Managing Parathyroid Disorders: Primary Hyperparathyroidism

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 hypercalcaemia (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 hypercalcaemia as in primary hyperparathyroidism (PHPT). PTH levels >2-fold above upper limit of normal are suggestive of PHPT.

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).

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 upon 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 un-suppressed 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 replaced. 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 24th 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 24th 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.

Table 2. Potential risk factors for hungry bone syndrome.

<table>
<thead>
<tr>
<th>Potential risk factors for hungry bone syndrome</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>High preoperative PTH level</td>
<td>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)</td>
</tr>
<tr>
<td>Large volume (weight and mass) of parathyroid adenoma</td>
<td>Positive correlation between PTH levels and volume of adenoma</td>
</tr>
<tr>
<td>High preoperative calcium levels</td>
<td>Explained as increased calcium resorption from bone and calcium reabsorption from renal tubules in case of preoperatively elevated PTH levels</td>
</tr>
<tr>
<td>Radiological evidence of PHPT-related bone disease</td>
<td>Brown tumors, multiple fractures, osteitis fibrosa cystica as an effect of long-lasting high circulating levels of PTH on the skeleton</td>
</tr>
<tr>
<td>Significantly elevated alkaline phosphatase</td>
<td>Reflects the state of bone turnover and the degree of osteoclast activity and bone resorption</td>
</tr>
<tr>
<td>Preoperatively low 25(OH)D concentrations</td>
<td>HBS develops indirectly by skeletal demineralization due to low circulating levels of 1,25(OH)2D with postoperative increased skeletal calcium requirements</td>
</tr>
</tbody>
</table>

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 Marzocchi, (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/paratz

Last updated Feb 2022.