Managing Parathyroid Disorders: **Primary Hyperparathyroidism**

European Society of Endocrinology

This guide summarizes the 13 primary hyperparathyroidism (PHPT) consensus recommendations published within "European Expert Consensus on Practical Management of Specific Aspects of Parathyroid Disorders in Adults and in Pregnancy". *European Journal of Endocrinology* 186 (2) February 2022'. Please access the article for recommendations in full.

Q1 How do we differentially diagnose familial hypocalciuric hypercalcemia (FHH)?

Calcium creatinine clearance ratio (CCCR) <0.01 is a screening tool for FHH, but the 'cut-off' is of limited clinical value due to low diagnostic sensitivity and specificity.

A positive family history is a key feature of FHH. Historic calcium values are important to exclude progressive hypercalcemia as in primary hyperparathyroidism (PHPT). PTH levels >2-fold above upper limit of normal are suggestive of PHPT.

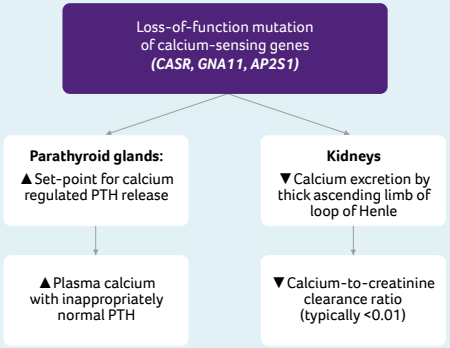

Figure 1. Alterations in calcium metabolism caused by FHH

Genetic testing is recommended for all patients with suspected FHH, but negative genetic testing does not exclude FHH, and ongoing follow-up of mutation negative patients is recommended.

Q2 What is normocalcemic primary hyperparathyroidism (PHPT)?

Normocalcemic PHPT is characterised by persistently (>3 months) increased PTH levels in the setting of consistently normal total, albumin-adjusted and / or free ionized serum calcium. Normocalcemic PHPT is a diagnosis of exclusion.

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).

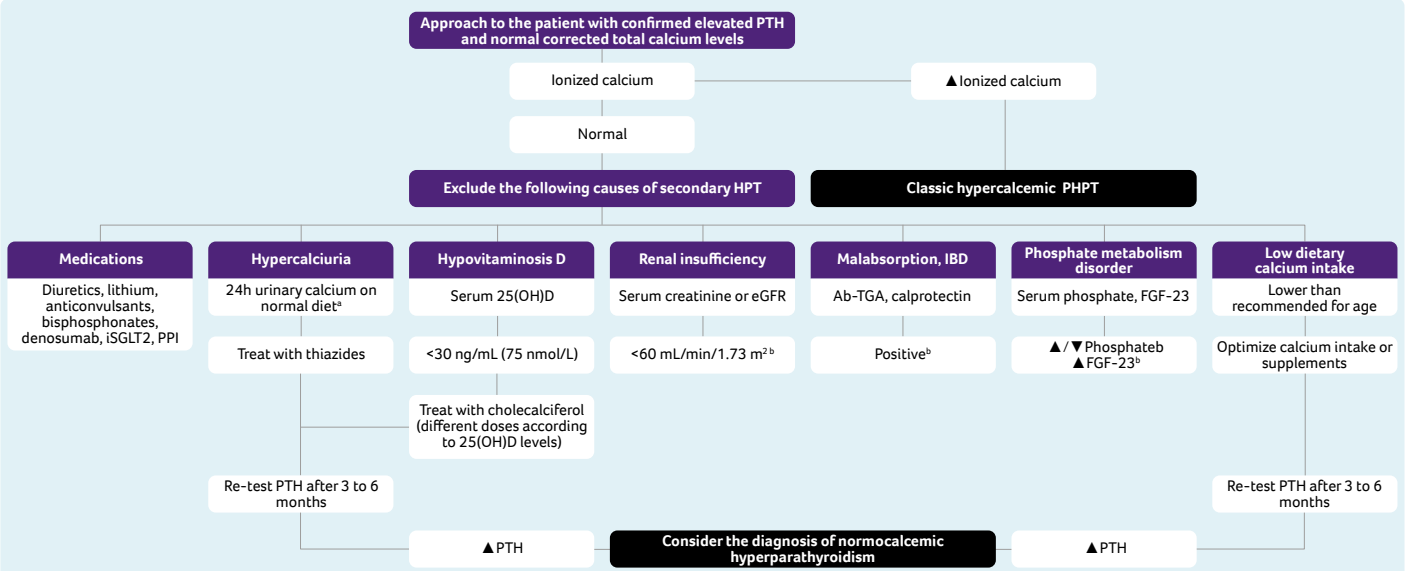

Figure 2. A clinical approach to patients with confirmed normocalcemic primary hyperparathyroidism. [a]Reference range >4 mg/kg/ day, >250 mg/day in females, and >300 mg/ day in males. [b]Evaluate for these disorders and manage as appropriate. 25(OH) D, serum 25-hydroxyvitamin D; Ab-TGA, anti-tissue 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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