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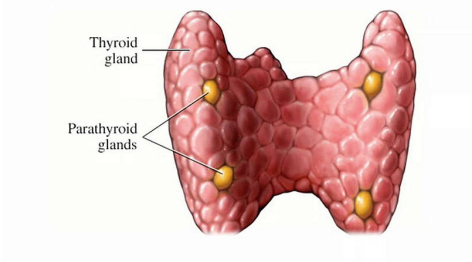

Primary hyperparathyroidism

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Confirm hyperCA: Calculator: Calcium correction in hypoalbuminemia (SI units)

- Calcium (mmol/L)
  - = Serum calcium + 0.02 * (Normal albumin – Patient albumin)
- Calcium (mg/dL)
  - = Serum calcium + 0.8 * (Normal albumin – Patient albumin
- And look at paraprotein (MM)

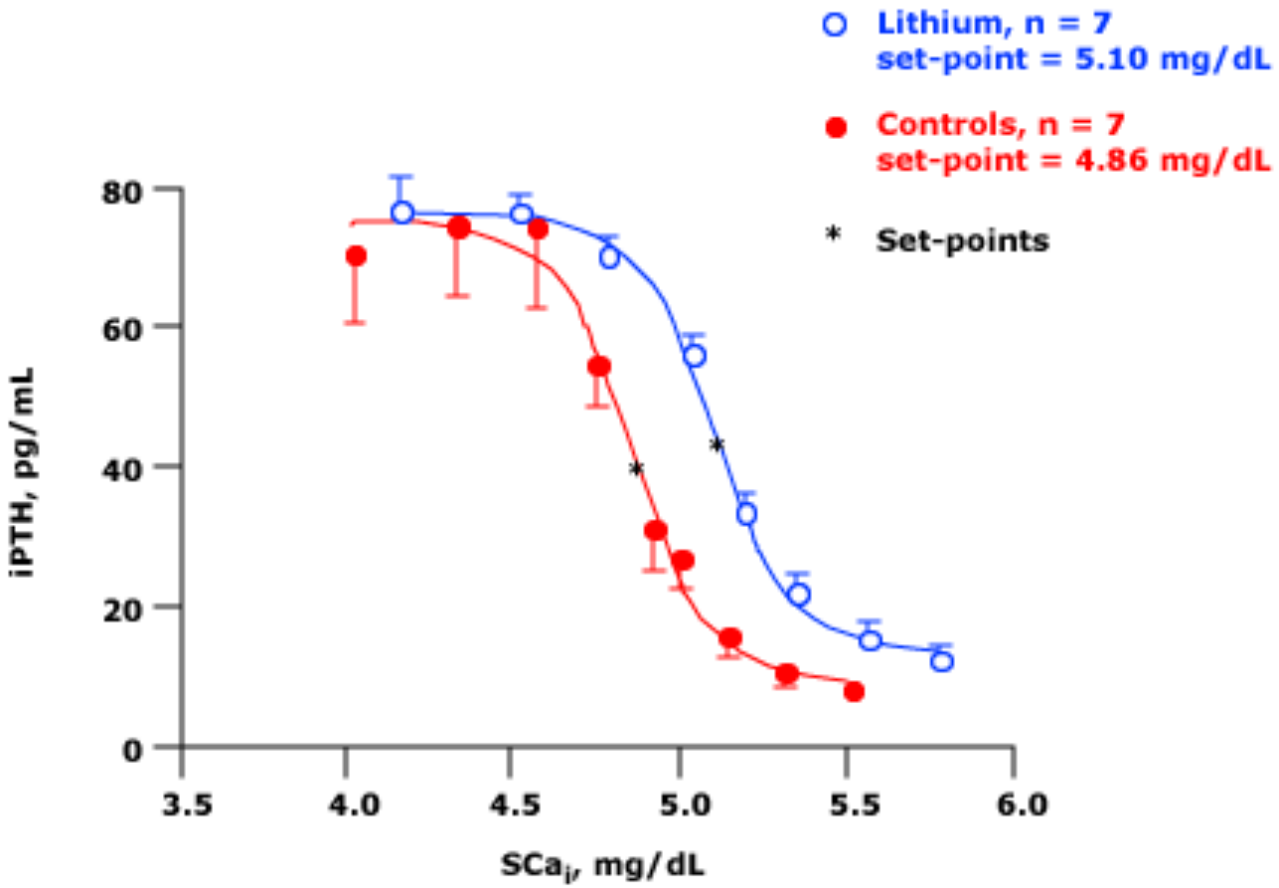
Figge J, Jabor A, Kazda A, Fencl V. Anion gap and hypoalbuminemia. *Crit Care Med*. 1998 Nov; 26(11):1807-10.
Payne RB, Little AJ, Williams RB, Milner JR. Interpretation of serum calcium in patients with abnormal serum proteins. *Br Med J*. 1973 Dec 15;4(5893):643-6.

Causes of hypercalcemia

Parathyroid mediated
Primary hyperparathyroidism (sporadic)
Inherited variants
Multiple endocrine neoplasia (MEN) syndromes
Familial isolated hyperparathyroidism
Hyperparathyroidism-jaw tumor syndrome
Familial hypocalciuric hypercalcemia
Tertiary hyperparathyroidism (renal failure)
Non-parathyroid mediated
Hypercalcemia of malignancy
PTHrp
Increased calcitriol (activation of extrarenal 1 alpha-hydroxylase)
Osteolytic bone metastases and local cytokines
Vitamin D intoxication
Chronic granulomatous disorders
Increased calcitriol (activation of extrarenal 1-alpha-hydroxylase)
Medications
Thiazide diuretics
Lithium
Teriparatide
Abaloparatide
Excessive vitamin A
Theophylline toxicity
Miscellaneous
Hyperthyroidism
Acromegaly
Pheochromocytoma
Adrenal insufficiency
Immobilization
Parenteral nutrition
Milk-alkali syndrome

High PTH
Or « non suppressed »

Mean (±SD) calcium-PTH dynamics in normal subjects and patients receiving lithium carbonate

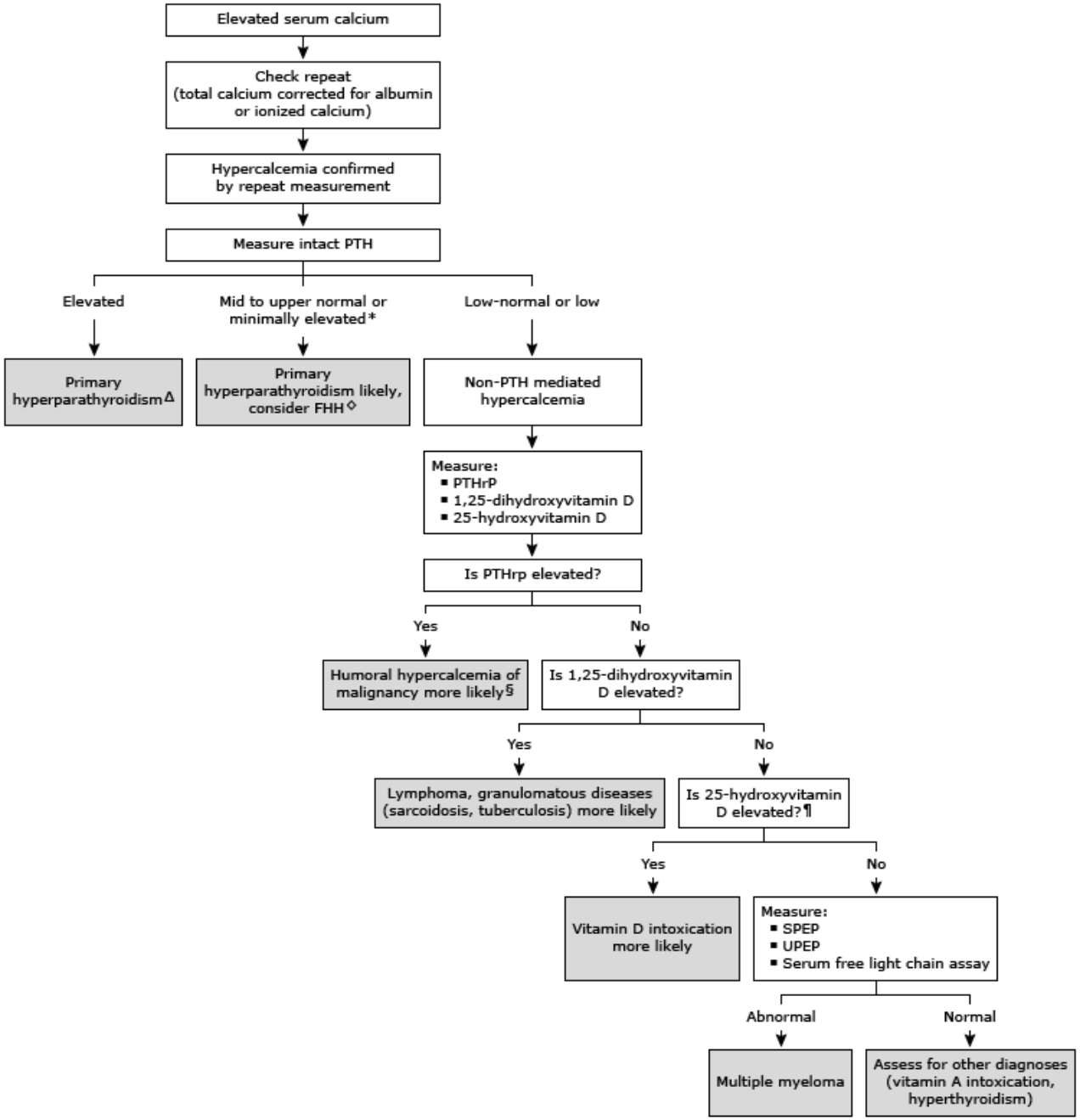


Pepersack T, Corazza F, Demulder A, Guns M, Fondu P, Bergmann P. Lithium inhibits calcitriol-stimulated formation of multinucleated cells in human long-term marrow cultures. J Bone Miner Res. 1994 May;9(5):645-50.

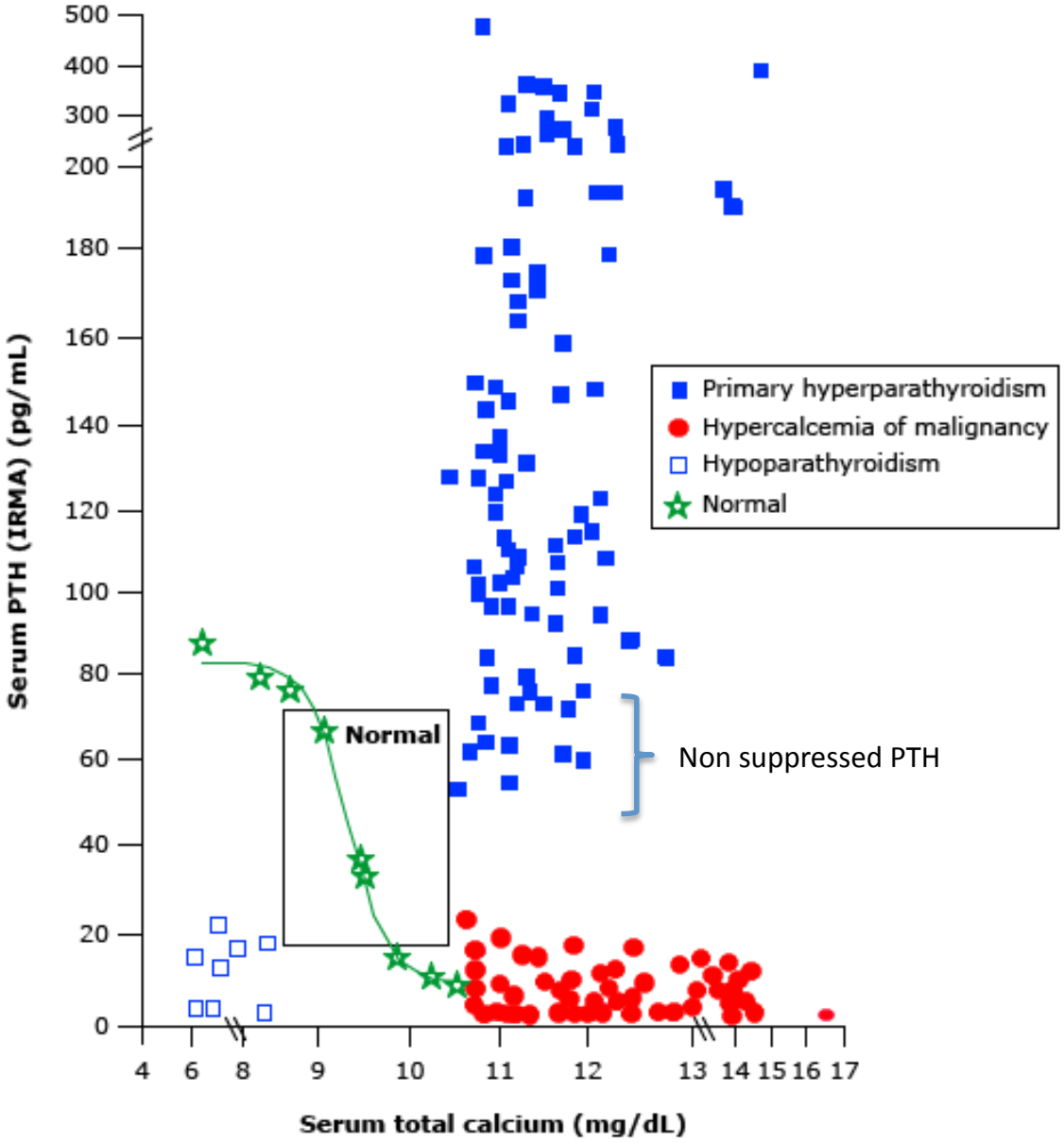
Pepersack T, Corvilain J, Bergmann P. Effects of lithium on bone resorption in cultured foetal rat long-bones. European journal of clinical investigation. 1994 Jun;24(6):400-5.

Haden ST, Stoll AL, McCormick S et al. Alterations in parathyroid dynamics in lithium-treated subjects. J Clin Endocrinil Metab 1997;82:2844.

Diagnostic approach to hypercalcemia



PTH: parathyroid hormone; FHH: familial hypocalciuric hypercalcemia; PTHrp: parathyroid hormone-related peptide; SPEP:



The degree of hypercalcemia also may be useful diagnostically

MW Ca= 40
10 mg/dL=2,5 mmol/L

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Haden ST, Brown EM, Hurwitz S, et al. The effects of age and gender on parathyroid hormone dynamics. Clin Endocrinol 2000; 52:329.

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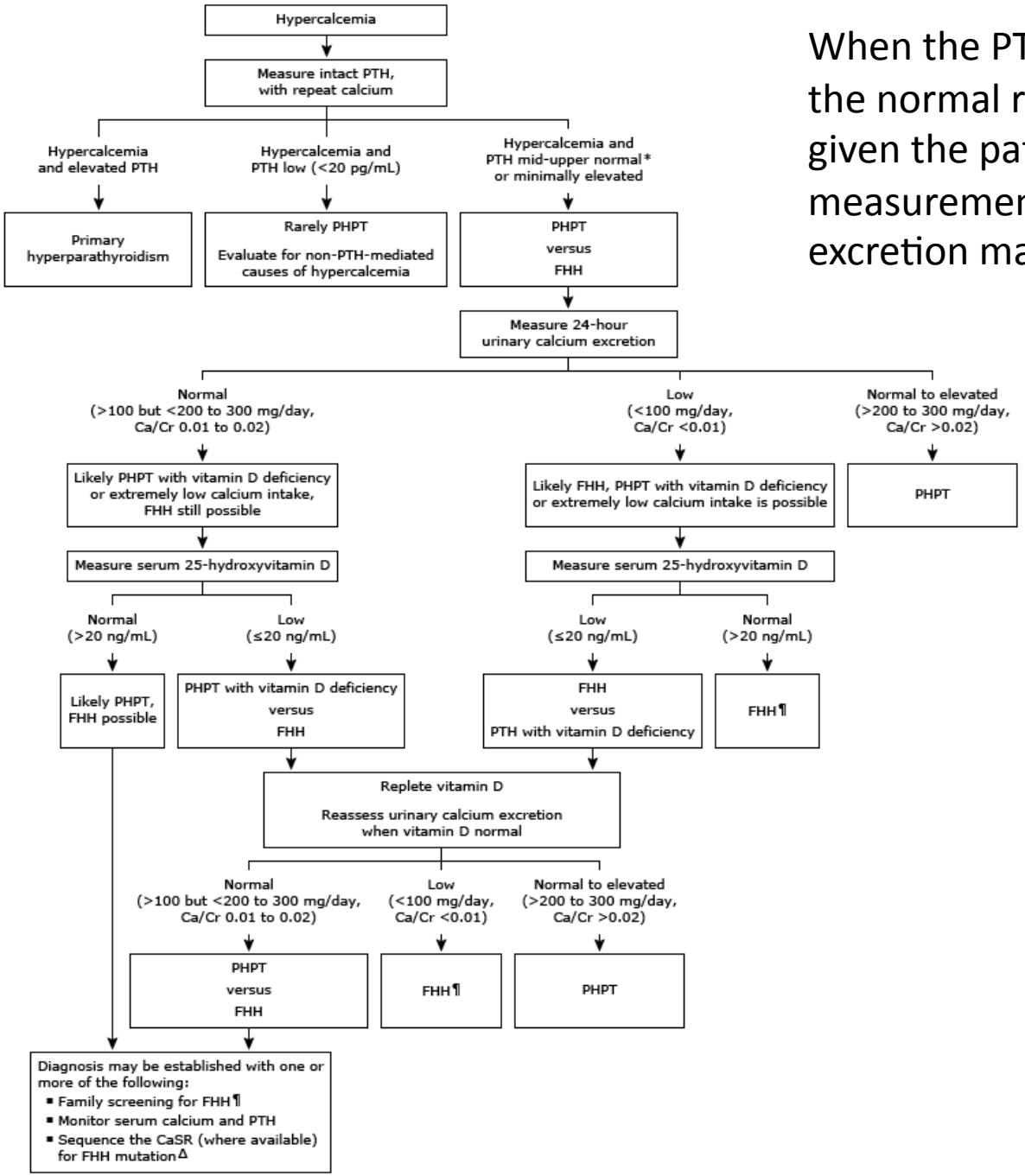
Diagnosis of primary hyperparathyroidism



When the PTH is minimally elevated or within the normal range (but inappropriately normal given the patient's hypercalcemia), measurement of 24-hour urinary calcium excretion may help distinguish PHPT from FHH

Differential diagnosis of primary hyperparathyroidism, typical laboratory findings

Disease	Laboratory test				
	Intact PTH	Serum calcium	Urinary calcium (mg/24 hours)	Ca/Cr clearance	25OHD
PHPT	High-normal or elevated	Elevated	Normal or elevated	0.01 to 0.05 (>0.02)	Normal, low-normal, or low
Malignancy	Low (<20 pg/mL)	Elevated	Generally high		Depends on malignancy*
FHH	Normal, mildly elevated in 15 to 20 percent	Elevated	Generally low (<100)	<0.01	Normal
PHPT with vitamin D deficiency	Elevated	Normal or elevated	Low-normal or low (<200)		Low (<20 ng/mL)
Normocalcemic PHPT	Elevated	Normal	Normal		Normal
Secondary hyperparathyroidism due to vitamin D deficiency	Elevated	Normal or low	Low		Low (<20 ng/mL)

Diagnosis: summary

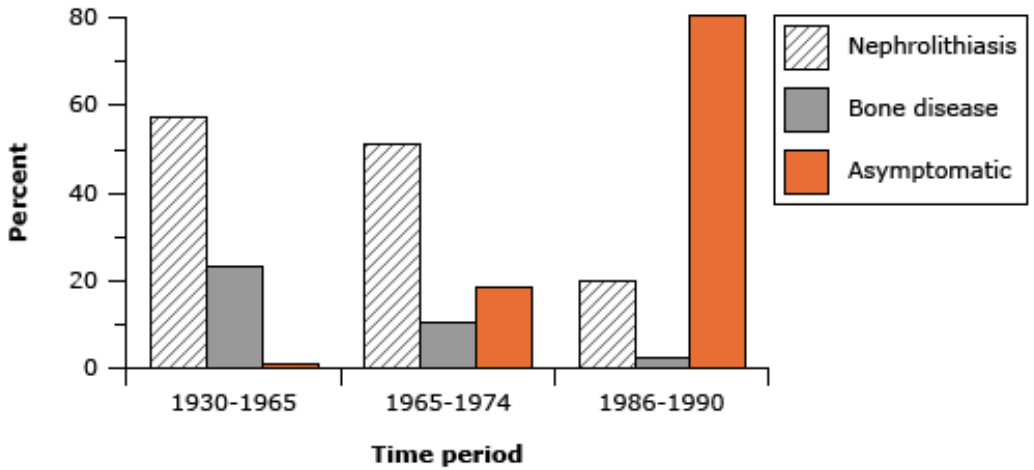
- Ca alb PTH Ca++
- 25OH-vitD
- calciuria

Clinical features

- The most common clinical presentation is ***asymptomatic*** *PHPT* !
- The classical manifestations of PHPT ("bones, stones, abdominal moans, and psychic groans") are uncommon in the United States but are still prevalent in other countries, especially developing ones

- Atypical presentations include normocalcemic PHPT and parathyroid crisis.

Changing presentation of primary hyperparathyroidism



Different patterns of presentation of primary hyperparathyroidism in three different time periods.
The latest survey shows that **80 percent of patients are asymptomatic** and discovered incidentally on routine blood screening;
bone disease (osteitis fibrosa cystica), on the other hand, has virtually disappeared as a presenting symptom.

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Silverberg SJ, Bilezikian JP . Evaluation and management of primary hyperparathyroidism. J Clin Endocrinol Metab. 1996;81(6):2036.

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Asymptomatic patients

- have *mild* and sometimes only *intermittent* hypercalcemia.
- In most asymptomatic patients, the mean serum calcium concentration *is less than 1.0 mg/dL* (0.25 mmol/L) above the upper limit of the normal range. (MW Ca= 40)
- In most patients, serum calcium and PTH levels remain stable, although they may increase over time in a small subset (<5%) of subjects

Siperstein AE, Shen W, Chan AK, Duh QY, Clark OH . Normocalcemic hyperparathyroidism. Biochemical and symptom profiles before and after surgery. Arch Surg. 1992;127(10):1157
Bilezikian JP, Silverberg SJ. Clinical practice. Asymptomatic primary hyperparathyroidism. N Engl J Med. 2004;350(17):1746.
Rubin MR, Bilezikian JP, McMahon DJ, Jacobs T, Shane E, Siris E, Udesky J, Silverberg SJ. The natural history of primary hyperparathyroidism with or without parathyroid surgery after 15 years. J Clin Endocrinol Metab. 2008;93(9):3462.

"*presumed* asymptomatic"…

- Some patients with PHPT presumed asymptomatic , when carefully questioned, have ***nonspecific symptoms***, such as:
  - fatigue,
  - weakness,
  - anorexia,
  - mild depression,
  - and mild cognitive or neuromuscular dysfunction, and others simply miss work often

Perrier ND . Asymptomatic hyperparathyroidism: a medical misnomer? Surgery. 2005; 137(2):127
Trombetti A, Christ ER, Henzen C, Gold G, Brändle M, Herrmann FR, Torriani C, Triponez F, Kraenzlin M, Rizzoli R, Meier C . Clinical presentation and management of patients with primary hyperparathyroidism of the Swiss Primary Hyperparathyroidism Cohort: a focus on neuro-behavioral and cognitive symptoms. J Endocrinol Invest. 2016;39(5):567.
Pepersack T, Jabbour N, Fuss M, Karmali R, Van Geertruyden J, Corvilain J. Hyperuricemia and renal handling of urate in primary hyperparathyroidism. Nephron. 1989;53(4):349-52.

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Pepersack T, Jabbour N, Fuss M, Karmali R, Van Geertruyden J, Corvilain J. Hyperuricemia and renal handling of urate in primary hyperparathyroidism. Nephron. 1989;53(4):349-52.

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"*presumed* asymptomatic" Cognitive function

- PHPT patients often present elevated *depression* and *anxiety* scores and *cognitive dysfunction*, but rarely as isolated manifestations.
- These alterations *may be relieved* upon treatment by parathyroidectomy.

Trombetti A, Christ ER, Henzen C, Gold G, Brändle M, Herrmann FR, Torriani C, Triponez F, Kraenzlin M, Rizzoli R, Meier C . Clinical presentation and management of patients with primary hyperparathyroidism of the Swiss Primary Hyperparathyroidism Cohort: a focus on neuro-behavioral and cognitive symptoms. J Endocrinol Invest. 2016;39(5):567.

"*presumed* asymptomatic" Cognitive function

Table 2 Clinical presentation of patients included in the Swiss Primary Hyperparathyroidism Cohort Study

	PHPT and symptomatic disease 143 (43) *n* (%)	PHPT and asymptomatic disease 189 (57) *n* (%)	*P* value
Renal lithiasis, *n* (%)	41 (29)	–	
Clinical vertebral fractures	20 (6)	–	
Non-vertebral fractures	41 (12)	–	
Any fractures, *n* (%)	55 (38 %)	–	
Muscle weakness, *n* (%)	53 (37)	20 (11)	0.0001
Age <50 years	18 (13)	24 (13)	0.976
Age (years)	68 ± 15	67 ± 15	0.474
Kidney dysfunction, *n* (%)	16 (11)	11 (6)	0.08
Osteoporosis[a], *n* (%)	38 (43)	71 (38)	0.373
Serum calcium ≥2.85 mmol/l, *n* (%)	27 (22)	34 (20)	0.670
Serum calcium (*N*: 2.25–2.60 mmol/l)	2.7 ± 0.3	2.7 ± 0.2	0.846
Serum PTH (*N*: 1.1–6.8 pmol/l)	18.3 ± 20.5	14.8 ± 9.4	0.052
25-Hydroxyvitamin D (75–120 nmol/l)	61 ± 33	55 ± 27	0.139

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Trombetti A, Christ ER, Henzen C, Gold G, Brändle M, Herrmann FR, Torriani C, Triponez F, Kraenzlin M, Rizzoli R, Meier C . Clinical presentation and management of patients with primary hyperparathyroidism of the Swiss Primary Hyperparathyroidism Cohort: a focus on neuro-behavioral and cognitive symptoms. J Endocrinol Invest. 2016;39(5):567.

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"*presumed* asymptomatic" Cognitive function

Table 3 Changes in neuro-behavioral and cognitive symptoms according to parathyroidectomy using paired data: Swiss Primary Hyperparathyroidism Cohort Study

	Normal range	Parathyroidectomy				Follow-up			
		N	T0 (baseline)	Evaluation 2	*P**	*N*	T0 (baseline)	Evaluation 2	*P**
MMSE	≥24	44	28.5 (28.0–29.0)	29 (28.0–30.0)	0.01	15	28 (19.9–29)	29 (24.2–30.0)	ns
MMSE ≤24, *n* (%)			7 (16 %)	2 (5 %)	0.0001		5 (33 %)	4 (27 %)	0.05
Clock drawing test		36	9.5 (8.0–10.0)	8.0 (8.0–9.0)	ns	11	7.0 (5.0–9.0)	7.0 (3.7–9.0)	ns
<8, *n* (%)			9 (25 %)	11 (31 %)	ns		7 (64 %)	7 (64 %)	ns
HADS anxiety subscale		44	6.5 (5–8)	5 (5.0–9.0)	0.05	17	5.0 (3.0–6.0)	4.0 (3.0–6.0)	ns
≥8, *n* (%)			7 (16 %)	10 (23 %)	0.001		2 (17 %)	0 (0 %)	ns
HADS depression subscale		44	3.5 (3.0–4.0)	3 (2.0–4.0)	0.05	17	2.0 (1.0–4.0)	3.0 (2.0–5.0)	ns
			4 (9 %)	0 (0 %)	0.007		0 (0 %)	0 (0 %)	ns

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Trombetti A, Christ ER, Henzen C, Gold G, Brändle M, Herrmann FR, Torriani C, Triponez F, Kraenzlin M, Rizzoli R, Meier C . Clinical presentation and management of patients with primary hyperparathyroidism of the Swiss Primary Hyperparathyroidism Cohort: a focus on neuro-behavioral and cognitive symptoms. J Endocrinol Invest. 2016;39(5):567.

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Normocalcemic primary hyperparathyroidism

- High parathyroid hormone (PTH) levels in the absence of hypercalcemia
- In order to make this diagnosis, certain conditions must be met:
  - In particular, all secondary causes for hyperparathyroidism must be ruled out,
  - and ionized calcium levels should be normal

Silverberg SJ, Lewiecki EM, Mosekilde L, Peacock M, Rubin MR. Presentation of asymptomatic primary hyperparathyroidism: proceedings of the third international workshop. J Clin Endocrinol Metab. 2009;94(2):351.

Causes of secondary hyperparathyroidism

Renal failure
Impaired calcitriol production
Hyperphosphatemia
Hypocalcemia
Decreased calcium intake
Calcium malabsorption
Vitamin D deficiency
Bariatric surgery
Celiac disease
Pancreatic disease (fat malabsorption)
Renal calcium loss
Idiopathic hypercalciuria
Loop diuretics
Inhibition of bone resorption
Bisphosphonates
Denosumab
Hungry bone syndrome

Parathyroid crisis

- Rare
- Ca >15 mg/dL (3.8 mmol/L)
- marked symptoms of hypercalcemia:
  - in particular, central nervous system dysfunction.
- In some cases, the syndrome occurs in patients with previously documented PHPT that is not severe. In others, it is the first evidence of parathyroid disease.
- may be related to an intercurrent illness (often of a life-threatening nature), volume depletion, or infarction of a parathyroid adenoma

Ahmad S, Kuraganti G, Steenkamp D. Hypercalcemic crisis: a clinical review. Am J Med. 2015 Mar;128(3):239-45.
Fitzpatrick LA, Bilezikian JP. Acute primary hyperparathyroidism. Am J Med. 1987;82(2):275.

Clinical manifestations of hypercalcemia

Renal
Polyuria
Polydipsia
Nephrolithiasis
Nephrocalcinosis
Distal renal tubular acidosis
Nephrogenic diabetes insipidus
Acute and chronic renal insufficiency
Gastrointestinal
Anorexia, nausea, vomiting
Bowel hypomotility and constipation
Pancreatitis
Peptic ulcer disease
Musculoskeletal
Muscle weakness
Bone pain
Osteopenia/osteoporosis
Neurologic
Decreased concentration
Confusion
Fatigue
Stupor, coma
Cardiovascular
Shortening of the QT interval
Bradycardia
Hypertension

Peacock M. Primary hyperparathyroidism and the kidney: biochemical and clinical spectrum. J Bone Miner Res. 2002;17.

Symptoms and signs of excess parathyroid hormone hormone secretion

Symptoms and signs of hypercalcemia
Bone disease
Nephrolithiasis
Hypophosphatemia
Increased production of calcitriol
Proximal renal tubular acidosis
Hypomagnesemia
Hyperuricemia and gout
Anemia

Neuromuscular

- *weakness and fatigue* are common among patients with PHPT
  - atrophy of type II muscle fibers was seen
- . However, that syndrome, as well as any objective evidence of myopathy or weakness, is rarely seen today
- In some more severely affected patients, neuromuscular symptoms *may improve after cure.*

Lundgren E, Ljunghall S, Akerström G, Hetta J, Mallmin H, Rastad J. Case-control study on symptoms and signs of "asymptomatic" primary hyperparathyroidism. Surgery. 1998;124(6):980

Neuropsychiatric disturbances

- lethargy, depressed mood, psychosis, decreased social interaction, and cognitive dysfunction

- But:
  - lack of rigorous assessment for symptoms in many studies,
  - small size of the studies,
  - and wide variations in the instrument

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Coker LH, Rorie K, Cantley L, Kirkland K, Stump D, Burbank N, Tembreull T, Williamson J, Perrier. Primary hyperparathyroidism, cognition, and health-related quality of life. Ann Surg. 2005;242(5): 642.

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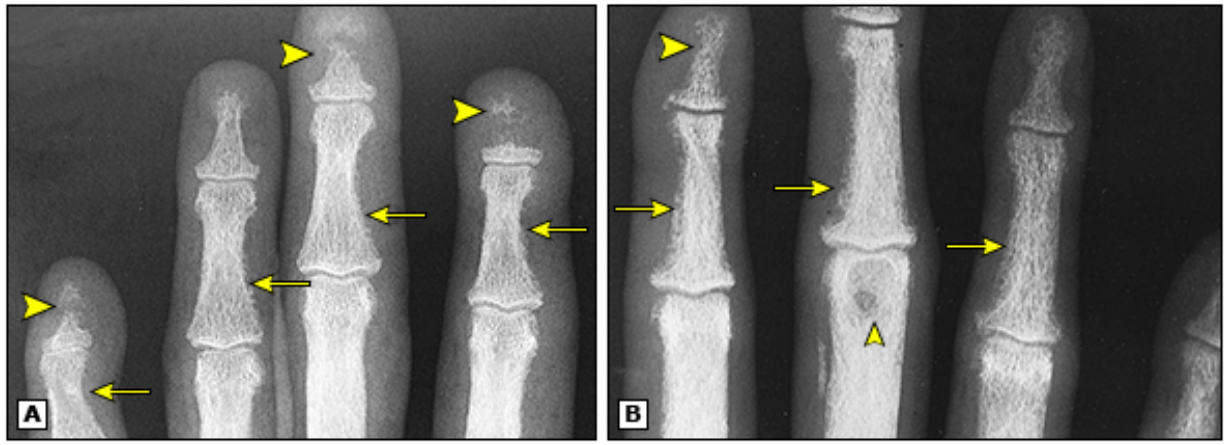
Skelettal

- Decreased BMD
  - more cortical sites (forearm and hip) as compared with more trabecular sites (spine)
- Fractures?
  - controversal

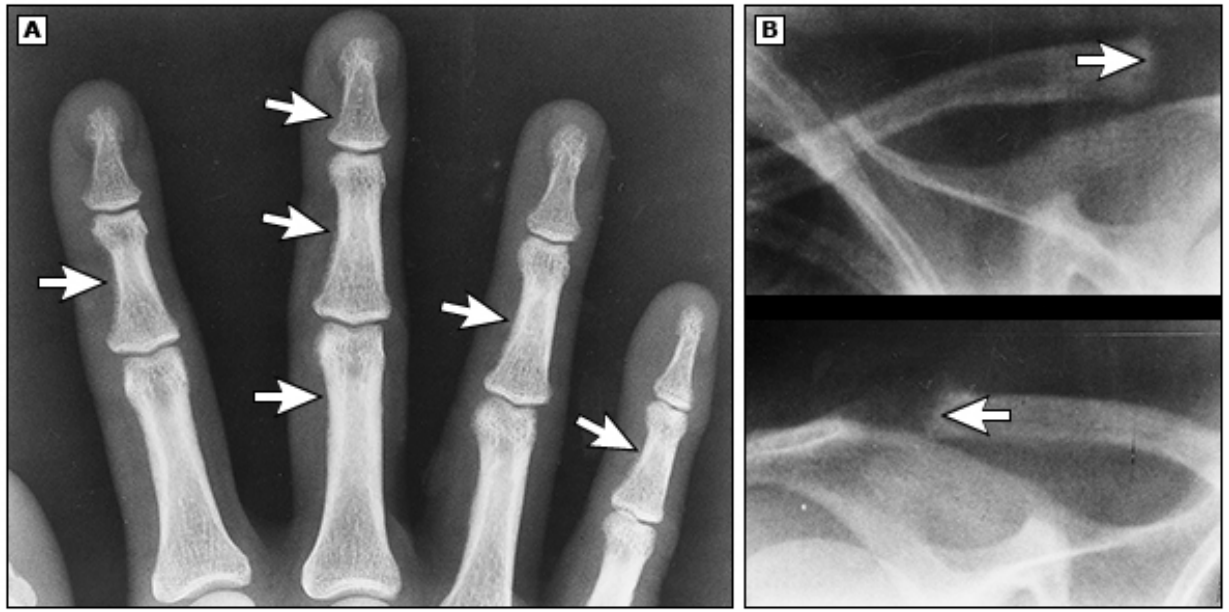
Silverberg SJ, Shane E, de la Cruz L, Dempster DW, Feldman F, Seldin D, Jacobs TP, Siris ES, Cafferty M, Parisien MV . Skeletal disease in primary hyperparathyroidism. J Bone Miner Res. 1989;4(3):283.
De Geronimo S, Romagnoli E, Diacinti D, D'Erasmo E, Minisola S. The risk of fractures in postmenopausal women with primary hyperparathyroidism. Eur J Endocrinol. 2006;155(3):415.
Vignali E, Viccica G, Diacinti D, Cetani F, Cianferotti L, Ambrogini E, Banti C, Del Fiacco R, Bilezikian JP, Pinchera A, Marcocci C. Morphometric vertebral fractures in postmenopausal women with primary hyperparathyroidism. J Clin Endocrinol Metab. 2009;94(7):2306.

Osteitis fibrosa cystica: Findings on radiograph of the phalanges



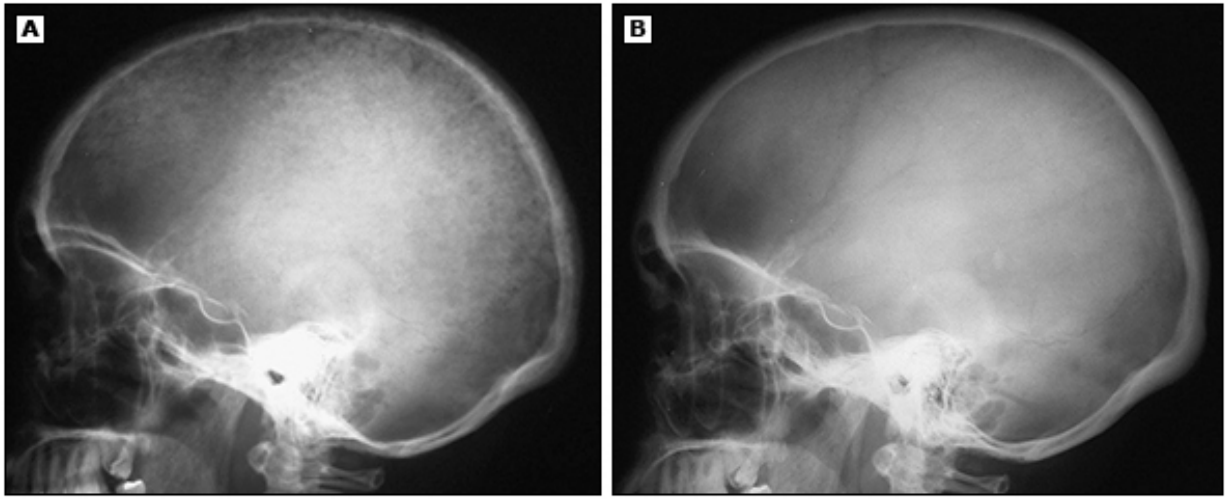
(A and B) Posteroanterior (PA) hands. Note the radial margins of the proximal and middle phalanges bilaterally are frayed, irregular, and lace-like (arrows) owing to characteristic subperiosteal resorption. Also note the brown tumor (small arrowhead) and osteolysis of the distal phalanges (large arrowheads).

Osteitis fibrosa cystica: Findings on radiographs of the phalanges and clavicles



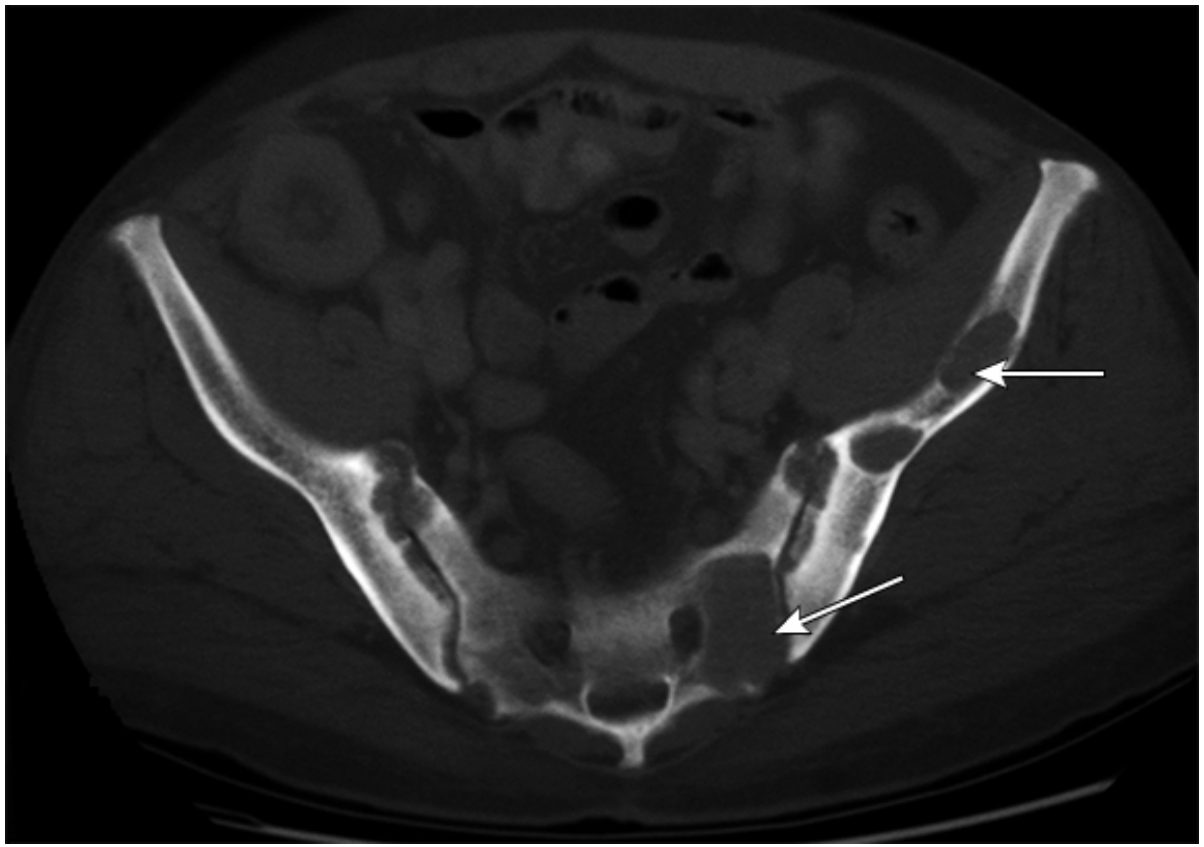
A) Detail view of the hands shows subperiosteal resorption in the phalanges (arrows).
(B) Detail views of both distal clavicles show subchondral resorption bilaterally (arrows).

Osteitis fibrosa cystica: Findings on skull radiograph



Skull radiograph shows the typical "salt and pepper" appearance caused by osteitis fibrosa cystica (A). Skull radiograph of same patient six months after removal of the patient's parathyroid adenoma (B). The bones have returned to normal.

Brown tumors of pelvic bones: Findings on CT



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Subclinical renal disease

- nephrolithiasis, hypercalciuria, nephrocalcinosis, chronic renal insufficiency, and several abnormalities in renal tubular function: in particular, *decreased concentrating ability*

Tassone F, Gianotti L, Emmolo I, Ghio M, Borretta G. Glomerular filtration rate and parathyroid hormone secretion in primary hyperparathyroidism. J Clin Endocrinol Metab. 2009 Nov;94(11): 4458-61.
Rejnmark L, Vestergaard P, Mosekilde L. Nephrolithiasis and renal calcifications in primary hyperparathyroidism. J Clin Endocrinol Metab. 2011 Aug;96(8):2377-85.

Cardiovascular

- hypertension,
- arrhythmia,
- ventricular hypertrophy,
- vascular and valvular calcification

Walker MD, Silverberg SJ. Cardiovascular aspects of primary hyperparathyroidism. J Endocrinol Invest. 2008;31(10):925.
Näppi S, Saha H, Virtanen V, Limnell V, Sand J, Salmi J, Pasternack A. Left ventricular structure and function in primary hyperparathyroidism before and after parathyroidectomy. Cardiology. 2000;93(4):229.
Iwata S, Walker MD, Di Tullio MR, Hyodo E, Jin Z, Liu R, Sacco RL, Homma S, Silverberg SJ. Aortic valve calcification in mild primary hyperparathyroidism. J Clin Endocrinol Metab. 2012;97(1): 132.

Body weight and abnormalities in glucose metabolism

- A higher than normal frequency of impaired glucose tolerance and type 2 diabetes have been reported in some, but not all, studies of PHPT

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Procopio M, Magro G, Cesario F, Piovesan A, Pia A, Molineri N, Borretta G. The oral glucose tolerance test reveals a high frequency of both impaired glucose tolerance and undiagnosed Type 2 diabetes mellitus in primary hyperparathyroidism. Diabet Med. 2002;19(11):958.

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Rheumatologic manifestations

- Hyperuricemia and gout.
- Pseudogout with pyrophosphate crystals into the joint.

Pepersack T, Jabbour N, Fuss M, Karmali R, Van Geertruyden J, Corvilain J. Hyperuricemia and renal handling of urate in primary hyperparathyroidism. Nephron. 1989;53(4):349-52.
Rubin MR, Silverberg SJ, Bilezikian JP. Primary hyperparathyroidism: Rheumatologic manifestations and bone disease. In: Bone Disease in Rheumatology, Maricic M, Gluck OS (Eds), Lippincott Williams & Wilkins, Philadelphia 2005. p.190.

Clinical manifestations: summary

- in western populations is *asymptomatic hypercalcemia* detected by routine biochemical screening
- Patients with *normocalcemic hyperparathyroidism* typically come to medical attention in the setting of an evaluation for low bone mineral density
- Parathyroid crisis, which is rare
- The classical symptoms and signs of PHPT, such as osteitis fibrosa cystica and nephrolithiasis, is rarely seen in the United States and Europe,
- Patients with PHPT may have *decreased bone mineral density* (BMD), in particular at more cortical sites (forearm and hip)
- renal manifestations : nephrolithiasis, hypercalciuria, nephrocalcinosis, chronic renal insufficiency, and several abnormalities in renal tubular function: in particular, decreased concentrating ability

Management

- Symptomatic:nephrolithiasis, symptomatic hypercalcemia
  - Parathyroidectomy is an effective therapy that cures:
    - the disease,
    - decreases the risk of kidney stones,
    - improves bone mineral density (BMD),
    - and may decrease fracture risk and
    - modestly improve some quality of life measurements
  - For “poor “surgical candidate” R/ cinacalcet 30 mg twice daily rather than bisphosphonates.

Silverberg SJ, Bone HG 3rd, Marriott TB, Locker FG, Thys-Jacobs S, Dziem G, Kaatz S, Sanguinetti EL, Bilezikian JP Short-term inhibition of parathyroid hormone secretion by a calcium-receptor agonist in patients with primary hyperparathyroidism. Silverberg SJ, Bone HG 3rd, Marriott TB, Locker FG, Thys-Jacobs S, Dziem G, Kaatz S, Sanguinetti EL, Bilezikian JP. N Engl J Med. 1997;337(21):1506.

Management

- Asymptomatic:
- Preventive measures:
  - Avoid thiazides, Li, volume depletion, prolonged bed rest or inactivity, and a high-calcium diet (>1000 mg/day).
  - physical activity to minimize bone resorption
  - adequate hydration
  - Maintain a moderate calcium intake (1000 mg/day)
  - Maintain moderate vitamin D intake (400 to 800 international units daily)

Bilezikian JP, Brandi ML, Eastell R, Silverberg SJ, Udelsman R, Marcocci C, Potts JT Jr Guidelines for the management of asymptomatic primary hyperparathyroidism: summary statement from the Fourth International Workshop. J Clin Endocrinol Metab. 2014;99(10):3561.

Guidelines for surgery in asymptomatic PHPT: A comparison of current guidelines with the previous one*

Measurement ¶	2008	2014
Serum calcium (>upper limit of normal)	1.0 mg/dL (0.25 mmol/L)	1.0 mg/dL (0.25 mmol/L)
Skeletal	1. BMD by DXA: T-score <–2.5 at any site ¶ 2. Previous fragility fracture Δ	1. BMD by DXA: T-score <–2.5 at lumbar spine, total hip, femoral neck, or distal 1/3 radius ¶ 2. Vertebral fracture by radiograph, CT, MRI, or VFA
Renal	1. eGFR <60 mL/min 2. 24-hour urine for calcium not recommended	1. Creatinine clearance <60 mL/min 2. 24-hour urine for calcium >400 mg/day (>10 mmol/day) and increased stone risk by biochemical stone risk analysis ◇ 3. Presence of nephrolithiasis or nephrocalcinosis by radiograph, ultrasound, or CT
Age (years)	<50	<50

Management: summary

- Symptomatic
  - -> surgery
  - ->cinacalcet
- Asymptomatic:
  - assess the risk for end organ effect
  - Preventive measures