In the name of ***ALLAH***

European Expert Consensus on Practical Management of Specific Aspects of Parathyroid Disorders in Adults and in Pregnancy:

Recommendations of the ESE Educational Program of Parathyroid Disorders

(PARAT 2021)

Primary Hyperparathyroidism

PHPT is a common endocrine disease for which surgery is the only curative treatment .

However, **various aspects of PHPT** are often managed based **on local practices and expert opinions,** rather than evidence-based recommendation

Q1 How do we differentially diagnose FHH?

FHH is an **autosomal dominant** **disorder** affecting the calcium sensing receptor (**CaSR**) – especially at the parathyroid glands and kidneys

It is characterized by:

- ✓ **lifelong non-progressive elevations of calcium concentrations**
- ✓ ***mild hypermagnesemia***
- ✓ **normal or mildly raised PTH concentrations**
- ✓ **typically low urinary calcium excretion**

FHH has a similar biochemical phenotype to PHPT, but FHH does not require surgical intervention.

FHH is genetically heterogeneous and comprises **3 distinct variants, designated *FHH types 1-3*, which are caused by loss-of-function mutations of the:**

- ✓ **CASR**
- ✓ **guanine nucleotide-binding protein subunit alpha-11(GNA11)**
- ✓ **adaptor protein complex-2 subunit sigma (AP2S1) genes**

respectively

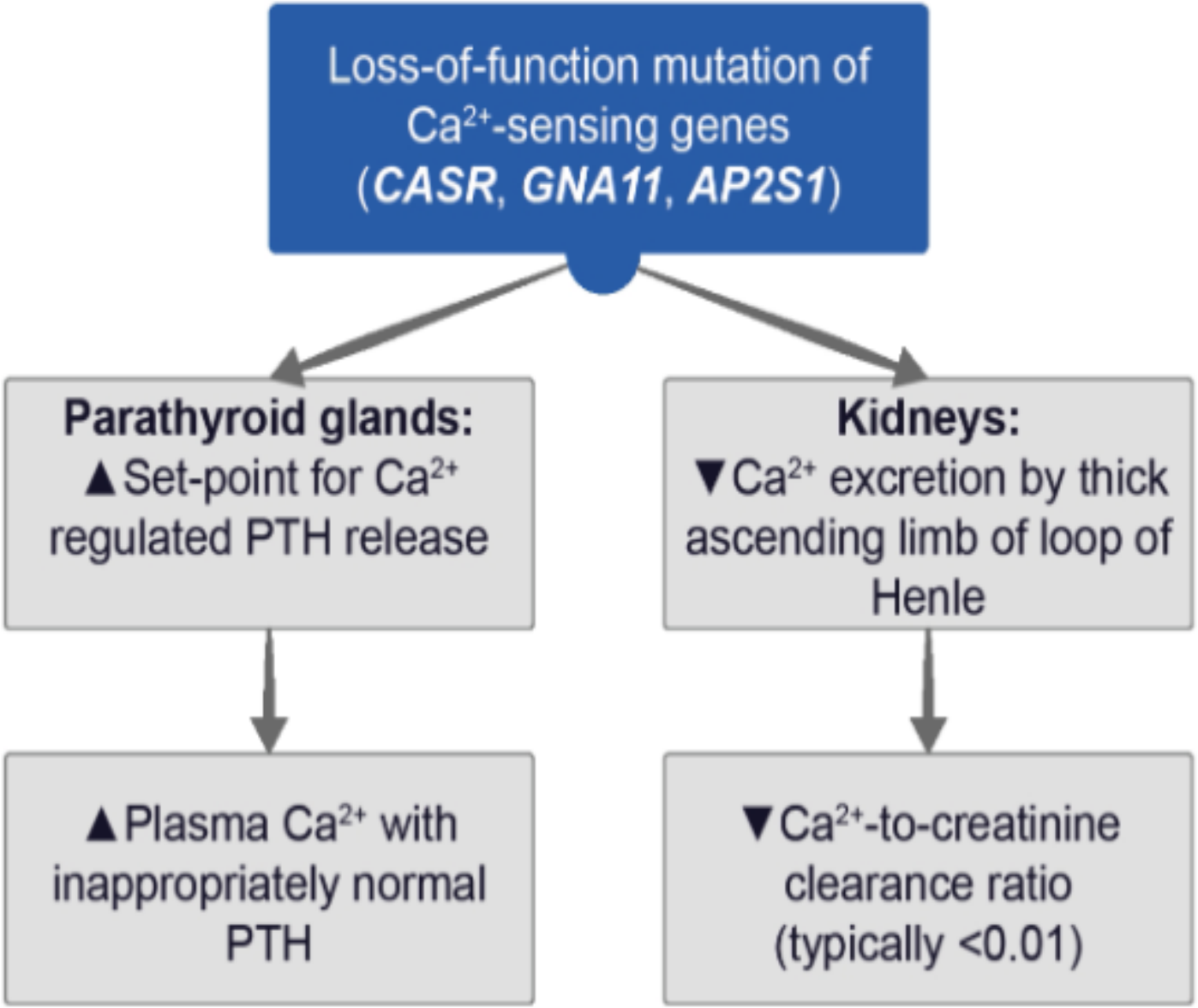

Figure 1.Alterations in calcium metabolism caused by familial hypocalciuric hypercalcemia (FHH). Hypercalcemia arises due to an increase in the parathyroid set-point for parathyroid hormone (PTH) release, and possibly also from decreased renal calcium excretion [11, 12]. Alterations in bone metabolism are not usually observed in FHH [13].

There is a **role for family testing in** FHH as it is a disease with **a familial penetrance of >90% (i.e., proportion of hypercalcemic relatives)**

Thus, a **positive family history is a key feature** and blood calcium testing of family members (especially first-degree relatives) is helpful in establishing the diagnosis.

In addition to family testing, biochemical testing contributes to distinguishing FHH from PHPT.

Calcium levels:

The degree of hypercalcemia does not discriminate FHH from PHPT.

This is due to the **marked variation** in calcium values in FHH, **overlapping with that of PHPT.**

A review of **patient records** can help to establish the presence of lifelong non-progressive hypercalcemia, which is a key feature of FHH.

Although **significantly increased in FHH compared to PHPT serum magnesium values are usually within the reference range** in FHH and are not useful for discriminating FHH from PHPT

PTH levels:

PTH levels **overlap** between FHH and PHPT

However, PTH concentrations **>2-fold above the upper limit of normal** (ULN) are suggestive of PHP

Vitamin D insufficiency should be corrected before interpreting PTH concentrations

Urine calcium excretion:

This **should** be assessed **using** the calcium / creatinine clearance ratio (**CCCR**), which requires concurrent blood and 24-hour urine measurements

A CCCR of <0.01 (i.e., an excretion fraction of calcium <1%) is generally considered a well- planned screening method for FHH

However, this 'cut-off' is of **limited clinical value** due to **reduced diagnostic sensitivity** **(only captures ~65% of FHH type 1 patients) and reduced specificity** **(~18% of surgically confirmed PHPT cases have CCCR <0.01)**

The positive predictive value of the CCCR cut-off is affected by **disease prevalence.**

Thus, as **FHH is less common than PHPT**, this condition may represent a **minority diagnosis in hypercalcemic patients with CCCR <0.01**

CCCR has **not been validated** for diagnosing FHH in patients:

- **with renal impairment,**
- **in vitamin D insufficiency,**
- **in pregnancy.**

Thiazide usage can lead to low CCCR values, as these drugs stimulate proximal tubular sodium reabsorption as a compensation of their natriuretic action in the distal tubule, resulting in enhanced proximal passive calcium transport

Hence, it is recommended to measure 24-hour urine calcium and creatinine **after withholding thiazide diuretics for at least 1 week**

As individual biochemical parameters cannot reliably distinguish FHH from PHPT, an algorithm termed pro-FHH has been proposed to help discriminate these two conditions.

Pro-FHH is a risk prediction tool that incorporates calcium, PTH, a biochemical marker of bone turnover and CCCR

More work is needed before pro-FHH can be advised for wider use in clinical practice

Pro-FHH Calculation

Pro-FHH is a validated formula that allow assessing if a genetic testing (by molecular biology) is required (or not) in order to make the diagnosis of a PTH-related hypercalcemia with a concomitant PTH value within the 'normal' range

VARIABLES

Fasting calcemia (mmol/L) *

mmol/L | mg/L

Fasting PTH (pg/mL) *

PTH upper limit of normal value (pg/mL) *
Please, make sure you used the same unit

Creatininemia (µmol/L) *

µmol/L | mg/L

Creatininuria assessed in 24-h urine (mmol/L) *

mmol/L | mg/L

Calciuria assessed in 24-h urine (mmol/L) *

mmol/L | mg/L

Fasting creatininuria (mmol/L)
Not required for the Pro-FHH score (24h-Pro-FHH)

mmol/L | mg/L

Fasting calciuria (mmol/L)
Not required for the Pro-FHH score (24h-Pro-FHH)

mmol/L | mg/L

Bone remodeling marker *

Bone remodeling marker upper limit of normal value *
Please, make sure you used the same unit

RESULTS

Refresh results

PTH Ratio

BRM ratio

24h-CCCR

Fasting-CCCR

24h-Pro-FHH

Fasting-Pro-FHH

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Article Navigation

Pro–FHH: A Risk Equation to Facilitate the Diagnosis of Parathyroid–Related Hypercalcemia

FREE

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Genetic testing **is recommended for all patients with suspected FHH** as identification of a pathogenic mutation, or likely pathogenic variants will confirm the diagnosis and differentiate between types of FHH. **However, genetic testing is not a panacea**

FHH type 1 is associated with a wide range of CASR missense variants , many of which are unique to individual families and are of unclear pathogenicity.

Variants of unknown significance are therefore commonly detected during FHH genetic testing.

Genetic testing has however, limited sensitivity, as >25% of patients with a clinical diagnosis of FHH do not harbour germline CASR/GNA11/AP2S1 genetic variation.

Thus, negative genetic testing does not exclude FHH, and we recommend ongoing follow-up of mutation negative patients, e.g., historic calcium measurements, family screening etc

Q2 What is normocalcemic PHPT

Normocalcemic PHPT can be considered when there is :

- ✓ a biochemical signature of **persistently** **(>3 months)** increased PTH levels
- ✓ in the setting of consistently **normal** total, albumin-adjusted and / or free ionized calcium, based on **serial laboratory measurements**,
- ✓ when all secondary causes of PTH elevation have been **excluded** .

Consequently, normocalcemic PHPT represents a diagnosis of exclusion and can only be considered following a careful evaluation of causes of secondary hyperparathyroidism

Q3 What are the causes of hyperparathyroidism with normal calcium that should be excluded before considering a diagnosis of normocalcemic PHPT?

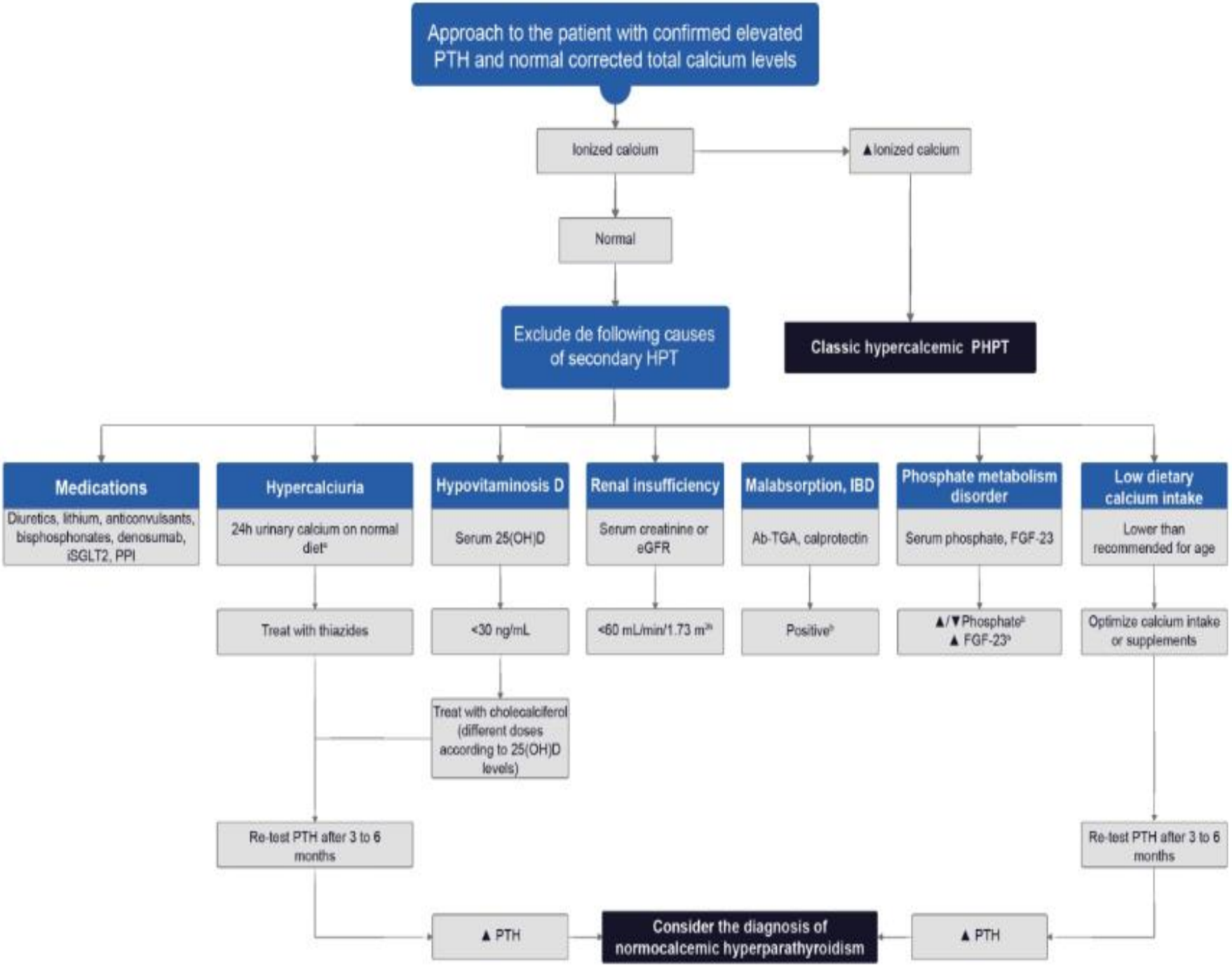
Detailed, and standardized tests are required before making a positive diagnosis of normocalcemic PHPT.

The causes of secondary hyperparathyroidism should be excluded before diagnosing normocalcemic PHPT

Table 1 Most common causes of secondary hyperparathyroidism

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 to 12 months and optimization of calcium intake is mandatory [31].
Low dietary calcium intake	1200 mg/day recommended for postmenopausal women 1000 mg/day for men 51-70 years, and 1200 mg/day for older men [32]	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/24h (6.25 mmol/24h) in females, >300 mg/24h (7.5 mmol/24h) in males, or >4mg/kg/24h (0.1mmol/kg/24h) [33, 34]	"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 [35]

Renal insufficiency	eGFR <60 mL/min/1.73 m² [36, 37]	As kidney function declines, 1α-hydroxylation activity decreases and, consequently, active vitamin D levels fall, calcium levels decline and PTH levels increase [36, 37]
Gastrointestinal disorders associated with calcium malabsorption	**Celiac disease,** **inflammatory bowel disease, and bariatric surgery** [38-41]	Measure anti-tissue transglutaminase antibodies and fecal calprotectin to consider celiac disease and inflammatory bowel disease respectively [39, 40].
Medications	Diuretics [42, 43], lithium, anticonvulsants [44, 45], bisphosphonates [46, 47], denosumab [48, 49], SGLT2 inhibitors [50-52], proton pump inhibitors [53].	Non-thiazide diuretics can increase PTH levels [42, 43]. If possible, discontinue and reevaluate PTH. Lithium therapy can raise PTH levels [44, 45]. However, the decision to withdraw from therapy in these patients 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 [7, 46, 47, 49]. Bisphosphonate effects may last for a long time after discontinuation [54]. 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 [50-52].
Phosphate metabolism disorders	Hyperphosphatemia and FGF-23-mediated hypophosphatemia are both associated with secondary	Extracellular phosphate regulation involves changes in PTH levels. Both high and low phosphate levels may be associated with secondary hyperparathyroidism [56-58].


Approach to the patient with confirmed elevated PTH and normal corrected total calcium levels
Ionized calcium
▲Ionized calcium
Normal
Exclude de following causes of secondary HPT
Classic hypercalcemic PHPT
Medications
Diuretics, lithium, anticonvulsants, bisphosphonates, denosumab, iSGLT2, PPI
Hypercalciuria
24h urinary calcium on normal diet[a]
Hypovitaminosis D
Serum 25(OH)D
Renal insufficiency
Serum creatinine or eGFR
Malabsorption, IBD
Ab-TGA, calprotectin
Phosphate metabolism disorder
Serum phosphate, FGF-23
Low dietary calcium intake
Lower than recommended for age
Treat with thiazides
<30 ng/mL
<60 mL/min/1.73 m²[b]
Positive[b]
▲/▼Phosphate[b] ▲ FGF-23[b]
Optimize calcium intake or supplements
Treat with cholecalciferol (different doses according to 25(OH)D levels)
Re-test PTH after 3 to 6 months
Re-test PTH after 3 to 6 months
▲ PTH
Consider the diagnosis of normocalcemic hyperparathyroidism
▲ PTH

Q4 What are the manifestations of normocalcemic PHPT, and does it progress to hypercalcemic PHPT?

Normocalcemic PHPT may be an early biochemical manifestation of hypercalcemic PHPT

Over an 8-year follow up of 64 subjects identified through community screening, only 1 person developed hypercalcemic PHPT and only 13 retained the biochemical findings of normocalcemic PHPT

Published series have used inconsistent definitions of normocalcemic PHPT and it is thus difficult to estimate the true prevalence and complication rate

Reported complication rates **vary from zero in population-based studies to 11-35% of patients with renal stones and 5-40% with low-traumatic fractures and osteoporosis, as assessed in tertiary referral center**

These **discrepancies** might reflect that many patients or cohorts are diagnosed when being **evaluated for nephrolithiasis or a suspected metabolic bone disease**.

Thus, selection bias might lead to an overestimation of the clinical impact of the disorder.

It is ***controversial*** whether ***surgery*** should be ***considered*** in ***expert*** centers for ***selected*** normocalcemic PHPT patients, when ***disease-associated progression occurs.***

However, evidence is limited, and the published, retrospective surgical series do not fulfil the diagnostic criteria stated herein and above, i.e. repeated measurements under standardized conditions and over time

In summary, normocalcemic PHPT must be diagnosed by exclusion, and laboratory testing over time is necessary to distinguish normocalcemic PHPT from secondary hyperparathyroidism.

Evidence on the effect of parathyroidectomy (PTX) or any other management of normocalcemic PHPT is scarce and there are no clear data on the natural history of normocalcemic PHPT.

However, unless longitudinal studies prove the opposite, established normocalcemic variant of PHPT requires standard PHPT diagnostic procedures and surgical intervention should be considered only after experienced endocrine review;

in this case only if there are compelling indications and a surgical target

Q5 What is the definition, prevalence and causes of recurrent PHPT?

The most widely accepted definition of recurrent PHPT is a **new finding of hypercalcemia, after a period of 6 months**, in patients successfully operated and in whom normocalcemia was previously documented

This is distinct from **persistent PHPT, defined as hypercalcemia within 6 months** following surgery.

The definition of recurrent PHPT primarily considers **calcium levels;** isolated elevation of PTH levels with normocalcemia does not represent this condition

As a first step to consider when confronted with apparent recurrent PHPT, it is fundamental to:

- **confirm the diagnosis (particularly exclude FHH),**
- **repeat measurement of albumin-adjusted calcium (or free ionized calcium)**
- **together with documentation of increased and unsuppressed PTH concentration**

There are only few data on the epidemiology of recurrent PHPT.

Most authorities consider **prevalence between 2.5 and 9.8%** .

Importantly, as recurrent PHPT can **occur many years after initial** presentation and predictive factors for recurrence are insufficiently sensitive, **long term yearly monitoring** of calcium concentrations after initially successful parathyroid surgery is recommended

Q6 Do we need to act upon persistent elevations of PTH levels, despite normocalcemia?

Up to one third of patients present elevated PTH concentrations following successful surgery for sporadic PHPT .

The mechanism of this increase is unclear.

In this context, elevated PTH is associated with:

- **higher preoperative PTH levels,**
- **older age**
- **impaired renal function.**

It is not, however, consistently associated with an increased risk of recurrent PHP

Although elevated PTH has been associated with recurrence in some series it is not sufficiently discriminatory to recommend routine monitoring (i.e., **most individuals with elevated PTH will not have recurrence of the disease**).

As such, ***PTH should not be routinely measured in normocalcemic individuals following parathyroid surgery.***

Despite recommending against routine PTH testing, **clinicians will frequently be faced with the dilemma** of interpreting results in this context.

It is important to ensure that patients are **vitamin D replete** and have **sufficient dietary calcium intake** , as dietary calcium deficiency can drive PTH elevation

Where diagnostic uncertainty persists, the **suppressibility of PTH in response to a calcium load** can be considered .

There are parallels between this situation and diagnosing normocalcemic PHPT

In the absence of clear evidence that elevated levels of PTH with normocalcemia represent persistent or recurrent PHPT, the appropriate course is to **carefully monitor serum calcium concentrations**, especially in those with calcium levels towards the upper part of the reference range.

Q7 What is the optimal work-up of patients with recurrent PHPT?

The first step in evaluating recurrent PHPT is to **accurately confirm or refute the diagnosis of PHPT.**

This requires a thorough **review of the pre- and postoperative medical, laboratory and pathology records, exploration of the personal and family history, and repeated laboratory analyses**

When persistent or recurrent PHPT is **confirmed** and a surgical approach is favored, it should be considered that:

- **about two thirds of recurrent disease is due to a single adenoma,**
- **up to a third due to multiglandular disease,**
- **rarely due to parathyroid carcinoma,** a distinctly different profile from de novo PHPT

Thus, **pre-operative localization procedures** that are more **sensitive** to detect multiglandular disease and /or small lesions should be preferred (**18F-Fluorocholine** positron emission tomography/computed tomography [**PET-CT**], with or without **enhanced arterial imaging**, and **4D-CT**)

This is especially so when conventional pre-operative imaging before the first intervention was inconclusive.

Moreover, localization for possible ectopic parathyroid tissue should be considered

Importantly, an **active search for potential underlying etiologies** should be considered for **all** patients with recurrent PHPT.

These could be acquired, e.g., **lithium-induced** parathyroid hyperplasia or **parathyromatosis**, a rare cause of PHPTdue to **several hyperfunctioning parathyroid nodules in the neck and mediastinum, as a result of seeding from a ruptured parathyroid adenoma during previous parathyroid surgery**

Other reasons relate to clinically important syndromes, such as **MEN syndromes, familial isolated hyperparathyroidism, or hyperparathyroidism-jaw tumor syndrome, where genetic tests might be useful**

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 centre's with **considerable experience in re-operative parathyroid 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 co-morbidities

The **European Society of Endocrine Surgeons** (ESES) suggest that **challenging procedures** (PHPT without unequivocal preoperative localization, hereditary variants, pediatric patients and re-interventions) should be confined to **high-volume centers performing at least 40 such procedures annually**

Depending on the results and etiology, **bilateral neck exploration** or **a focused minimal-invasive PTX** should be performed. Surgical adjuncts, like **intraoperative PTH assay** and **intraoperative nerve-monitoring** is recommended in cases of repeated parathyroid surgery.

Q9 What is the risk and prevention of hypoparathyroidism following surgery for recurrent PHPT?

In the re-operative setting, the risk of **transient hypoparathyroidism** can be as high as **81%**, while the rate of **chronic hypoparathyroidism** **is** **3-13%**

Since there is an **increased risk of hypoparathyroidism**, **autotransplantation** of parathyroid tissue may be considered if a remaining gland is intraoperatively injured or devascularized

Recurrence of disease can occure however, within the autotransplanted tissue.

Additionally, **autotransplanted grafts** **may fail to function in up to half of the cases** , wherefore **some** centers have **stopped** performing the procedure.

Q10 Why and when should calcium levels be measured after PTX?

Calcium levels should be measured postoperatively, in parallel to evaluation for **hypocalcemic symptoms.**

For those at **high risk of Hungry Bone Syndrome (HBS)** calcium levels should be checked frequently (**multiple times per day**) in the **first postoperative days .**

To define cure of PHPT after parathyroid surgery, **reestablishment of normocalcemia should last a minimum of 6 months**

Q11 What preoperative advice should be offered to patients awaiting PTX?

Patients with PHPT do **not need to restrict dietary calcium intake.**

However, the normal daily intake recommendation should not be exceeded

Preoperatively, patients with **vitamin D depletion** are recommended to **start vitamin D supplementation**

Several studies have confirmed it to be safe when **calcium levels are <3 mmol/L (12 mg/dL).**

Patients with PHPT should be advised to keep **well hydrated**.

Patients with hypercalcemic crises require parenteral hydration and may benefit from further medical management, such as bisphosphonates, denosumab, cinacalcet and calcitonin, or combinations of these.

Prioritized surgery may be considered in this setting after medical stabilization

Q12 What causes hypocalcemia after PTX?

Postoperative hypocalcemia can be related to **hypoparathyroidism** or to massive transfer of calcium to bone tissue, **HBS**.

The **biochemical profile** usually allows distinction between these two situations:

postoperative PTH deficiency is associated with low / inappropriately "normal" PTH concentrations, increased serum phosphate concentrations, and normal or elevated 24-h urinary calcium excretion with calcium replacement

whereas ***HBS*** is typically accompanied by:

normal or high PTH concentrations, low serum phosphate, low serum magnesium concentrations, and a low 24-h urinary calcium excretion despite parenteral calcium replacement, as calcium is transferred into the bone tissue

The hypocalcemia of **HBS** starts typically from **third to fifth** postoperative day .

.

Hypocalcemia is **usually temporary** but can be permanent if all parathyroid glands are accidentally removed or devascularized

The risk of permanent HypoPT is increased for patients undergoing re-operation.

PTH levels on the first postoperative day predict temporary hypocalcemia

Q13 What is optimal follow-up after (successful) PTX?

- ✓ The surgical field should be checked for **cervical hematoma or infection**
- ✓ Referral for **genetic panel testing** **is appropriate in** **patients <30 years.**
- ✓ Genetic testing should be considered in PHPT **patients with** **multi-glandular disease at any age,** if not performed before surgery

Patients with parathyroid carcinoma or with genetic forms of PHPT (i.e., MEN types 1, 2A, 4, hyperparathyroidism-jaw tumor syndrome, familial isolated primary hyperparathyroidism) **require an individually planned follow-up in a specialized endocrine unit**

Although bone density (BMD) improves after successful surgery , PHPT patients with osteoporosis need an individual recommendation regarding follow-up, BMD measurement, length of calcium / vitamin D treatment,

putative need for osteoporosis medication after surgery

Patients with persisting hypercalcemia at 6 months after surgery should be considered for re-operation after detailed reassessment.

In the presence of normocalcemia, risk of recurrence is low, but 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

Table 3. Patients at risk for postsurgical HypoPT and risk mitigation

Topic	Comment	References
General	Higher rates in • thyroid cancer with central lymph node dissection • Graves' disease Risk mitigation • awareness • preoperative screening of parathyroid function • vitamin D status	[102, 118, 119]
Comorbidities	• obesity • gastrointestinal malabsorption, e.g. post gastric bypass, severe IBD Risk mitigation • awareness	[118]
Primary exploration *versus* repeated surgery	Higher risk in • case of repeated surgery Risk mitigation • critical assessment for additional/repeated surgeries	[102]
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)	[102]
Total thyroidectomy *vs.* less extensive surgery	Risk bilateral surgery > risk unilateral surgery Risk mitigation • individualized surgical strategy	[120]
Bilateral cervical exploration in parathyroid disease	Risk bilateral exploration > focused PTX Risk mitigation • preoperative localization (ultrasound and nuclear medicine techniques) • exclusion of FHH (no surgery, see also PHPT Chapter 3, Q1) **lack of localization in clearly established PHPT should not delay surgery**	[121]

Table 2. Potential risk factors for Hungry Bone Syndrome

Potential risk factors for Hungry Bone Syndrome	**Explanation**
High preoperative PTH level	High preoperative PTH [95]. 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) [94].
Large volume (weight and mass) of parathyroid adenoma	Positive correlation between PTH levels and volume of adenoma [93, 95].
High preoperative calcium levels	Explained as increased calcium resorption from bone and calcium reabsorption renal tubules in case of preoperative elevated PTH levels [95]
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 [91, 94]
Significantly elevated alkaline phosphatase	Reflects the state of bone turnover and the degree of osteoclast activity and bone resorption [91, 94]
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 [95]

HBS, Hungry bone syndrome; PHPT, primary hyperparathyroidism; PTH, parathyroid hormone; $1,25(OH)_2D$, 1,25-dihydroxy-vitamin D; 25(OH)D, 25-hydroxyvitamin D.

Chronic Hypoparathyroidism in Adults

HypoPT is a **rare** endocrine disease characterized by low calcium concentrations due to insufficient PTH secretion from the parathyroid glands

In adults, the **most common** **cause is** **previous anterior neck surgery**, **in approximately 75% of cases**

Non-surgical causes **include genetic, autoimmune, or idiopathic causes or functional HypoPT related to magnesium depletion, and account for the remaining 25% of case**

Genetic causes can be isolated or occur as a part of genetic syndromes.

In all patients with non-surgical HypoPT, detailed diagnostic work-up is mandatory

The chronic PTH deficiency results in :

- ✓ decreased intestinal calcium absorption,
- ✓ decreased bone resorption,
- ✓ decreased renal calcium reabsorption in the distal tubule,
- ✓ accompanied by enhanced phosphate reabsorption in the proximal tubule, causing chronic **hypocalcemia and hyperphosphatemia**

Urinary calcium excretion may vary according to dietary calcium intake and decreased reabsorption, but is usually lower than after conventional treatment has been started.

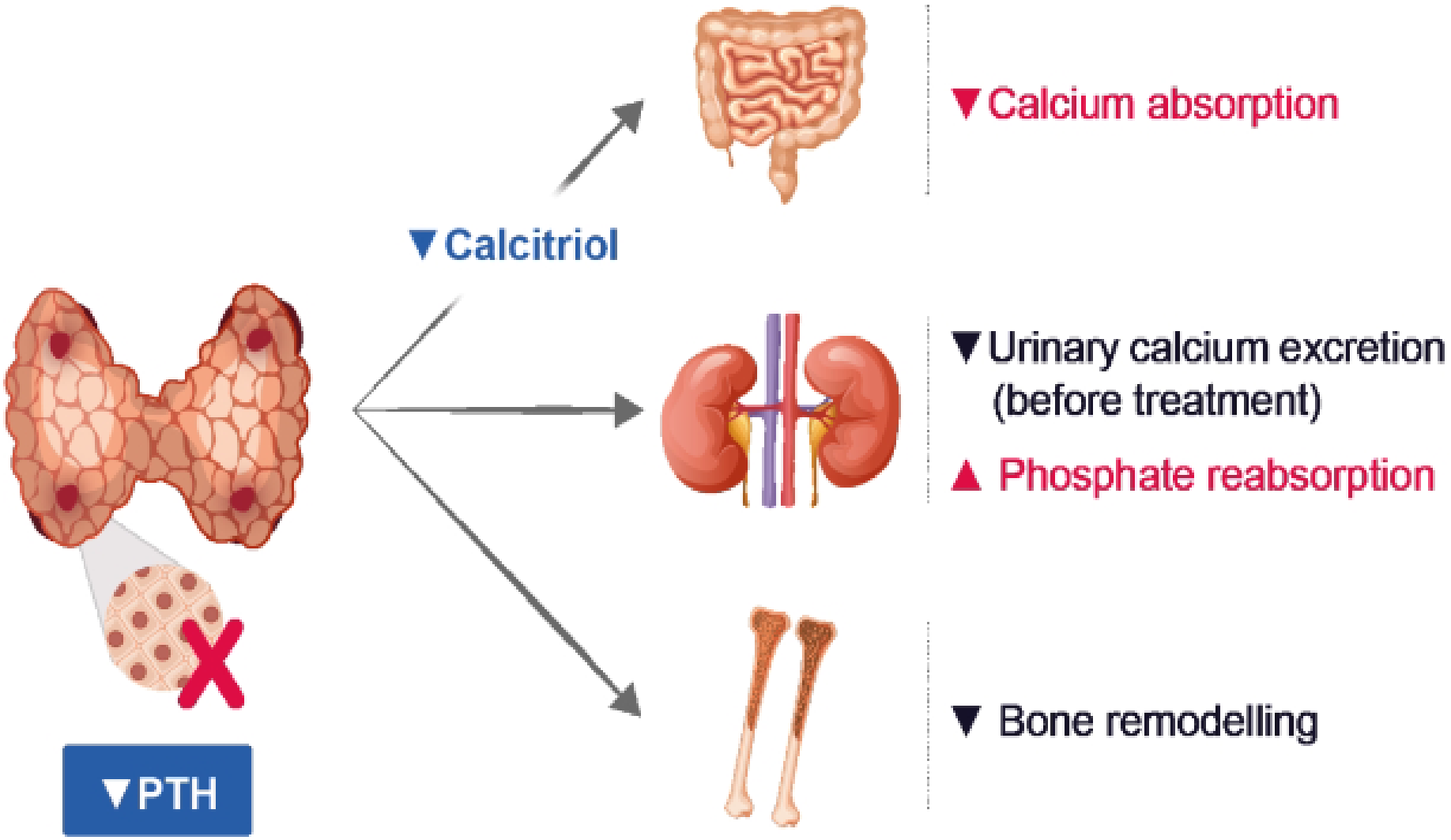


Figure 3. Pathophysiology of hypoparathyroidism. PTH, parathyroid hormone

321x169mm (118 x 118 DPI)

Symptoms, related to hypocalcemia, vary from paresthesia and muscle cramps to seizures and life-threatening laryngospasm

*Q1 How do we define **chronic** postsurgical HypoPT?*

HypoPT following anterior neck surgery (mostly thyroid and less frequently parathyroid surgery) is suspected in patients with symptomatic or asymptomatic hypocalcemia and low PTH concentrations, or inappropriately normal PTH concentrations despite hypocalcemia.

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

Calcium and PTH should be assessed repeatedly when the diagnosis is uncertain.

The definitions of HypoPT differs widely in the medical literature

However, to compare the incidence of chronic HypoPT in different countries and among different centers, agreement on diagnostic criteria is essential.

We recommend to differentiate between transient and chronic post-surgical HypoPT

Chronic post-surgical HypoPT should be diagnosed **at least six months after the anterior neck surgery**, **if active vitamin D analogues are still necessary to maintain calcium concentrations low normal**.

Occasionally, the recovery of the parathyroid tissue may occur later than six months.

We further recommend to confirm the chronicity of post-surgical HypoPT by carefully **taper active treatment** in order to avoid misclassification of patients with recovered endogenous parathyroid function

Q2 How can postoperative hypoparathyroidism be prevented?

The **rate of postsurgical hypoparathyroidism** is an internationally accepted outcome variable and an **important quality control indicator** for endocrine neck surgery

Parathyroid preservation with intact gland perfusion and sufficient postoperative function is paramount in endocrine neck surgery

Surgeons performing endocrine neck surgery should be aware of the, sometimes, dramatic impact of permanent HypoPT and the individual risk factors for developing parathyroid dysfunction

Volume and expertise of the center and the individual surgeon influence the rate of postoperative HypoPT significantly .

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 value of autotransplantation of devascularized or intracapsular parathyroids remains controversial

Intraoperative fluorescent imaging of parathyroid glands, as an additional method of visualization and marker of gland viability, may help to reduce postoperative complication rate

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 day following surgery, PTH and ionized calcium should measured to identify patients at risk of developing HypoPT

postoperative PTH monitoring is an integral part of surgical management and allows for early identification of patients at risk of post-surgical PTH deficiency.

Keeping the patient symptom-free and allowing risk-free discharge is the primary goal in the early postoperative phase.

Surgeons should initiate interdisciplinary care early for all patients at risk for transient or permanent HypoPT.

When immediate post-surgical hypoparathyroidism is diagnosed, it is important to ensure close follow-up in collaboration between the endocrinologist and general practitioner.

***Several important questions remain unanswered and require further research*:**

- ✓ ***Is parathyroid "splinting" helpful?*** The concept of parathyroid splinting refers to the hypothesis that high- normal postoperative calcium levels are putting the injured parathyroid parenchyma at rest after thyroidectomy thereby improving long-term parathyroid function
- ✓ ***Is identification of the parathyroids beneficial?***
- ✓ ***What is the value of parathyroid tissue cryopreservation?***
- ✓ ***How to estimate how much parathyroid tissue has been removed or damaged?***

Q3 How can parathyroid gland injury be predicted?

The prediction of HypoPT from PTH levels following thyroid or neck surgery has to be distinguished from intraoperative PTH measurement in parathyroid surgery.

Also with respect to the need to make decisions quickly post-surgically, the **assay used for intraoperative measurements provides a rapid result, whereas the routine intact PTH assay may not be appropriate for fast decision-making.**

With regard to the subsequent threshold levels, different reference ranges dependent on the assay and institution have to be taken into account.

A very low PTH level on the first postsurgical day was associated with HypoPT

Thresholds of PTH concentrations associated with the development of chronic HypoPT have been suggested to be <5.5 pg/mL (<0.58 pmol/L)

On the other hand, PTH concentrations on the first postsurgical day >10 pg/mL (>1.06 pmol/L) seem to predict normal parathyroid function 6 months following surgery

Another approach is to calculate the ratio between pre-and postsurgical PTH concentrations: **a decrease >70% in the normal PTH value was associated with chronic HypoPT**

Postsurgical **PTH** measurement has a **higher specificity** and **predictive value** compared to calcium measurement

Thus, the earliest opportunity to predict hypoPT reliably is through measurement of **serum PTH level at either the conclusion of or immediately following surgery**

The optimal timing of post-surgical assessment of PTH and the appropriate interpretation of the PTH kinetics remain controversial, as described above

Q4 What is the management of acute hypocalcemia following anterior neck surgery?

So far, there is no consensus or guideline on when to initiate post-surgical hypocalcemia with active vitamin D analogues and calcium supplements, or PTH substitution.

In case of acute severe hypocalcemic symptoms, such as carpal or pedal spasm or even seizures and laryngospasm, iv calcium supplementation has to be initiated

The emergency treatment of acute symptomatic hypocalcemia consists of iv administration of 200 to 300 mg (5 to 7.5 mmol) of elemental calcium by slow intravenous injection, i.e., 2 to 3 ampules of 10 mL of 10% calcium gluconate (N.B. 10 mL of 10% calcium gluconate contains 93 mg / 2,3 mmol of elemental calcium) followed by continuous iv. 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.

Milder post-surgical hypocalcemia is treated with oral calcium supplements and active vitamin D analogues(alphacalcidol or calcitriol)

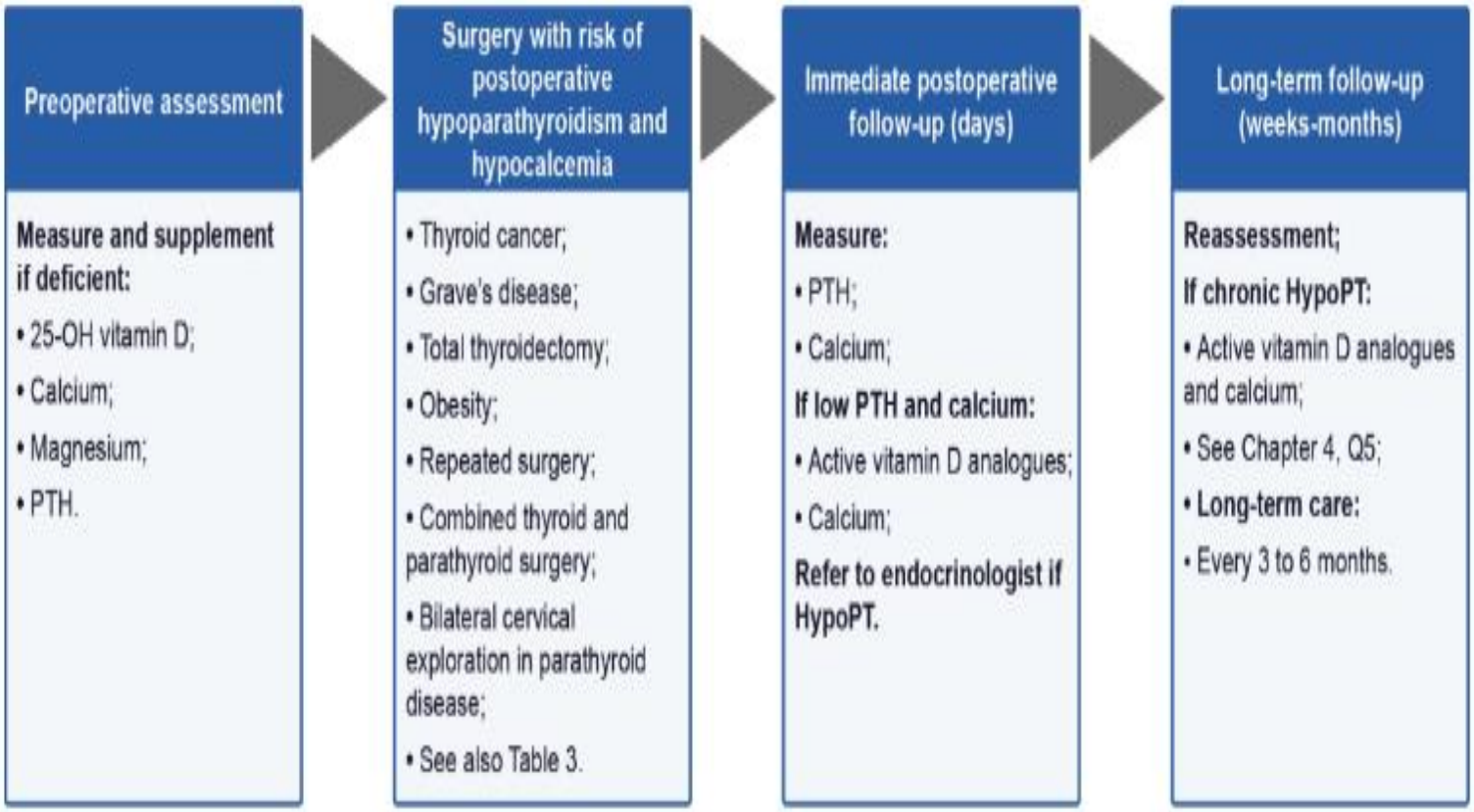


Figure 4. Perioperative management of patients at risk of postoperative hypoparathyroidism. HypoPT, chronic hypoparathyroidism; PTH, parathyroid hormone.

490x160mm (118 x 118 DPI)

Q5 What is the first line treatment of chronic HypoPT?

Chronic HypoPT is conventionally treated with active vitamin D analogues and calcium supplements.

As PTH drives 1α-hydroxylation of vitamin D in the proximal tubule, the treatment is based on 1α-hydroxylated analogues of vitamin D.

In adults, 0.5 to 2 µg/day of alfacalcidol (e.g., Un-Alfa®, Etalpha®) once a day or **0.5 to 1.0 µg/day of calcitriol** (e.g., Rocaltrol®) taken twice a day usually allows to obtain acceptable calcium levels

During adolescence, the doses of active vitamin D analogues and calcium supplements can be higher because of growth requirements

Calcium supplements are only needed if dietary calcium is insufficient.

They are prescribed in order to increase oral calcium intake, while, when taken with meals, they also act as a phosphate binder.

Calcium carbonate, containing 40% of elemental calcium is most widely used, **but calcium citrate, calcium gluconate or calcium acetate may be preferred in patients taking proton pump inhibitors or suffering from atrophic gastritis .**

An adequate vitamin D status with a serum concentration of **25(OH)D above 50 nmol/l should be ensured**

The goal of "conventional" treatment of HypoPT is to maintain calcium concentrations in the lower part or slightly below the lower limit of the reference range with patients being free of symptoms or signs of hypocalcemia

No data exist on optimal calcium concentrations during treatment of HypoPT.

Normalization of calcium concentrations very frequently leads to an increase in calciuria, facilitated by the lack of PTH-driven reabsorption of calcium in the distal convoluted and connecting tubule, with **the risk of nephrolithiasis and nephrocalcinosis** Some patients may, however, need higher calcium concentrations to be symptom free

The management of severe episodes of acute symptomatic hypocalcemia defined by calcium concentrations <1.8 mmol/L (**<7.21 mg/dL**) (or ionized calcium <0.9 mmol/L [<3.61 mg/dL]), clinical symptoms, or ECG signs, requires emergency treatment with iv calcium gluconate and ECG monitoring

Episodes of acute hypercalcemia related to overtreatment should be treated rapidly with iv fluids, due to the danger of renal impairment following phases of hypercalcemia

Q6 In which patients should second line therapies be considered?

The conventional treatment by oral calcium supplements and active vitamin D analogues **does not always** make it possible to obtain an **acceptable clinical and biochemical control** of HypoPT, since these treatments do not replace the functions of PTH.

In addition, this treatment can lead to short and long-term complications, including **hypercalcemia or increased urinary calcium excretion, resulting in nephrocalcinosis or kidney stone formation.**

The **ESE clinical guidelines** provide useful treatment goals, but **do not explicitly recommend when to switch to substitution with the lacking hormone - second line treatments**

Different groups and guidelines have suggested that second line treatment (hormone substitution) could be considered in patients:

- inadequate control of the calcium concentrations;
- in whom calcium supplementation exceeds 2.5 g of elemental calcium / daily or large amounts of active vitamin D analogues are required to control calcium levels or symptoms;
- with hypercalciuria, renal stones, nephrocalcinosis, or reduced renal function;
- with hyperphosphatemia and / or increased calcium-phosphate product;
- with gastrointestinal tract disorder associated with malabsorption;
- with significantly reduced quality of life (QoL).

However, as the clinical benefits and efficacy so far remain unknown, more clinical research is warranted to further define patients not adequately controlled by conventional treatment, and which patients would benefit from the second line treatments.

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

Two principal therapeutic options may be considered in patients insufficiently controlled by conventional treatment:

Thiazide diuretics (in association with a low salt diet), that reduce urinary calcium excretion and should be considered in patients with hypercalciuria

Thiazides are orally administered and are inexpensive.

However, they cause a renal loss of sodium, chloride, potassium, and magnesium.

Potassium concentrations should be regularly controlled when using thiazides. It should be noted that the clinical benefit of thiazides in HypoPT has so far not been documented.

Substituting the PTH deficiency by subcutaneous administration of recombinant human PTH (***rhPTH***) represents another strategy.

PTH 1–84 in a daily dose of **25 - 100 µg** has been approved by the U.S. Food and Drug Administration (FDA) and conditionally by the European Medicines Agency (EMA), as an adjunct to conventional treatment for the management of adult patients with HypoPT refractory to conventional treatment.

However, it is not available in all European countries.

Hence, **teriparatide, a PTH 1–34 fragment**, administered **once or twice daily** has **been used** **and** **has proven its efficacy** in maintaining normal calcium levels in such patients .

However, data on reduction of hypercalciuria, preservation of renal function and on bone metabolism with PTH substitution are limited and warrant further investigations

More long-acting PTH analogues are currently under development

Q8 How to evaluate patient's symptoms and QoL?

Patient reported outcome measures (PROM) are standardized, validated questionnaires that patients complete by themselves to **measure perception symptoms, functional status and wellbeing**

In endocrinology, several disease specific PROMs have been established (eg. AcroQol, Pituitary disease LBNQ-Pituitary)

QoL is reduced in HypoPT assessed by generic tools as SF-36

The current ESE guidelines do not address PROM

More recently, three disease specific PROMs for HypoPT have been developed,

- the Hypoparathyroid Patient Questionnaire (***HPQ*** 28, 28 items/questions),
- the HypoPT Symptom Diary (***HSD***; 13 items/questions),
- the Hypoparathyroidism Patient Experience Scale-Symptom (***HPES-Symptom***, 17 items/questions)
- Hypoparathyroidism Patient Experience Scale-Impact (***HPES-Impact***, 26 items/questions)

The ***HPQ 28*** and the ***HPES*** have been validated, while the shorter HSD so far lacks validation

In contrast to most methods of biochemical monitoring, PROM may reflect calcium metabolism better over time, include the patients' perspective and support shared decision-making.

Furthermore, a semi-quantitative approach to the patient's perception may improve the traditionally qualitative character of most patient consultations

We agree upon the importance of a standardised assessment of symptoms and QoL. However, awareness for unintended effects on the patients and patient communication must be considered.

The repeated reminders to symptoms and discomfort may have a negative effect on the patients overall well-being

The present PROMs for HypoPT need, however, a broader validation, both as research and clinical tools.

A meaningful, efficient and successful clinical implementation requires the development of user-friendly electronic applications for the patients and health care providers, and broad validation

Q9 Which biochemical parameters should be monitored to adjust treatment?

The principal parameter to monitor in patients with HypoPT is serum **calcium concentration**.

A discussion is ongoing about which calcium to measure: free ionized, total, or albumin-adjusted calcium concentrations.

One recent study suggests that adjustment formulas misclassify patients and add no value as compared to total calcium concentrations, while new equations are still being developed

At steady state, we recommend measuring **calcium** concentrations **every 3 to 6 months**.

Calcium should be monitored **more often** in patients requiring **dose adjustment of calcium or vitamin D treatment or during intercurrent illness, pregnancy,lactation, etc**

Serum **phosphate** concentrations and the **calcium-phosphate product** should be monitored.

Some observational studies have shown a **strong association with any kidney disease, nephrocalcinosis, the development of brain calcification and QoL**

However, it is still **unclear** whether decreasing levels of phosphate / calcium-phosphate product would improve renal outcomes,

kidney function should be monitored (through a measure of creatinine) at least every year in patients with HypoPT, but it is unclear whether it is possible to prevent a renal function decline.

So far, no clinical interventional study has shown improvement of renal function by any HypoPT treatment.

A study suggested a benefit of rhPTH(1–84) treatment as compared to the standard of care, but groups were too heterogeneous to draw firm conclusions

We recommend that **phosphate** and **creatinine** concentrations should be measured **every 3 to 6months** depending on **disease control** and stability of the patient.

Serum **magnesium** concentrations should be measured at **least annually**, **but more frequently if low.**

Biochemical markers of bone turnover could be useful in assessing the effect of **PTH replacement therapy** on bone homeostasis

Urinary calcium excretion measurement is often neglected during follow-up.

The assessment of urinary calcium excretion identifies patients at risk of developing kidney stones and / or nephrocalcinosis, and decline of renal function.

Even if recent studies did not find a clear correlation between kidney stones and hypercalciuria , or between urinary biochemical parameters and kidney outcomes , patients with HypoPT should be considered at a high risk of developing nephrolithiasis, nephrocalcinosis , as well as chronic kidney diseas

Current guidelines suggest monitoring **24h-urine calcium excretion** in all HypoPT patients without clarifying its frequency, or recommend an evaluation **every 6 or 12 months** .

This evaluation usually includes 24h-urine creatinine excretion to ensure a complete 24h- collection.

Some debate still exists on the value of measuring calcium-to-creatinine ratio rather than a 24h-urine collection.

Assessment of urinary biochemical profile, including the excretion of sodium, urea, citrate, oxalate, urate, and other analyses like pH and osmolarity is of importance, in particular in patients with history of nephrolithiasis,

Q10 Which imaging techniques are useful to monitor treatment or to evaluate tissue complications of chronic HypoPT?

The **ESE guideline** on management of HypoPT **did not comment** on the approach of patient surveillance by **imaging** during follow-up

Therefore, **questions remain unanswered** on the **optimal imaging approach** for baseline evaluation and long-term surveillance of patients with chronic HypoPT.

Clinicians should be aware of common adverse end organ manifestations(e.g., renal or central nervous system [CNS] calcification) and organize imaging to detect these accordingly depending on the clinical situation

Renal and urinary tract imaging

Regular surveillance renal imaging (**every 1 to 2 years**) is required to detect calcification or stones at an early stage in **asymptomatic individuals**.

Renal ultrasound has advantages in terms of wide availability, acceptability and safety.

In patients with prior stones, involvement of a urologist is indicated with interval scans depending on determination of individual risk.

CT scan of the renal tract has higher sensitivity and we would advocate its use in symptomatic individuals.

However, it should be indicated with caution with regards to regular long-term surveillance imaging to minimize risk from **radiation dosing**.

Clinical parameters such as urinary calcium excretion and dynamics of renal function should also be used to stratify patient risk of stone formation and determine timing of scans.

CNS effects

Basal ganglia calcification and other brain tissue calcifications are **commonly** associated with chronic HypoPT, particularly in patients with **genetic and autoimmune disease**, although studies of **post-surgical cases** had **limited duration of follow-up** .

There is a wide spectrum of CNS manifestations of this condition, including **movement disorders, seizures and neuropsychiatric symptoms**.

A **careful clinical assessment** including **brain imaging** is recommended in patients with **these manifestations. CT is commonly used** to detect basal ganglia calcification, however it is associated with exposure to ionizing radiation

Standard magnetic resonance imaging (MRI) has **low sensitivity** for the detection of **calcification**, whereas **susceptibility-weighted MRI (SW-MRI)** is validated for this indication, but **CT seems to be more sensitive**.

Prospective assessment of the natural history of basal ganglia calcification in HypoPT with clinical correlation would be helpful to develop protocols in this area.

Data for guidance on mode and **frequency** of corresponding imaging surveillance in **asymptomatic patients is lacking**

Monitoring of bone mineral density (BMD)

BMD tends to be increased in patients with chronic HypoPT with evidence of reduced bone turnover , but the **clinical implication is unclear.**

In preexisting conditions affecting the bone (PHPT, osteoporosis, hyperthyroidism) BMD measurement should be considered.

Assessment of BMD and fracture risk, in line with standard guidelines, follows a pragmatic approach.

Prospective data on meaningful clinical bone outcomes, such as fracture rates, are needed

We do agree on the importance of biomarkers for bone turnover in these patients;

however, it is questionable if BMD measurement is helpful in monitoring.

DXA could be considered in patients receiving long-term PTH replacement therapy with increase bone turnover markers

Table 4: Biochemical parameters in hypoparathyroidism

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 analogue 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 post-surgical hypoparathyroidism (6 to 12 months after the surgery).
Phosphate	Hyperphos-phatemia	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 [143]
Calcium-phosphate product			Should be calculated. Associated with brain calcifications and reduced QoL in some [145, 146] but not all studies [3].
Kidney function	Renal insufficiency	At every check	To detect decline in renal function. Advise patients to be careful with nephrotoxic medications, and with dehydration [147].
25-OH Vitamin D	Vitamin D deficiency		Often high vitamin D doses needed, especially under PTH replacement therapy. 25OHD recommended goal: >30 ng/mL and <50 ng/mL (>75 nmol/L and <125 nmol/L) (expert opinion, [21]).
Calciuria	Hypercalciuria	Every 6 to 12 months	24-hour 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.

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

Table 5: Imaging 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 *versus* 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

Parathyroid disorders during preconception, pregnancy and lactation

Changes in bone and mineral metabolism during pregnancy and lactation occur to **ensure an adequate mineral supply** to meet the **growing needs** of the fetal skeleton and the newborns while preserving maternal health

During pregnancy, the **plasma volume expansion** with subsequently **reduced albumin** levels causes a decrease in **total** calcium concentrations.

Ionized (free) and albumin-adjusted calcium remain unchanged in pregnant women with normal parathyroid function and should therefore be **used for clinical decisions** on calcium and parathyroid related disorders during pregnancy

Fetal mineral demands are mainly met by **approximately doubling the intestinal absorption of calcium, phosphate and magnesium**, that is, at least in part, a consequence of increases in **1,25(OH)2D and estrogen.**

This and glomerular hyper-filtration lead to **increased postprandial** and 24-h urine calcium excretion with **normal fasting** urine calcium excretion (i.e., **absorptive hypercalciuria**) .

Required minerals are **actively** transported by the placenta and circulate at higher concentrations in the fetus as compared to the mother .

This facilitates mineralization of the fetal skeleton before birth, with **80% of mineral accretion occurring in the third trimester**

Despite this mineral supply, pregnancy itself **usually does not alter maternal BMD if the maternal calcium intake is adequate**, or result in **only a modest 1 to 4% decrease in BMD .**

During lactation, mineral supply to **breast milk mainly derives from the maternal skeleton that is exposed to increased bone resorption and osteocytic osteolysis**

This translates into a **significant decrease of about 5 to 10% in lumbar spine BMD after 6 months of exclusively nursing a singleton, with about half of this effect at the hip and radius**

Six to twelve months after weaning, the maternal BMD reaches its pre-pregnancy values or may even exceed them

Therefore, and although the literature on this issue is not fully consistent, **parity and lactation itself do usually not increase the long-term risk for osteoporosis and fractures, but might even confer some protection**

During pregnancy, maternal PTH, which does not cross the placenta, is usually suppressed to the lower normal range or even below, while 25(OH)D remains materially unchanged and 1,25(OH)2D increases 2- to 3-fold .

Parathyroid hormone-related peptide (**PTHrP**) that is virtually **not detected in non-pregnant women, increases steadily** during pregnancy and appears to be mainly produced by **breast tissue and placent**

The **precise physiological role** of PTHrP is **still not fully clarified**, but has been shown to exert **PTH-like effects**.

Excess PTHrP production may cause hypercalcemia, a disease termed ***pseudohyperparathyroidism*** .

During lactation, **PTHrP release is stimulated via suckling and high prolactin,** as exemplified by the **successful treatment of pseudohyperparathyroidism with prolactin suppressing dopamine agonists**

After delivery and during lactation, 1,25(OH)2D concentrations normalize, while inconsistent data have been reported on PTH concentration

No RCTs are available to guide management decisions for parathyroid disorders during pregnancy and lactation.

Accordingly, all recommendations and suggestions are based on (limited) evidence from **observational studies** and **personal experience**

In general, we consider it as a reasonable approach to **measure calcium concentrations** (preferably albumin corrected and / or ionized calcium) **at least once** as part of otherwise indicated **routine screening** programs or visits during **preconception** and **early pregnancy**, and consult an endocrinologist in case of calcium levels outside the reference ranges

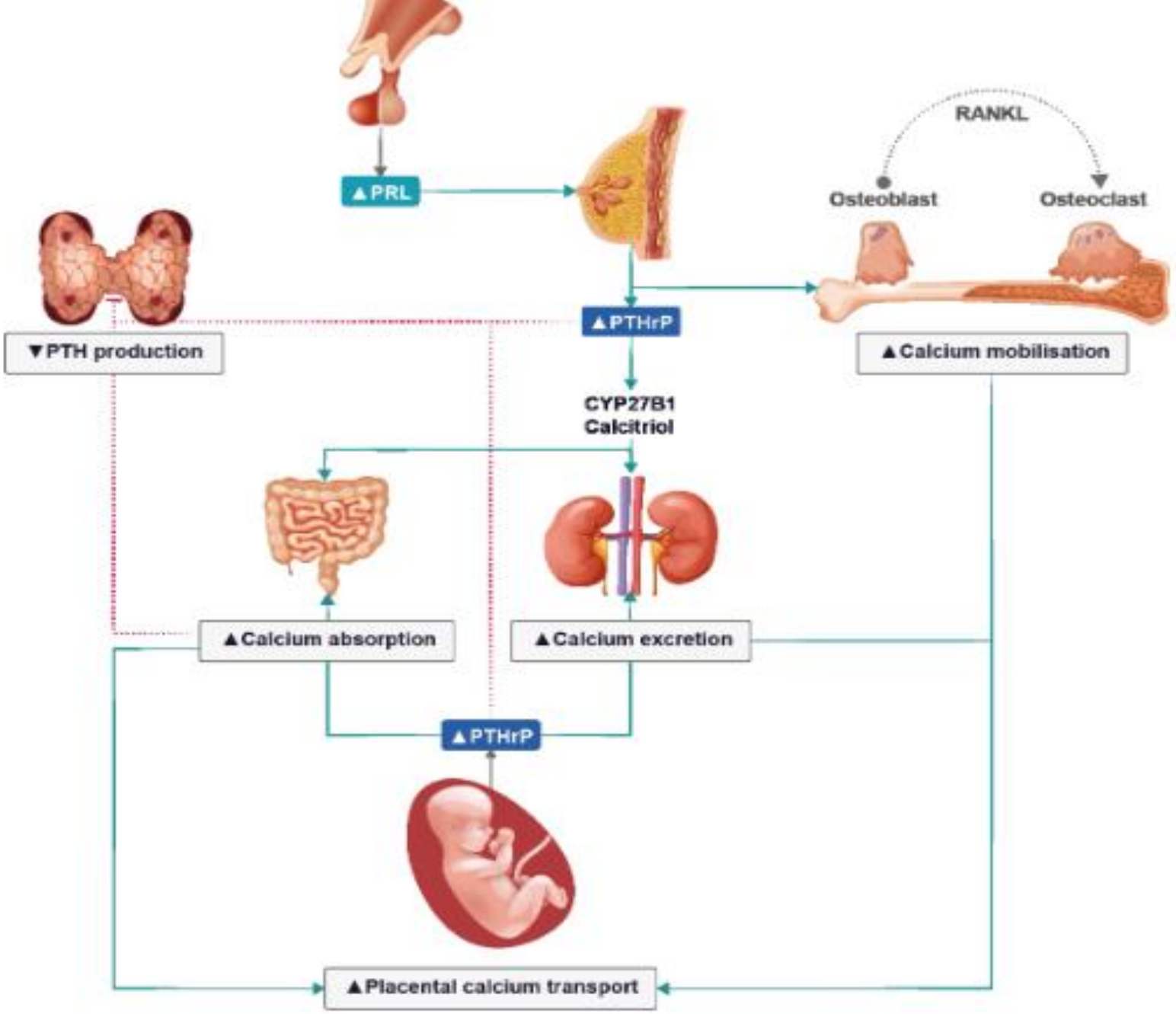


Figure 5. Overview of calcium homeostasis and calciotropic hormones in pregnancy. Parathyroid hormone related protein (PTHrP) production in the placenta will gradually decrease endogenous parathyroid hormon

Management of patients with PHPT in relation to pregnancy

PHPT during pregnancy is relatively rare accounting for roughly 1% of the total of PHPT patients .

PHPT diagnosed during pregnancy requires consideration of alterations in PTH concentrations and associated changes in mineral metabolism

Distinguishing PHPT from FHH in pregnancy is challenging in view of absorptive hypercalciuria resulting in a significant increase of the CCCR

Therefore, **laboratory values of first-degree relatives** and of the **patient** before pregnancy, as well as **genetic testing** are of particular importance in this setting

In case reports and case series, **maternal clinical symptoms** of PHPT during pregnancy vary considerably and resemble frequent complaints during normal pregnancy, such as:

- **malaise,**
- **nausea,vomiting,**
- **fatigue,**
- **polyuria,**
- **muscle weakness.**

Polyhydramnios may develop due to osmotic polyuria of the fetus

The **vast majority** of investigations on gestational PHPT report on **significantly increased risk** of fetal / neonatal and maternal complications which might reflect **publication bias.**

In general, calcium levels are **usually only slightly elevated** and **relatively stable,** and **many cases of mild PHPT** go **undiagnosed** in pregnancy with no particular increase in maternal or fetal health risk

Nevertheless, PHPT during pregnancy has been reported to increase the risk of:

- **miscarriages,**
- **premature birth,**
- **intrauterine growth retardation**
- **maternal nephrolithiasis, pancreatitis and preeclampsia**

There seems to be a **strong positive correlation** between calcium concentrations and **pregnancy complications**, with the risk being particularly increased **if total calcium levels are >2.85 mmol/L (>11.42 mg/dL)**

By contrast, there is **still some controversy** whether **mild hypercalcemia** is associated with adverse pregnancy outcome

Q1 *What preconception advice should be given to women with PHPT?*

We recommend that pregnancy, if possible, should be **deferred** until **curative surgery for PHPT** has been performed and calcium levels have normalized.

Q2 *How to treat PHPT during pregnancy?*

International guidelines recommend PTX in patients **below the age of 50 years**

Therefore, the main question is the **timing and mode of surgery**, while conservative management should **only be regarded as temporary** until surgery

Conservative treatment options primarily include **oral and intravenous rehydration**, **and cinacalcet for severe hypercalcemia**

Cinacalcet has been used in **several pregnant women** without significant safety concerns, although it **crosses the placenta** and **safety evidences** are still considered **insufficient** for official approval.

Safety concerns argue against the use of ***bisphosphonates*** that also **cross the placenta.**

Calcitonin does **not cross the placenta** but its efficacy to control hypercalcemia declines after a few days due to **tachyphylaxis.**

Importantly, **a systematic review** of observational studies including **382** women with **gestational PHPT**, of whom **108** underwent **PTX** during pregnancy, reported a **significantly lower infant complication rate for surgery versus medical therapy** (9.1% versus 38.9%), with similar results when restricting the analyses to asymptomatic cases .

Adverse outcomes were less likely when surgery was performed in the **second** versus the third trimester (4.5% versus 21.1%).

Accordingly, we recommend that pregnant women with PHPT and an

- **albumin adjusted total calcium** level >2.85 mmol/L ***(>11.42 mg/dL***)
- and / or >0.25 mmol/L ***(>1mg/dL) above ULN***
- and / or an ***ionized calcium >1.45*** mmol/L (>5.81 mg/dL)

should undergo PTX in the second trimester

For pregnant PHPT women with calcium levels **below** **the above-mentioned cut-offs, an individual shared decision** should be made regarding the therapeutic options.

However, PTX may be considered in selected cases, but factors such as only **mild hypercalcemia** and / or **doubts** regarding the correct diagnosis of PHPT might justify a **conservative approach**

For surveillance, we consider it as a reasonable approach to monitor **calcium levels and eGFR approximately every 4 weeks** in pregnant women with PHPT and even more frequently **(e.g., all 1 to 2 weeks) after changes in the medical treatment of PHPT.**

In case of PTX, perioperative laboratory measurements and calcium plus vitamin D supplementation are recommended, as in non-pregnant patients

Q3 What is the preferred surgical approach for PTX during pregnancy?

In sporadic PHPT, minimally invasive PTX in combination with intraoperative PTH monitoring is preferred.

Bilateral neck exploration may be needed in:

- **hereditary forms** of PHPT (i.e., MEN1, MEN2A, MEN4, hyperparathyroidism-jaw tumor syndrome and familial isolated hyperparathyroidism),
- other causes of **parathyroid hyperplasia** with potential indication for surgery, such as **lithium intake**

Q4 Which parathyroid imaging modalities should be used in pregnant women with PHPT and indication for surgery?

Preoperative localization of abnormal parathyroid glands is crucial for the success of **minimally invasive PTX**, and **concordance of 2 imaging methods may result in very high positive predictive values** for a correct localization of adenoma(s)

Avoiding radiation exposure in pregnancy is critical for guiding decisions on the choice of imaging methods for PHPT.

- **Ultrasound and 4D-dynamic contrast-enhanced MRI lack ionizing radiation, but if needed, also**
- **99mTc-methoxyisobutylisonitrile (99mTc-MIBI) scans,**
- **sestamibi single-photon emission computed tomography (SPECT/CT),**
- **18F-Fluorocholine PET/CT**
- **methionine PET/CT**

are acceptable choices after careful consideration of potential risks and benefits

The fetal exposure by a 99mTc-MIBI scan is lower than the exposure associated with fetal harm.

18F-Fluorocholine PET/CT is even considered to have a **lower overall (maternal) radiation dose than 99mTc-MIBI SPECT/CT, but the fetal radiation exposure by 18F- Fluorocholine PET/CT is not exactly known and might even be higher due to increased fetal tracer uptake .**

4D-CT has the highest radiation dose and **should be avoided** during pregnancy

To provide a rough guidance for pregnant women with PHPT and an indication for surgery, we consider it reasonable to aim for **two different preoperative imaging methods**, **preferably ultrasonography in combination with either 99mTc-MIBI scan or 4D- dynamic contrast-enhanced MRI.**

Other imaging methods or ultrasonography without additional imaging may be considered for selected cases and taking into account the **local expertise** and the **individual risks and benefits.**

However, any imaging method with radiation exposure should only be performed if considered to have a favorable benefit to risk ratio for the individual pregnant woman.

Q5 What are important considerations for the postpartum and lactation period for the mothers with PHPT and their newborns?

In ***pregnant*** women with PHPT, it should be considered that **fetal PTH is likely suppressed** due to elevated maternal calcium levels, but **immediately after birth the calcium** transfer via the placenta is abruptly stopped.

Consequently, there is an **increased risk of hypocalcemia and hypocalcemic seizures** (**clonic movements**) in the newborns and of **maternal hypercalcemic crisis** in the postpartum period

During ***lactation***, we consider it reasonable to measure **maternal calcium levels and eGFR approximately every 4 to 8 weeks starting within the first week after delivery**

PTX should be performed **a few weeks after delivery** when the mother hasfully recovered.

With respect to medical treatment, ***cinacalcet*** **is excreted in the milk of lactating rats with a high milk to plasma ratio.**

Therefore, a ***careful benefit / risk assessment decision*** should be made to discontinue either breast-feeding or treatment with ***cinacalcet*** in lactating women who require this treatment for PHPT.

We recommend close clinical monitoring for the ***newborns of mothers*** with PHPT as **neonatal hypocalcemia may occur within the first 2 to 3 weeks of life.**

We **suggest to measure ionized calcium in the newborns at least every 2 days starting on day 2, and continue this, depending on disease severity, until about 1 to 2 weeks of life,** with usually no further testing in case of mild disease with normal neonatal calcium levels within the first week of life

Consider active vitamin D treatment (e.g., alfacalcidol or calcitriol) in case of neonatal hypocalcemia that usually occurs around day 2 or 3.

Regular native vitamin D supplementation(usually 400 international units cholecalciferol [vitamin D3 per day] is recommended.

Management of HypoPT patients in relation to pregnancy

Management of chronic HypoPT during pregnancy constitutes a **challenge**, **as there are scarce data on this topic.**

Most published studies are based on **case reports** **or** **small case series**, which suggest that maternal HypoPT is associated with **significant maternal and fetal morbidity, including fetal loss and preterm delivery**.

Importantly, the by far largest study on this topic, a recently published register study from **Sweden** of **97 pregnant women** with chronic HypoPT and 1,030 pregnant age-matched controls, showed a **significantly higher prevalence of diabetes mellitus and chronic kidney disease in chronic HypoPT compared with control**

In **multivariate adjusted analyses**, chronic HypoPT versus controls was associated **with higher risk of induction of labor and a slightly lower birth weight, but no other adverse pregnancy outcomes**

Calcium requirements increase during pregnancy.

It is important to ensure an adequate intake of calcium and active vitamin D, as **maternal hypocalcemic** may cause **secondary hyperparathyroidism in the fetus** with fetal skeletal demineralization

In contrast, if the **mother is hypercalcemic,** the fetal parathyroid tissue may become suppressed and the **fetus** may develop **hypocalcemia**

It is therefore of particular importance to closely monitor women with HypoPT during pregnancy.

Calcium and activated vitamin D supplements were recommended as the mainstay of treatment for HypoPT during pregnancy

Q6 What are the treatment targets and surveillance recommendations during pregnancy in women with chronic HypoPT?

The goal of therapy is to achieve an ionized and / or albumin adjusted calcium level in the **lower end of the normal reference range** and to avoid both maternal hypo- and hypercalcemia

As it is difficult to predict precise doses of calcium and active vitamin D needed to maintain the concentrations within the recommended range, **careful monitoring of calcium, phosphate, eGFR, and magnesium should be performed during pregnancy, i.e., every 3 to 4 weeks,** and **more frequently (e.g., weekly) within 1 month before giving birth**

If changes in the dose of calcium and / or active vitamin D are recommended, measurement of calcium should be **repeated in 1 to 2 weeks.**

It is recommended to maintain 25(OH)D levels in the reference range

Q7 What are the required doses of calcium and active vitamin D during pregnancy in women with chronic HypoPT?

The literature describes a **wide variation in the required doses** of calcium and active vitamin D (alfacalcidiol or calcitriol)to maintain normocalcemia during pregnancy in women with chronic HypoPT .

Some women require higher doses of active vitamin D, whereas others require lower doses. **These dose requirements may also change during the course of pregnancy**

Individual variations may, amongst others, reflect variations in dietary intakes, and variations in PTHrP production, and in calcitriol production from the maternal kidneys

Notably, **inadequate calcium intake in the first trimester may contribute to inadequate mineral accrual of the developing fetus**

Q8 Is treatment with PTH analogues and hydrochlorothiazide safe during pregnancy?

Adjunctive therapy with ***PTH analogues*** **has not been evaluated during pregnancy (FDA *Category C* drugs),**

Hydrochlorothiazide **(FDA *Category B* drug) should be stopped during** pregnancy in the **first trimester**, and should **only** be used **after careful risk evaluation in the second and third trimester**

Q9 How to manage chronic HypoPT during lactation?

Close monitoring of calcium is recommended during lactation as

- ✓ **calcitriol levels normalize (i.e., endogenous calcitriol synthesis decreases after delivery)**
- ✓ **PTHrP levels are increased**
- ✓ **bone resorption increases**
- ✓ **renal calcium reabsorption increases**

These effects **may lower the dose requirements for active vitamin D and calcium supplementation during lactation** in women with chronic HypoPT

Therefore, it is recommended to continue monitoring maternal calcium **levels weekly within the first month after delivery** **and then** **every 4 weeks during lactation**

Abrupt cessation of breastfeeding can be associated with maternal hypocalcemia

Q10 What are the surveillance and treatment recommendations for Newborns of mothers with HypoPT?

Newborns should be monitored **clinically** and we suggest **measuring ionized calcium** concentrations **every second day for the first week of life**

Regular native vitamin D supplementation is recommended.

Table 6. Summary of recommendations for PHPT and HypoPT during preconception, pregnancy and lactation.

	PHPT	HypoPT
Mother (preconception)	Pregnancy should be avoided until curative surgery has been performed and calcium concentrations are normalized.	Counselling regarding frequent surveillance and potential changes in vitamin D and calcium requirements during pregnancy. Most mothers will have a healthy baby.
Mother (pregnancy)	Surgery is advised, preferentially in the second trimester, and especially if albumin adjusted calcium is >2.85 mmol/L (>11.42 mg/dL) and / or >0,25 mmol/L (>1 mg/dL) ULN and /or ionized calcium is >1.45 mmol/L (>5.81 mg/dL). Surveillance every 4 weeks.	Calcium and vitamin D supplements as well as active vitamin D treatment can be used. Aim for ionized and / or albumin adjusted calcium levels in the lower end of the reference range. Surveillance every 3 to 4 weeks.
Mother (lactation)	Surveillance every 4 to 8 weeks. Surgery a few weeks after delivery.	Surveillance weekly within the first month after birth and then every 4 weeks.
Newborns	Measure ionized calcium every second day until about 1 to 2 weeks of life. In case of hypocalcemia, consider active vitamin D treatment.	Measure ionized calcium every second day during the first week of life.

HypoPT, chronic hypoparathyroidism; PHPT, primary hyperparathyroidism; ULN, upper-limit of normal.


Tnx for your attention
And he is the best preservoir…