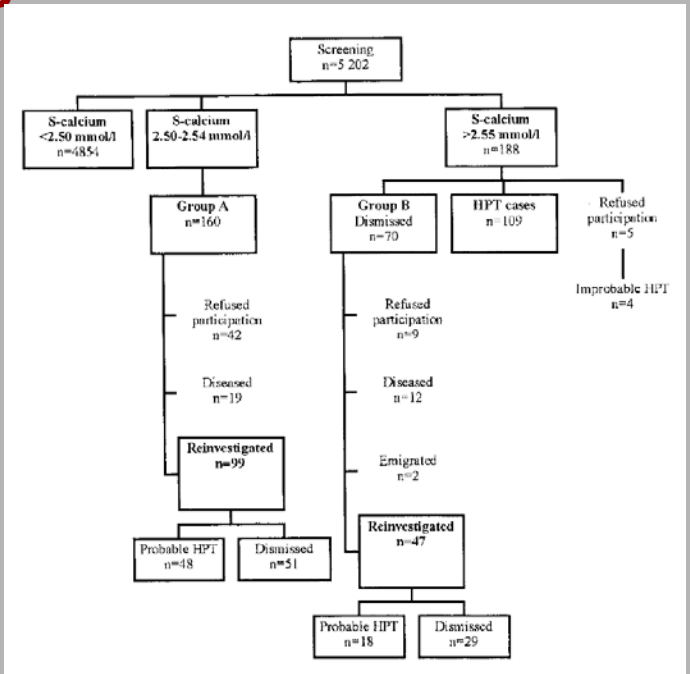


Table 1. Variables for presently examined women in groups A and B at screening and follow-up 8 years later.

Characteristic	All	At screening		At 8-year follow-up	
		Present material	pHPT in present material	Present material	pHPT in present material
Group A					
No.	160	99	48	99	48
Age (years)	67.2 ± 5.6	66.6 ± 5.4	66.9 ± 5.1	75.6 ± 5.4	75.9 ± 5.1
Total s-calcium (mmol/L)	2.52 ± 0.01	2.52 ± 0.01	2.52 ± 0.01	2.56 ± 0.10*	2.59 ± 0.08**
Intact s-PTH[a] (ng/L)	ND	ND	ND	40.0 ± 21.9	54.0 ± 23.7
s-Creatinine[a] (μmol/L)	ND	ND	ND	87.0 ± 18.4	86.0 ± 15.1
Group B					
No.	70	47	18	47	18
Age (years)	65.6 ± 5.2	64.8 ± 4.9	65.6 ± 5.2	73.7 ± 5.1	74.6 ± 5.2
Total s-calcium (mmol/L)	2.59 ± 0.07	2.62 ± 0.07	2.60 ± 0.11	2.57 ± 0.10*	2.62 ± 0.09
Intact s-PTH (ng/L)	31.0 ± 9.6[b]	31.0 ± 10.0[b]	36.0 ± 10.4[b]	32.0 ± 13.0	41.0 ± 10.6
s-Creatinine (μmol/L)	86.0 ± 12.2[b]	84.0 ± 12.7[b]	85.0 ± 10.9[b]	88.0 ± 19.2	84.0 ± 19.4

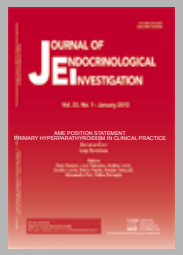
A summary of the new phenomenon of normocalcemic hyperparathyroidism and appropriate management

Carneiro-Plaa D and Solorzanob C

Curr Op Onc 24-1 2012

Indications for parathyroidectomy in patients with NCHPT are not standardized and patients should be evaluated on an individual basis taking into consideration the higher incidence of multiglandular disease and the potential lower success rates in the surgical treatment of this condition.

The presence of an enlarged parathyroid gland on a preoperative localization study might help in deciding toward parathyroidectomy as opposed to observation in these patients. Localization studies in this disease also suffer from inaccuracies, therefore, the diagnosis should always be established clinically and biochemically.



AME recommendations

We suggest that subjects with NCPHPT should be monitored regularly for progression of their disease, referring them to surgery in case of worsening

Curr Op Onc 24-1 2012

Indications for PTX in patients with NCHPT are not standardized and pts should be evaluated on an individual basis taking into consideration the higher incidence of multiglandular disease and the potential lower success rates in the surgical treatment of this condition.

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ARQUIVOS BRASILEIROS DE ENDOCRINOLOGIA & METABOLOGIA
BRAZILIAN ARCHIVES OF ENDOCRINOLOGY AND METABOLISM

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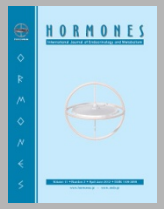
Journal of Osteoporosis



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