Parathyroid Disease

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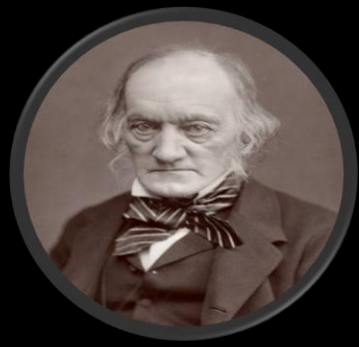
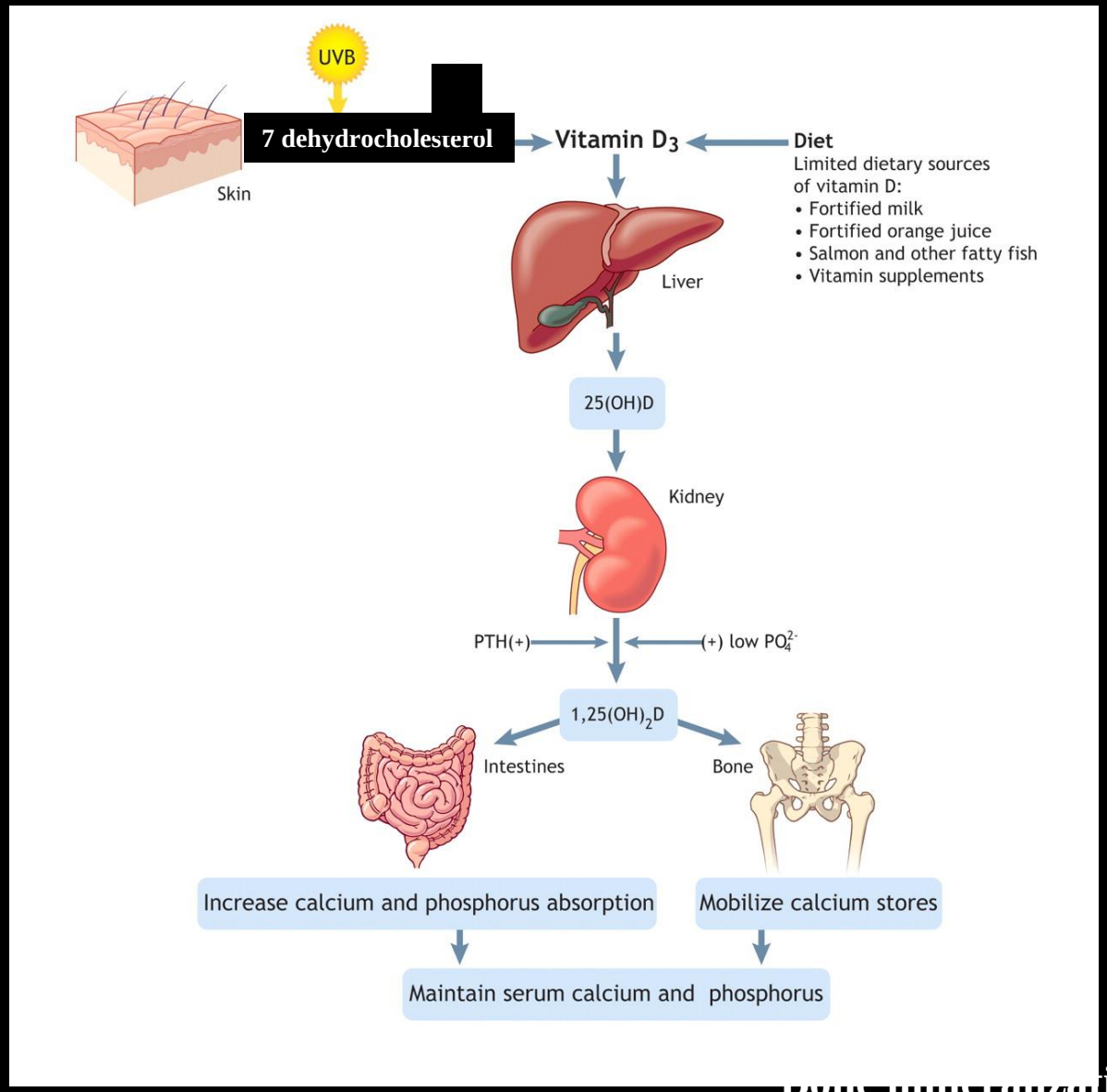
Parathyroid Glands



1862

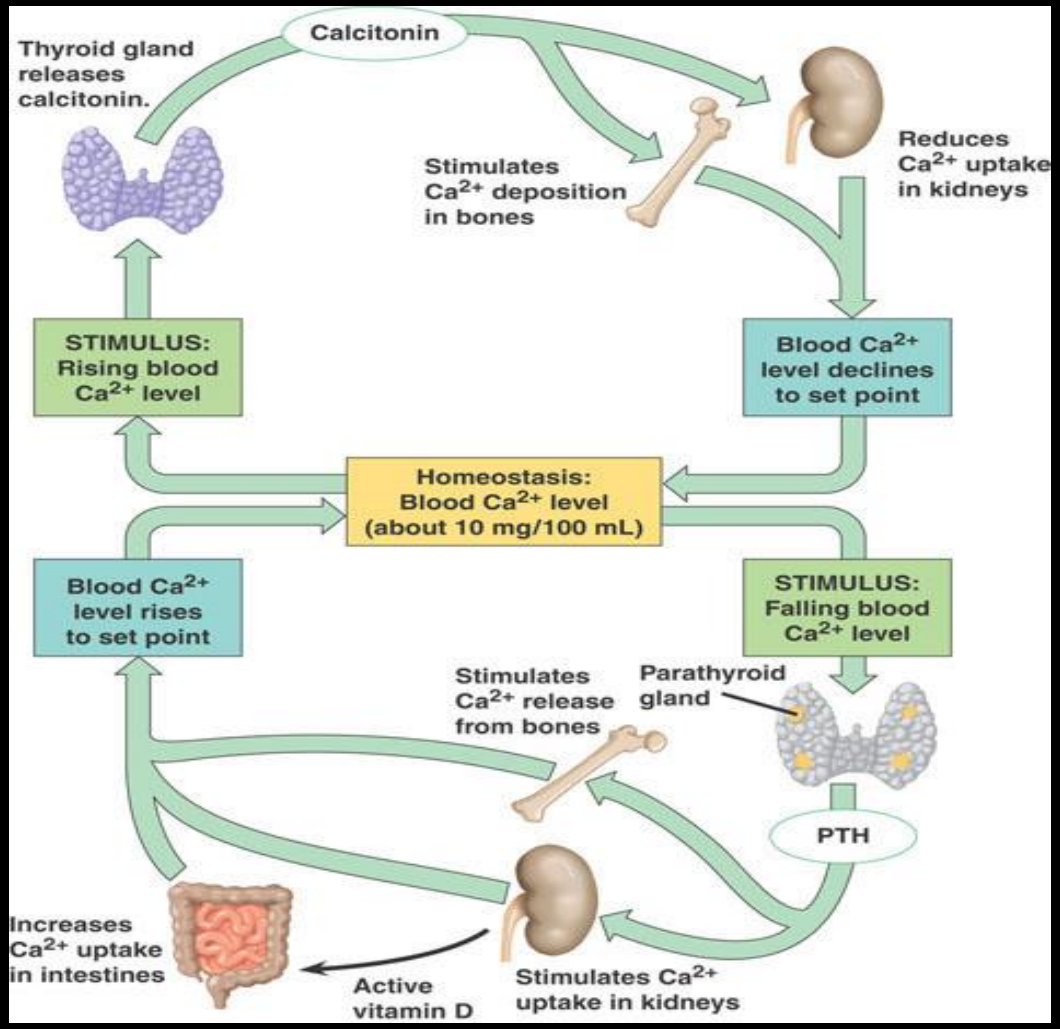
Modarai B, Sawyer A, Ellis H. The glands of Owen. J R Soc Med 2004; 97(10):494-495.

Vitamin D metabolism



Bone mineralization

Calcium Homeostasis



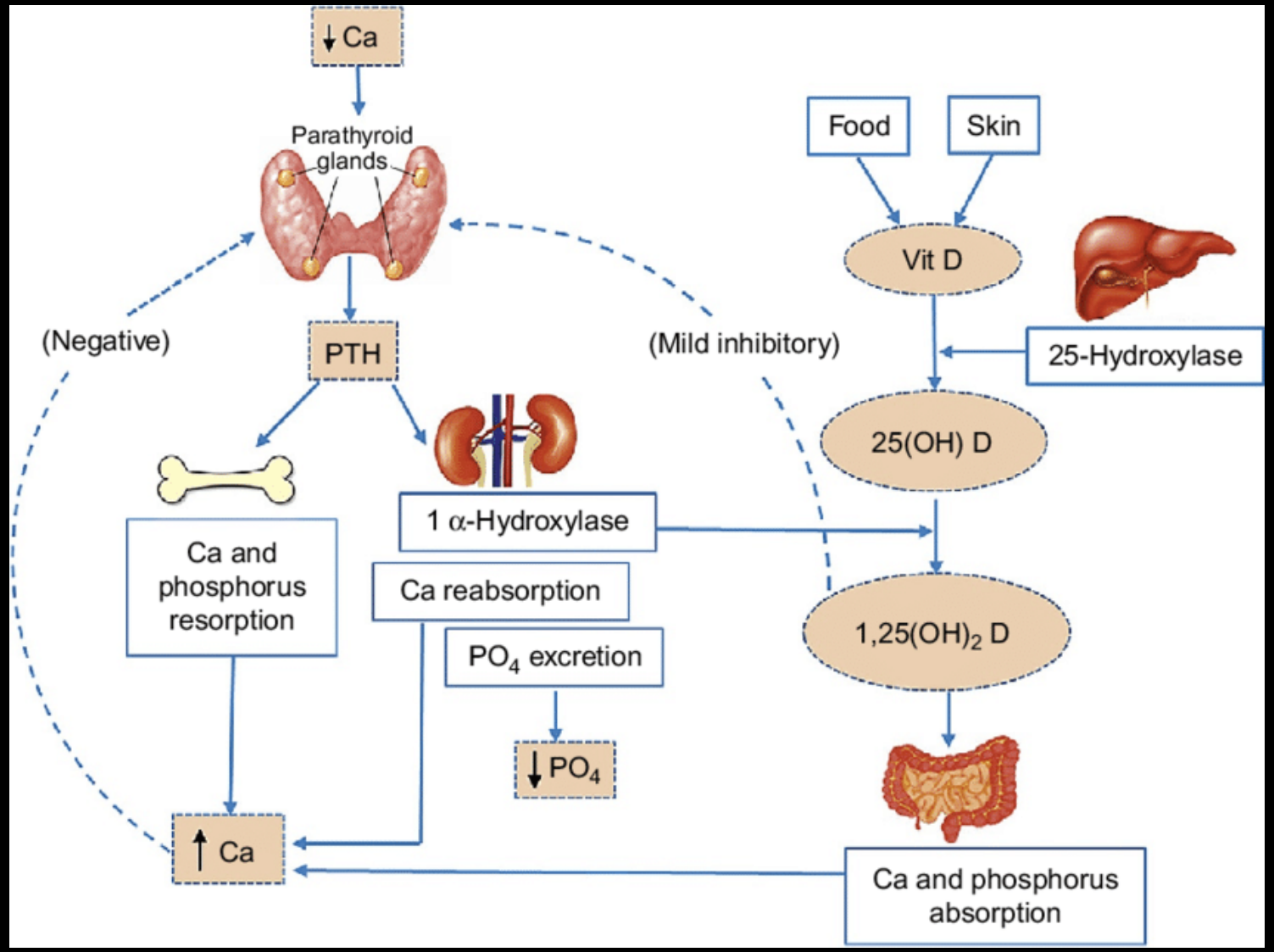
3 hormones:

Active form of vit D

PTH

Calcitonin

Calcium Homeostasis



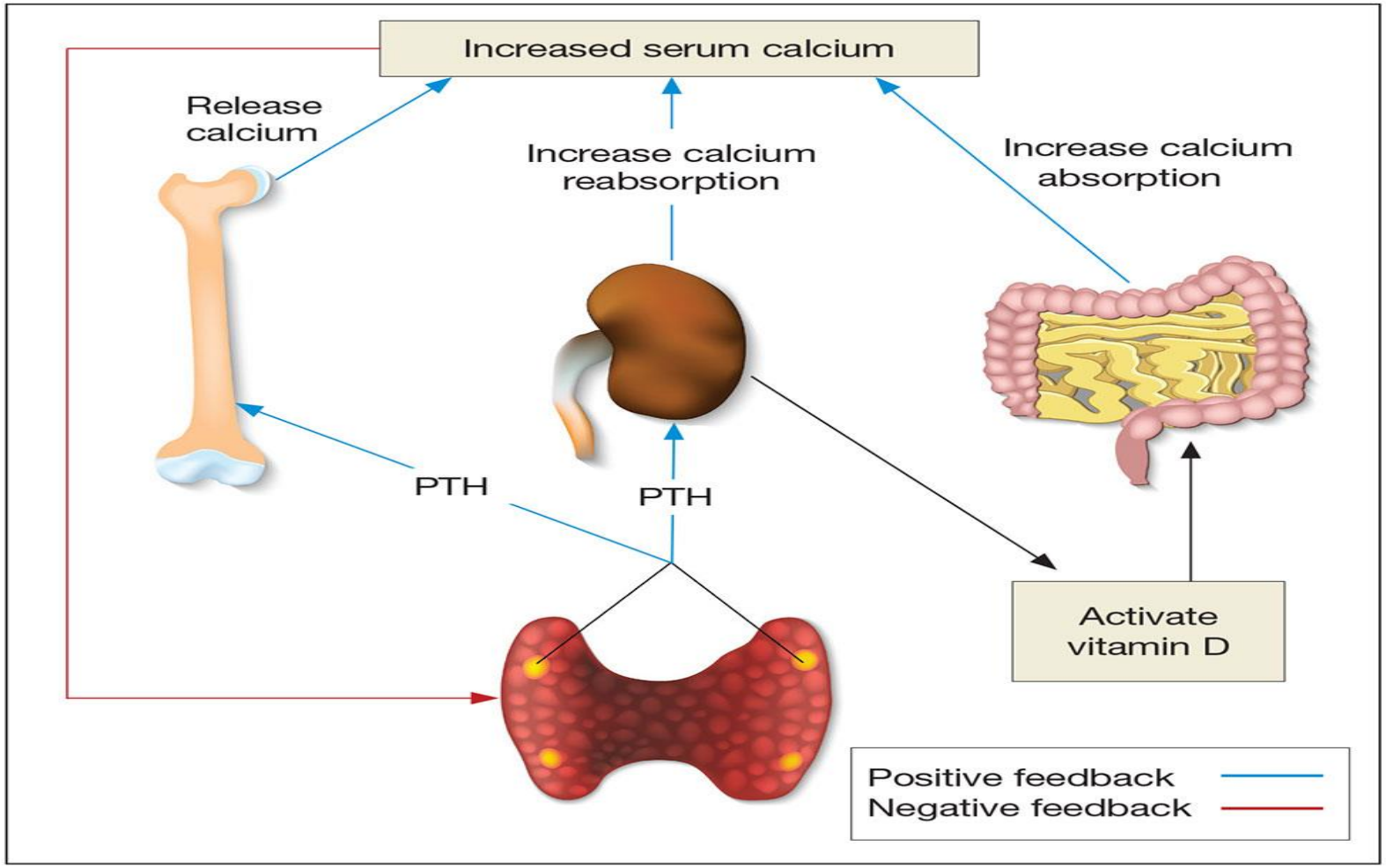
Calcium forms:

50% free (ionized)

40% albumin bound

10% Anion bound (Phosphorous, citrate)

Parathyroid Hormone–Calcium Feedback



Serum calcium levels are modulated by PTH secretion by action on bone, kidneys, and intestines. PTH stimulates osteoclastic release of calcium directly into the blood. Kidneys are stimulated to increase reabsorption of calcium and convert 25-hydroxy-vitamin D to the active form of vitamin D. Vitamin D prompts gastrointestinal calcium absorption. All three pathways in the positive feedback loop result in increased serum calcium levels. In the negative feedback loop, high serum levels suppress PTH secretion; low levels stimulate PTH secretion.

Sources: Kapustin and Schofield. *Nurse Pract.* 2012[3]; Michels and Kelly. *Am Fam Physician.* 2013.[8]

The parathyroid glands (unlike other endocrine glands) are not controlled by the hypothalamic-pituitary axis. They are controlled by ionized serum calcium levels (active form of calcium).

Ionized calcium receptors on parathyroids are G-protein membrane receptors

Calcium Homeostasis

	PTH	Calcitriol	Calcitonin
Stimulus for secretion	↓ serum [Ca^{2+}] ↑ serum [PO_4^{3-}] ↓ serum [calcitriol]	↓ serum [Ca^{2+}] ↓ serum [PO_4^{3-}] ↑ PTH	↑ serum [Ca^{2+}]
Actions:			
Bone	↑ resorption of bone	↑ resorption of bone	↓ resorption of bone
Kidney	↑ Ca^{2+} reabsorption ↓ phosphate reabsorption	↑ Ca^{2+} and phosphate reabsorption ↑ Ca^{2+} and phosphate absorption	↑ excretion of Ca^{2+} and phosphate
Intestines	↑ Ca^{2+} absorption (via activation of calcitriol)		None
Net effect	↑ serum [Ca^{2+}] ↓ serum [PO_4^{3-}]	↑ serum [Ca^{2+}] ↑ serum [PO_4^{3-}]	↓ serum [Ca^{2+}]

Causes of Hyperparathyroidism

Primary	Secondary- In response to hypocalcemia	Tertiary
•Parathyroid Adenoma, Hyperplasia, Carcinoma •MEN 1 or MEN 2a •Familial hypocalciuric hypercalcemia •Hyperparathyroid-jaw tumor (HPT-JT) syndrome •Familial isolated hyperparathyroidism (FIHPT)	•Renal Failure -Impaired calcitriol production -Hyperphosphatemia •Decreased calcium -Low oral intake -Vit D deficiency -Malabsoption -renal calcium loss – lasix •Inhibition of bone resorption -Bisphophonates -Hungry Bone Syndrome	•Autonomous hypersecretion of parathyroid hormone -chronic secondary hyperparathyroidism -After renal transplantation

Parathyroid carcinoma accounts for only 1% of cases of primary hyperparathyroidism

	Primary Hyperparathyroidism	Secondary Hyperparathyroidism	Tertiary Hyperparathyroidism
Calcium	↑	↓/N	↑
PTH	↑	↑	↑↑
Phosphate	↓	↑/N	↑

Manifestations of Primary Hyperparathyroidism

System	Signs and symptoms	Mechanism
Renal	Nephrolithiasis, nephrocalcinosis, recurrent urinary tract infections, renal impairment	Hypercalcemia, hypercalciuria, and hyperphosphaturia
		Calcium phosphate precipitates in alkaline urine, calcium oxalate stones form; stones formed in the renal pelvis or collecting ducts are associated with increased risk of infection
	Polyuria, dehydration	Hypercalcemia has a direct effect on renal tubules, causing a decreased response to antidiuretic hormone
Musculoskeletal	Osteoporosis, osteitis fibrosa cystica, fractures, muscle weakness, myalgia	Excess PTH excretion leads to metabolic acidosis, bone resorption, and myopathic changes
	Arthralgia, arthritis	Hyperuricemia leads to gout, pseudogout
Gastrointestinal	Abdominal pain, constipation, anorexia, nausea, vomiting	Hypercalcemia decreases gastrointestinal motility, stimulates the central vomiting center, and increases gastrin secretion
	Peptic ulcer disease	Hypercalcemia stimulates elevated hydrochloric acid secretion
	Pancreatitis (less common)	Exact mechanism unknown; gastrin weakly stimulates pancreatic enzymes and gallbladder contraction
Neurologic/ psychiatric	Memory impairment, depression, anxiety, confusion, stupor, coma	Hypercalcemia induces neuropathy, electroencephalographic changes
Cardiovascular	Hypertension	Hypercalcemia has direct effect on arterial smooth muscle and elevates plasma renin activity

Sources: Brashers et al. *Pathophysiology.* 2015[6]; Michels and Kelly. *Am Fam Physician.* 2013[8]; Bilezikian et al. *J Clin Endocrinol Metab.* 2014.[19]

Hypercalcemia / Hyperparathyroidism Signs

Mnemonic: "Bones, Stones, Groans, Moans"

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Painful Bones	Painful bone condition (Classically osteitis fibrosa cystica)
Renal Stones	Kidney Stones (Can ultimately lead to Renal failure)
Abdominal Groans	GI symptoms: Nausea, Vomiting, Constipation, Indigestion
Psychiatric Moans	Effects on nervous system: lethargy, fatigue, memory loss, psychosis, depression

Most cases of primary hyperparathyroidism are asymptomatic

Accuracy of Imaging Studies

Imaging Study	Sensitivity, % (95% CI)	Specificity, % (95% CI)	Positive Predictive Value, % (95% CI)
MIBI	69 (66-73)	92 (90-94)	89 (85-92)
US	63 (59-67)	90 (87-92)	89 (86-92)
MIBI and US imaging positive for same site (concordant)	56 (51-60)	60 (56-64)	99 (97-100)

2014 Guidelines for Surgery in Asymptomatic Primary Hyperparathyroidism (Bilezikian et al. JCEM, 2014)

Recommended Index	3rd Int'l Workshop (Bilezikian et al. JCEM 2009)	4th Int'l Workshop (Bilezikian et al., 2014)
Serum calcium (above normal)	>0.25 mmol/L	> 0.25 mmol/L
Skeletal	DXA: T-Score <-2.5 at any site; any fragility fracture	DXA: T-Score < -2.5 at any site; Vert Fx by X-ray or VFA
Renal	eGFR< 60 mL/min 24 hr urine: Not recommended	eGFR< 60 mL/min Stone by X-ray, CT, or ultrasound Urinary calcium: >10 mmol/d plus other urinary biochemical indices of increased stone risk
Age	<50	< 50

PHP

Patients suitable for surgical treatment

Patients unsuitable for surgical treatment

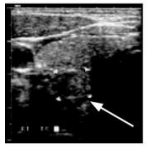
Clinical observation
Non-surgical techniques
Medical therapy

Ultrasound + ^{99m}Tc-MIBI scan

Concordant

Discordant

Negative



Minimally invasive parathyroidectomy
+
Intraoperative determination of PTH

Inadequate ↓ PTH
- Multiglandular disease
- Double adenoma
- Intrathyroid adenoma

Difficulty in dissection
Negative exploration
Parathyroid carcinoma suspicion

Multiglandular disease
- Familial disease (MEN)
- Renal chronic disease
- Lithium

Concomitant thyroid pathology

Bilateral cervical exploration
+
Intraoperative determination of PTH

↓ PTH > 50%

Cure

Persistence / recurrence

CT / MR / PET / arteriography / selective venous sampling

Cervical reintervention
Mediastinum surgery

Medical therapy