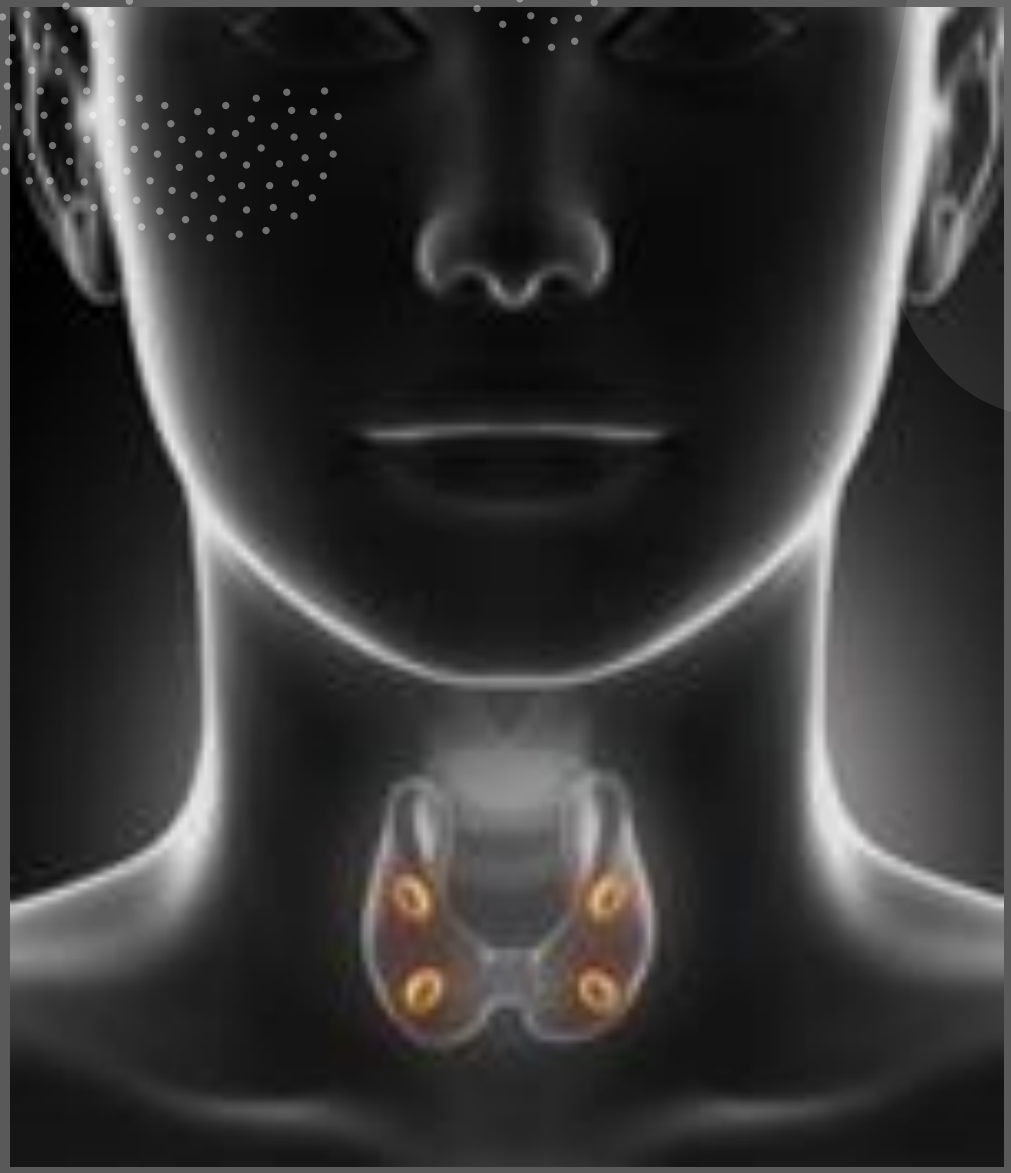
Οδηγίες διάγνωσης και αντιμετώπισης πρωτοπαθούς υπερπαραθυρεοειδισμού



Ζωή Α. Ευσταθιάδου, MD, PhD

Διευθύντρια ΕΣΥ

Ενδοκρινολογικό Τμήμα

«Ιπποκράτειο» ΓΝ Θεσσαλονίκης

ΕΕΜΜΟ: Βιβλιογραφική ενημέρωση

Ιωάννινα 2023

REVIEW

JBMR®

Evaluation and Management of Primary Hyperparathyroidism: Summary Statement and Guidelines from the Fifth International Workshop

John P. Bilezikian,[1] Aliya A. Khan,[2] Shonni J. Silverberg,[1] Ghada El-Hajj Fuleihan,[3] Claudio Marcocci,[4] Salvatore Minisola,[5] Nancy Perrier,[6] Antonio Sitges-Serra,[7] Rajesh V. Thakker,[8] Gordon Guyatt,[9] Michael Mannstadt,[10] John T. Potts,[10] Bart L. Clarke,[11] and Maria Luisa Brandi,[12] On behalf of the International Workshop on Primary Hyperparathyroidism

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[11]Mayo Clinic Division of Endocrinology, Diabetes, Metabolism, and Nutrition, Mayo Clinic, Rochester, MN, USA
[12]Fondazione Italiana sulla Ricerca sulle Malattie dell'Osso (F.I.R.M.O. Foundation), Florence, Italy

- *Minisola S. Arnold A. Belaya Z. et al. Epidemiology, pathophysiology and genetics of primary hyperparathyroidism. J Bone Miner Res. 2022;37(11):2315-2329.*
- *El-Hajj Fuleihan G. Chakhtoura M. Cipriani C. et al. Classical and nonclassical manifestations of primary hyperparathyroidism. J Bone Miner Res. 2022;37(11):2330-2350.*
- *Ye Z. Silverberg SJ. Sreekanta A. et al. The efficacy and safety of medical and surgical therapy in patients with primary hyperparathyroidism: a systematic review and meta-analysis of randomized controlled trials. J Bone Miner Res. 2022;37(11):2351-2372.*
- *Perrier N. Lang B. Yeh MW. et al. Surgical aspects of primary hyperparathyroidism. J Bone Miner Res. 2022;37(11):2373-2390.*
- *Bilezikian JP. Silverberg SJ. Bandeira F. et al. Management of primary hyperparathyroidism. J Bone Miner Res. 2022;37(11):2391-2403.*
- *Yao L. Guyatt G. Ye K. et al. Methodology for the guidelines on evaluation and management of hypoparathyroidism and primary hyperparathyroidism. J Bone Miner Res. 2022;37(11):2404-2410.*

Ενημέρωση των δεδομένων

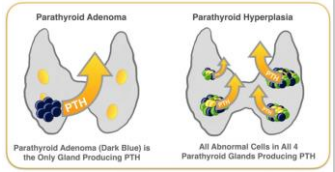
- ✓ Διάγνωση και διαφορική διάγνωση
- ✓ Επιδημιολογία
- ✓ Γενετική
- ✓ Φυσιολογία & παθοφυσιολογία
- ✓ Κλινικές εκδηλώσεις
- ✓ Βιοχημική εικόνα
- ✓ Εκτίμηση κλασσικών εκδηλώσεων
- ✓ Εκτίμηση μη-κλασσικών εκδηλώσεων
- ✓ Χειρουργική θεραπεία
- ✓ Φαρμακευτική θεραπεία
- ✓ PHPT και εγκυμοσύνη

Πρωτοπαθής υπερπαραθυρεοειδισμός

Ορισμός

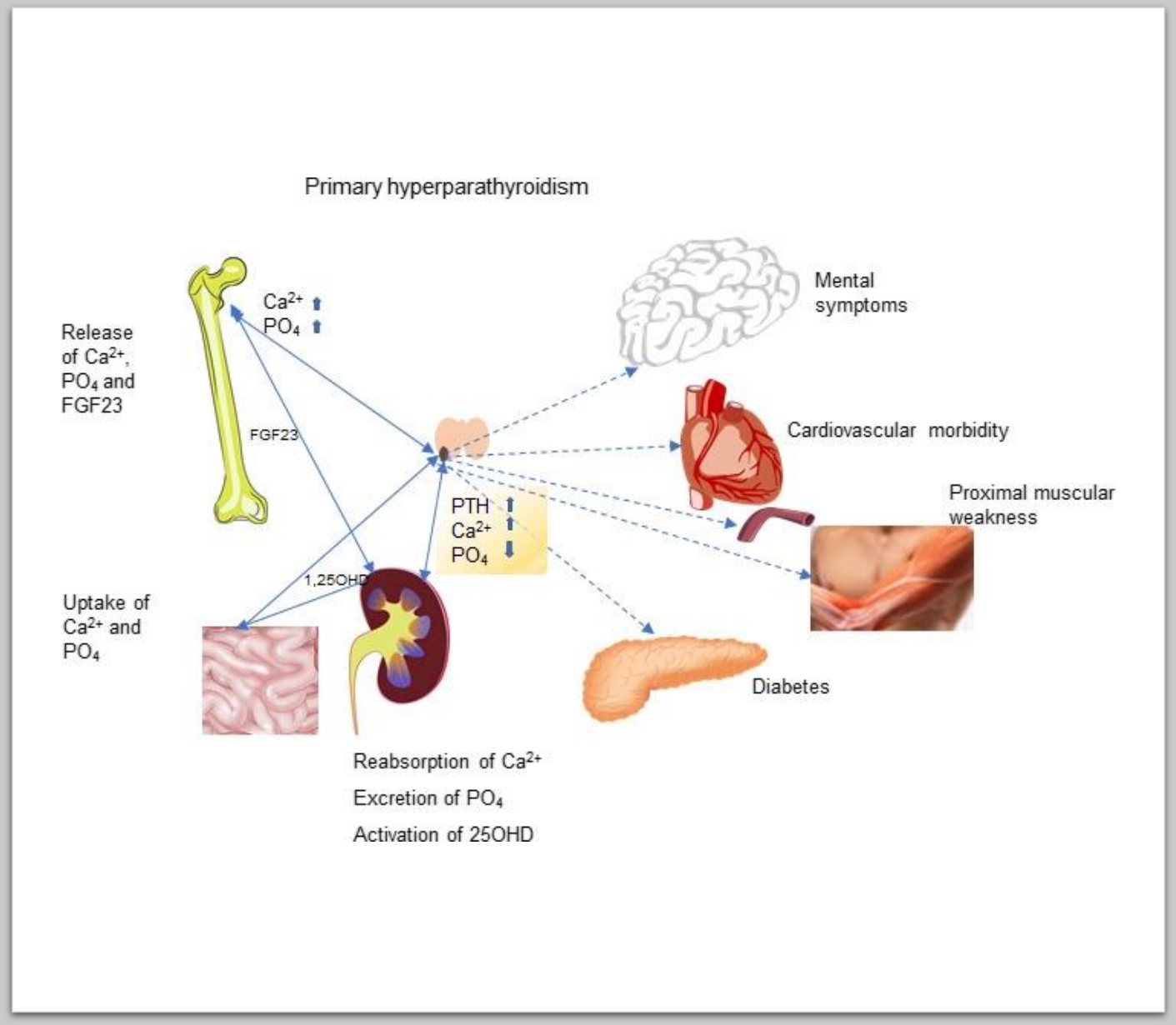
Σποραδική ή οικογενής διαταραχή που χαρακτηρίζεται από ανεπαρκώς ρυθμιζόμενη, χρόνια, υπερβολική έκκριση παραθορμόνης, από έναν ή περισσότερους παραθυρεοειδείς αδένες.

Ιστοπαθολογικοί τύποι



- **Single benign adenoma including atypical (85%)**
- **Multiple gland involvement (15%)**
- **Cancer (< 1%)**

Bilezikian JP. JCEM. 2018;
Cetani et al. . Front HormRes. 2019;
Cetani et al. Endocr Relat Cancer. 2019



Διάγνωση

Hypercalcemic PHPT	Normocalcemic NPHPT
↑ Ca (total)	= Ca (total) και Ca^{++}
↑/= PTH	↑ PTH
2 μετρήσεις	2 μετρήσεις
>2 εβδομάδες	> 3-6 μήνες
ΔΔ υπερασβεστιαιμίας	Αποκλεισμός β'παθούς HPT

Διαφορική Διάγνωση

- **Familial Hypocalciuric Hypercalcemia (FHH)**
  - Εμφάνιση σε νεότερα άτομα (<30 ετών)
  - Λόγος Ca/Creatinine clearance <0.01
  - Οικογενειακό ιστορικό υπερασβεστιαιμίας
- **Thiazide diuretics and lithium**
- **Ectopic secretion of PTH (very rare)**

Αίτια δευτεροπαθούς HPT

- Vitamin D deficiency (25 OH D < 30 ng/mL)
- Renal insufficiency (eGFR < 60 mL/min)
- Medications (Thiazide diuretics, Lithium)
- Hypercalciuria
- Malabsorption
- Other metabolic bone diseases that could be associated with elevated PTH (e.g., Paget's disease)

Ομάδες εργασίας 5ου Διεθνούς workshop

- Επιδημιολογία, Παθοφυσιολογία και Γενετική
- Κλασσικές και μη κλασσικές εκδηλώσεις
- Χειρουργικές πτυχές
- Εκτίμηση και αντιμετώπιση

- ✓Διάγνωση και διαφορική διάγνωση
- ✓Επιδημιολογία
- ✓Γενετική
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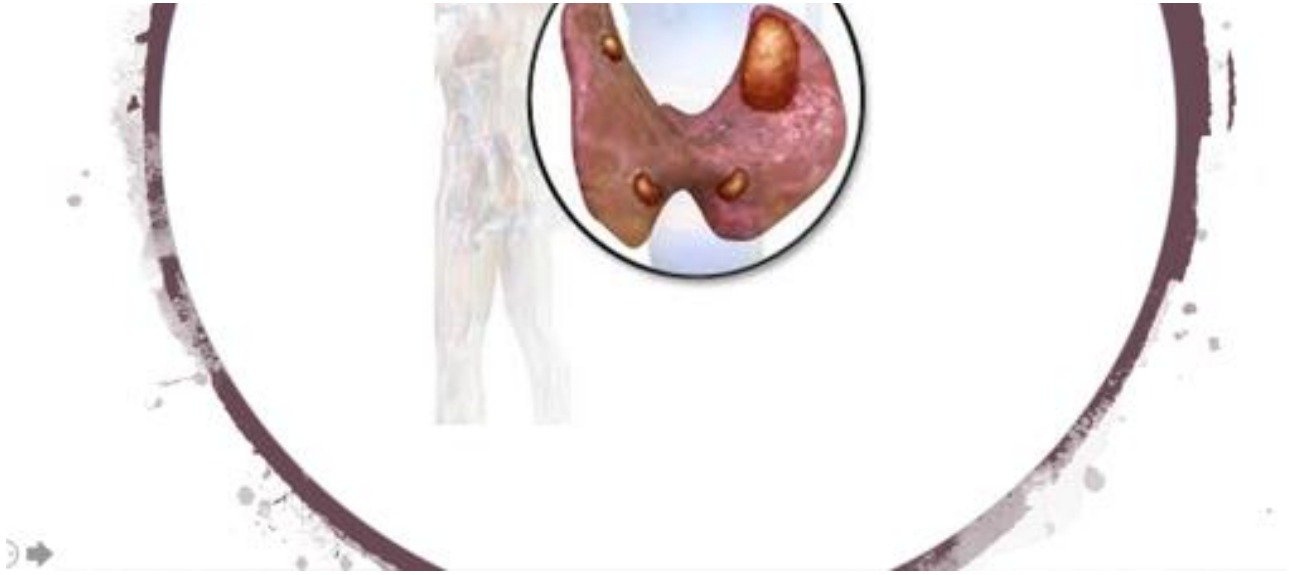
- Εκτίμηση και αντιμετώπιση

REVIEW

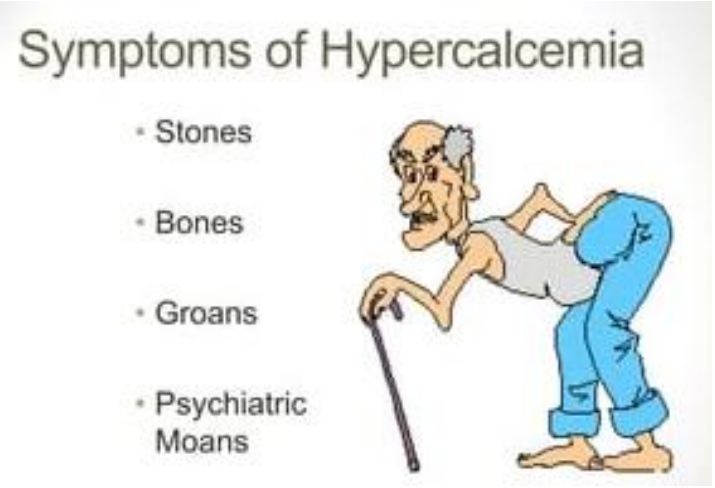
JBMR®

Epidemiology, Pathophysiology, and Genetics of Primary Hyperparathyroidism

Salvatore Minisola,[1] Andrew Arnold,[2] Zhanna Belaya,[3] Maria Luisa Brandi,[4] Bart L. Clarke,[5] Fadil M. Hannan,[6,7] Lorenz C. Hofbauer,[8] Karl L. Insogna,[9] André Lacroix,[10] Uri Liberman,[11] Andrea Palermo,[12] Jessica Pepe,[1] René Rizzoli,[13] Robert Wermers,[14] and Rajesh V. Thakker[6,15]

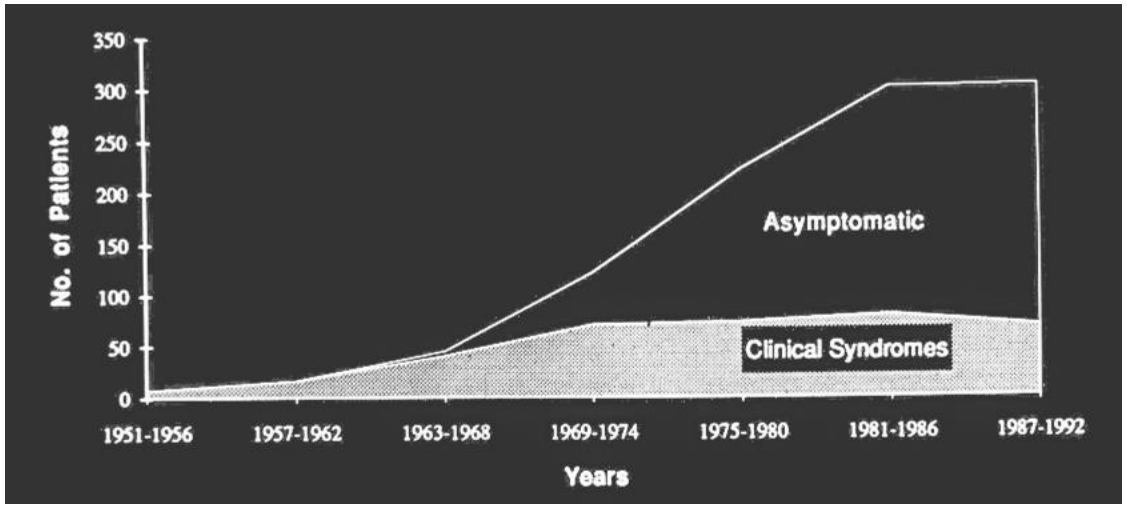


Επιδημιολογία



Αλλαγή της αναλογίας των ασυμπτωματικών ασθενών με υπερπαραθυρεοειδισμό ανά 6ετία

Η βιοχημική ανίχνευση οδηγεί σε αύξηση της επίπτωσης, όπου και όποτε υιοθετείται.



Επίπτωση και επιπολασμός PHPT στον κόσμο

Η συχνότητα στις γυναίκες είναι Χ 3-5 φορές υψηλότερη από ότι στους άνδρες

Area	Incidence per 100,000 person-years	Prevalence per 100,000 people	
USA	48.3–50.4	Women	233
		Men	85
		Black women, 70–79 years old	1409
		White women, 70–79 years old	1110
Spain	Unspecified type of hyperparathyroidism		
Women	40.3		
Men	13.7		
Denmark	16		
Scandinavian countries		Observational studies in perimenopausal and postmenopausal women	2000–5000
Sweden		Men	730
Czech Republic	24		
Serbia		General population	300
China		Middle-aged and elderly	200
South Africa (hospital inpatients)	78		

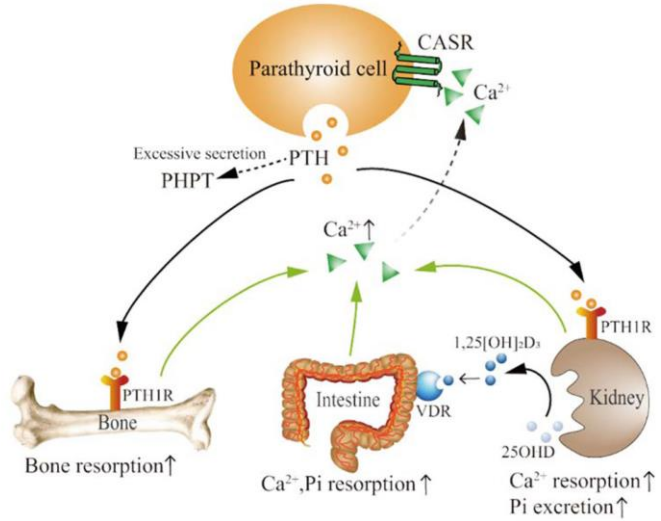
Minisola et al. J Bone Miner Res 2022;37(11):2315-2329

Παθοφυσιολογία PHPT

Table 2. PTH Actions and Their Pathophysiology

Target organ	PTH cell target	PTH-regulated function	Pathophysiological changes	Clinical implications
Kidney	Distal tubule	Calcium reabsorption	Hypercalcemia (with contributions from gut and bone)	Hypercalcemic syndrome Increased mortality
	Proximal and distal tubules	Phosphate reabsorption	Hypophosphatemia	Fatigue/muscle weakness
	Distal tubule	Bicarbonate reabsorption	Hyperchloremic acidosis	Nephrocalcinosis
	Proximal tubule	1-Alpha hydroxylase	Hypercalciuria (indirectly)	Renal stones
Gut	Proximal and distal intestine	Indirect through 1,25OH2D-dependent Increased calcium intestinal absorption	Hypercalciuria	Renal stones
Bone	Osteoblast	Bone turnover	High bone turnover Bone loss	Fracture
Cardiovascular system	Cardiomyocyte	Hypercalcemia-dependent	Arrythmias	Possible increase in mortality
		Interaction with RAAS	Left ventricular hypertrophy Heart failure Soft tissue calcification	Heart failure
	Cardiac valves	Hypercalcemia-dependent	Soft tissue calcification	
	Smooth muscle cells	Vasodilatation	Decreased blood pressure	Decreased blood pressure
		Interaction with RAAS	Hypertension* Soft tissue calcification	Hypertension
Central nervous system		Hypercalcemia	Apoptosis*	
	Axons	Cross-reactivity with PTH2R	Stress response, anxiety*	
Skeletal muscle	Myotube		Muscle weakness	
Dermis	Fibroblasts/hair follicles	Possible role hair growth/ differentiation	None known in nongenetic forms of PHPT	No known

*Possible.



Μονοκλωνική –συχνότερα- αύξηση παραθυρεοειδικού ιστού με υπερέκκριση PTH

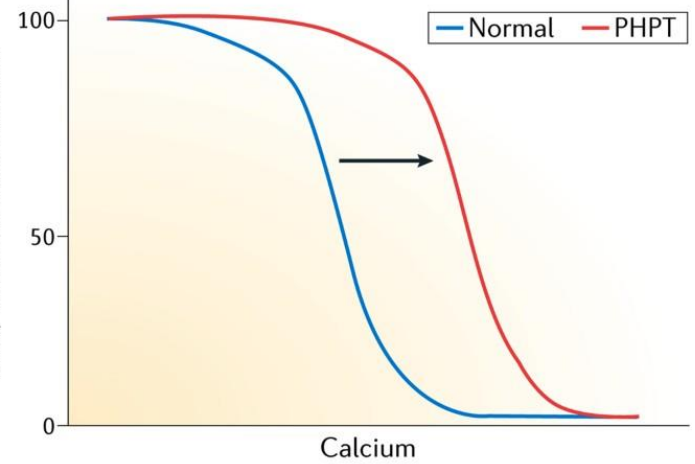
+

Μειωμένη έκφραση CaSR

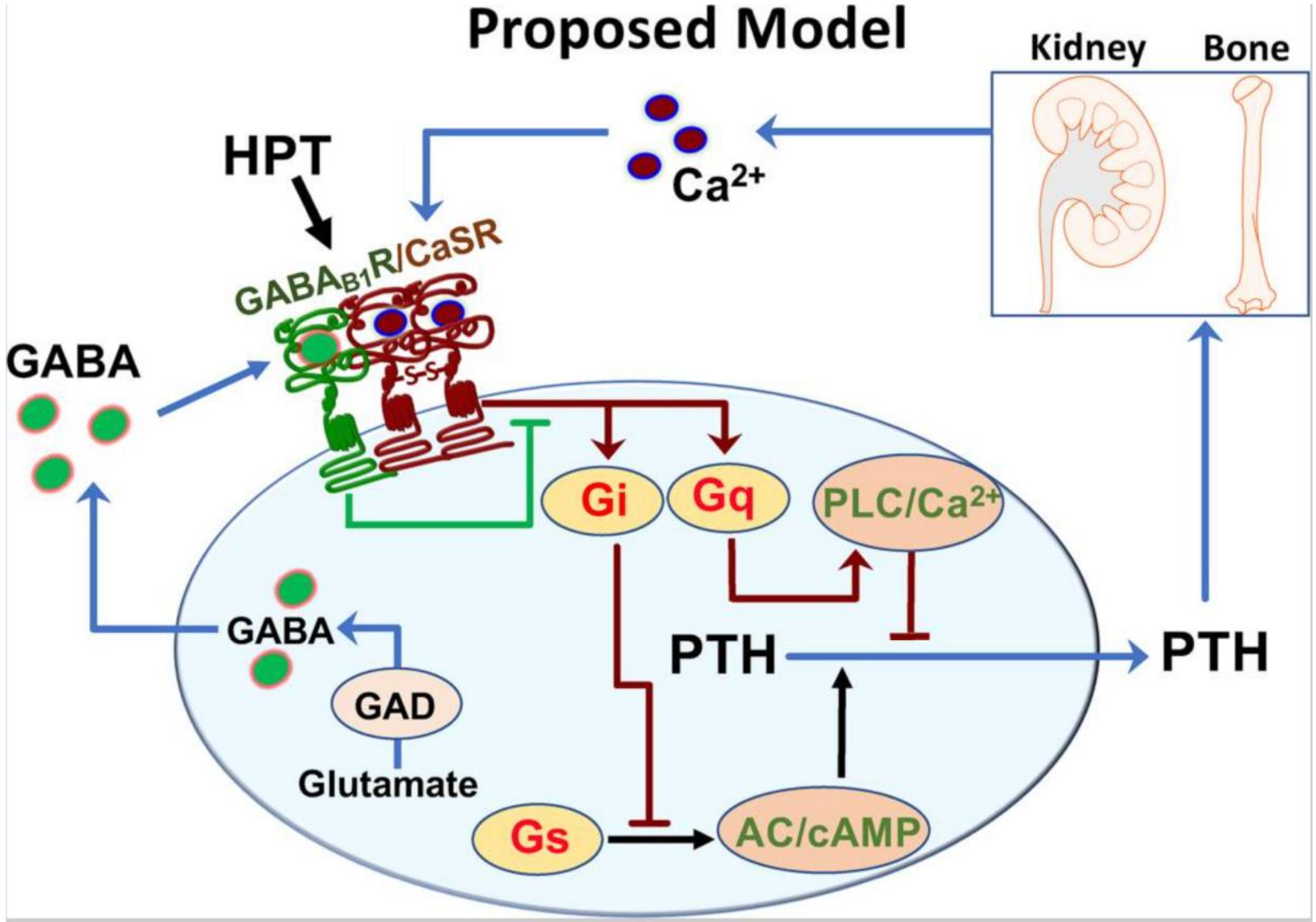
↓

Παθοφυσιολογικές συνέπειες

- Μει
- Αύξ
- Αύξ ασβ
- Μει φω
- Αύξ



Minisola et al. J Bone Miner Res 2022;37(11):2315-2329



Chang et al. Nat Metab 2020; 2(3):243-255

Γενετική του PHPT

- Το 10% των περιστατικών φέρει μετάλλαξη σε ένα από τα 10 περιγραφέντα γονίδια
- Δεν απαιτείται γενετικός έλεγχος για τη διάγνωση του PHPT
- Ο γενετικός έλεγχος πιθανά χρήσιμος σε:
  - **Hyperparathyroidism – jaw tumor syndrome**
  - **MEN 1 και MEN 2A**
  - **Επί υποψίας FHH**
- Συνιστάται σε
  - Ηλικία <30 έτη
  - Πολυαδενική νόσο (από ιστορικό ή απεικόνιση)
  - Θετικό οικογενειακό ιστορικό
  - Atypical adenoma ή καρκίνωμα

Table 3. Familial Primary Hyperparathyroidism—Major Genetic Basis and Key Features

Clinical diagnosis	Major gene/ protein	Distinguishing aspects of hyperparathyroidism	Additional features/considerations
FHH		Autosomal dominant	Low CCCR
FHH1	*CASR*/CaSR[a]	Lifelong hypercalcemia (otherwise rare in first decade of life in other syndromes)	Often increased serum Mg
FHH2	*GNA11*/Gα11	PTH levels inappropriately normal or mildly elevated	No increase in nephrocalcinosis or stones
FHH3	*AP2S1*/adaptor-protein 2 σ-subunit	Calcium-PTH setpoint curve shifted to right = decreased sensitivity of PTH release to suppression by ambient calcium Normal or mildly hypercellular parathyroid glands Persistent hypercalcemia after subtotal PTX. PTX to be generally avoided Rare individuals/kindreds with *CASR* mutation have phenotype on spectrum to typical sporadic PHPT, can include hypercalciuria and benefit from PTX	Normal bone mass No or minimal symptoms of hypercalcemia suggesting decreased sensitivity in other tissues expressing CASR eg, brain, GI tract Antibodies against CaSR can give similar picture, but usually with other autoimmune features and nonfamilial Heterozygosity for the defective CASR, GNA11, or AP2S1 allele
NSHPT	*CASR*/CaSR	Autosomal recessive or dominant Severe hypercalcemia begins at birth; very high PTH levels Parathyroid glands all exceedingly large, hypercellular Requires urgent total PTX	Fractures, hypotonia, respiratory distress; neurodevelopmental impairment if survives without early treatment Low CCCR Compound heterozygosity or homozygosity for inactive CASR alleles - parental consanguinity as one cause of latter
MEN1	*MEN1*/menin CDK inhibitor genes (other than *CDKN1B*) in rare families: *CDKN1A*, *CDKN2B*, *CDKN2C*/p21, p15, p18	Autosomal dominant Multigland parathyroid disease; gland size asymmetry but all glands hypercellular; avoid minimally invasive PTX Onset often in second/third decade	Enteropancreatic endocrine tumors with malignant potential are main life-threatening feature; also tumors of anterior pituitary, adrenal, skin, and bronchial/thymic carcinoids, lipomas, others
MEN4	*CDKN1B*/p27	High recurrence rate years after successful subtotal PTX Thymus as common location for pathologic parathyroid tissue upon recurrence of HPT; thymectomy advised on initial PTX	
MEN2A	*RET*	Autosomal dominant Generally mild multigland disease, less likely to recur after subtotal PTX than in MEN1	Medullary thyroid carcinoma Pheochromocytoma RET DNA testing enables lifesaving prophylactic thyroidectomy
HPT-JT	*CDC73* (*HRPT2*)	Autosomal dominant Hypercalcemia at times in first decade, usually later All glands at risk of neoplasia, which may develop asynchronously Mostly benign adenomas and atypical adenomas, with marked increased risk of parathyroid cancer (15%) Evidence for evolution from benign to malignant neoplasia At times cystic or microcystic histopathology Tumors may grow rapidly Germline mutations in subset of patients with sporadic parathyroid carcinoma Close surveillance of normocalcemic mutation-positive carriers to enable early curative surgery Reports of poorly functioning parathyroid carcinomas Bilateral exploration advised for PTX: resection of abnormal glands; avoid prophylactic total PTX	Benign ossifying fibromas of mandible and maxilla, renal cysts, uterine tumors
FIHP	*CASR*, *MEN1*, or *CDC73* in 30% Additional causes/ contributors pending investigation/ confirmation[b]	Genetic heterogeneity, different modes of inheritance, different patterns of parathyroid pathology	No other clinical features (as per definition) Emergence of a syndromic feature redefines patient/kindred out of this category

Ομάδες εργασίας 5ου Διεθνούς workshop

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- Εκτίμηση και αντιμετώπιση

Κλινική εικόνα

Τρεις φαινότυποι

- **Symptomatic PHPT**
  - Skeletal complications
    - Osteitis fibrosa cystica
    - Fractures
  - Renal complications
    - Chronic kidney disease
    - Nephrolithiasis
    - Nephrocalcinosis
- **Normocalcemic PHPT**
  - Symptomatic
  - Asymptomatic with or without target organ involvement
- **Asymptomatic PHPT**
  - with target organ involvement
  - without target organ involvement

El-Hajj Fuleihan et al. JBMR 2022; 37(11):2330

Εκτίμηση ασθενών με PHPT

Βιοχημικός έλεγχος

- **25OH Vit D**
- **Creatinine clerarance or eGFR**
- **24h urine calcium (preferred)**
- **Phosphate**
- **Bone turnover markers (not generally recommended)**

Hypercalcemia (albumin corrected calcium)

- **Mild hypercalcemia**
  - 10.4-11.4 mg/dL
- **Moderate**
  - 11.4-14 mg/dL
- **Severe**
  - >14 mg/dL

Εκτίμηση ασθενών με PHPT

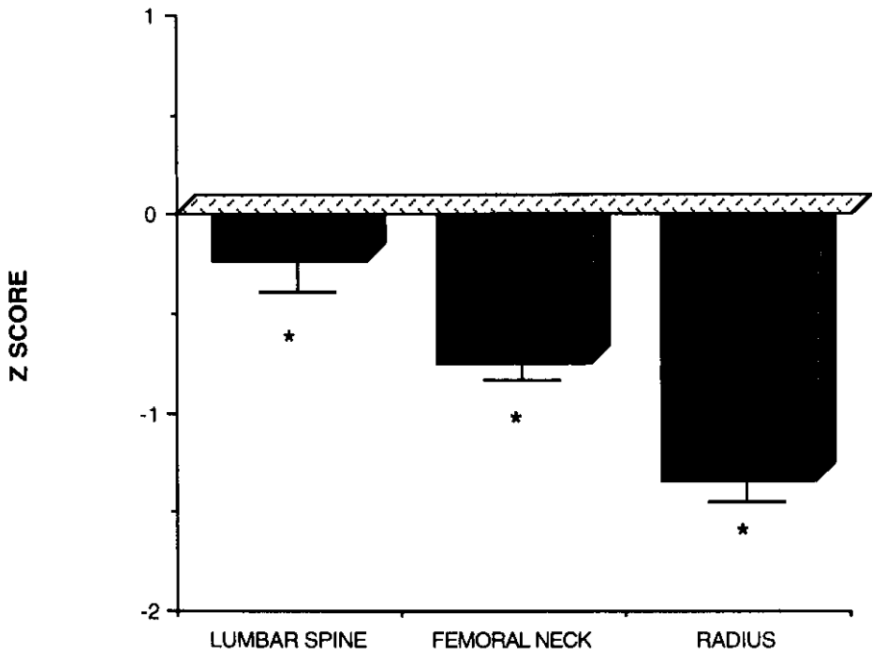
Οστικός έλεγχος

- **DEXA**
  - ΟΜΣΣ
  - Ισχίο
  - Αποκακρυσμένο 1/3 κερκίδας
- **Απεικόνιση σπονδύλων**
  - Α/α ΟΜΣΣ-ΘΜΣΣ ή VFA
  - TBS, εφόσον είναι διαθέσιμο

Morphometric Vertebral Fractures in Postmenopausal Women with PHPT

Εκτίμηση σκελετού

N=66pts without PTX f/up for 7ys



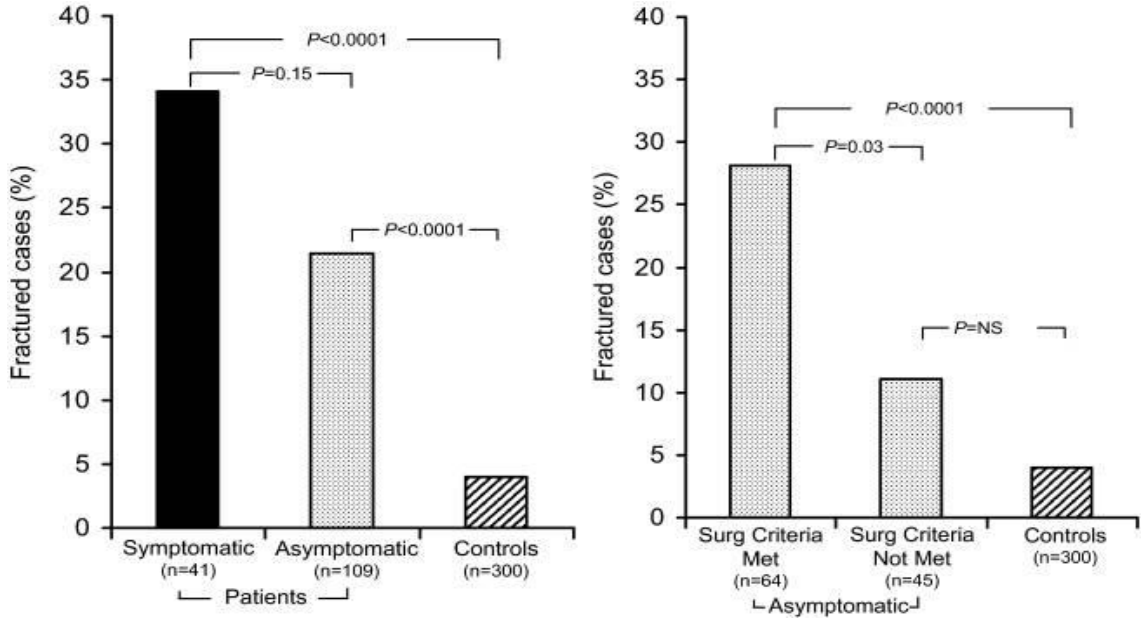
Baseline Z-scores
The asterisk denotes difference by site at the lumbar spine, femoral neck and radius (by analysis of variance, p<0.0005)

Silverberg et al. Clin Endocrinol Metab 80: 723-728. 1995

Case-control study

N=150 post-meno ♀ vs 300 controls, 61ys

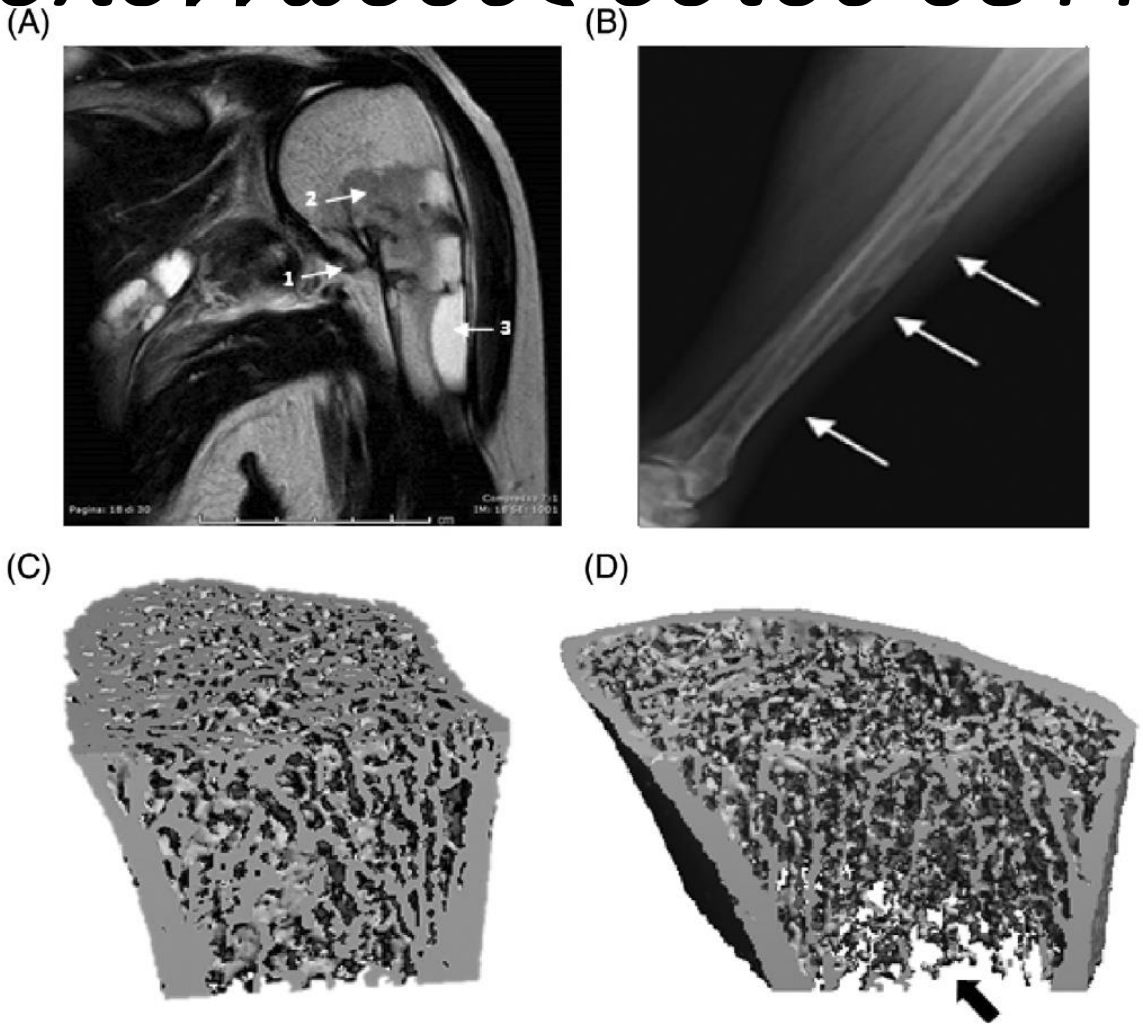
109 mild disease with no surg criteria



- OR 95% CI: 7.9 (4.0–15.6)
- Η BMD στην ΟΜΣΣ, ο μόνος ανεξάρτητος παράγοντας παρουσίας μορφομετρικών καταγμάτων στον PHPT

Vignali et al. JCEM 2009; 94(7):2306-12

Προσβολή τόσο του φλοιώδους όσο και του σπονγώδους οστού σε PHPT



Risk of fractures in primary hyperparathyroidism: a systematic review and meta-analysis
12 observational studies, n=5233 PHPT 13154 controls

Περιοχή	Odds ratio (%Cis)
Any fracture	2.01 (1.61-2.5)
Distal forearm	2.36 (1.64-3.38)
Vertebral	3 (1.41-6.37)
Vertebral fx in mild PHPT	4.22 (2.2-8.12)
hip	1.27 (0.97-1.66)

El-Hajj Fuleihan et al. JBMR 2022; 37(11):2330

Ejlsmark-Svensson et al. Osteopors Int 2021; 32(6):1053-1060

Εκτίμηση ασθενών με PHPT

Έλεγχος νεφρών

- Κάθαρση κρεατινίνης ή eGFR
- 24ωρη συλλογή ούρων για ασβέστιο (έναντι του spot ούρων) και, ίσως, προσδιορισμός άλλων παραγόντων κινδύνου νεφρολιθίασης.
- Απεικονιστικών έλεγχος νεφρών:
  - U/S
  - Spiral CT
  - X-rays

PHPT και νεφρική λειτουργία

Κλινική	(5-55%)
Υποκλινική	(11-35%)

👍 Τεκμηριωμένη γνώση

- Η νεφρολιθίαση/ νεφρασβέστωση αποτελούν συχνή επιπλοκή του PHPT.
- Η ασβεστιουρία παρατηρείται στο 1/3 όσων ασθενών με PHPT παρουσιάζουν νεφρολιθίαση.
- Συνεκτιμώμενοι παράγοντες κινδύνου: υπερουρικοζουρία, υπομαγνησιουρία, υπεροξαλουρία, υποκιτρικουρία και κυστινουρία.

👉 Χρειάζεται επιβεβαίωση

- Το κατώφλι κάθαρσης κρεατινίνης 60cc/min για PTX.
- Υπάρχει προϊούσα έκπτωση της νεφρικής λειτουργίας χωρίς χειρουργείο;
- Το eGFR< 60 ml/min σχετίζεται με μεγαλύτερη έκπτωση BMD και αυξημένο καταγματικό κίνδυνο;

⍰ Ερωτήματα προς απάντηση

- Κατά πόσο η μειωμένη νεφρική λειτουργία οφείλεται στον PHPT ή σε άλλους παράγοντες

Μη κλασσικές εκδηλώσεις του PHPT

Neurobehavioural
- Altered mental status*
- Depression and anxiety
- Impaired cognition*
- Reduced quality of life

Renal
- Polyuria
- Nephrolithiasis, nephrocalcinosis
- Impaired renal function

Gastrointestinal
- Anorexia, nausea, vomiting and constipation
- Cholelithiasis
- Pancreatitis
- Peptic ulcer disease

Biochemical abnormalities
- Hypercalcemia
- Hypercalciuria
- Hyperchloremic acidosis
- Hyperuricemia
- Hypophosphatemia

Cardiovascular
- Atherosclerosis
- Cardiac arrhythmias
- CV risk factors (insulin resistance, cholesterol, etc.)
- Hypertension
- Left ventricular hypertrophy
- Vascular stiffness

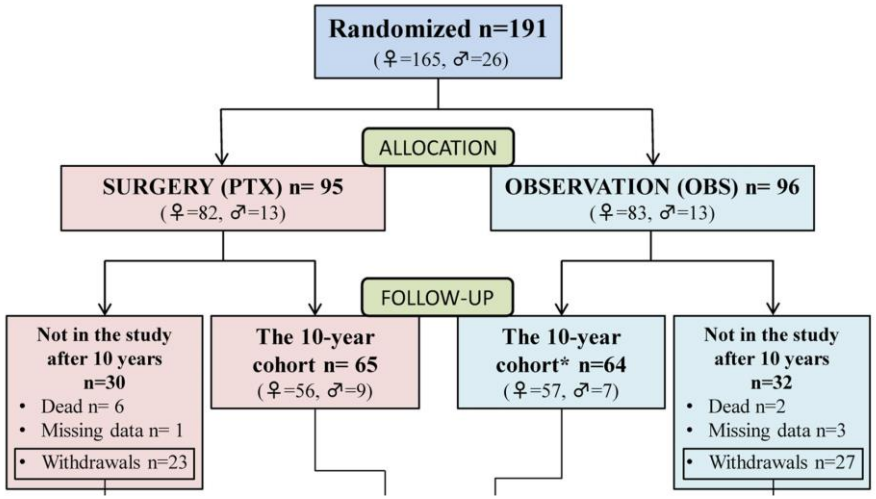
Skeletal
- Bone pain
- Osteitis fibrosa cystica/brown tumours
- Osteoporosis (fractures)
- Pseudogout

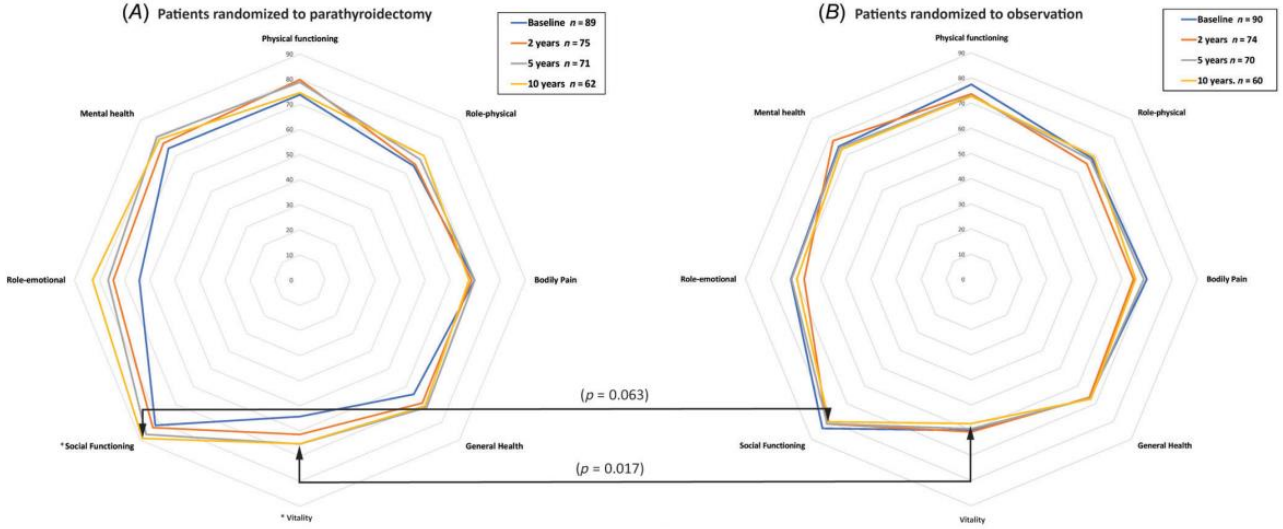
Neuromuscular
- Myopathy
- Impaired neuromuscular function

El-Hajj Fuleihan et al. JBMR 2022; 37(11):2330

Νευροψυχιατρικές διαταραχές *Επίδραση PTX ?*

The Scandinavian Study on Primary Hyperparathyroidism (SIPH)





Σχεδιασμός:

- **RCT με 10ετή παρακολούθηση (1998 -2005)**
- **Σύγκριση ποιότητας ζωής ασθενών με ασυμπτωματικό PHPT που τυχαιοποιήθηκαν σε παραθυρεοειδεκτομή ή παρακολούθηση χωρίς καμία θεραπεία.**
- **Έκβαση: SF-36 και CPRS (Comprehensive Psychopathological Rating Scale)**

Αποτελέσματα:

- **Τα score στις δύο κλίμακες παρέμειναν εντυπωσιακά σταθερά κατά την παρακολούθηση.**
- **Μικρές βελτιώσεις σε δύο υποκλίμακες του SF-36, στην ομάδα PTX, ακαθορίστου κλινικής σημασίας.**
- **Ήπια βελτίωση στο CPRS και στις δύο ομάδες.**

Συμπεράσματα:

- **«Thus, from a QoL perspective it seems safe to observe patients with mild PHPT for several years»**

Pretorius et al JBMR 2021; 36(1), pp 3–11

Καρδιαγγειακές και μεταβολικές εκδηλώσεις

Table 3. Summary of Studies on Cardiovascular Manifestations of PHPT 2013–2020

CV manifestation	? Mechanism	Association observational studies	Improvement observational studies	Improvement RCTs	Details
Hypertension	PTH or renin-aldosterone ratio	✓[172]	✓[175]	X[196]	Conflicting data; SIPH RCT trial negative
Impaired glucose insulin resistance		✓[169]		X[170]	Conflicting data; SIPH RCT trial negative
Fat mass/BMI		X[169]		X[170]	SIPH RCT trial negative
Cholesterol				X,[170] ✓[171]	Conflicting; SIPH RCT trial negative at 5 years; Danish RCT positive at 3 months post-PTX
Coronary calcification Aortic calcification Femoral calcification	? Calcium effect	✓,[183] X,[184] X[187] ✓[185] X[173]	X[187]		Limited, conflicting data
Vascular stiffness Flow mediated dilation	PTH associated with stiffness? Calcium	✓[178,185] X,[179] ✓[180]	X,[179] ✓[180]	X[171]	Conflicting data; Danish RCT negative but subgroup with highest calcium improved
Left ventricular mass	PTH → cardiac myocyte hypertrophy?	✓[190]	✓[192]	X[192,196]	Meta-analysis shows LVM improvement, but tends to be in observational studies with higher PTH
Short QT, VPBs	Calcium shortens QT	✓[195]		✓[195]	Small study size
CV events	? PTH	X[188]	✓[189]	X[73]	Limited data; SIPH trial no reduction CV events, limited events

- Πολύ ήπιες ή ανεπιβεβαίωτες καρδιαγγειακές εκδηλώσεις στον ασυμπτωματικό υπερπαραθυρεοειδισμό.
- Απουσία ενδείξεων υποστροφής καρδιαγγειακού κινδύνου μετά PTX

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Table 5. Summary of Studies on All-Cause Mortality in Patients with Hypercalcemia and PHPT and Its Predictors*

Source, Country	Setting Population	*n*	Gender (% women)	Age (years)	Follow up years	Death rate (%)	Predictors of mortality on multivariate analysis
Palmér and colleagues[217] (1987) Sweden	Mild to moderate hyperCa[a] in health screening in 1969 Control: normocalcemic cohort matched for sex, age and date of screening	172[a]	85[a]	59.3 (12.1)	14	HyperCa: 33 Controls: 22.7 ($p = 0.0135$, log rank)	Data derived from HyperCa and control cohorts: Age β 1.51 (p = NA) (calculated HR 4.52) Gender (reference being men) β −1.07 (p = NA) (calculated HR 0.34) Calcium β 4.97 (p = NA) (only at age <79 years) (calculated HR 144) PTH NA
Hedbäck and Odén[210] (1995) Sweden	Single institution, PHPT with single adenoma, surgical cohort (1953–1982)	713	74	57.8 (12.9)	10.3 (5.6)	PHPT 33	Data derived from PHPT cohort: Age β 0.1 (p = NA) (calculated HR 1.1) Gender (reference being men) β −0.63 (p = NA) (calculated HR 0.53) Calcium,[b] PTH NA
Söreide and colleagues[215] (1997) Rochester	Single institution, PHPT, surgical cohort (1980–1984) Control: matched patient population from the upper Midwest	1052	73	Median 59 (range 12–89)	Median 12 (0–15)	PHPT 24 Risk of death similar PHPT versus control	Data derived from PHPT cohort: Age[c] RR 2.17 (1.86; 2.54) Men RR 2.07 (1.48; 2.88) Calcium NA PTH >100 µLEq/mL RR 1.48 (1.09; 2.02)
Hedbäck and Odén[211] (1998) Sweden	National patient registry, PHPT surgical cohort (1987–1994) Control: general population, to derive expected death, using the Swedish Central Bureau of Statistics.	4461	79	Range of means 61.3–64.7	3.6	11.3 RR of death 1.53 (PHPT versus control) (p = NA)	Data derived from PHPT cohort, by gender: Age: significant predictor, risk was significantly increased for both categories: age >65 years or <65 years Calcium, PTH NA
Wermers and colleagues[214] (1998) Rochester	Population-based, PHPT surgical and nonsurgical cohort (1965–1992) Control: Minnesota white residents matched for age and gender	435	76	56.1 (range 15.8–89.4)	Up to 20	NA Observed versus expected death: no difference ($p = 0.23$)	Data derived from PHPT cohort: Age (per 10 years increase) HR 2.6 (2.2, 3.1) Gender NS Highest calcium (per mg/dL increase) HR 1.3 (1.1, 1.6) PTH NA
Yu and colleagues[213,216] (2011 and 2013) Scotland	Population based[d] PHPT nonsurgical cohort (1997–2006) Control: general population matched for age, gender, calendar year of PHPT diagnosis	2097	70	68 (13.7)	3.5 (max 10)	31 HR for mortality 1.64 (1.43–1.87) PHPT versus control	Data derived from PHPT cohort: Age HR 1.04 (1.03; 1.05) Gender (reference men) HR 0.81 (0.68; 0.97) PTH HR 1.46 (1.25; 1.71) for ≤1000 days; HR 3.13 (2.37; 4.14) for >1000 days Ca HR 1.21 (1.11; 1.31) for <1000 days; HR 0.71 (0.57–0.85) for >1000 days
Clifton and colleagues[212] (2015) Australia	Single institution PHPT surgical and nonsurgical cohort (1961–1994) Control: Australian population at large matched for age, sex, the year observation began, duration of observation	561	NA	Range of means 52.9–55.5	10	22 Survival rate in PHPT versus control: 86.8% (84.9;86.2)	Data derived from PHPT and control cohorts: Age and gender: matching terms Ca and PTH: NA Data derived from PHPT cohort: Surgically treated ($n = 448$): Age NA; Gender, Calcium, PTH: NS Non-surgically treated ($n = 113$): Age NA; Gender, Calcium: NS PTH HR 1.59 (1.20; 2.11)
Reid and colleagues[68] (2019) Edinburg, Scotland	Single institution PHPT surgical and nonsurgical cohort (2006–2014)	611	82	Range of means 61–69 (49–77)	Median 6.2	16	Data derived from PHPT cohort: Age HR 1.05 (1.02;1.08) Gender NA Calcium HR 8.584 (1.68; 44.95) PTH NS[e]

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Ολική και καρδιαγγειακή θνησιμότητα

- **Μελέτες με αυξημένη ολική θνησιμότητα από καρδιαγγειακά αίτια και καρκίνο στην Ευρώπη και Αυστραλία (RR 1,2-1,6), όχι όμως στις ΗΠΑ.**
- **Προγνωστικοί δείκτες τα**
  - **επίπεδα ασβεστίου**
  - **βαρύτητα νόσου και μέγεθος αδένων**
  - **Επίπεδα PTH**
  - **Ηλικία?**
- **Ωστόσο, οι περισσότερες προ 20ετίας**

Μη κλασσικές εκδηλώσεις του PHPT
Συμπεράσματα

- ✓**Προς το παρόν οι μη κλασσικές εκδηλώσεις του PHPT δεν μπορούν να χρησιμοποιηθούν στη λήψη αποφάσεων για χειρουργική παρέμβαση**

- ✓**Προτείνονται στρατηγικές για περαιτέρω έρευνα αυτών των πεδίων**

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Ομάδες εργασίας 5ου Διεθνούς workshop

- Επιδημιολογία, Παθοφυσιολογία και Γενετική
- Κλασσικές και μη κλασσικές εκδηλώσεις
- **Χειρουργικές πτυχές**
- Εκτίμηση και αντιμετώπιση

ORIGINAL ARTICLE

JBMR®

The Efficacy and Safety of Medical and Surgical Therapy in Patients With Primary Hyperparathyroidism: A Systematic Review and Meta-Analysis of Randomized Controlled Trials

Zhikang Ye,[1] Shonni J. Silverberg,[2] Ashwini Sreekanta,[1] Kyle Tong,[3] Ying Wang,[1] Yaping Chang,[1] Mengmeng Zhang,[1] Gordon Guyatt,[1] Wimonchat Tangamornsuksun,[1,4] Yi Zhang,[5,6] Veena Manja,[7] Layla Bakaa,[8] Rachel J. Couban,[9] Maria Luisa Brandi,[10] Bart Clarke,[11] Aliya A. Khan,[12] Michael Mannstadt,[13] and John P. Bilezikian[2]

ORIGINAL ARTICLE

JBMR®

Surgical Aspects of Primary Hyperparathyroidism

Nancy Perrier,[1] Brian H. Lang,[2] Leonardo Costa Bandeira Farias,[3] Leyre Lorente Poch,[4] Mark Sywak,[5] Martin Almquist,[6] Menno R. Vriens,[7] Michael W. Yeh,[8] Omair Shariq,[9] Quan-Yang Duh,[10] Randy Yeh,[11] Thinh Vu,[12] Virginia LiVolsi,[13] and Antonio Sitges-Serra[4]

ORIGINAL ARTICLE

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Φαρμακευτική και χειρουργική θεραπεία PHPT

2 συστηματικές ανασκοπήσεις και μετα-αναλύσεις

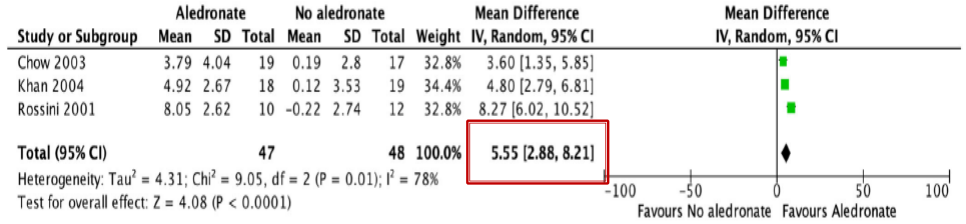
Alendronate
Denosumab
ERT
Vit D
Cinacalcet

? Impact of medical therapy versus no medical therapy in patients with PHPT who have declined surgery.

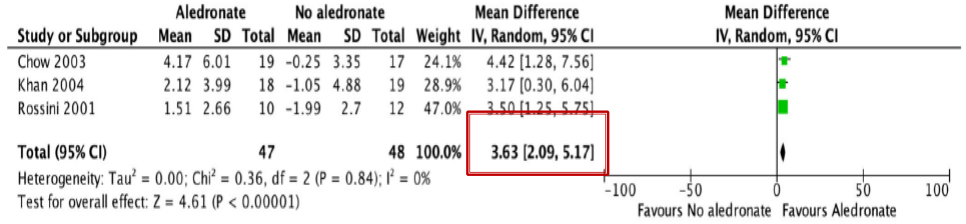
? The desirable and undesirable consequences of surgery in patients with asymptomatic PHPT.

? Impact of medical therapy versus no medical therapy in patients with PHPT who have declined surgery. BMD

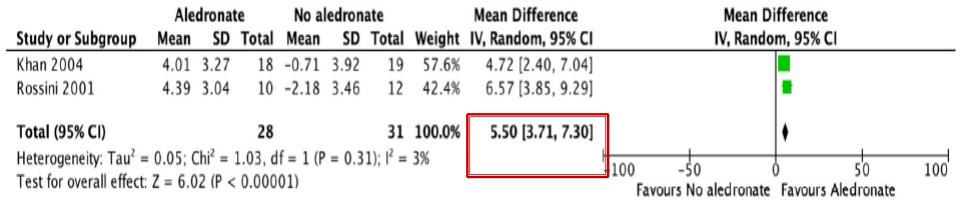
ALENDRONATE



(A) Lumbar spine

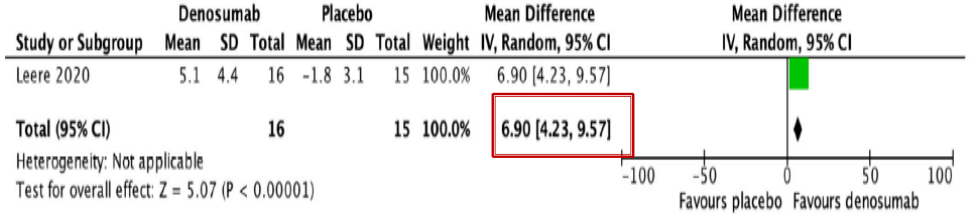


(B) Femoral neck

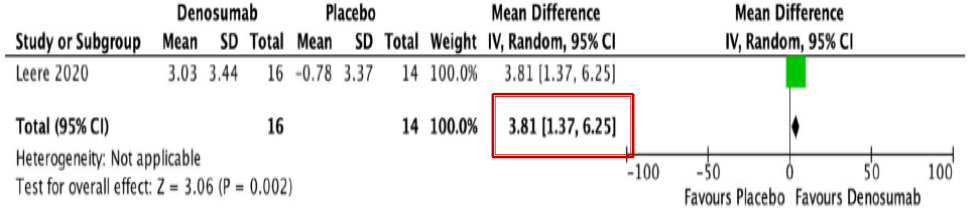


(C) Total hip

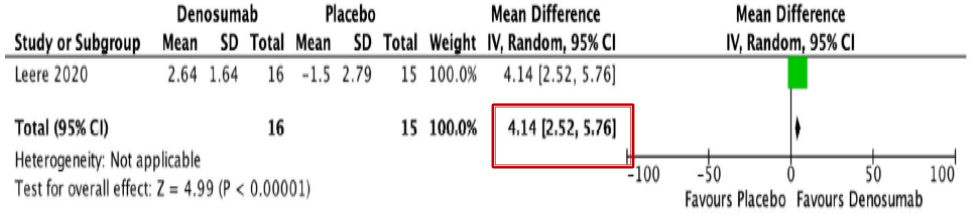
DENOSUMAB



(A) Lumbar spine



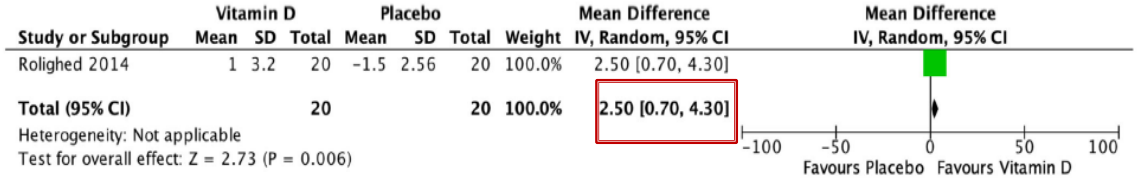
(B) Femoral neck



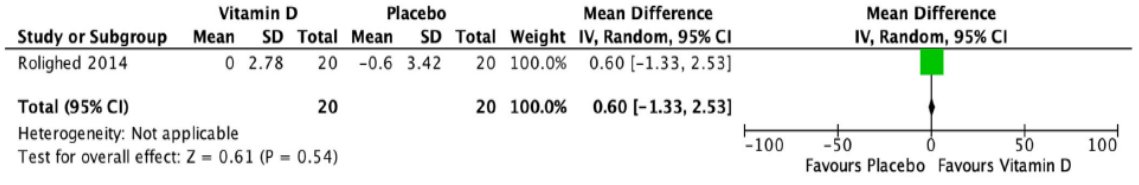
(C) Total hip

? Impact of medical therapy versus no medical therapy in patients with PHPT who have declined surgery. BMD

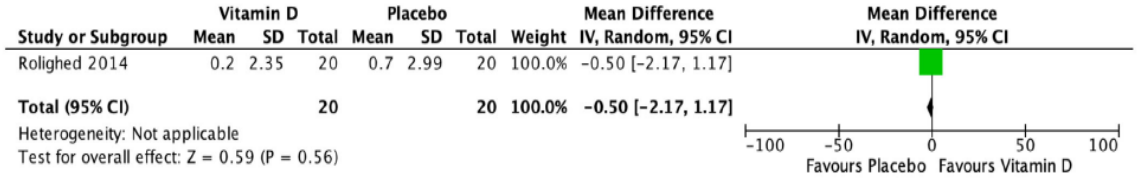
VITAMIN D



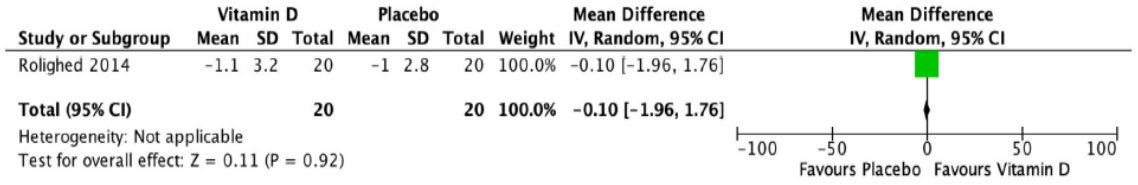
(A) Lumbar spine



(B) Femoral neck

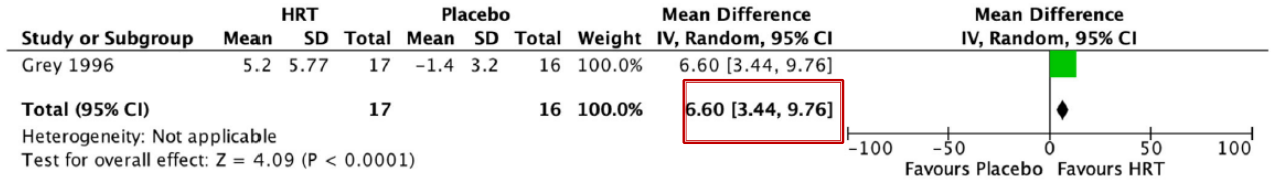


(C) Total hip

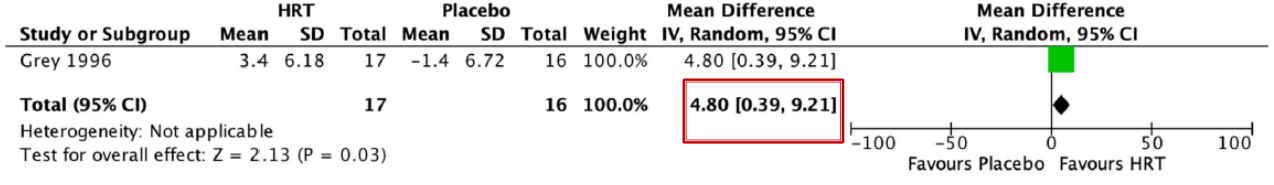


(D) Proximal 1/3 of distal forearm

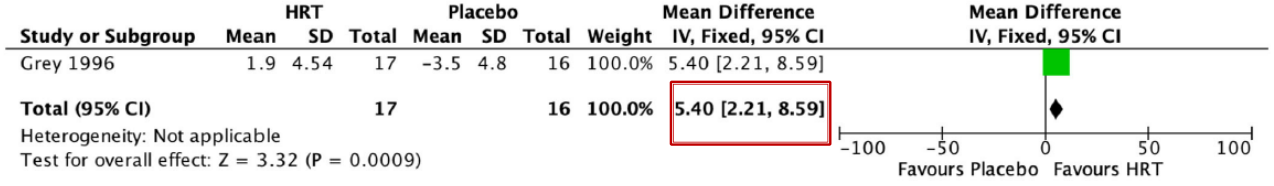
HRT



(A) Lumbar spine



(B) Femoral neck

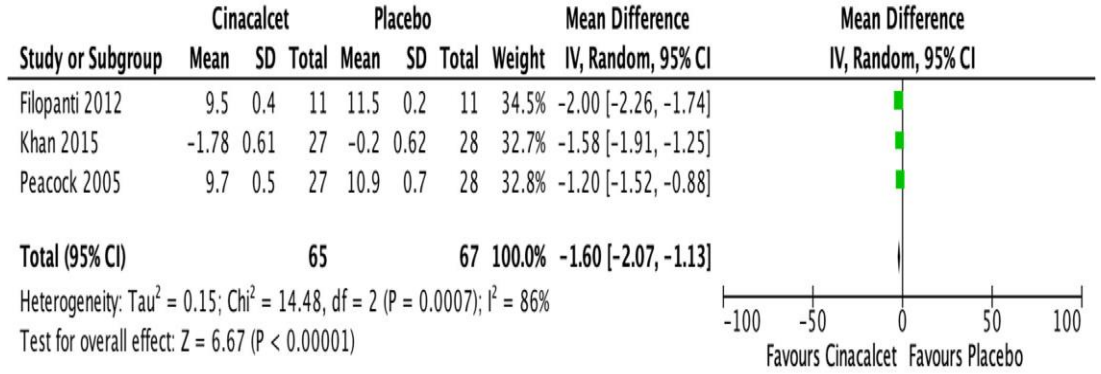


(C) Proximal forearm

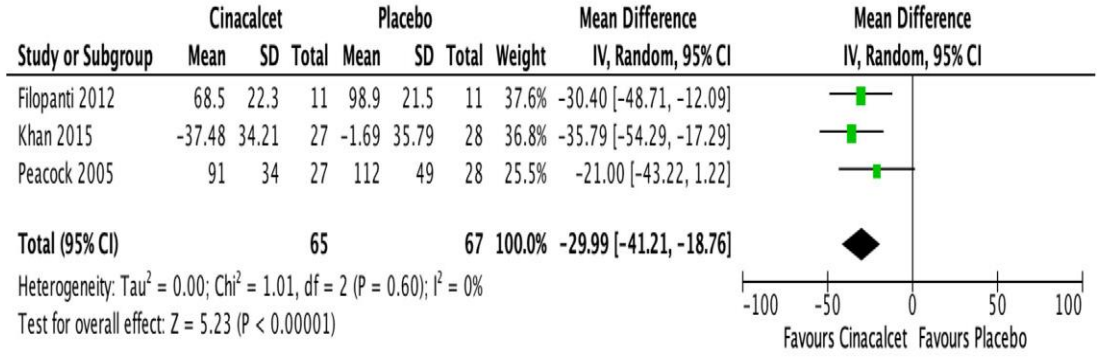
? Impact of medical therapy versus no medical therapy in patients with PHPT who have declined surgery.

Calcium & PTH

CINACALCET



(A) Serum calcium

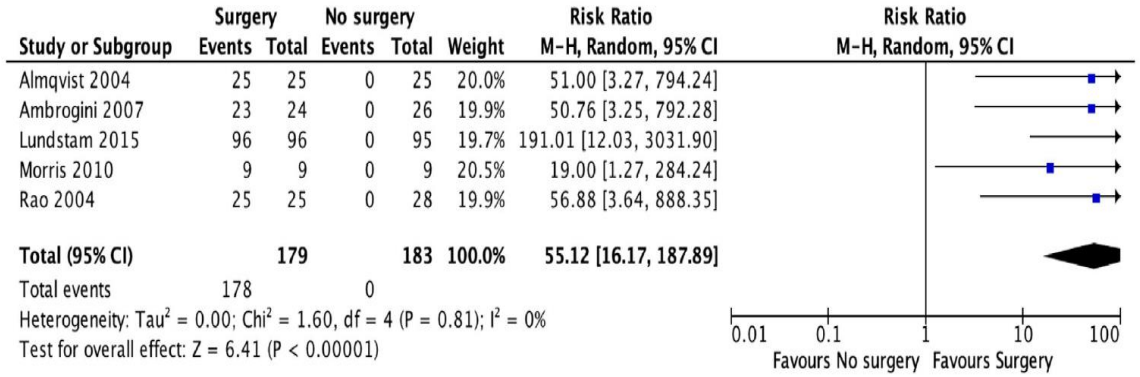


(B) Serum PTH

- ✓ Η cinacalcet μείωσε σημαντικά τα επίπεδα ασβεστίου και PTH.
- ✓ Η μείωση του ασβεστίου εντός ορίων αναφοράς παρατηρήθηκε σε μεγαλύτερο βαθμό σε σχέση με την αντίστοιχη της PTH.
- ✓ Χωρίς επίδραση στην απέκκριση ασβεστίου ή στο σχηματισμό λίθων (2 μελέτες)
- ✓ Χωρίς επίδραση στην BMD.

? Χειρουργείο ή όχι χειρουργείο σε ασυμπτωματικό PHPT?
Βιοχημική ύφεση και BMD

Effect of surgery on biochemical cure in asymptomatic patients with PHPT



Effect of Surgery on Bone Mineral Density by DXA in PHPT

Table 10. Effect of Surgery on Bone Mineral Density by DXA in Primary Hyperparathyroidism

Site	Lumbar spine	Femoral neck	Total hip	1/3 radius
Mean difference	4.82 (2.55 to 7.09)[a]	3.18 (−0.95 to 7.31)[a]	4.41 (2.62 to 6.20)[a]	0.28 (−1.25 to 9.58)[b] −1.47 (−10.13 to 7.19)[c]
Trial[c]	4	3	2	2[b]; 1[c]
Patient[c]	258	208	103	136[b]; 53[c]

Data presented as MDs with 95% CIs.
DXA = dual-energy X-ray absorptiometry.
[a]At 2–5 years.
[b]At 1–5 years.
[c]At 2 years.

? Χειρουργείο ή όχι χειρουργείο σε ασυμπτωματικό PHPT?

Κλινικές εκβάσεις

Table 9. GRADE Summary of Findings for Surgery Versus No Surgery in Patients with Asymptomatic PHPT

Outcomes (duration of follow-up in studies)	Relative effects and/or MD (95% CI); number of patients and trials	Absolute effect estimates (10 years)		Quality of evidence	Plain language summary
		Baseline risk for control group	Difference (95% CI)		
Biochemical cure (0.5 to 5 years)	316 patients in five trials	0	96.1% (92.1% to 98.4%)	High	Surgery results in a very high rate of biochemical cure; cure does not occur in patients who do not undergo surgery
Vertebral fracture (1 to 5 years)	RR 0.18 (0.02 to 1.48); 156 patients in two trials	Not applicable	−7% (−13% to −1%)[a]	Very low (serious risk of bias and very serious imprecision)	We are very uncertain of the effect of surgery on vertebral fracture
Nonvertebral fracture (2 to 5 years)	RR 0.81 (0.19 to 3.44); 159 patients in two trials	Not applicable	−1% (−6% to 5%)[a]	Very low (serious risk of bias and very serious imprecision)	We are very uncertain of the effect of surgery on non-vertebral fracture
Quality of life (1 to 10 years)	225 patients in three trials	Not applicable	Social functioning CI excluded no effect, other seven domains CI included both benefit and harm	All domains rated down for risk of bias and imprecision, some domains rated down twice for imprecision	We are very uncertain of the effect of surgery on Quality of Life.
Kidney stone (1 to 5 years)	RR 0.55 (0.10 to 3.10); 248 patients in three trials		−1% (−4% to 3%)[a]	Very low (serious risk of bias and very serious imprecision)	We are very uncertain of the effect of surgery on kidney stones
Renal failure (2 years)	RR not estimable; 53 patients in one trial	0	0 (−7%, 7%)[a]	Low (very serious imprecision)	Surgery may have a small or no effect on renal failure
Surgical complications (1 year)	RR not estimable; 50 patients in one trial	0	0 (−7%, 7%)[a]	Low (very serious imprecision)	Surgical complications may be very rare

Φαρμακευτική και χειρουργική θεραπεία PHPT

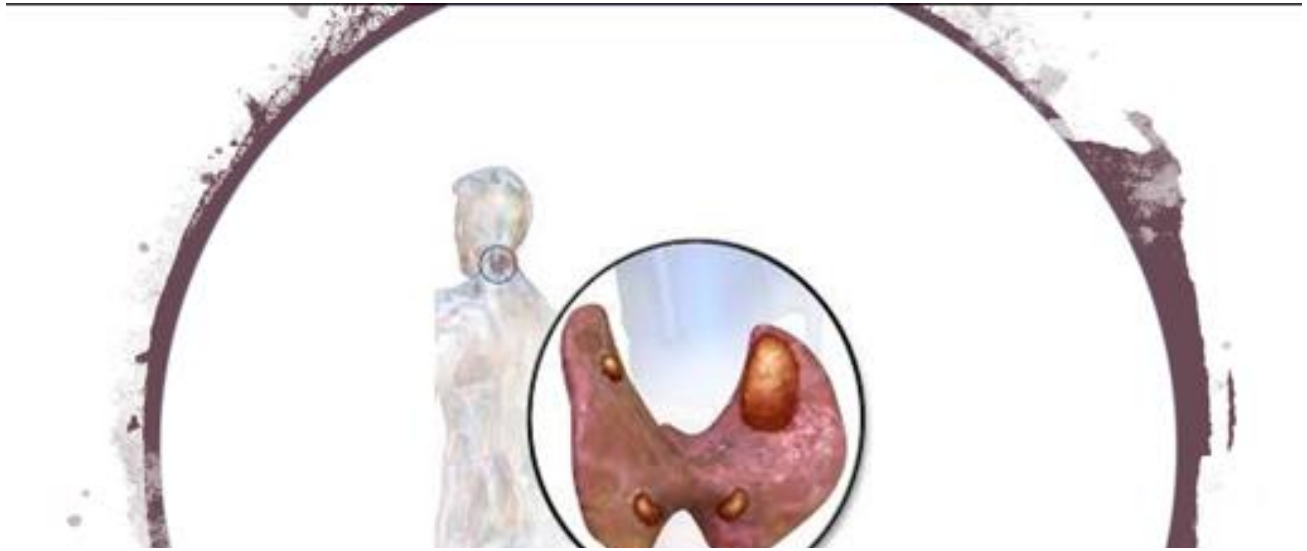
? Φαρμακευτική θεραπεία, απλή παρακολούθηση ή χειρουργική αντιμετώπιση ? ? ?

- Καμία φαρμακευτική θεραπεία δεν επιδρά στη νεφρική απέκκριση ασβεστίου.
- Οι ALD, Denosumab, vit D, ERT αύξησαν την BMD.
- Χωρίς ασφαλή συμπεράσματα για τη μείωση του καταγματικού κινδύνου με οποιαδήποτε παρέμβαση.

- Η χειρουργική αντιμετώπιση οδηγεί σε βιοχημική ύφεση στο 95%.
- Άγνωστη η επίδραση της PTX σε κατάγματα, νεφρολιθίαση και έκπτωση νεφρικής λειτουργίας.

Ομάδες εργασίας 5ου Διεθνούς workshop

- Επιδημιολογία, Παθοφυσιολογία και Γενετική
- Κλασσικές και μη κλασσικές εκδηλώσεις
- Χειρουργικές πτυχές
- **Εκτίμηση και αντιμετώπιση**



ORIGINAL ARTICLE

JBMR®

Management of Primary Hyperparathyroidism

John P. Bilezikian,[1] Shonni J. Silverberg,[1] Francisco Bandeira,[2] Filomena Cetani,[3] Manju Chandran,[4] Natalie E. Cusano,[5] Peter R. Ebeling,[6] Anna Maria Formenti,[7] Morten Frost,[8] Jessica Gosnell,[9] E. Michael Lewiecki,[10] Frederick R. Singer,[11] Neil Gittoes,[12] Aliya A. Khan,[13] Claudio Marcocci,[14] Lars Rejnmark,[15] Zhikang Ye,[16] Gordon Guyatt,[16] and John T. Potts[17]

A summary of panel recommendations for surgical management of PHPT (1)

1. **Symptomatic PHPT: <u>all symptomatic patients should be offered parathyroid surgery</u> unless medically contraindicated.**

2. **Asymptomatic PHPT**

   A. Serum calcium >1 mg/dL (0.25 mmol/L) above the upper limit of normal

   B. Skeletal involvement:

      a) A fracture by VFA or vertebral X-ray or

      b) BMD by T-score ≤ 2.5 at any site or

   C. Renal involvement:

      a) eGFR or creatinine clearance <60 mL/min or

      b) Nephrocalcinosis or nephrolithiasis by X-ray, ultrasound,or other imaging modality or

      c) Urinary calcium excretion: hypercalciuria (eg,>250 mg/day in women; >300 mg/day in men).

   D. Age <50 years (no other indications are necessary; age <50 years is a sufficient indication)

   E. If no aforementioned guidelines are met, PTX is still an option with concurrence of the patient and physician and if there are no contraindications

Table 2. Guidelines for Surgery in Asymptomatic Primary Hyperparathyroidism: A Comparison of Current Recommendations with Previous Ones

Parameter	1990	2002	2008	2013	2022
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)	1.0 mg/dL (0.25 mmol/L)
Skeletal	BMD by DXA: *Z*-score < −2.0 (site unspecified)	BMD by DXA: *T*-score < −2.5 at any site	BMD by DXA: *T*-score < −2.5 at any site Previous fragility fracture	a. BMD by DXA: *T*-score < −2.5 at lumbar spine, total hip, femoral neck or distal 1/3 radius b. Vertebral fracture by X-ray, CT, MRI, or VFA	a. BMD by DXA: *T*-score < −2.5 at lumbar spine, total hip, femoral neck or distal 1/3 radius* b.Vertebral fracture by X-ray, CT, MRI or VFA
Renal	a. eGFR reduced by >30% from expected. b. 24-Hour urine for calcium >400 mg/day (>10 mmol/day)	a. eGFR reduced by >30% from expected b. 24-Hour urine for calcium >400 mg/day (>10 mmol/day)	a. eGFR <60 cc/min b. 24-Hour urine for calcium not recommended	a. eGFR <60 cc/min b. 24-hour urine for calcium >400 mg/day (>10 mmol/day) and increased stone risk by biochemical stone risk analysis c. Presence of nephrolithiasis or nephrocalcinosis by X-ray, ultrasound, or CT	a. eGFR <60 cc/min** b. Complete 24-hour urine for calcium >250 mg/day in women (>6.25 mmol/day) or > 300 mg/day in men (>7.5 mmol/day) c. Presence of nephrolithiasis or nephrocalcinosis by X-ray, ultrasound, or CT
Age	<50 years	<50 years	<50 years	<50 years	<50 years

A summary of panel recommendations for surgical management of PHPT (2)

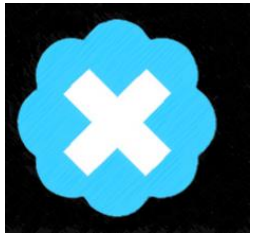
3. Normocalcemic PHPT: Because of limited data, we cannot recommend guidelines for surgery in normocalcemic PHPT at this time.

- **Surgery should be performed by an experienced parathyroid surgeon.**
- **Surgery cannot be recommended to improve neurocognitive function, quality of life and/or cardiovascular indices because the evidence is inconclusive.**

Ρόλος της προεγχειρητικού απεικονιστικού ελέγχου και της περιεγχειρητικής μέτρησης PTH

- Preoperative imaging is not recommended for diagnostic purposes.
- Preoperative imaging is recommended for those who are going to have parathyroid surgery in order to locate the abnormal parathyroid gland(s).
- Preoperative imaging modalities include
  - high resolution neck ultrasound.
  - technetium-99 m-sestamibi subtraction scintigraphy.
  - and contrast-enhanced four dimensional (4D) computed tomography (CT).
- With successful preoperative imaging, selective parathyroidectomy, combined or not with intraoperative PTH monitoring, achieves high cure rates in the hands of experienced surgeons.
- Advantages of the selective approach include (No head-to-head comparisons are available):
  - shorter operative time
  - less tissue scarring
  - less risk to surrounding structures
  - reduced hospital costs.

Διατροφική και φαρμακευτική αντιμετώπιση, όταν δεν προβλέπεται χειρουργείο (unGRADEd)



1. Ημερήσια λήψη ασβεστίου με βάση τις οδηγίες του Institute of Medicine.
   - 800 mg/day for women <50 years and men <70 years;
   - 1000 mg/day for women >50 years and men >70 years.

2. Πλάνο παρακολούθησης

- Biochemical monitoring: Serum calcium and 25OHD: annually. PTH levels can also be measured, as clinically indicated.
- Skeletal: Three-site DXA every 1 or 2 years unless the BMD is normal. Vertebral X-ray, VFA, or TBS if clinically indicated
- Renal:
  - Creatinine clearance (preferred over eGFR), annually
  - Abdominal imaging (X-ray, CT, or ultrasound) if clinically indicated
  - 24-Hour urine for calcium, if clinically indicated.

Διατροφική και φαρμακευτική αντιμετώπιση, όταν δεν προβλέπεται χειρουργείο (GRADEd)

1. In patients with PHPT who do not undergo PTX, pharmacological management should be used only for specific indications.

   a) In patients with low BMD who do not undergo PTX, we suggest bisphosphonates (eg, alendronate) or denosumab (weak recommendation based on very low-quality evidence).

   * Estrogen has been shown to increase BMD.
   * Raloxifene cannot be recommended

   b) In patients with PHPT and serum calcium levels >11.0 mg/dL above the upper limit of normal who do not undergo PTX, we suggest cinacalcet (weak recommendation based on low quality of evidence)

2. In patients with PHPT and vitamin D insufficiency (25OH vitamin D <30 ng/mL, or deficiency (<12 ng/mL), we suggest vitamin D supplementation (weak recommendation based on very low-quality evidence)

Πότε θα πρέπει να συσταθεί χειρουργείο σε PHPT υπό παρακολούθηση;

- Serum calcium becomes consistently >1 mg/dL above the upper limit of normal.
- A low trauma fracture.
- A kidney stone.
- A significant reduction in BMD to a T-score ≤ -2.5 at any site.
- A significant reduction in creatinine clearance.

Πρωτοπαθής υπερπαραθυρεοειδισμός και κύηση

- **Ήπιες περιπτώσεις αντιμετωπίζονται με διατήρηση:**
  - **Καλής ενυδάτωσης και παρακολούθησης ασβεστίου**
  - **Φάρμακα:**
    - X **Bisphosphonates και denosumab δεν πρέπει να χρησιμοποιούνται**
    - ? **Πολύ περιορισμένα δεδομένα για το cinacalcet**
- **Δυνατότητα χειρουργικής αντιμετώπισης στο 2ο τρίμηνο, σε ασθενείς**
  - **Με ασβέστιο ορού >11.0 mg/dL, όταν δεν υπάρχει αντένδειξη χειρουργείου**
- **Προεγχειρητική απεικόνιση μόνο με υπερηχογράφημα**
- **Εάν αποφευχθεί το χειρουργείο:**
  - **Στενή παρακολούθηση του νεογνού για υπασβεστιαιμία**
  - **Η PTX θα πρέπει να πραγματοποιηθεί μετά τον τοκετό και πριν από επόμενη κύηση.**

Προκλήσεις για το μέλλον

Presentations

- Global presentations and factors to account for differences
- Global differences in incidence and prevalence of the various forms of PHPT
- Long-term consequences/natural history of the various forms of PHPT with or without PTX.
- Definition of normocalcemic PHPT
- A global registry

Pathophysiology

- Differences among the hypercalcemic and normocalcemic variants
- Accounting for differences in predominant presentations of each form *vis a vis* single or multi-glandular disease
- Potential role of diet and the microbiome on clinical manifestations of PHPT.
- Potential role of CaSR signaling pathways in abnormal parathyroid tissue

Genetics

- CaSR mutations as they relate to PHPT vs FHH: similar or different?
- Potential role of GNA11 or AP2S1 on pathogenesis
- Role of genetic testing
- Utility of genetic testing modalities
- Identification of unidentified, causative genes

Serum calcium and vitamin D

- How/whether to adjust downward for a serum albumin of > 4 g/dL
- Is there a threshold at which PTX is indicated?
- Optimal levels of serum 25OHD
- What is the best way to replete vitamin D in PHPT?

Renal

- Stone Risk in PHPT.
- Can a predictive model be developed to document risk?
- Threshold values of renal function for recommending surgery
- Factors associated with worsening renal function
- Relationships between reduced creatinine clearance ,PTH, calcium, phosphorus, 1,25(OH)2D
- Medical and surgical therapeutics

Skeletal

- TBS, HRpQCT and other measures of bone quality
- FRAX tool as a risk factor in PHPT
- Factors associated with reduced bone density and/or fractures
- Fracture risk before and after PTX

Non-classical manifestations

- Neurocognitive
- Cardiovascular
- Metabolic

Surgical Aspects

- Complications of combined thyroid and parathyroid procedures
- Risk factors for parathyromatosis and local recurrence
- Timing of medical therapy for osteoporosis after PTX
- Review of complications
- Parathyroid cancer
- The role of genetics in decision-making for PTX

Review | J Bollerslev and others | Practical management of parathyroid disorders | 186:2 | R33–R63

European expert consensus on practical management of specific aspects of parathyroid disorders in adults and in pregnancy: recommendations of the ESE Educational Program of Parathyroid Disorders (PARAT 2021)

Jens Bollerslev[1,2], Lars Rejnmark[3], Alexandra Zahn[4], Ansgar Heck[1,2], Natasha M Appelman-Dijkstra[5], Luis Cardoso[6], Fadil M Hannan[7], Filomena Cetani[8], Tanja Sikjaer[3], Anna Maria Formenti[9], Sigridur Björnsdottir[10], Camilla Schalin-Jäntti[11], Zhanna Belaya[12], Fraser Gibb[13], Bruno Lapauw[14], Karin Amrein[15], Corinna Wicke[16], Corinna Grasemann[17], Michael Krebs[18], Eeva Ryhänen[11], Özer Makay[19], Salvatore Minisola[20], Sébastien Gaujoux[21], Jean-Philippe Bertocchio[22], Zaki Hassan-Smith[23], Agnès Linglart[24], Elizabeth M Winter[5], Martina Kollmann[25], Hans-Georg Zmierczak[26], Elena Tsourdi[27], Stefan Pilz[15], Heide Siggelkow[28], Neil Gittoes[23], Claudio Marcocci[8] and Peter Kamenický[29] on behalf of the 2021 PARAT Working Group*

? The differential diagnosis of familial hypocalciuric hypercalcemia (FHH),

? the definition and clinical course of normocalcemic PHPT, and

? the optimal management of its recurrence after surgery

https://doi.org/10.1530/EJE-21-1044

Managing Parathyroid Disorders: **Primary Hyperparathyroidism**

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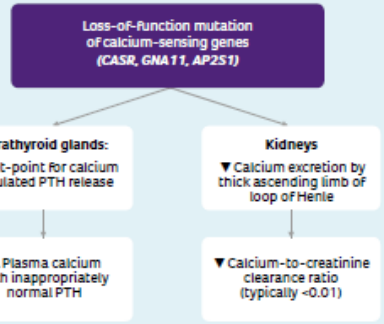

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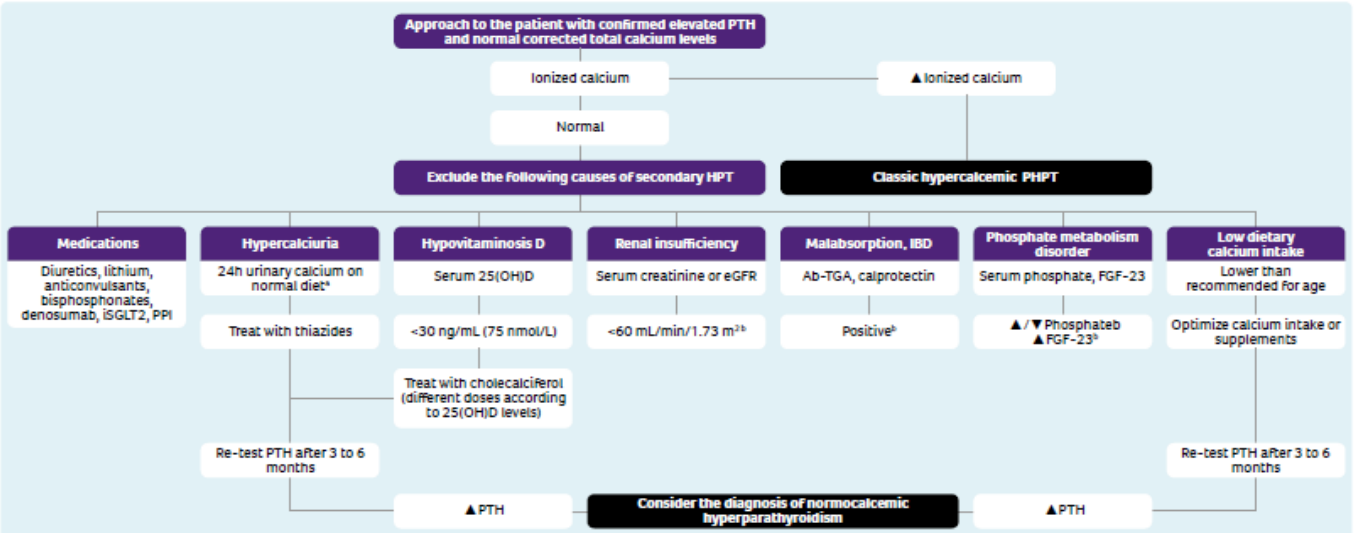

Figure 2. A clinical approach to patients with confirmed normocalcemic primary hyperparathyroidism. [a]Reference range >4 mg/kg/ day, >250 mg/day in females, and >300 mg/ day in males. [b]Evaluate for these disorders and manage as appropriate. 25(OH) D, serum 25-hydroxyvitamin D; Ab-TGA, anti-tissue transglutaminase antibodies; eGFR, estimated glomerular filtration rate; FGF-23, fibroblast growth factor-23; HPT, hyperparathyroidism; IBD, inflammatory bowel disease; iSGLT2, sodium-glucose cotransporter-2 inhibitors; PHPT, primary hyperparathyroidism; PPI, proton pump inhibitors; PTH, parathyroid hormone.

Cause of secondary hyperparathyroidism	Proposed intervention thresholds	Comments
Vitamin D deficiency	Aim for 25(OH)D concentrations of 30 ng/mL (75 nmol/L) to avoid secondary hyperparathyroidism	Re-test PTH when vitamin D replete. PTH concentrations may remain elevated for 6–12 months and optimization of calcium intake is mandatory
Low-dietary calcium intake	1200 mg/day for postmenopausal women 1000 mg/day for men 51–70 years and 1200 mg/ day for older men	Evaluate calcium intake using a dietary questionnaire. Patients should increase calcium intake or use calcium supplements
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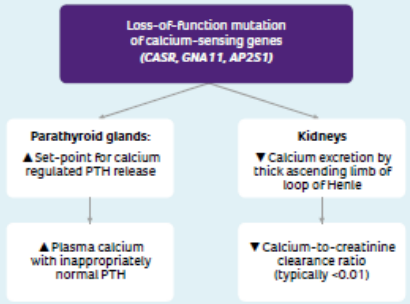

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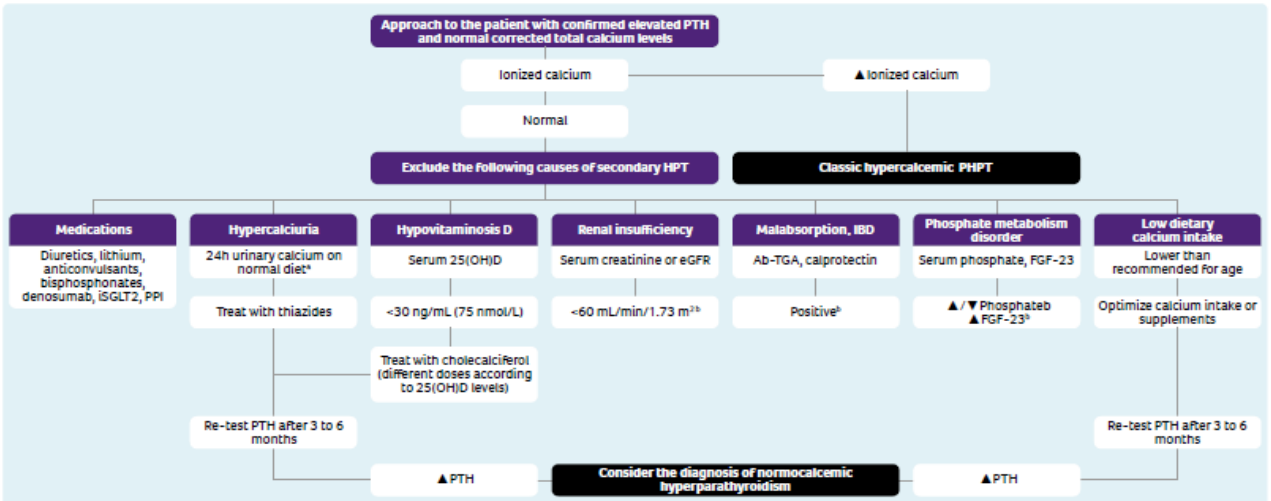

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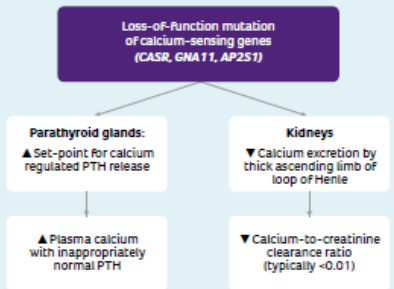

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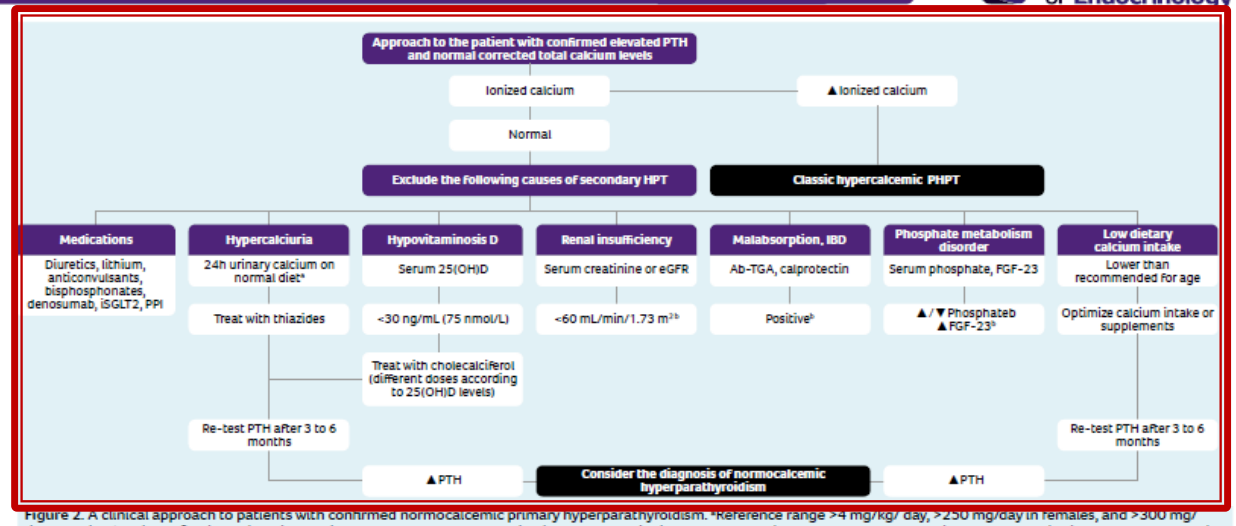

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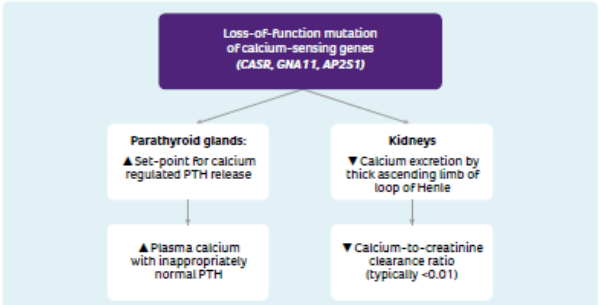

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Q3 What are the causes of hyperparathyroidism with normal calcium that should be excluded before considering a diagnosis of normocalcemic PHPT?

Secondary causes of hyperparathyroidism include medications, hypercalciuria, hypovitaminosis D, renal insufficiency, malabsorption syndromes, phosphate metabolism disorders and low dietary calcium intake (Figure 2, Table 1).

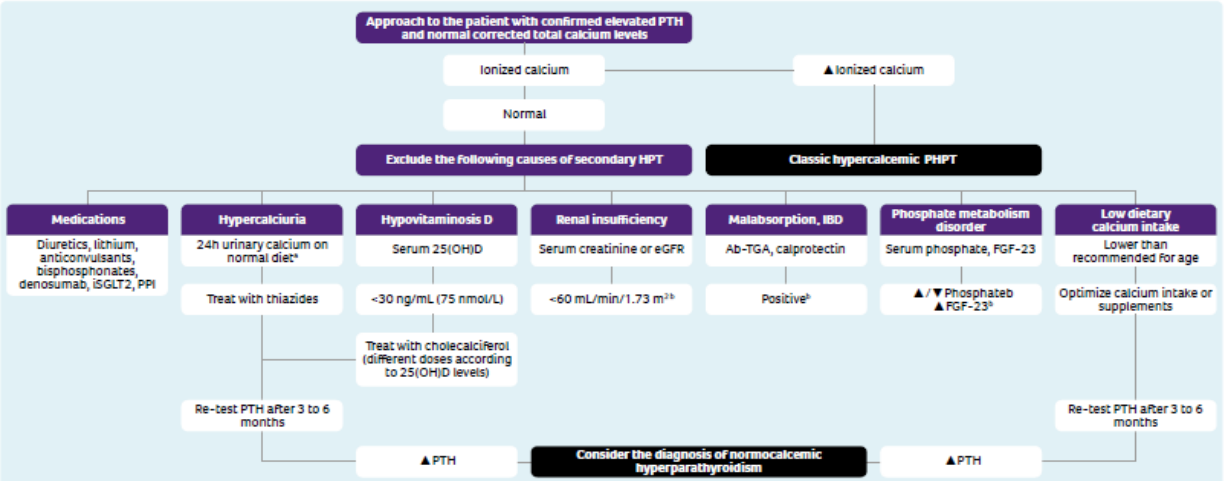

Figure 2. A clinical approach to patients with confirmed normocalcemic primary hyperparathyroidism. [a]Reference range >4 mg/kg/ day, >250 mg/day in females, and >300 mg/ day in males. [b]Evaluate for these disorders and manage as appropriate. 25(OH) D, serum 25-hydroxyvitamin D; Ab-TGA, anti-tissue transglutaminase antibodies; eGFR, estimated glomerular filtration rate; FGF-23, fibroblast growth factor-23; HPT, hyperparathyroidism; IBD, inflammatory bowel disease; iSGLT2, sodium-glucose cotransporter-2 inhibitors; PHPT, primary hyperparathyroidism; PPI, proton pump inhibitors; PTH, parathyroid hormone.

Cause of secondary hyperparathyroidism	Proposed intervention thresholds	Comments
Vitamin D deficiency	Aim for 25(OH)D concentrations of 30 ng/mL (75 nmol/L) to avoid secondary hyperparathyroidism	Re-test PTH when vitamin D replete. PTH concentrations may remain elevated for 6–12 months and optimization of calcium intake is mandatory
Low-dietary calcium intake	1200 mg/day for postmenopausal women 1000 mg/day for men 51–70 years and 1200 mg/ day for older men	Evaluate calcium intake using a dietary questionnaire. Patients should increase calcium intake or use calcium supplements
Hypercalciuria due to renal abnormalities	Urinary calcium excretion >250 mg/24 h (6.25 mmol/24 h) in females, >300 mg/24 h (7.5 mmol/24 h) in males, or >4 mg/kg/24 h (0.1 mmol/kg/24 h)	'Thiazide challenge' test (administer hydrochlorothiazide 25 mg twice a day for 2 weeks; check PTH levels prior to starting thiazide and after 2 weeks of therapy). PTH normalization supports renal secondary causes of PHPT
Renal insufficiency	eGFR <60 mL/min/1.73 m²	As kidney function declines, 1α-hydroxylation activity decreases and, consequently, active vitamin D levels fall, calcium levels decline, and PTH levels increase
Gastrointestinal disorders associated with calcium malabsorption	Celiac disease, inflammatory bowel disease, and bariatric surgery	Measure anti-tissue transglutaminase antibodies and fecal calprotectin to consider celiac disease and inflammatory bowel disease, respectively
Medications	1200 mg/day for postmenopausal women 1000 mg/day for men 51–70 years and 1200 mg/ day for older men	Non-thiazide diuretics can increase PTH levels (if possible, discontinue and reevaluate PTH). Lithium therapy can raise PTH levels (decision to withdraw from therapy is difficult and should be made by a psychiatrist). Treatment with bisphosphonates or denosumab can raise PTH levels as a result of positive calcium signaling to the parathyroid glands in the context of inhibited bone resorption. Bisphosphonate effects may last for a long time after discontinuation. Denosumab discontinuation should be avoided to prevent excessive bone loss. Recent studies showed that SGLT2 inhibitors have complex interactions with bone metabolism, including an increase in PTH
Phosphate metabolism disorders	Hyperphosphatemia and FGF-23-mediated hypophosphatemia are both associated with secondary hyperparathyroidism	Extracellular phosphate regulation involves changes in PTH levels. Both high and low phosphate levels may be associated with secondary hyperparathyroidism

25(OH)D, 25-hydroxyvitamin D; eGFR, estimated glomerular filtration rate; FGF-23, fibroblast growth factor 23; PTH, parathyroid hormone; SGLT2 inhibitors, sodium-glucose cotransporter-2 inhibitors.

Table 1. Most common causes of secondary hyperparathyroidism.

Q4 What are the manifestations of normocalcemic PHPT, and does it progress to hypercalcemic PHPT?

Normocalcemic PHPT may be an early biochemical manifestation of PHPT, but there are no clear data on the natural history of normocalcemic PHPT. Some studies reported the development of complications, e.g., renal stones, low-traumatic fractures and osteoporosis in patients assessed in tertiary referral centers.

Q5 What are the definition, prevalence and causes of recurrent PHPT?

Recurrent PHPT is defined by hypercalcemia, after a period of 6 months, in patients successfully operated by parathyroidectomy, and where normocalcemia was previously documented. Isolated elevation of PTH levels with normocalcemia does not represent recurrent PHPT.

When confronted with apparent recurrent PHPT, it is fundamental to confirm the diagnosis by excluding FHH and repeating calcium levels associated with increased and unsuppressed PTH concentrations.

Recurrent PHPT affects 2.5-10% of patients after successful parathyroidectomy and recurrence can be tardive, therefore long-term follow-up is recommended.

Q6 Do we need to act upon persistent elevations of PTH levels despite normocalcemia?

PTH should not be routinely measured in normocalcemic individuals following parathyroid surgery.

Q7 What is the optimal work-up of patients with recurrent PHPT?

When evaluating recurrent PHPT, it is mandatory to accurately confirm or refute the diagnosis of PHPT. About 2/3 of recurrent disease is due to a single adenoma, up to 1/3 due to multiglandular disease, and rarely due to parathyroid carcinoma. Thus, preoperative localization procedures that are more sensitive to detect multiglandular disease and/or small lesions are preferred. (18F-fluorocholine PET/CT, with or without enhanced arterial imaging, and 4D-CT).

If confirmed, an active search for potential underlying etiologies should be considered, which include acquired forms (lithium-induced parathyroid hyperplasia or parathyromatosis) or genetic forms (MEN syndromes, familial isolated hyperparathyroidism, or hyperparathyroidism-jaw tumor syndrome).

Q8 What is the best surgical approach in patients with recurrent PHPT?

A thorough preoperative work-up is imperative and repeat surgery should only be performed in highly experienced centers.Depending on the results and etiology, bilateral neck exploration or a focused minimal-invasive parathyroidectomy should be performed. Intraoperative PTH assay and nerve-monitoring are recommended in repeated parathyroid surgery.

A lack of localization in clearly established PHPT should not delay surgery.

Conservative medical management using cinacalcet and bone protecting agents is an adjunctive or even alternative approach to be considered, especially in patients with mild disease and/or severe comorbidities.

Q9 What is the risk of hypoparathyroidism following surgery for recurrent PHPT?

In the re-operative setting, the risk of transient hypoparathyroidism can be as high as 80%, while the rate of chronic hypoparathyroidism is 3-13%.

Q10 Why and when should calcium levels be measured after parathyroidectomy?

Calcium levels should be measured postoperatively, in parallel to evaluation for symptoms of hypocalcemia. Patients at risk for hungry bone syndrome should be checked more than once per day in the first postoperative days. To define cure of PHPT after parathyroidectomy, normocalcemia should last ≥6 months.

Q11 What preoperative advice should be offered to patients awaiting parathyroidectomy?

Patients with PHPT should not exceed recommended calcium daily intake (Table 1), but do not need to restrict dietary intake.

Low 25(OH)D levels should be repleted. Several studies have confirmed it to be safe, when calcium levels are <3 mmol/L (12 mg/dL).

Patients should stay well-hydrated. Hypercalcemic crises require parenteral hydration and may benefit from further medical management (e.g., bisphosphonates, denosumab, cinacalcet, and calcitonin, or combinations of these). Surgery might be prioritized in selected cases after medical stabilization.

Q12 What causes hypocalcemia after parathyroidectomy?

Postoperative hypocalcemia can be related to:

- Hypoparathyroidism is characterized by low/inappropriately 'normal' PTH concentrations, increased serum phosphate concentrations, and normal or elevated 24h urinary calcium excretion with calcium replacement.
- Hungry bone syndrome (massive transfer of calcium to bone, starting typically from 3rd-5th postoperative day) is characterized by normal or high PTH concentrations, low serum phosphate, low serum magnesium concentrations, and a low 24h urinary calcium excretion despite parenteral calcium replacement. (Table 2)

Q13 What is optimal follow-up after (successful) parathyroidectomy?

Patients with persisting hypercalcemia at 6 months after surgery should be considered for reoperation after detailed reassessment.

Annual checks of calcium levels should be performed. If hypercalcemia emerges, PTH measurement is warranted, but as stated, routine PTH monitoring (without hypercalcemia) is not recommended.

Special cases (parathyroid cancer, syndromic forms) should be followed with a personalized plan in a specialized endocrine center.

Genetic testing in young patients (<30 years) and multiglandular disease at any age. Patients with concomitant osteoporosis are in need of individualized management.

Potential risk factors for hungry bone syndrome	Comments
High preoperative PTH level	Sudden removal of the effect of high circulating levels of PTH on osteoclastic resorption leads to increased influx of calcium into bone (new remodeling sites)
Large volume (weight and mass) of parathyroid adenoma	Positive correlation between PTH levels and volume of adenoma
High preoperative calcium levels	Explained as increased calcium resorption from bone and calcium reabsorption from renal tubules in case of preoperatively elevated PTH levels
Radiological evidence of PHPT-related bone disease	Brown tumors, multiple fractures, osteitis fibrosa cystica as an effect of long-lasting high circulating levels of PTH on the skeleton
Significantly elevated alkaline phosphatase	Reflects the state of bone turnover and the degree of osteoclast activity and bone resorption
Preoperatively low 25(OH)D concentrations	HBS develops indirectly by skeletal demineralization due to low circulating levels of $1,25(OH)_2D$ with postoperative increased skeletal calcium requirements

$1,25(OH)_2$ D, 1,25-dihydroxyvitamin D; 25(OH)D, 25-hydroxyvitamin D; HBS, hungry bone syndrome; PHPT, primary hyperparathyroidism; PTH, parathyroid hormone

Table 2. Potential risk factors for hungry bone syndrome.

This guide is an output of PARAT - the ESE educational programme on parathyroid disorders developed by an expert Steering committee and International community. Faculty members Elena Tsourdi, (Germany), Luis Cardosa, (Portugal), Claudio Marcocci, (Italy) and Nik Screen (ESE/Versatility.org.uk) prepared this guide.

Further summaries covering hypoparathyroidism and preconception, pregnancy and lactation are also available, plus other educational materials at **www.ese-hormones.org** or by searching; **bit.ly/paratlz**

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European Society of Endocrinology

Πρωτοπαθής υπερπαραθυρεοειδισμός και κύηση

	PHPT
Mother (preconception)	Pregnancy should be avoided until curative surgery has been performed and calcium concentrations are normalized
Mother (pregnancy)	Surgery is advised, preferentially in the second trimester, and especially if albumin-adjusted calcium is >2.85 mmol/L (>11.42 mg/dL) and/or >0,25 mmol/L (>1 mg/dL) ULN and/or ionized calcium is >1.45 mmol/L (>5.81 mg/dL) Surveillance every 4 weeks
Mother (lactation)	Surveillance every 4–8 weeks Surgery a few weeks after delivery
Newborns	Measure ionized calcium every second day until about 1–2 weeks of life In case of hypocalcemia, consider active vitamin D treatment

Bollerslev et al. (PARAT 2021) EJE 2022; 186(2): R33-R63

Συμπεράσματα

- ✓Ο PHPT είναι συχνή ενδοκρινική διαταραχή, ιδιαίτερα σε περιοχές όπου ασκείται ενεργή ανίχνευση.
- ✓Διακρίνονται 3 ξεχωριστοί φαινότυποι της νόσου, συμπτωματικός, ασυμπτωματικός και νορμοασβεστιαιμικός (συμπτωματικός ή μη).
- ✓Η χειρουργική θεραπεία είναι απαραίτητη στη συμπτωματική νόσο, αλλά μπορεί να προταθεί και σε όσους δεν πληρούν τις προϋποθέσεις.
- ✓Η φαρμακευτική θεραπεία συνιστάται μόνο υπό προϋποθέσεις (υψηλό ασβέστιο ή χαμηλή BMD), όταν δεν είναι εφικτή η χειρουργική αντιμετώπιση.
- ✓Η μακροχρόνια παρακολούθηση, είναι απαραίτητη σε όλους τους ασθενείς και ιδιαίτερα σε όσους ασθενείς δεν έχουν δεν έχουν υποβληθεί σε PTX.

ΕΥΧΑΡΙΣΤΩ!!