Managing Parathyroid Disorders: **Chronic Hypoparathyroidism**

European Society of Endocrinology

This guide summarizes the 10 hypoparathyroidism (HypoPT) 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 define chronic post-surgical hypoparathyroidism (HypoPT)?

Postsurgical HypoPT should be suspected in patients with symptomatic or asymptomatic hypocalcemia and low PTH concentrations, or inappropriately normal PTH concentrations despite hypocalcemia.

Chronic postsurgical HypoPT is diagnosed ≥6 months after anterior neck surgery, if medication is still necessary to maintain calcium concentrations in the lower normal range.

Calcium should be measured preferably as ionized calcium, or as albumin-adjusted calcium concentration.

Q2 How can postoperative HypoPT be prevented?

We recommend that anterior neck surgery is performed only by experienced surgeons, particularly in patients at risk of postsurgical hypoparathyroidism (Table 1).

We further recommend measuring calcium, magnesium, 25-hydroxyvitamin D (25(OH)D), and PTH in advance of any anterior neck surgery and that vitamin D and magnesium deficiency should be treated.
The value of autotransplantation of devascularized or intracapsular parathyroids remains controversial. However, anatomical expertise, early visualization of the parathyroid glands with surgical loupes, meticulous surgical technique, and operative strategies personalized to each patient minimize risk and ensure a favorable outcome.

The day following surgery, PTH and ionized calcium should be measured to identify patients at risk of developing HypoPT. When immediate postsurgical hypoparathyroidism is diagnosed, we recommend a close and coordinated follow-up team including the surgeon, the endocrinologist and general practitioner (Figure 1). Keeping the patient symptom-free and allowing risk-free discharge are the primary goal in the early postoperative phase.

Q3 How can parathyroid gland injury be predicted?

We recommend early postoperative PTH monitoring (rather than isolated calcium assessments) to identify patients at risk of postsurgical parathyroid deficiency.

PTH levels <5.5 pg/mL (<0.58 pmol/L) are associated with the development of chronic HypoPT; on the contrary, PTH concentrations on the first postoperative day >10 pg/ mL (>1.06 pmol/L) seem to predict normal parathyroid function 6 months following surgery; a decrease in PTH levels >70% on the first postoperative day, when compared to preoperative PTH, was also associated with chronic HypoPT.

Risk factor postsurgical hypoparathyoidism	Comments
General	**Higher rates in** • Thyroid cancer with central lymph node dissection • Graves' disease **Risk mitigation** • Awareness • Preoperative screening of parathyroid function • Vitamin D status
Comorbidities	Obesity Gastrointestinal malabsorption, for example, post gastric bypass, severe IBD **Risk mitigation** • Awareness
Primary exploration vs repeated surgery	**Higher rates in** • Case of repeated surgery **Risk mitigation** • Critical assessment for additional/repeated surgeries
Combined thyroid and parathyroid surgery	Thyroid and parathyroid disease often co-exist but unnoticed if not specifically evaluated **Risk mitigation** • Preoperative evaluation for elective thyroid surgery must include parathyroid function (and vice versa)
Total thyroidectomy vs less extensive surgery	Risk bilateral surgery > risk unilateral surgery **Risk mitigation** • Individualized surgical strategy
Bilateral cervical exploration in parathyroid disease	Risk bilateral exploration > focused parathyroidectomy. **Risk mitigation** • Preoperative localization (ultrasound and nuclear medicine techniques) • Exclusion of familial hypocalciuric hypercalcemia

Table 1. Patients at risk for postsurgical hypoparathyoidism and risk mitigation.

Q4 How should acute hypocalcemia be treated?

Severe acute hypocalcemia is defined by:

- Symptoms of hypocalcemia (e.g., carpal or pedal spasm, seizures or laryngospasm), and/or
- Albumin-adjusted calcium levels <1.8 mmol/L (<7.21 mg/dL), or ionized calcium <0.9 mmol/L (<3.61 mg/dL) with clinical symptoms, and/or
- ECG signs.

The emergency treatment of hypocalcemia consists of:

- i.v. administration of 200 to 300 mg (5 to 7.5 mmol) of elemental calcium (i.e., 2 to 3 ampules of 10 mL of 10% calcium gluconate) over a period of 10 to 15 minutes, followed by
- Continuous i.v. calcium administration, at a rate of 0.13–0.75 mmol/kg/h (0.5–3 mg/kg/h), in 5% glucose under cardiac monitoring.

N.B. 10 mL of 10% calcium gluconate contains 93 mg/2.3 mmol of elemental calcium. Mild postsurgical hypocalcaemia should be treated with oral calcium supplements and active vitamin D analogues.

Q5 What is the recommended first-line treatment of chronic HypoPT?

- Active vitamin D analogues (0.5-2 µg/day alfacalcidol once a day or 0.5-1.0 µg/day calcitriol taken twice a day);
- Oral calcium supplements in divided dosages, are only needed, when dietary calcium is insufficient. Calcium carbonate (40% of elemental calcium), taken during meals, is the most widely used formulation; however, calcium citrate (21% elemental calcium), calcium gluconate (9% elemental calcium), or calcium acetate (25% elemental calcium) may be preferred in patients taking proton pump inhibitors or suffering from atrophic gastritis;
- Maintain adequate vitamin D status, .i.e., 25(OH)D >20 ng/mL (50 nmol/L).

The goal of treatment is to maintain calcium levels in the lower part or slightly below the lower limit of the reference range with patients being free of symptoms. Some patients may, however, need higher calcium concentrations to be symptom free.

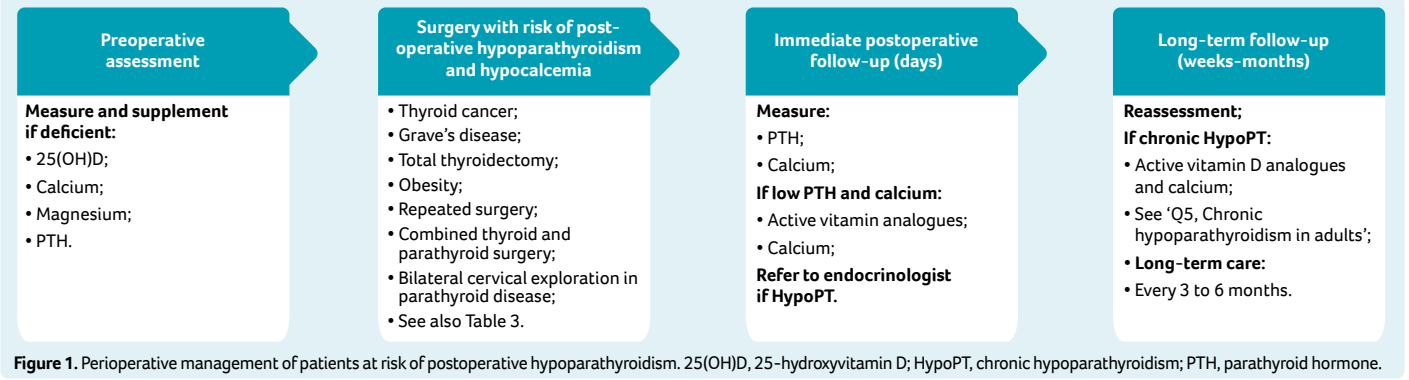

Figure 1. Perioperative management of patients at risk of postoperative hypoparathyroidism. 25(OH)D, 25-hydroxyvitamin D; HypoPT, chronic hypoparathyroidism; PTH, parathyroid hormone.

Q6 In which patients should second line therapies be considered?

The conventional treatment does not fully replace PTH actions and does not permit obtaining an acceptable disease control in all patients. We recommend considering second line treatments (hormone substitution) in patients with:

- Inadequate calcemic control;
- Calcium supplementation exceeding 2.5 g of elemental calcium/daily or large amounts of active vitamin D analogs to control calcium levels or symptoms;
- Hypercalciuria, renal stones, nephrocalcinosis, or reduced renal function;
- Hyperphosphataemia and/or increased calcium-phosphate product;
- Gastrointestinal tract disorder with malabsorption;
- Significantly reduced quality of life (QoL).

Q7 What are the treatment options for chronic HypoPT refractory to conventional treatment?

We recommend adjunction to the conventional therapy of:

- Thiazide diuretics to reduce urinary calcium excretion in patients with low sodium diet. Potassium concentrations should be regularly monitored;
- Substitution therapy with 25-100 µg daily of rhPTH(1–84) s.c., or, if unavailable, with rhPTH(1–34) once or twice daily, may be considered in patients where conventional therapy is not optimized. Long-term consequences of PTH replacement therapy on the kidney and bone warrant further investigations.

Q8 How to evaluate patient's symptoms and QoL?

The following patient reported outcome measurement tools are valuable to evaluate the fluctuations of calcium homeostasis over time, but necessitate a broader validation both as research and clinical tools.

- Hypoparathyroid Patient Questionnaire (HPQ 28)
- HypoPT Symptom Diary (HSD)
- Hypoparathyroidism Patient Experience Scale-Symptom and Impact (HPES-Symptom, HPES-Impact)

Q9 Which biochemical parameters should be monitored to adjust treatment? (See Table 2)

- Free ionized or albumin-adjusted calcium concentrations every 3 to 6 months, and more frequent monitoring in patients requiring treatment adjustment or during intercurrent illness;
- Phosphate every 3 to 6 months and strongly suggest calcium-phosphate product calculation at every check;
- Renal function with creatinine measurement every check;
- Magnesium at least annually, and at every check if hypomagnesemia;
- 24-h urinary calcium and creatinine excretions should be performed every 6 to 12 months to identify patients at risk of developing kidney stones and/or nephrocalcinosis. Urinary calcium/creatinine ratio calculated from fasting morning spot urine is a potential alternative.

Lab test	Looking for	Interval	Comments
Calcium	Hypocalcemia and hypercalcemia	At every check, every 6 months at steady state	Ionized calcium is preferable. If not available, total calcium (and albumin-corrected) is acceptable Timing of assessment is dependent on previous/daily calcium intake by food or supplements, as well as treatment Calcium levels should be assessed several days after changes in active vitamin D analog doses or PTH doses to detect iatrogenic hypercalcemia
PTH		Only for diagnosis	Not required for follow-up in chronic HypoPT Should be assessed to detect recovery in transient postsurgical hypoparathyroidism (6-12 months after surgery)
Phosphate	Hyperphosphatemia	At every check	Hyperphosphatemia can be related to high dietary phosphate intake (soft drinks, products with preservatives, acidifier, and flavor enhancer). Hyperphosphatemia is associated with higher risk of infections and with increased mortality
Calcium–phosphate product			Should be calculated Associated with brain calcifications and reduced QoL in some but not all studies
Kidney function	Renal insufficiency	At every check	To detect decline in renal function Advise patients to be careful with nephrotoxic medications and with dehydration
25-hydroxyvitamin D	Vitamin D deficiency		Often high vitamin D doses needed, especially under PTH replacement therapy 25(OH)D recommended goal: >30 ng/mL and <50 ng/mL (>75 nmol/L and <125 nmol/L) (expert opinion)
Calciuria	Hypercalciuria	Every 6–12 months	24 h calcium excretion is reliable and spot easier to obtain
Urinary stone profile		As clinically indicated	Sodium, urea, citrate, oxalate, pH, osmolarity, urate excretions, and others
Magnesium	Hypomagnesemia	Yearly or as clinically indicated	Serum magnesium does not reflect intracellular levels well and magnesium depletion is possible with normal values. Hypomagnesemia reduces response to PTH and may cause hypokalemia
Thyroid status		At every check	In patients with thyroid replacement therapy

25(OH)D, 25-hydroxyvitamin D; HypoPT, chronic hypoparathyroidism; PTH, parathyroid hormone; rhPTH, recombinant human parathyroid hormone.

Table 2. Biochemical parameters in hypoparathyroidism.

Organ	Looking for	Interval	Comments
Kidney	Nephrolithiasis, nephrocalcinosis	At diagnosis As clinically indicated Every 5 years	Ultrasound + no radiation - highly operator-dependent Non-contrast renal CT + accurate - accumulation of radiation exposure *Sensitivity of CT vs ultrasound in nephrocalcinosis detection uncertain*
Brain	Intracerebral calcifications	As clinically indicated	Non-contrast CT MRI (only special MRIs usable for this assessment). *Sensitivity of even specialized MRI for detection of calcifications uncertain*
Bone	Changes in bone density/ quality, vertebral fx	As clinically indicated	DXA + cheap + low radiation + Vertebral fracture assessment (VFA) X-ray spine and VFA + detection of unknown vertebral fracture
Eyes	Cataract	At diagnosis As clinically indicated	Ophthalmologist check in non-surgical patients

DXA, dual-energy X-ray absorptiometry; HypoPT, chronic hypoparathyroidism; Fx, fractures.

Table 3. Imaging in hypoparathyroidism.

Q10 Which imaging techniques are useful to monitor treatment or to evaluate tissue complications of chronic HypoPT? (See Table 3)

- Renal imaging every 1 to 2 years to detect nephrolithiasis or nephrocalcinosis. Repeated renal CT scans should be indicated with caution to minimize risk from radiation dosing;
- Brain CT scans to search for basal ganglia or other brain tissue calcifications in patients with neurologic symptoms including movement disorders, seizures, and neuropsychiatric symptoms;

Whether BMD measurement helps the regular care of hypoPT patients is questionable.

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 primary hyperparathyroidism 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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