European Journal of Endocrinology, 2025, **193**, G83–G112
https://doi.org/10.1093/ejendo/lvaf222
Advance access publication 13 November 2025
Clinical Practice Guideline

Revised European Society of Endocrinology Clinical Practice Guideline: Treatment of Chronic Hypoparathyroidism in Adults

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Abstract

In the present European Society of Endocrinology (ESE) clinical guideline, we present recommendations for the diagnosis, management, and monitoring of chronic hypoparathyroidism (HypoPT) in adults. Management of HypoPT has changed since the first ESE clinical guideline was published in 2015, as has the knowledge on patient burden of the disease, and the understanding of associated morbidities. In line with the ESE policy, the 2015 guidelines were updated based on up-to-date scientific evidence.

As HypoPT is an orphan disease, strong evidence for most outcomes is scarce and recommendations were based on careful synthesis of the literature and expert opinion. Postsurgical HypoPT should be defined as persisting more than 12 months following surgery; recovery could be expected even thereafter (clinical question I [Q I]). For Q II (optimal treatment of chronic HypoPT), relevant data regarding conventional treatment are lacking for clinically relevant endpoints and long-term effects. PTH replacement therapy reduces the pill burden of conventional therapy, improves various biochemical parameters, and potentially improves QoL. We cannot recommend a substantial role for parathyroid allotransplantation in the treatment of chronic HypoPT (Q III).

In conclusion, we present recommendations for the diagnosis, management, and monitoring of chronic HypoPT in adults, to give health care providers practical clinical guidance on the management of this condition. The guideline can serve as a source for preparation of educational materials to empower patients and clinicians.

Keywords: Hypoparathyroidism, hypocalcaemia, PTH replacement therapy, vitamin D

Received: October 25, 2025. **Accepted:** October 27, 2025

1. Summary of Recommendations

1. Diagnosis
   - R.1.1 We recommend considering a diagnosis of chronic hypoparathyroidism (HypoPT) in a patient with persistent hypocalcaemia and inappropriately low or inappropriately normal parathyroid hormone (PTH) levels.
   - R.1.2 We recommend genetic testing and/or family screening in a patient with nonsurgical HypoPT without other obvious aetiology.
2. General goals of management in chronic hypoparathyroidism
   - R.2.1 We recommend treatment for HypoPT to be personalised and centred on the patient's overall well-being with therapeutic goals that optimise quality of life (QoL), minimise symptoms of hypocalcaemia, improve long-term prognosis, and maintain calcium levels within the lower part or slightly below the reference range. (Good clinical practice)
   - R.2.2 We recommend providing information/education that enables patients to recognise the possible symptoms of hypo- or hypercalcaemia and/or complications of their disease. (Good clinical practice)
   - R.2.3 We suggest aiming for normal 24-hour urinary calcium excretion. (⊕OOO)
   - R.2.4 We suggest aiming for phosphate levels within the reference range. (⊕OOO)
   - R.2.5 We suggest aiming for magnesium levels within the reference range. (⊕OOO)
   - R.2.6 We suggest aiming at an adequate vitamin D status (25(OH)D level ≥ 75 nmol/L [> 30 ng/mL]). (⊕OOO)
3. Treatment
   - R.3.1 We recommend treatment of all patients with chronic HypoPT who have symptoms of hypocalcaemia and/or an albumin-adjusted calcium level < 2.0 mmol/L (< 8.0 mg/dL) ≈ ionised calcium (iCa^{2+}) < 1.00 mmol/L.
   - R.3.2 We suggest offering treatment to patients with chronic HypoPT, even if apparently asymptomatic, if albumin-adjusted calcium levels are between 2.0 mmol/l (8.0 mg/dL or iCa^{2+} 1.00 mmol/L) and the lower limit of the reference range to assess whether this may improve their well-being. (Good clinical practice)
   - R.3.3 We recommend treatment with vitamin D.
     - R.3.3.1 We recommend treatment with an activated vitamin D analogue if available (e.g., alfacalcidol or calcitriol). (⊕OOO)
     - R.3.3.2 If activated vitamin D analogues are not available, we suggest treatment with supraphysiological doses of calciferol (preferentially cholecalciferol, i.e., vitamin D3). (⊕OOO)
     - R.3.3.3 We recommend titration of vitamin D analogue doses aiming at calcium levels within the target range with patients being free of symptomatic hypocalcaemia and biomarkers within the target range. (⊕OOO)
   - R.3.4 We recommend assuring an adequate calcium intake.
     - R.3.4.1 We suggest a dietary elemental calcium intake of about 800-1000 mg/day in adults (non-pregnant) (European Food Safety Authority[1]).
     - R.3.4.2 We suggest using calcium supplements if blood calcium levels in the target range cannot be achieved by treatment with activated vitamin D analogues in combination with an adequate dietary calcium intake. (⊕OOO)
     - R.3.4.3 We recommend that elemental calcium supplementation greater than 500 mg daily should be taken in smaller doses and spread throughout the day.
   - R.3.5 We recommend PTH replacement therapy patients with chronic HypoPT who continue to have signs or symptoms of HypoPT despite optimised treatment with (activated) vitamin D and adequate calcium intake. (⊕⊕OO)
     - R.3.5.1 We suggest to titrate the dose of PTH replacement therapy to achieve sustained calcium levels in the target range without the need for concurrent activated vitamin D treatment or calcium supplements.
     - R.3.5.2 We suggest to consider treatment with PTH replacement therapy in patients with one of the following despite optimised conventional treatment:
       - Frequent fluctuations in calcium levels, or symptomatic hypocalcaemia
       - Impaired quality of life attributable to chronic HypoPT
       - Reduced kidney function (eGFR < 60 mL/min per 1.73m²)
       - Hypercalciuria (calcium excretion > 7.5 mmol/24-hour [300 mg/24-hour] in men, and > 6.25 mmol/24-hour in women [250 mg/24-hour]; or > 0.1 mmol/kg/24-hour [4 mg/kg/24-hour] in both sexes)
       - Hyperphosphataemia
     - R.3.5.3 If PTH replacement therapy is initiated, we suggest evaluating the treatment effects after 6-12 months, depending on treatment goals. (Good clinical practice)
   - R.3.6 In the presence of hypercalciuria, we suggest measures to lower urinary calcium excretion, which may include decreased doses of calcium supplements and/or activated vitamin D analogues, a low sodium chloride intake (< 6 g NaCl or < 2.4 g sodium/day), and/or addition of treatment with a thiazide diuretic. If these measures are not effective in normalising hypercalciuria, while maintaining calcium levels within the target range, we suggest PTH replacement therapy. (⊕OOO)
   - R.3.7 In the presence of hyperphosphataemia, we suggest dietary interventions and/or adjustment of treatment with calcium supplements and vitamin D analogues. If these measures are not effective in normalising hyperphosphataemia while maintaining calcium levels within the target range, we suggest PTH replacement therapy. (⊕OOO)
   - R.3.8 In a patient with hypomagnesaemia, we suggest measures to increase magnesium levels. (⊕OOO)
   - R.3.9 Ensure replete levels of vitamin D by using a daily vitamin D supplement (cholecalciferol or ergocalciferol; vitamin D_3 or D_2) of 800-2000IU (20–50 µg).
4. Monitoring
   - R.4.1 We suggest measuring PTH levels once a year, as appropriate, to assess endogenous function for potential recovery.

R.4.2 We recommend routine biochemical monitoring of circulating levels of ionised, or albumin-adjusted total calcium, phosphate, magnesium, and creatinine (estimated glomerular filtration rate [eGFR]), as well as assessment of symptoms of hypocalcaemia and hypercalcaemia at regular time intervals (e.g., every 3-6 months).

R.4.3 Following changes in therapy, we recommend biochemical monitoring every 1-2 weeks.

R.4.4 When receiving conventional treatment, we suggest monitoring of 24-hour urinary calcium at regular time intervals (e.g., every 1-2 years).

R.4.5 We recommend against routine renal imaging, but perform renal imaging (ultrasound or computed tomography) if there are clinical or laboratory features suggestive of nephrolithiasis, nephrocalcinosis, or unexplained decline in renal function.

R.4.6 We suggest monitoring for the development of signs or symptoms of co-morbidities at regular time intervals (e.g., yearly).

R.4.7 We suggest assessing fracture risk as recommended for the general population.

5. Special circumstances

Autosomal dominant hypocalcaemia

R.5.1 We recommend close monitoring of patients with autosomal dominant hypocalcaemia (ADH), who are being treated with calcium and/or activated vitamin D, as such patients may be at greater risk of hypercalciuria and renal complications.

Pregnancy and breastfeeding

R.5.2 We suggest treatment with activated vitamin D analogues and calcium supplements as in non-pregnant women.

R.5.3 We recommend monitoring ionised calcium and/or albumin-adjusted calcium levels regularly (e.g., every 3 - 4 weeks) throughout pregnancy and lactation and even more frequently (e.g., weekly) during the 4 weeks before and after delivery, aiming to keep calcium levels at the lower end of the normal range.

R.5.4 We recommend that a paediatrician and/or neonatologist be informed of maternal HypoPT and be involved in the immediate care and monitoring of the infant for potential consequences related to both maternal treatment and the underlying maternal disorder.

2. Clinical considerations in chronic hypoparathyroidism

2.1 Aetiology and Epidemiology

Hypoparathyroidism (HypoPT) is an endocrine disease characterised by low calcium and undetectable or inappropriately low (insufficient) circulating parathyroid hormone (PTH) levels[2-5]. It is a rare condition, designated an orphan disease by the European Commission in January, 2014, (EU/3/13/1210), http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/orphans/2014/01/human_orphan_001301.jsp&mid=WC0b01ac058001d12b.

HypoPT is the only major endocrine disorder in which the missing hormone, PTH, is not routinely replaced[6-8]. Functionally, HypoPT represents a dual hormonal deficiency, as levels of activated vitamin D (1,25-dihydroxyvitamin D [1,25$(OH)_2$D], calcitriol) are reduced due to absent PTH stimulation of renal 1α-hydroxylase[9].

The prevalence of HypoPT ranges from 6.4 to 38/100.000, and the vast majority (75% or more) is due to neck surgery[6,8,10-12], i.e., secondary to thyroid or parathyroid surgery, termed postsurgical HypoPT[6-8,13]. The annual incidence of HypoPT varies by region, ranging from 0.8 to around 7 per 100.000 inhabitants, most likely reflecting differences in the completeness and representativeness of background registries[14]. HypoPT may have an autoimmune pathogenesis[13,15], and in many such patients, the cause is a bi-allelic mutation in the *AIRE* (autoimmune regulator of endocrine function) gene[13,16-18]. The main targets of autoantigens in AIRE-related autoimmunity are the calcium-sensing receptor (CaSR) and NACHT leucine-rich protein 5 (NALP5)[19]. In general, autoimmune parathyroid diseases occur in the setting of autoimmune polyendocrine syndromes, but isolated autoimmune forms of HypoPT may also occur[20], such as that caused by activating antibodies to CaSR[21]. In addition, other rare genetic conditions can cause HypoPT, either as part of a syndrome (e.g., DiGeorge Syndrome[22], which tends to be sporadic but can be familial), or as an isolated endocrinopathy (e.g., autosomal dominant hypocalcaemia type 1 [ADH1]), caused by pathogenic gain-of-function variants in *CASR*)[13] (see **Table 1**). An emerging mechanism of nonsurgical HypoPT relates to the increasing use of immune therapies, including immune checkpoint inhibitors for malignancies and related diseases[23,24]. Other rare causes of HypoPT include, for example, parathyroid gland radiation injury, haemochromatosis, granulomatous diseases, or metastatic cancers[25].

2.2 Postsurgical Hypoparathyroidism

Postsurgical HypoPT persisting for more than 6–12 months in adults is usually secondary to thyroid surgery but may occur following parathyroidectomy or other operations on the neck[26]. Overall, between 2-10% of patients undergoing total thyroidectomy, particularly when combined with central/lateral lymph node dissection for thyroid cancer, will develop permanent HypoPT[27,28].

Postsurgical HypoPT is associated with young age, female sex, underlying Graves' disease, unilateral or bilateral lymphadenectomy, gross extrathyroidal extension of thyroid cancer, early postoperative hypocalcaemia (within 24 hours of thyroidectomy), accidental parathyroidectomy, intraoperative parathyroid biopsies during surgery for hyperparathyroidism, the presence of parathyroid tissue in the operative specimen, and parathyroid auto-transplantation[29]. Most importantly, the number of functioning parathyroid glands remaining *in situ* postoperatively is a key determinant of the risk of developing postoperative hypocalcaemia (16% for cases with 1-2 preserved glands, 6% for 3 glands, and 2.5% for four glands)[28-30]. All these factors correlate with reduced PTH secretion immediately following surgery. If the PTH concentration is > 10 pg/mL (1.05 pmol/L) 12 to 24 hours after surgery, progression to permanent HypoPT is very unlikely. However, many patients with lower PTH levels may still recover from postoperative HypoPT[13].

Notably, in patients with preoperative hypercalcaemia, such as in primary hyperparathyroidism, calcium levels may take several days to normalise after surgery, during which PTH levels may be very low[28-31]. Additional risk factors for postsurgical HypoPT include obesity[32] and severe vitamin D deficiency[33].

Table 1. Genetic Aetiologies of Hypoparathyroidism.

Condition	OMIM Phenotype #	Gene/Chromosome	Syndromic features
Isolated hypoparathyroidism due to pathogenic variants or deletions/insertions in:			
ADH1	601198	*CASR*	Hypomagnesemia, hypercalciuria, possible Bartter syndrome
ADH2	615361	*GNA11*	Hypomagnesemia, hypercalciuria
FIH1	146200	*PTH*	
FIH2	618883	*GCM2*	
HYPX	307700	Chromosome Xq27.1 (*SOX3*)	
Syndromes of hypoparathyroidism with damage to the parathyroid glands due to pathogenic variants in:			
APS1	240300	*AIRE*	Primary adrenal insufficiency, mucocutaneous candidiasis, other autoimmune conditions, ectodermal dystrophy
Syndromes of hypoparathyroidism with impaired parathyroid gland formation due to pathogenic variants or deletions in:			
DiGeorge syndrome 1	188400	Chromosome 22q11 (*TBX1*)	Thymic hypoplasia with immune deficiencies, heart malformations, cleft palate, dysmorphic facies, cognitive impairment, developmental delay, psychiatric disorders
DiGeorge syndrome 2	601362	Chromosome 10p14 (*NEBL*)	
Barakat syndrome	146255	*GATA3*	Sensorineural deafness, renal dysplasia
CHARGE syndrome (Hall-Hittner syndrome)	214800	*CHD7*	Coloboma, Heart defects, Atresia choanae, Retardation of growth and development, Genital abnormalities, Ear abnormalities
Kabuki syndrome	147920	*KMT2D**	Dysmorphic facies, developmental delay, growth retardation, cardiac, and skeletal abnormalities
Sanjad-Sakati syndrome (Kenny-Caffey syndrome type 1)	241410/ 244460	*TBCE***	Growth retardation, short stature, dysmorphic facies, developmental delay, seizures, intellectual disability
Kenny-Caffey syndrome, dominant (type 2)	127000	*FAM111A***	Growth retardation, short stature, craniofacial abnormalities, seizures, and cortical thickening and medullary stenosis of long bones
Osteocraniostenosis	602361		Gracile bone dysplasia with thin and fragile bones, craniofacial abnormalities, microphthalmia
Kearns-Sayre syndrome	530000	Mitochondrial DNA	Mitochondrial encephalomyopathy, progressive ophthalmoplegia, pigmentary retinopathy, cardiac abnormalities
Pearson marrow-pancreas syndrome	557000		Anaemia, cytopenias, pancreatic insufficiency, lactic acidosis
MELAS	540000		Mitochondrial encephalomyopathy, lactic Acidosis, stroke-like episodes, seizures
Mitochondrial trifunctional protein deficiency syndrome	609015/ 620300	*HADHA/HADHB*	Cardiomyopathy, hypoglycaemia, lethargy, hypotonia, rhabdomyolysis, neuropathy, liver disease
Long-chain hydroxyacyl-CoA dehydrogenase deficiency	609016	*HADHA*	Hypoglycaemia, myopathy, rhabdomyolysis, cardiomyopathy, hepatomegaly, neuropathy, pigmentary retinopathy, liver disease
Medium-chain acyl-CoA dehydrogenase deficiency	201450	*ACADM*	Hypoglycaemia, lethargy, vomiting, seizures, fatty liver
Smith-Lemli-Opitz syndrome	270400	*DHCR7*	Microcephaly, intellectual dysfunction, hypotonia, facial dysmorphism, syndactyly, genital abnormalities

Data in Table 1 were derived from Mannstadt et al[13], *Cerqueira et al[273], and **Schight *et al.*[274].
ADH1, autosomal dominant hypocalcaemia 1; ADH2, autosomal dominant hypocalcaemia 2; FIH1, Familial isolated hypoparathyroidism 1; FIH2, Familial isolated hypoparathyroidism 2; HYPX, hypoparathyroidism X-linked recessive; APS1, autoimmune polyendocrine syndrome type 1; MELAS, mitochondrial encephalopathy, lactic acidosis, and stroke-like episodes.

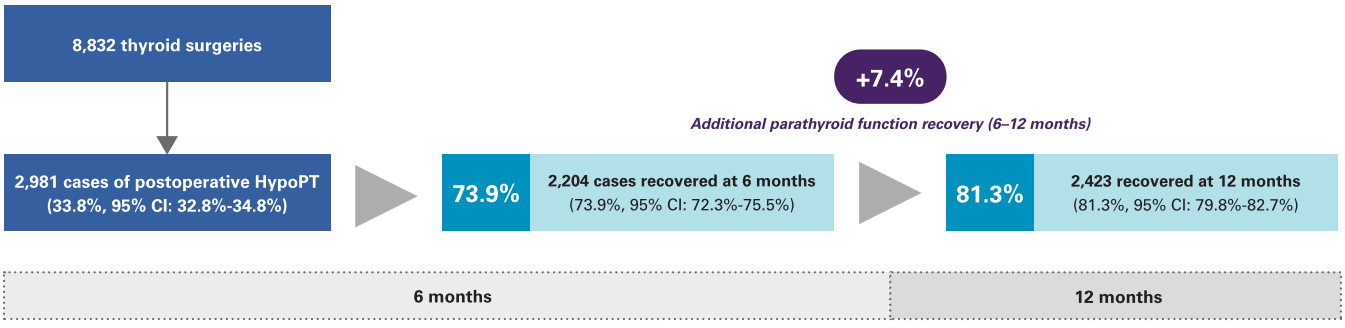

Figure 1. Recovery of postsurgical HypoPT 6 and 12 months after thyroid surgery.

About 60-70% of cases of postoperative hypocalcaemia resolves within four to six weeks after surgery (transient HypoPT); the rest remains with HypoPT characterised by low PTH levels and the need for continued treatment, at least for a period, but still with a chance for recovery; other clinical variables lose predictive value at this stage[28,30].

Importantly, a substantial proportion of patients with postoperative HypoPT will recover in the period between 6 to 12

months following surgery[34-37], see Figure 1. Therefore, we here define postoperative chronic HypoPT in adults as HypoPT of more than 12 months duration following neck surgery. However, it is important to stress that some patients may still regain sufficient parathyroid function even several years after surgery[35].

Overdiagnosis of thyroid cancer can lead to unnecessary surgery and is a potential contributor to preventable HypoPT cases and should be carefully minimised[38,39]. Efforts to preserve parathyroid gland function and reduce the risk of postsurgical HypoPT have led to the introduction of near-infrared autofluorescence (NIRAF), as an intraoperative adjunct to improve parathyroid gland visibility during surgery[40]. By using near-infrared light and NIRAF characteristics of the parathyroid tissue, surgeons can obtain high-contrast imaging in real-time, with the potential to preserve the glands. The use of indocyanine green (ICG) to enhance fluorescence imaging enables the real-time assessment and direct imaging of tissue perfusion and vascularisation[41]. Standardisation of the technique, as well as long-term randomised controlled studies, are required to truly assess any sustained beneficial effect of NIRAF on parathyroid function[42].

2.3 Complications and Renal Implications of Chronic Hypoparathyroidism in Adults

Compared to the general population, patients with chronic HypoPT experience a lower quality of life (QoL), characterised by musculoskeletal and neuropathic pain, fatigue, weakness, increased anxiety, and a potentially higher risk of depression[6,8,10,43-48]. Similarly, cohort studies have shown an increased risk of hospitalisation for depression and affective disorders, as well as for renal impairment and infections[8,44,48-50]. The risk of ischaemic heart disease and cataracts is increased in nonsurgical HypoPT, whereas data from patients with postsurgical HypoPT are inconsistent[8,10,44,50,51]. The discrepancy between the two conditions may be disease- and exposure-time-specific[4].

HypoPT is associated with an increased circulating calcium-phosphate product. Loss of renal PTH action decreases renal tubular reabsorption of calcium and the excretion of phosphate, causing hypercalciuria and hyperphosphataemia, respectively[52]. Patients with chronic HypoPT have an increased risk of renal complications, such as renal stones, renal insufficiency, and a higher risk of needing renal replacement therapy[8,48,49,51,53,54]; see Table 2. Impaired renal function has been associated with duration of disease and time with hypercalcaemia[48,53]. However, despite keen interest in improving the management of HypoPT, large cohort studies describing typical treatment patterns, optimised target laboratory parameters, and rates of complications are scarce. Data on mortality have been conflicting so far. A recent study found increased mortality in patients with nonsurgical HypoPT[51], while others did not find this association[10]. A recent synthesis of these studies showed an increased all-cause mortality of 80% (Hazard Ratio 1.8, 95% CI 1.49–2.17) in patients with HypoPT in general[50].

2.4 Pregnancy and breastfeeding

Pregnancy and lactation pose substantial short-term challenges to maternal calcium homeostasis. These challenges are met by production of parathyroid hormone-related protein (PTHrP) by the placenta followed by a vigorous production of activated vitamin D, stimulating intestinal calcium and phosphate absorption. These changes result in a low to suppressed endogenous PTH secretion and higher levels of urinary calcium[55-57]. As pregnancy progresses, PTHrP production increases. PTHrP synthesis rises even further during nursing because it is abundantly produced in lactating mammary tissue[56].

Pregnant and nursing women with HypoPT are at considerable risk for both hypercalcaemia and hypocalcaemia[55-57]. Poor control of maternal HypoPT and resulting hypocalcaemia during pregnancy can cause miscarriage, stillbirth, premature labour, and even neonatal death[56-59]. Maternal hypocalcaemia can impair neonatal skeletal development and trigger compensatory hyperparathyroidism in the newborn. This may lead to skeletal deformities, fractures, parathyroid hyperplasia, and other complications (e.g., respiratory distress, poor feeding, hypotonia)[56,57]. Conversely, maternal overtreatment, resulting in hypercalcaemia, can suppress foetal parathyroid development, causing neonatal hypocalcaemia[57,59].

Table 2. Co-morbidities which may occur with an increased prevalence in patients with hypoparathyroidism[8,10,44,48,50,51,111,125,216,229,275-279].

Organ system	Co-morbidity
Renal	Renal stone disease[§]
	Impaired renal function[§]
	Renal calcifications[§]
Immunological	Infections[§]
Neuropsychiatric	Neuropsychiatric diseases
	Seizures[§]
	Depression[§]
	Anxiety
	Sleep disorders
	Fatigue
	Impaired quality of life[§]
Musculoskeletal	Muscle stiffness/pain
	Joint/bone pain
	Proximal humerus fractures*
Cardiovascular	Ischemic heart disease[§]*
	Heart failure
	Cardiac arrhythmias[§]*
	Stroke*
Central nervous system	Intracerebral calcifications *
Eyes	Cataract [§]

[§]Co-morbidities with a statistically significant association with hypoparathyroidism. *An increased risk has only been documented in nonsurgical hypoparathyroidism.

2.5 Conventional treatment

Treatment of chronic HypoPT aims to relieve symptoms of hypocalcaemia, improve patients' well-being (QoL), and long-term prognosis. Conventional treatment includes sufficient calcium intake by diet, with or without calcium supplements, plus activated vitamin D treatment (e.g., calcitriol, alfacalcidol or calcifediol (referred to as activated vitamin D analogues for ease of reading throughout the manuscript), while maintaining adequate vitamin D and magnesium status (see Figure 2 and Table 3). Hyperphosphataemia[60,61] and hypercalciuria[62,63] should be addressed, if needed.

Seemingly asymptomatic patients with mild hypocalcaemia and without hypocalcaemic symptoms should be considered to receive oral therapy, as nonspecific symptoms (e.g., fatigue, brain fog, anxiety) may improve with treatment. Dietary calcium intake should be optimised, according to guidelines for the general population[64,65]. Magnesium deficiency should be

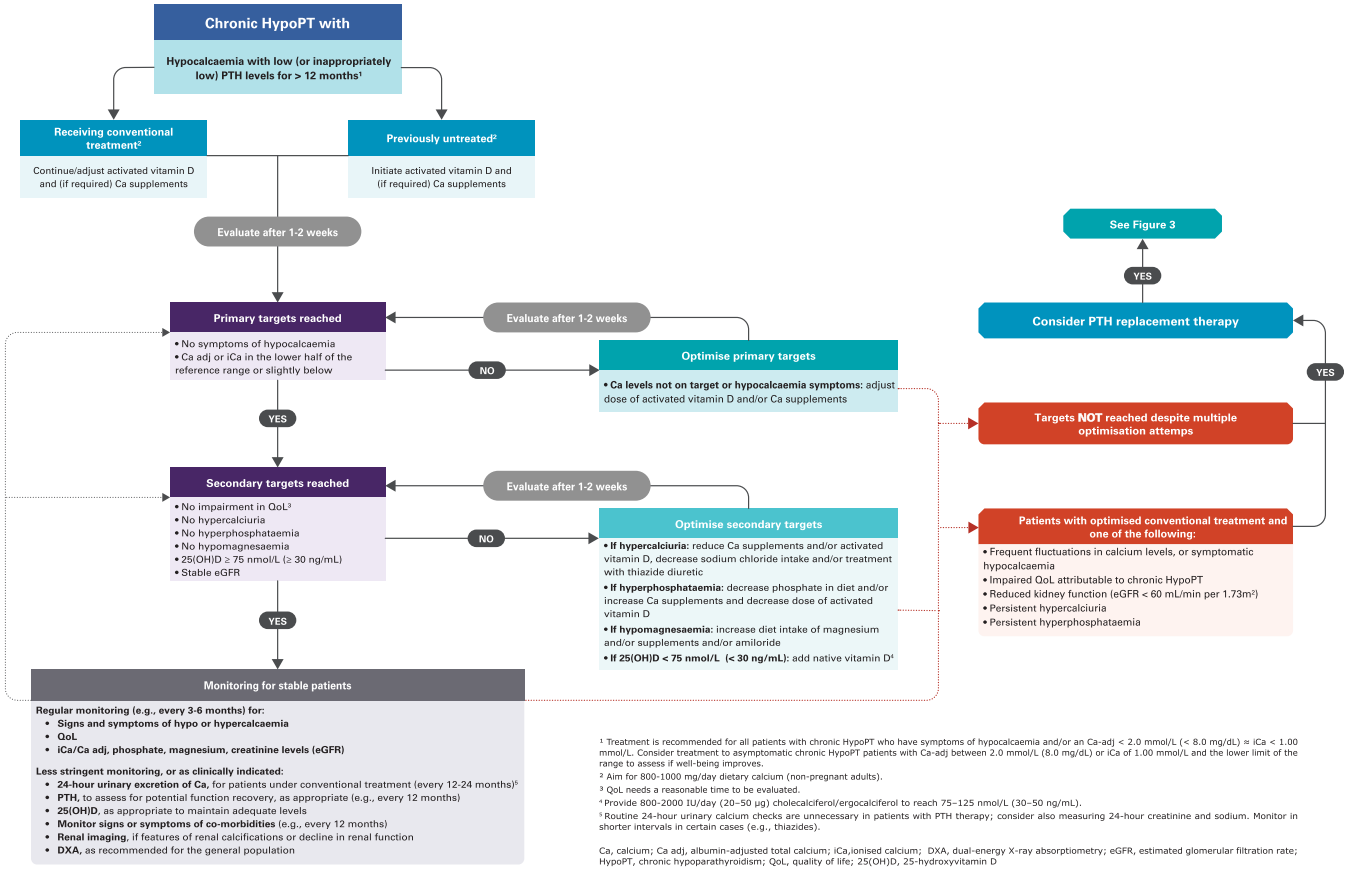

Figure 2. Chronic hypoparathyroidism treatment algorithm.

Table 3. Vitamin D metabolites in the management of chronic hypoparathyroidism[1].

Medication	Typical dose	Time to onset of action	Time to offset of action
Calcitriol $1,25(OH)_2D$	0.25-2.0 µg once or twice daily	1-2 days	2-3 days
Alfacalcidol[2] $1\alpha(OH)D_3$	0.5-4 µg once daily	1-2 days	5-7 days
Dihydrotachysterol[2]	0.3-1.0 mg once daily	4-7 days	7-21 days
Vitamin D_2 (ergocalciferol) or vitamin D_3 (cholecalciferol)[3]	25,000–200,000 IU daily	10-14 days	14-75 days

[1]Derived from Shoback[121].
[2]Alfacalcidol and dihydrotachysterol are rapidly activated in the liver to $1,25(OH)_2D$ and 25(OH)D dihydrotachysterol, respectively.
[3]These compounds could be used in a setting where activated vitamin D metabolites are not available and/or too expensive.

corrected, as profound hypomagnesaemia *per se* inhibits PTH secretion and action (functional hypoparathyroidism)[66]. In cases of symptomatic severe hypocalcaemia, the use of intravenous calcium should be considered for a limited period (see **5.3 Treatment**).

2.6 PTH replacement therapy

PTH replacement therapy with synthetic or recombinant human (rh) PTH analogues is an attractive option for patients with persistent signs and symptoms of chronic HypoPT. The N-terminal part of the PTH molecule [PTH(1-34)] binds with high affinity to the PTH receptors (PTHR1 and PTHR2), which are widely distributed in the human body[67].

Since the first ESE Guideline on the management of chronic HypoPT in 2015[3], numerous initiatives have emerged for new treatment strategies. rhPTH(1-84) (Natpara®, US and Natpar®, Europe) was approved by the FDA (U.S. Food and Drug Administration) in 2015, later by the EMA (European Medicines Agency) based on multiple clinical trials. However, the drug was withdrawn from the market at the end of 2024 (Takeda Discontinuation of NATPARA® [parathyroid hormone]).

In general, substitution therapy with intact PTH(1-84) or PTH(1-34), has been promising in maintaining normocalcaemia, lowering phosphate levels, reducing urinary calcium excretion, and potentially improving patient well-being (QoL) (see **Clinical Question II**)[68-72]. In most studies, PTH has

been administered in a non-physiological manner (i.e., once-daily injection), compared to its continuous episodic endogenous pattern of secretion. Due to the short plasma half-life after subcutaneous injection, i.e., about 1 hour for PTH(1-34)[73] and 3 hours for PTH(1-84)[74,75], once-daily injections are not expected to cause sustained PTH activity. Studies on injections twice a day so far have been scarce. However, a recent study comparing once daily versus twice-daily equipotent injections of PTH(1-84) in patients with chronic HypoPT, without supplemental calcium intake, found no clinically significant differences between the two regimes, although the statistical power was low[76]. For PTH(1-34), twice-daily injections for HypoPT showed less fluctuations in calcium levels compared with once daily injections[77,78]. The same authors compared twice-daily injections with infusion pumps of PTH(1-34) in patients with postsurgical HypoPT, and found the latter application superior for various biochemical endpoints, and the most physiological approach[79]. However, in the clinic, PTH(1-34) has until recently only been available for the treatment of osteoporosis, administered as a fixed 20 microgram once-a-day injection. Although off-label use of this drug for HypoPT (once or twice injections daily) has been tried, this application has been limited by challenges in achieving precise dose titration[69,80].

Several pharmacodynamic, safety, and clinical studies have recently demonstrated promising results with palopegteriparatide, a pegylated form of PTH(1-34) that provides active PTH within the physiological range over a 24-hour dosing interval[81-84]. Following pivotal clinical trials, palopegteriparatide (Yorvipath®) was approved by the EMA and the FDA for the treatment of chronic HypoPT in 2023 and 2024, respectively, and is currently the only approved PTH replacement treatment on the market. Additional therapies are currently under development, including and oral PTH analogue[113], a calcilytic agent (encaleret) and a selective PTHR1 agonist (eneboparatide), with phase 2 results recently published for the latter two[85,86].

3. Methods

3.1 Guideline working group

This guideline revision was initiated by the European Society of Endocrinology (ESE). The chair (J.B.) was appointed by the ESE Clinical Committee. O.D. served as the methodology lead, L.v.H. joined the guideline working group for methodology and organisational support. Members of the working group (authors) were appointed by the chairs and approved by the ESE Clinical Committee: endocrinologists (N.G., C.M., J.C.P. (Endocrine Society Representative), S.P., L.R., and M.Y.), a nephrologist (P.H.), and an endocrine surgeon (O.M.). O.B. served as ESE Nurse Representative and L.M.C. (endocrinologist) as EYES Representative. The working group had in-person meetings in May and October 2024 and several virtual meetings. All participants completed conflict of interest forms (see Supplementary Table 1).

The guideline panel collaborated with the following patient representatives: Liz Glenister (UK), Natalie Grosset (France), Tanja Richter and Frauke Sieger (Germany), and Helen Dahl-Hansen and Perny-Ann Nilsen (Norway). Before publication, a draft of the guideline was reviewed by three experts in the field (see **Acknowledgements**). Revision of the guideline was based on feedback from the Endocrine Society's Clinical Committee, and ESE members following a presentation at the Joint Congress of ESE and ESPE (European Society of Paediatric Endocrinology) 2025, in Copenhagen. All comments and suggestions were discussed and implemented as deemed appropriate by the working group (see Supplementary Table 10).

3.2 Target group

This document was developed for healthcare providers of patients with chronic HypoPT and serves as a source document for the preparation of educational materials to be published on the ESE website to empower patients with chronic HypoPT and their clinicians.

3.3 Aims

The overall purpose of this guideline is to provide clinicians with practical guidance for the management of patients with chronic HypoPT in adults. In clinical practice, both the recommendations and the clinical judgment of treating physicians should be considered. Recommendations may need adaptation to local circumstances.

3.4 Endorsement by other societies

To achieve wide acceptance of the guideline within the clinical community of the different disciplines involved in the management of chronic HypoPT in adults, the draft of the guideline document was submitted to several other professional/learned societies. The following societies endorsed the present guideline: the European Society of Endocrine Surgeons, the Endocrine Society of Australia.

3.5 Summary of methods used for guideline development

The methods used have been described in more detail previously[3,87]. In short, the guideline used GRADE (Grading of Recommendations Assessment, Development and Evaluation) as a methodological base. The first step was to define clinical questions (see section 3.6), the second being a systematic literature search (see section 3.7). After including relevant articles, we 1) estimated an average effect for specific outcomes (if possible), and 2) rated the quality of the evidence. The quality of evidence behind the recommendations is classified as very low (⊕OOO), low (⊕⊕OO), moderate (⊕⊕⊕O) or high (⊕⊕⊕⊕).

For the recommendations we considered: 1) the quality of the evidence, 2) the balance of desirable and undesirable outcomes, and 3) values and preferences (patient preferences, goals for health, costs, management inconvenience, feasibility of implementation, etc)[3,87]. The recommendations are worded as "***recommend***" (strong recommendation) or "***suggest***" (weak recommendation). It is important to emphasise that there is no direct translation from the (quality of) evidence to the strength of a recommendation, and there might be situations when a recommendation is strong even if the quality of evidence is low[88]. Recommendations based on good clinical practice were not graded. Recommendations were derived from a majority consensus of the guideline development panel, but substantive disagreements could be acknowledged in the manuscript. All recommendations provided are accompanied by an explanation ("reasoning").

3.6 Clinical questions and eligibility criteria

In the 2015 guideline, chronic HypoPT was defined as HypoPT persisting for more than 6 months[3]. Acknowledging that the statement from the Second International Workshop on the management of HypoPT defined postsurgical chronic HypoPT as persisting for more than 12 months after surgery[89], we decided to systematically review the literature on the time to recovery of parathyroid function after surgery.

We updated the literature review of optimal treatment for chronic HypoPT in adults, both for conventional treatment and PTH replacement therapy. Since the 2015 guideline[3], more data have become available regarding the use of PTH replacement therapy[84,90,91]. For PTH replacement therapy, results were stratified according to the biological half-life of the drug. In addition, the guideline panel noticed an emerging interest of patients in parathyroid allotransplantation, especially those with uncontrolled HypoPT despite medical treatment[92], and decided to explore the evidence.

The clinical questions for the systematic reviews are summarised in Table 4. Eligible study designs were observational cohort studies, crossover studies, case-control studies, and RCTs. To answer questions on treatment effects in a meaningful way, studies had to compare two different treatment regimens, either in a direct comparison or in a formal pre-post design. Surveys were excluded. Eligible articles were required to present data on adult patients (≥ 18 years), with a minimum of 10 patients to reduce the risk of selection bias. Studies primarily selecting patients with end-stage renal disease were excluded. Eligible studies were restricted to languages familiar to the authors (English, French, German, and Dutch).

For clinical question I (recovery of HypoPT after 6 and 12 months), the number of persons with recovery of HypoPT at re-testing (numerator) and the total number of persons with HypoPT at baseline (denominator) were used to estimate the incidence of recovery. For intervention studies, the duration of intervention needed to be ≥ 4 weeks. The outcomes of treatment effects of the updated literature review included endpoints of the original guideline[3] (i.e., mortality, QoL, calcium levels in serum or plasma and urine - including the incidence of hypercalcaemia, chronic kidney disease (CKD), and renal calcifications - defined as symptoms or episodes of nephrolithiasis or nephrocalcinosis, cramps, tetany and seizures, cardiovascular disease - defined as the incidence of major adverse cardiovascular events, and disability or sick leave), supplemented with the following endpoints after discussion within the guideline panel and consultation with patient representatives (see section 3.1): phosphate levels, neuropsychological endpoints, bone markers, fractures or bone mineral density (BMD), pill burden, increased susceptibility to infection, cataract, gastrointestinal symptoms, and pain (bone, muscle, and nerves).

3.7 Description of search and selection of literature

PubMed, MEDLINE, Embase, Web of Science, and Cochrane Library were searched with the help of a specialised librarian to identify potentially relevant studies. The literature searches for questions I, II, and III were performed in June 2024, September 2024, and November 2024, respectively. Searches can be found in Appendix 1 (see section on supplementary materials at the end of this guideline). Since clinical question II (optimal treatment) was an update of the literature review of the original guideline[3], the search was conducted from the date of the search of the original guideline, i.e., from 2013 onwards. The outcome "bone" was not assessed in the original guideline but deemed an outcome of major interest by the guideline panel; for reasons of completeness, studies published before 2013 were also included for this outcome.

All studies obtained from the searches were entered into reference manager software (EndNote X21, Clarivate Analytics, Philadelphia, PA) and titles and abstracts were screened. Potentially relevant studies were retrieved for detailed assessment. References of included studies were assessed for additional relevant articles.

4. Summary and interpretation of evidence from the systematic reviews

4.1 Clinical question I: What is the incidence of recovery from postoperative HypoPT 6 and 12 months after thyroid surgery?

Fourteen studies assessing the recovery of postsurgical HypoPT were included[34-37,93-102]. See Supplementary Table 2 and Supplementary Table 3 for details and the GRADE assessment. Overall, the evidence quality was moderate based on a serious risk of bias concerning outcome measurement (i.e., no standard protocol for assessing recovery of parathyroid function) and loss to follow-up (mostly not reported). It was not possible to stratify results for patients undergoing parathyroid auto-transplantation.

Of the 8,832 patients (data from 14 studies) undergoing thyroid surgery, 2,981 developed postoperative hypoparathyroidism (33.8%, Figure 1). Six months after surgery, 73.9% of these 2,981 patients had recovered parathyroid function (i.e., 91.2% of the total cohort had normal parathyroid function), while 12 months after surgery, this number had increased to 81.3% (93.7% of the total cohort). In total, 558 of 8832 patients undergoing thyroid surgery had chronic HypoPT 1 year after thyroid surgery, i.e., 6.3% of the total cohort.

From these data, we conclude that between 6 and 12 months after thyroid surgery, an additional 7.4% of patients recovered parathyroid function. The guideline panel deemed this a clinically relevant proportion and decided to define postsurgical HypoPT from 6 months following surgery in the original guideline[3] to 12 months after surgery, in accordance with recent recommendations[89]. Several studies reported patients regaining parathyroid function ≥ 1 year after surgery[34,35,95,98,102]; however, since standard follow-up protocols were lacking, it is uncertain if this resulted from delayed weaning from supplementation therapy rather than actual recovery.

4.2 Clinical question II: What is the optimal treatment for adult patients with chronic HypoPT?

4.2.1 Conventional treatment

Although many studies have published prevalence data on outcomes of interest in chronic HypoPT patients on conventional treatment, these studies did not compare different conventional treatment *strategies*, e.g., different supplement dosages or different target calcium levels. Therefore, these studies did not inform regarding optimal conventional treatment regimens. Another complicating factor was that several outcomes, e.g., CKD, QoL, and fractures are dependent on disease duration (time exposure) and ageing by itself. These

Table 4. Clinical questions.

Clinical question	Search criteria				Papers included (*n*)
	Population	Intervention	Comparison	Outcome	
Question I: What is the incidence of recovery from postoperative HypoPT 6 and 12 months after surgery?	Adults with postsurgical HypoPT	-	-	Incidence of HypoPT recovery, assessed by biochemical testing at 6 and 12 months	14 [34-36,37,93-102]
Question II: What is optimal treatment for adult patients with chronic HypoPT?	Adults with chronic (≥ 1 year) HypoPT	PTH/conventional therapy ≥ 4 weeks	PTH/conventional therapy/placebo/no intervention	Mortality QoL Calcium and phosphate levels CKD and renal calcifications Cramps, tetany, seizures, neuropsychological endpoints CVD Disability or sick leave Bone markers, fracture, BMD Pill burden Increased susceptibility to infection Cataract Digestion Pain (bone, muscle, nerves)	Conventional treatment: 4[103-106] PTH replacement therapy: 19[46,69,71,72,80,82,83,85,90,107-116]
Question III: What is the effect of parathyroid allotransplantation in HypoPT treatment?	Individuals with HypoPT	Parathyroid allotransplantation	PTH/conventional therapy/placebo/no intervention	As for question II + functioning graft/graft survival	3 [117-119]

HypoPT = hypoparathyroidism, PTH = parathyroid hormone, QoL = quality of life, CKD = chronic kidney disease, CVD = cardiovascular disease, BMD = bone mineral density.

time-dependent outcomes require long-term observational studies to adequately disentangle underlying disease effects (i.e., chronic HypoPT) versus treatment effects.

We defined conventional treatments as treatment regimens based on formulations of activated vitamin D and/or calcium. We could only include two observational studies and two RCTs assessing optimal treatment regimens of conventional treatment; a total of 170 patients with chronic HypoPT, ~75% females, were included[103-106]. See **Supplementary Table 4** for study details and description of outcomes; GRADE evidence is presented in **Supplementary File 5**. Overall, the quality of the evidence was very low, based on concerns regarding the selection of patients, confounding factors and small study cohorts.

A small, double-blind crossover study (n = 24) reported no difference in serum calcium and phosphorus, or urinary calcium between calcium carbonate versus calcium citrate; however, gastrointestinal tolerance of calcium citrate was higher[104]. Biochemical control also did not differ between various preparations of activated vitamin D analogues in two studies with a total of 79 patients[105,106]. Biochemical control did appear to improve in patients with an adequate increase in dietary calcium intake (i.e., elemental 1000 - 1200 mg daily), while maintaining their regular doses of activated vitamin D and calcium supplements[103]. Importantly, the intervention duration was too short, and the sample sizes were too small in these four studies to draw firm conclusions. From the results of this systematic review, it is apparent that relevant data regarding optimal conventional treatment regimens are lacking, particularly for clinically relevant endpoints and long-term effects.

4.2.2 *PTH replacement therapy*

Nineteen studies assessing the efficacy of PTH replacement therapy in a total of 2069 patients (79% women) with chronic HypoPT were included. Eleven studies assessed PTH(1-84) treatment[46,71,72,90,107-113] and seven studies PTH(1-34) treatment[69,80,82,83,114-116], of which four used teriparatide[69,80,114,116], two palopegteriparatide[82,83], and one oral PTH[115]. A single study reported on the PTHR1 agonist, eneboparatide[85]. There were six RCTs[46,72,82,83,111,116], two cohort studies with historical controls[107,109], and eleven open-label intervention studies making pre-post comparisons[69,71,80,85,90,108,110,112-115]. Details of included studies and descriptive results per outcome can be found in **Supplementary Table 6**; the description of the GRADE evidence is in **Supplementary File 7**. Except for the RCT's on pill burden, for which the quality of evidence was moderate (large effect), the quality of the evidence was very low for all other outcomes, with concerns on small sample sizes, selection of patients, and, depending on the outcome, concerns on possible confounder adjustment and assessment of outcome.

Pill burden and biochemical parameters. The results of the systematic review showed that PTH replacement therapy reduced the pill burden of conventional therapy (as assessed by 11 studies) while improving biochemical parameters (as assessed by 13 studies). Reductions in activated vitamin D analogues and calcium supplementation were observed by PTH(1-84) therapy[72,90,108,112], with some studies reporting discontinuation of these supplements in over 60% of the study cohort[108]. With PTH(1-34) therapy, conventional therapy dosages could also be markedly reduced[69,80,83,115] or completely discontinued in a majority of the study cohort[80,82,83]. PTHR1 agonist therapy enabled the discontinuation of activated vitamin D analogues in 92% and calcium supplements in 88% of patients[85].

With PTH(1-84) treatment, an increase in calcium levels[108,110,111] and a decline in, or continuous normalisation of phosphate levels were observed[72,90,108,110-113]. There were mixed results for 24-hour urine calcium excretion. Two studies reported a decrease in urinary calcium excretion[90,112] with percentages of hypercalciuria decreasing from 69.2% at baseline to 33.3% after three years of treatment for women, and 66.7% to 34% for men[112]. Two other studies reported an increase in 24-hour urine calcium excretion, albeit remaining within the normal range[108,110].

With PTH(1-34) treatment, calcium levels either increased[69,80] or remained within normal range[82,83,115]. Phosphate levels remained within the normal range (palopegteriparatide)[82,83] or decreased[69,80]. All studies with PTH(1-34) treatment observed a significant, or a trend towards, a decrease in 24-hour urine calcium excretion[69,80,82,83,114,115].

These results apply to the short- as well as the long-acting PTH(1-34) preparations, although too few studies were included to make proper comparisons between the two therapies.

QoL. There are limited data indicating that short-term PTH(1-34) treatment can improve various aspects of QoL compared to baseline (teriparatide, oral PTH)[69,80,115] or to placebo (palopegteriparatide)[82,83]. For PTH(1-84) treatment, results were inconsistent; two studies found improvement in several QoL domains compared to baseline[71,90,113], while others found no difference[110,111].

Renal and cardiovascular outcomes. PTH(1-84) treatment did seem to improve renal and cardiovascular outcomes in observational studies. PTH(1-84) treatment maintained renal function within the normal range[108] and lowered the risk of developing CKD, eGFR decline or a cardiovascular event compared to conventional treatment; adjusted Hazard Ratio 0.47 (95%CI 0.25-0.87), 0.35 (95%CI 0.13-0.89) and 0.25 (95% CI 0.08-0.81), respectively, after five years of follow-up[107,109]. Renal function also improved with palopegteriparatide: after 26 weeks, mean eGFR rose by 7.9 ± 10.4 ml/min per 1.73 m^2 with treatment and generally remained unchanged by 1.9 ± 8.6 ml/min per 1.73 m^2 in the placebo group ($p < 0.001$)[83]. Well-designed, long-term RCT's are, however, needed to confirm these potential positive results, with adequate outcome measures assessing renal function, e.g., cystatin C.

No data were found on cardiovascular outcomes for PTH(1-34) treatment or PTHR1 agonist treatment.

Bone. Biochemical markers of bone turnover were assessed in eight studies and consistently increased after initiation with PTH treatment[46,80,82,85,90,116], stabilising to steady-state values above pretreatment levels during long-term treatment[110,112]. Although this reflects exposure to the physiologic bone-remodelling effects of PTH, effects on BMD were inconsistent[46,110,112,113,116], and it is currently not known if this translates to a clinically relevant endpoint such as fracture rates.

Overall, most studies have so far been hypothesis-generating only, with the need for future prospective,

randomised controlled studies (hypothesis testing) on hard endpoints such as patient outcomes and markers of morbidity, to establish the true value of PTH replacement therapy beyond biochemical control.

We were not able to stratify results for HypoPT aetiology.

4.3 Clinical question III: What is the effect of parathyroid allotransplantation in HypoPT treatment?

Three studies assessing the results of 141 parathyroid allotransplantations in 109 patients were included[117-119]. Details of the included studies can be found in Supplementary Table 8, and the description of the GRADE evidence is provided in Supplementary Table 9. Overall, the evidence was very low, based on a serious risk of bias concerning adjustment for confounding factors, heterogeneity of intervention and measurement of outcome, and imprecision due to small patient numbers.

A small cohort study ($n = 10$) reported functioning allografts in 70% of patients after one year, which led to the discontinuation of conventional therapy in these patients[117]. Another study ($n = 14$) reported a reduction of daily conventional therapy dosages two years after parathyroid allotransplantation, but discontinuation in none[118]. The largest study, comprising 85 patients, reported 57% functioning allografts directly after transplantation, and a mean cellular allograft survival of 6.3 ± 13.1 months[119].

In conclusion, small, short-term studies show functioning allografts one year after transplantation although this comes at the cost of immunosuppression use.

Based on the available evidence, we cannot recommend a role for parathyroid allotransplantation in the treatment of chronic HypoPT.

5. Recommendations and rationale for the recommendations

5.1 Diagnosis

R.1.1 We recommend considering a diagnosis of chronic hypoparathyroidism (HypoPT) in a patient with persistent hypocalcaemia and inappropriately low or inappropriately normal parathyroid hormone (PTH) levels.

Reasoning: Hypocalcaemia is defined as an ionised or albumin-adjusted total calcium level below the lower limit of the reference range. Measurements of ionised or total calcium mostly reflect local traditions. However, ionised calcium measurements might improve diagnostic accuracy[120], and may be preferred in pregnancy, see section 5.5. A specific cut-off limit for PTH levels in the presence of hypocalcaemia cannot be defined. If parathyroid function is intact, hypocalcaemia is normally associated with (markedly) increased PTH levels (secondary hyperparathyroidism). In accordance, a diagnosis of HypoPT may be considered in a patient with hypocalcaemia if PTH levels are low in the reference range, which is inappropriately normal in the setting of hypocalcaemia[121,122].

Remarks: Magnesium. Magnesium depletion impairs the secretion of PTH, causing a state of functional HypoPT and impairs effective PTH actions in target tissues. If magnesium levels are low, this should be corrected before diagnosing a patient with chronic HypoPT[123].

Remarks: Postsurgical HypoPT. Recovery of parathyroid function in patients with postsurgical HypoPT increased from 73.9% to 81.3% between six months and one year after surgery (see **Clinical Question I**). Therefore, chronic HypoPT should not be diagnosed within the first year following surgery (12-month cut-off). In the case of postoperative HypoPT, we advise close monitoring of calcium and PTH levels.

R.1.2 We recommend genetic testing and/or family screening in a patient with nonsurgical HypoPT without other obvious aetiology.

Reasoning: Nonsurgical HypoPT may be due to various reasons[13]. If no obvious cause can be established, we recommend genetic testing for inherited forms of HypoPT, which include isolated or syndromic aetiologies[13]. Family history may be negative when pathogenic variants occur *de novo* or have variable clinical features. Genetic testing refines the clinical diagnosis, may guide targeted therapies, could help predict other medical conditions, and can help to assess the risk for family members. For example, individuals with autosomal dominant hypocalcaemia type 1 (ADH1) caused by activating variants in *CASR* may benefit from a targeted negative allosteric modulator of the calcium-sensing receptor that can promote PTH secretion and renal calcium reabsorption[86]. Genetic testing may be of particular importance to younger individuals, as a genetic diagnosis may allow for genetic counselling about future pregnancy plans. Genetic information may also prompt monitoring for other possible complications that may accompany HypoPT (see Table 1)[13]. Access to genetic testing may vary in different settings and may be limited by availability and costs.

5.2 General goals of management in chronic hypoparathyroidism

R.2.1 We recommend treatment for HypoPT to be personalised and centred on the patient's overall well-being with therapeutic goals that optimise QoL, minimise symptoms of hypocalcaemia, improve long-term prognosis, and maintain calcium levels within the lower part or slightly below the reference range. (Good clinical practice)

Reasoning: Patients with chronic HypoPT suffer from varying degrees of physical, mental, and emotional health impairments. Although treatment may alleviate symptoms, QoL is not fully normalised in most cases[124]. Fluctuations in calcium levels, a high pill burden, hyperphosphataemia, hypercalciuria, and renal complications are limitations of conventional therapy with calcium and activated vitamin D.

The main therapeutic goals are to enhance the patient's overall well-being and maintain albumin-adjusted calcium levels or ionised calcium levels in the lower part of the reference range or slightly below. Based on normal physiology, maintaining circulating calcium levels in the low-normal range may reduce urinary calcium excretion, lower the risk of hypercalcaemia and hyperphosphataemia, and potentially support residual parathyroid function recovery[125,126]. Some patients may require higher calcium levels for symptom relief. If raising calcium levels to the upper part of the normal range improves well-being, this may be acceptable, as there is no evidence of specific harm from this approach. However, the elevated

calcium level resulting from conventional treatment comes at the expense of increased urinary calcium excretion.

It is important to emphasise that no firm evidence exists on the long-term benefits (or harms) of achieving these therapeutic goals. Consequently, treatment decisions should avoid compromising QoL or imposing significant burdens on the patient, such as undesirable lifestyle changes (i.e., dietary habits) or adverse effects of therapy.

For patients not adequately managed with conventional therapy, PTH replacement therapy may improve biochemical parameters and enhance QoL (see **R.3.5.2** and **Clinical Question II**). However, these therapies are significantly more expensive, posing accessibility challenges for many individuals and limiting their widespread use. Therefore, where available and affordable, PTH replacement therapy should be considered for patients not adequately controlled on conventional therapy and based on the individual needs of the patient.

R.2.2 We recommend providing information/education that enables patients to recognise the possible symptoms of hypo- or hypercalcaemia and/or complications of their disease. (Good clinical practice)

Reasoning: As stated in section 5.4, we suggest monitoring patients at regular time intervals. Circulating calcium levels may, however, change, and complications may emerge at any time, with or without apparent reasons. Thus, we find it of importance to empower patients with knowledge of symptoms and of co-morbidities and drugs that may affect the course of their disease.

Table 5. Symptoms patients should be informed of to allow for early detection of hypo- or hypercalcaemia.

	Hypocalcaemia[50,61,66]	Hypercalcaemia[66,280]
CNS	Depression Irritability Confusion or disorientation Seizures	Weakness Headache Drowsiness Confusion or disorientation Poor memory Reduced concentration
Neuromuscular	Numbness and tingling (paraesthesia) in circumoral and acral areas (fingers, toes) Spasms/twitches Cramps	Muscle weakness
Cardiovascular	Fast, slow, or irregular heart rate Symptoms of congestive heart failure	Fast, slow, or irregular heart rate Hypertension
Gastrointestinal	Abdominal cramps	Loss of appetite Nausea/vomiting Abdominal pain Constipation
Renal	-	Polyuria Hypotension due to renal NaCl wasting Dry mouth and/or increased thirst
Respiratory	Shortness of breath Wheezing Throat tightness	

Table 2 shows co-morbidities which may occur with an increased prevalence in HypoPT.

Table 5 shows symptoms of hypo- and hypercalcaemia, of which patients should be informed.

Table 6 lists drugs, conditions, and diseases which may interfere with calcium homeostasis. If a patient is diagnosed with one of the diseases or initiates treatment with one of the drugs, this may necessitate changes in the medical treatment of HypoPT to maintain target calcium levels. For further useful information, we suggest referring patients to the Patient Information Leaflet on the treatment of Chronic Hypoparathyroidism in Adults (hypoparathyroidismpatientleaflet.pdf). A standardised European Emergency Card for Adult Patients with Hypoparathyroidism has been published, containing relevant medical information to guide emergency management of either hypocalcaemia or hypercalcaemia (A Standardised European Emergency Card for Adult Patients with Hypoparathyroidism | ESE). The Patient Information Leaflet and the Emergency Card are available in several languages.

R.2.3 We suggest aiming for normal 24-hour urinary calcium excretion. (⊕OOO)

Reasoning: In a patient with intact parathyroid function, hypercalciuria is considered a risk factor for renal stone formation. Because PTH increases the renal tubular reabsorption of calcium, chronically low PTH levels make hypercalciuria a common feature of HypoPT on conventional therapy. The risk of renal stone disease is increased in HypoPT[8,44]. It is not possible to predict 24-hour urinary calcium excretion based on a circulating calcium value, and there is limited and conflicting evidence as to whether the risk of forming or passing renal stones is associated with the amount of urinary calcium excreted in patients with HypoPT[49,127-133]. Moreover, it is important to note that other urine parameters besides calcium may increase (e.g., low volume, low urinary citrate or high uric acid, oxalate, or phosphate) or decrease (e.g., high volume or magnesium) the risk of renal stone formation. However, assuming that the pathogenesis of renal stone disease is similar in HypoPT, as in hypercalciuric individuals with normal parathyroid function, it is reasonable to aim for a normal 24-hour urinary calcium excretion[126], in order to decrease renal stone formation[134]. Algorithms using 24-hour urinary collection and spot samples for estimating stone risk have also been proposed[127,135,136], offering potential avenues for future research and clinical application.

Remarks: autosomal dominant hypocalcaemia. Particular attention should be paid to patients with ADH in whom hypercalciuria may occur at low-normal serum calcium levels because of both decreased PTH action and increased renal CaSR signalling. In patients with symptoms of hypocalcaemia, hypercalciuria may be further increased when treated with conventional therapy[13,137,138].

General Remarks: We recommend measuring 24-hour urinary calcium excretion when stable serum calcium target values and satisfactory well-being have been obtained, particularly when using conventional therapy, since hypercalciuria is less common using PTH replacement therapy, see **4.2.2 Clinical question II**. Urinary calcium excretion is higher in men compared to women. No clinical intervention studies have been conducted to guide target calcium excretion. The risk of

Table 6. Drug therapy and diseases that may interfere with calcium and phosphate homeostasis potentially necessitating changes in monitoring and therapy of patients with chronic hypoparathyroidism.

Drug/disease	Mechanism	Possible adverse effects in HypoPT	Action
Loop diuretics	Increased urinary calcium losses	May aggravate hypercalciuria and lower serum calcium levels[281]	Avoid if possible
Thiazide diuretics	Decreased urinary calcium losses[282]	May increase serum calcium levels[283]	May be used in a patient with HypoPT (see text, **section 5.3**)
Systemic glucocorticoids	Decreased intestinal calcium absorption	May precipitate hypocalcaemia[284]	Avoid if possible Otherwise, use minimum effective dose and consider steroid sparing medications
Antiresorptive drugs	Decreased bone turnover	May cause hypocalcaemia[285,286]	Rarely needed, as HypoPT is a state of (very) low bone turnover
Proton pump inhibitors (PPI)	May cause hypomagnesaemia[287] May impair bioavailability of calcium in the intestine	May lower serum calcium levels[288] and cause symptoms similar to hypocalcaemia	Avoid if possible – otherwise magnesium supplements as needed, and use calcium citrate
Chemotherapy: Cisplatin, 5-Fluorouracil, Leucovorin	Cisplatin causes renal damage leading to a functional defect in magnesium reabsorption, while it also decreases the activity of 1-alpha-hydroxylase. Leucovorin/5-fluorouracil can also independently induce hypocalcaemia[289]	May lower serum calcium levels and cause symptoms similar to hypocalcaemia	Magnesium and/or vitamin D supplements, as needed
Cardiac glycosides (e.g., digoxin)	Cardiac glycosides inhibit the Na^+/K^+ ATPase, which in turn increases intracellular calcium, through reducing Na^+/Ca^{2+} exchange Hypercalcaemia may predispose to digoxin toxicity, while hypocalcaemia may reduce the efficacy of digoxin[290]	Arrhythmias	Avoid if possible. If needed, close monitoring by a cardiologist
Diarrhoea/gastrointestinal disease	May reduce intestinal absorption of calcium and vitamin D	May cause hypocalcaemia	Close monitoring of serum calcium levels with dose adjustments as needed
Changes in (correction of) acid-base balance*[291]	The affinity of calcium to bind to proteins in serum is highly pH dependent – only the free fraction is physiological active	Correction of metabolic alkalosis may cause hypercalcaemia Correction of metabolic acidosis may cause hypocalcaemia**	
Immobilisation	Increased bone resorption. In healthy individuals, PTH and 1,25-dihydroxyvitamin D levels are suppressed.	May cause hypercalcaemia	
Hungry bone syndrome	Severe and prolonged hypocalcaemia due to rapid calcium shift into the bone[292]	Except for parathyroidectomy may also occur in thyroidectomy due to thyrotoxicosis[293] and osteoblastic metastasis due to prostate cancer[294]	Close monitoring of serum calcium levels with dose adjustments as needed
Intravenous iron infusion (notably ferric carboxymaltose)[295]	Increases circulating concentrations of biologically active FGF-23 in patients with iron deficiency anaemia	May cause transient[296] or even severe and protracted[297,298] hypophosphataemia	Avoid if possible/close monitoring of Ca/PO4 product for several weeks after intravenous iron infusion, particularly in patients under PTH replacement therapy[299]
Tenofovir disoproxil fumarate (TDF) used in first-line treatment of human immunodeficiency virus infection and in hepatitis B virus infection[300,301]	Induces renal proximal tubular dysfunction	May cause hypophosphataemia and osteomalacia	Consider changing to tenofovir alafenamide or other non-tenofovir-based regimen
Immune check point inhibitors (mainly PD-1 and PD-L1 inhibitors)[24,302-306]	Immune tolerance disruption- Antiparathyroid and calcium-sensing receptor-activating autoantibodies may be detectable	May rarely cause autoimmune HypoPT (largely irreversible) between 3 weeks and 7 months of treatment	Close monitoring/Long-term treatment with an activated vitamin D and calcium supplements

(*continued*)

Table 6. Continued

Drug/disease	Mechanism	Possible adverse effects in HypoPT	Action
Pregnane X receptor ligands***[307]	Upregulate the expression of the 24-hydroxylases (CYP24A1 and CYP3A4) leading to increased degradation of 1,25-dihydroxy vitamin D	May induce hypocalcaemia	Consider modifying doses of activated vitamin D

HypoPT, hypoparathyroidism; PD-1, programmed cell death protein 1; PD-L1, programmed cell death-ligand 1; PTH, parathyroid hormone.
*Changes in the free (ionised) fraction of calcium (Ca^{2+}) cannot be monitored by measuring total calcium levels. Many laboratories report serum Ca^{2+} levels adjusted to a neutral pH value (pH 7.4), which does not reflect the actual serum Ca^{2+} level in a patient with disturbances in acid-base balance. If so, patients may have symptoms despite (apparently) normal calcium levels and Ca^{2+} levels at actual pH should be requested.
**As pH decreases, more H^+ ions compete for binding sites on proteins like albumin, causing more calcium to be released and increasing the physiologically active free fraction. Conversely, increasing pH values increase the negative charge on proteins, leading to increased calcium binding and a decrease in free ionized calcium.
***Including antibiotics (rifampicin), anti-epileptic drugs (phenytoin, carbamazepine), anti-inflammatory/steroids (dexamethasone), antiretroviral drugs (ritonavir, saquinavir), antineoplastic drugs (cyclophosphamide, taxol (paclitaxel), epirubicin, tamoxifen), other drugs (nifedipine, spironolactone, cyproterone acetate, clotrimazole) or herbal products (hyperforin, Kava kava).

developing calcium stone disease increases continuously, in a nonlinear manner, with urinary calcium excretion. It is therefore difficult to provide a threshold below which the risk becomes negligible. Nevertheless, we suggest aiming at calcium excretion <7.5 mmol/24-hour (300 mg/24-hour) in men, and < 6.25 mmol/24-hour in women (250 mg/24-hour); or < 0.1 mmol/kg/24-hour (4 mg/kg/24-hour) in both sexes. Creatinine and sodium excretion should be measured in parallel to assess the completeness of the collection and sodium intake, respectively. In patients with hypercalciuria, reduction in calcium intake, a sodium-restricted diet, and thiazide diuretic use can be considered (see **R.3.5**).

R.2.4 We suggest aiming for phosphate levels within the reference range. (⊕OOO)

Reasoning: HypoPT is characterised by a relatively high circulating phosphate level and a higher-than-normal calcium-phosphate product. This is attributable to the lack of the phosphaturic effect of PTH, as well as an enhanced intestinal absorption of phosphorus, due to activated vitamin D treatment (conventional treatment)[25,121]. The risk of extra-skeletal calcifications, including nephrocalcinosis and cataracts, is increased in HypoPT. It is generally assumed that this is related to high phosphate levels and an increased calcium-phosphate product; therefore, it seems reasonable to aim for keeping phosphate levels within the normal range[139].

R.2.5 We suggest aiming for magnesium levels within the reference range. (⊕OOO)

Reasoning: Magnesium is central to several physiological processes, including the secretion and actions of PTH. Low circulating magnesium levels may cause functional HypoPT by blunting the (residual) capacity of the parathyroid glands to secrete PTH[140]. Moreover, low magnesium may cause hypocalcaemia-like symptoms by itself[141]. Accordingly, it seems reasonable to aim at keeping serum magnesium levels within the reference range.

Although more than 99% of the exchangeable total body magnesium is located intracellularly, routine clinical measurements are limited to serum or plasma magnesium levels. Hypomagnesaemia - considered when magnesium concentration is below 0.7 mmol/L - is common, particularly in subjects with comorbid conditions and medications (like diuretics and proton pump inhibitors)[141]. Despite its limitations as a proxy for intracellular magnesium status, circulating magnesium levels remain the standard measure in clinical practice and should be monitored and optimised in HypoPT.

R.2.6 We suggest aiming at an adequate vitamin D status (25(OH)D level ≥ 75 nmol/L [30 ng/mL]). (⊕OOO)

Reasoning: Vitamin D insufficiency has been associated with adverse effects on skeletal, as well as extra-skeletal health[142]. Severe vitamin D deficiency is associated with symptoms of myopathy, and patients with HypoPT frequently report neuromuscular symptoms, which may be exacerbated by concomitant vitamin D deficiency[25,111,143]. To ensure that symptoms are not caused by vitamin D deficiency, an adequate vitamin D status should be ensured. A concentration of

25-hydroxyvitamin D (25(OH)D) above 75 nmol/L (30 ng/mL) may be considered adequate[144].

Remarks: Treatment with activated vitamin D analogues does not guarantee an adequate vitamin D status, as measured by circulating 25(OH)D levels. As vitamin D (calciferol) and its metabolite 25(OH)D itself may be of importance to several cellular processes and may undergo hydroxylation to $1,25(OH)_2D$ catalysed by local hydroxylases in different tissues[145], it seems reasonable to ensure sufficient 25(OH)D levels, despite treatment with activated vitamin D analogues.

5.3 Treatment

R.3.1 We recommend treatment of all patients with chronic HypoPT who have symptoms of hypocalcaemia and/or an albumin-adjusted calcium level < 2.0 mmol/L (< 8.0 mg/dL) ≈ ionised calcium (iCa^{2+}) < 1.00 mmol/L.

R.3.2 We suggest offering treatment to patients with chronic HypoPT, even if apparently asymptomatic, if albumin-adjusted calcium levels are between 2.0 mmol/l (8.0 mg/dL or iCa^{2+} 1.00 mmol/L) and the lower limit of the reference range to assess whether this may improve their well-being. (Good clinical practice)

Reasoning: In chronic HypoPT, symptoms of hypocalcaemia may vary widely, from asymptomatic to life-threatening, such as seizures, cardiac failure, bronchospasm, and laryngospasm[25,121,125,146]. In a life-threatening hypocalcaemia emergency, 90-180 mg elemental calcium, e.g., preferably 1-2 ampules calcium gluconate (containing 1 g calcium gluconate per ampule) is administered over 10 to 20 minutes, followed by a slower intravenous calcium infusion, e.g., 10 ampules containing about 900 mg elemental calcium into 1 litre of 5% dextrose or saline at a starting rate of 100 ml/h. In addition to close monitoring of calcium levels and ECG, oral therapy with calcium supplements and activated vitamin D (e.g., calcitriol 0.25 or 0.5 µg twice daily) should be started[147].

While it is obvious to recommend treatment of patients with severe symptoms of hypocalcaemia, it is unclear whether asymptomatic patients with biochemical hypocalcaemia should be treated. No limit of calcium levels has been defined below which treatment is unquestionably needed. Symptoms of hypocalcaemia do not translate directly to circulating calcium levels. Sudden fluctuations in calcium levels may cause symptoms, even if average calcium levels are (almost) normal. On the other hand, no apparent symptoms may be present, despite low calcium levels, if the hypocalcaemia has developed slowly or has been present for a longer period. In a patient with intact parathyroid function, calcium levels are tightly regulated within a narrow range[145,148]. It seems likely that patients with no complaints of hypocalcaemia, despite (very) low calcium levels, have adapted to a new calcium homeostasis, which may have blunted their symptoms of hypocalcaemia. We consider it reasonable to offer treatment to asymptomatic patients with chronic HypoPT, since treatment might improve their well-being (**Figure 2**). An exception is for patients with ADH1, where lower calcium levels in asymptomatic patients might be tolerated, see section 5.1. If no improvements occur following 6-12 months of therapy, the need for treatment may be reconsidered, especially if hypocalcaemia is mild.

R.3.3 We recommend treatment with vitamin D.

R.3.3.1 If available, we recommend treatment with an activated vitamin D analogue (e.g., alfacalcidol or calcitriol). (⊕OOO).

R.3.3.2 If activated vitamin D analogues are not available, we suggest treatment with supraphysiological doses of calciferol (preferentially cholecalciferol, i.e., vitamin D3). (⊕OOO).

R.3.3.3 We recommend titration of vitamin D analogue doses aiming at calcium levels within the target range, with patients being free of symptomatic hypocalcaemia and biomarkers within the target range. (⊕OOO)

Reasoning: HypoPT is a disease with a deficiency of two hormones (PTH and $1,25(OH)_2D$), as PTH normally facilitates the hydroxylation of 25(OH)D to $1,25(OH)_2D$, and activated vitamin D stimulates the intestinal calcium absorption. There are no comparative studies guiding the optimal treatment with vitamin D (dose and type). Prior to the development of activated vitamin D analogues, calciferol (ergocalciferol [vitamin D_2] or cholecalciferol [vitamin D_3]) were used, as small amounts of 25(OH)D are converted to $1,25(OH)_2D$, even if PTH is low as in HypoPT[149]. If supraphysiological doses of calciferol (typical 25.000-200.000 IU/day, 625-5000 µg/day) are used, this may result in normocalcaemia with very high circulating concentrations of 25(OH)D (typically 500-1000 nmol/l, 200-400 ng/mL). Importantly, this treatment with supraphysiological calciferol doses should only be considered in special circumstances or in healthcare settings with no access to activated vitamin D analogues, as this therapy is only based on historical observations, rarely used today and associated with the risk of vitamin D toxicity. Following the development of activated vitamin D analogues, small case series showed that normocalcaemia could be achieved if HypoPT was treated with activated vitamin D analogues[150,151]. Today, activated vitamin D analogues are preferred due to shorter plasma half-life, allowing for dose titration at shorter time intervals compared with calciferol (**Table 3**). Moreover, in the case of intoxication, calcium levels normalise faster if patients are treated with activated vitamin D analogues[152,153]. Alfacalcidol (1α-hydroxyvitamin D) or calcitriol ($1,25(OH)_2D$) are mainly used. Effects on long-term clinical outcomes of the different analogues have not been compared head-to-head in HypoPT. In terms of calcaemic effects, calcitriol is approximately twice as potent as alfacalcidol, as shown in a randomised controlled trial[154]. To maintain calcium levels within the target range, the daily dose must be carefully titrated, as the dose needed varies between patients. Daily doses of calcitriol are typically 0.25-2.0 µg, equal to a daily dose of 0.5-4.0 µg of alfacalcidol[155] (**Table 3**). We suggest treatment with calcitriol once or twice daily or with using alfacalcidol, once daily as opposed to divided doses for the following reasons: 1) Changes in circulating or urinary calcium are similar regardless of whether identical calcitriol doses per day are given once daily or twice daily[156,157], 2) The onset of effect of active vitamin D analogues on intestinal calcium absorption and calcium levels is

delayed with no significant difference for intravenous versus oral calcitriol treatment[158], 3) Although the plasma half-life of calcitriol is only several hours, the half-life of its biological effects on calcium metabolism is more than 24 hours[159,160], and 4) To minimize pill burden. We acknowledge that there is limited evidence and controversy in the literature regarding whether once-daily doses or divided doses of active vitamin D analogues is preferred. We therefore encourage further studies on this issue.

If calcium levels are slightly outside the target range, or if a patient is complaining of symptoms, the daily dose of activated vitamin D can be gradually changed (**Figure 2**), i.e., the daily dose of alfacalcidol may be changed by 0.5 µg, corresponding to a 0.25 µg change in the dose of calcitriol. Larger changes in dose may be needed in case of severe hypo- or hypercalcaemia and treatment initiation (e.g., daily doses of 1.0 to 2.0 µg of alfacalcidol or 0.5 to 1.0 µg calcitriol, which roughly equals the normal daily calcitriol production rate of a human)[161]. To allow for the achievement of a new steady-state, dose adjustments should not be performed more frequently than at 2-3 day time intervals[162]. If only minor symptoms or biochemical disturbances are to be adjusted, weeks may be allowed to pass between dose adjustments. Of note, the measurement of calcium levels is subject to variations. Because of the long half-life of calciferol, if a patient is receiving treatment with supraphysiological doses of calciferol, 2-3 months are needed between dose adjustments before a new steady state has emerged.

R.3.4 We recommend assuring an adequate calcium intake.

R.3.4.1 We suggest a dietary elemental calcium intake of about 800-1000 mg/day in adults (non-pregnant) (European Food Safety Authority[1]).

R.3.4.2 We suggest using calcium supplements if blood calcium levels in the target range cannot be achieved by treatment with activated vitamin D analogues in combination with an adequate dietary calcium intake. (⊕OOO).

R.3.4.3 We recommend that elemental calcium supplementation greater than 500 mg daily should be taken in smaller doses and spread throughout the day.

Reasoning: An adequate daily intake of calcium from diet and/or supplements is advisable for several reasons, including for bone health. In HypoPT, hypocalcaemia is mainly caused by the lack of $1,25(OH)_2D$ due to PTH deficiency. Thereby, it seems rational to substitute with activated vitamin D and not to aim for obtaining normocalcaemia by supplying very high amounts of calcium supplements. Most patients with HypoPT have normal calcium absorption if conditions allow, i.e., if adequate $1,25(OH)_2D$ is present. Accordingly, most patients with HypoPT do not need a (very) high calcium intake to achieve normocalcaemia, and selected patients can be well managed without any calcium supplements[49,163]. A high calcium intake can help to achieve calcium levels in the target range (and lower the dose of activated vitamin D needed), but it is not feasible as the principal component in the treatment of HypoPT, as it causes a high pill burden. Intake of calcium causes only a transient increase in circulating calcium levels. Moreover, the absorptive capacity of the intestine is probably saturated by an intake of 500 mg of elemental calcium in one ingestion[164]. Thus, routine high-dose calcium supplements are discouraged, but higher doses may be selectively useful in defined situations and administered in divided doses throughout the day[165,166].

However, it is noteworthy that calcium binds phosphorus in the intestine and may thereby lower circulating phosphate levels[167]. Thus, in selected cases, high doses of calcium from supplements may be advantageous. Furthermore, extra intake of calcium alone may be recommended on an *as-required basis* if a patient is only experiencing symptoms of hypocalcaemia occasionally.

Intake of calcium from dietary sources is physiologic and considered equivalent to intake from supplements[103,168]. Different calcium salts are available as supplements. Of note, 500 mg elemental calcium equals to 1250 mg calcium carbonate (40% elemental calcium) and to 2385 mg calcium citrate (21% elemental calcium). Calcium carbonate is most often used and is less expensive than other calcium preparations. However, calcium carbonate requires an acidic environment for absorption and should, therefore, be taken together with a meal[168]. Calcium citrate can be used in patients with achlorhydria or receiving treatment with proton pump inhibitors (PPI), as well as in patients who prefer to take supplements outside mealtimes[166], see **Table 6**. Calcium citrate, compared with calcium carbonate, was also associated with lower urinary oxalate excretion and may therefore mitigate the risk of nephrolithiasis[104].

Bariatric surgery, especially Roux-en-Y gastric bypass, frequently causes intestinal calcium malabsorption[169,170]. Therefore, higher doses of oral calcium supplements than in patients with conserved intestinal absorption may be needed. Calcium citrate rather than calcium carbonate may be recommended because achlorhydria is frequently associated. Furthermore, high oral calcium intake is useful to decrease intestinal oxalate absorption and limit hyperoxaluria[171].

Coexistence of hypothyroidism is common in patients with postsurgical HypoPT. Due to interference with L-thyroxine absorption, calcium supplements should not be taken together with thyroxine substitution[172].

R.3.5 We recommend PTH replacement therapy in patients with chronic HypoPT who continue to have signs or symptoms of HypoPT despite optimised treatment with (activated) vitamin D and adequate calcium intake. (⊕⊕OO)

R.3.5.1 We suggest to titrate the dose of PTH replacement therapy to achieve sustained calcium levels in the target range without the need for concurrent activated vitamin D treatment or calcium supplements.

R.3.5.2 We suggest to consider treatment with PTH replacement therapy in patients with one of the following despite optimised conventional treatment.

- **Frequent fluctuations in calcium levels, or symptomatic hypocalcaemia**
- **Impaired quality of life attributable to chronic HypoPT**
- **Reduced kidney function (eGFR < 60 mL/min per 1.73m²)**
- **Hypercalciuria (calcium excretion >7.5 mmol/24-hour [300 mg/24-hour] in men, and > 6.25 mmol/24-hour in women [250 mg/24-hour]; or > 0.1 mmol/kg/24-hour [4 mg/kg/24-hour] in both sexes)**
- **Hyperphosphataemia**

R.3.5.3 If PTH replacement therapy is initiated, we suggest evaluating the treatment effects after 6-12 months, depending on treatment goals. (Good clinical practice).

Reasoning: There is a potential for recovering parathyroid function in postsurgical HypoPT (even after years; see **Clinical Question I**). Accordingly, in patients managed with conventional treatment, calcium levels should be in the lower half or slightly below the reference range (i.e., in the target range) to stimulate any remaining parathyroid cells to secrete PTH, and to avoid suppression of parathyroid gland function.

Target ranges for calcium levels may differ for patients on conventional treatment by activated vitamin D analogues versus replacement formulations with sustained PTH effects. As the PTH effects of increasing renal calcium reabsorption and decreasing renal phosphate reabsorption are minimal (if at all present) in chronic HypoPT patients, the aim to increase calcium levels with activated vitamin D treatment comes at the expense of increased risk of hypercalciuria (risk of urinary stones) and hyperphosphataemia. Therefore, aiming at low normal or slightly below the lower limit of normal calcium levels is reasonable for conventional treatment, to minimise adverse treatment effects when targeting higher calcium levels. Conversely, treatment with formulations with sustained PTH effects simultaneously increases endogenous activated vitamin D (calcitriol) levels (due to increased conversion of 25(OH)D to 1,25$(OH)_2$D/calcitriol), and restores PTH effects on renal calcium reabsorption and urinary phosphate excretion, thereby mitigating the risk of hypercalciuria and hyperphosphataemia[173]. Therefore, in patients with chronic HypoPT treated with PTH replacement therapy, the optimal trade-off between minimising hypocalcaemic symptoms while minimising the risk of adverse treatment effects by, e.g., hypercalciuria or hyperphosphataemia, may shift towards higher target ranges for calcium levels, as compared to conventional treatment. Thus, we consider it reasonable to aim for a target calcium level within the lower half of the normal range (but not below) in patients on PTH replacement therapy. For these patients, it may also be reasonable to aim for calcium levels within the normal range as recorded before the occurrence of HypoPT, even if in the upper half of the normal range. Targeting calcium levels in the upper half of the reference range may also be reasonable if required for optimising symptoms and QoL and when paying particular attention to avoid overtreatment reflected by, e.g., hypercalcaemia and hypercalciuria.

Palopegteriparatide is currently (i.e., 2025) the only available (EMA and FDA) PTH analogue approved for the treatment of chronic HypoPT and causes a sustained PTH effect[81]. Although clinical trials have shown beneficial effects of treatment with palopegteriparatide[82,83], the guideline panel acknowledges that long-term safety and outcome data (e.g., on fracture rates, cardiovascular health, or renal endpoints) are not yet available. Moreover, availability and reimbursement criteria may differ between countries, which must be considered when treatment decisions are made.

After a subcutaneous injection of palopegteriparatide, free PTH(1-34) is slowly released into the circulation, providing stable concentrations throughout the day (half-life is about 60 hours)[81]with steady circulating calcium concentrations and no need for treatment with activated vitamin D or calcium supplements in the majority of patients. The starting dose is one daily subcutaneous injection of 18 µg, see **Figure 3**. Activated vitamin D should be omitted on the same day that PTH treatment is initiated. However, reduced doses of activated vitamin D (usually half the dose) should be maintained if calcium levels are very low (e.g., total calcium < 2.07 mmol/L [< 8.3 mg/dL]). Doses of palopegteriparatide are adjusted according to calcium levels with up or down titration once a week (with a maximum change of ±3 µg/day each week). Concomitant doses of activated vitamin D and calcium are adjusted, aiming at calcium levels within the target range without the need for activated vitamin D or calcium supplements[83,174]. We acknowledge that some patients will remain in need of concurrent treatment with activated vitamin D and calcium supplements. Palopegteriparatide can be dosed in the range of 6-60 µg/day (the FDA limit is currently 30 µg/day, as per the label). A dose > 30 µg/day is administered as two subcutaneous injections (simultaneously). The package leaflet of the drug provides further information on how best to titrate the drug (Yorvipath®, INN-palopegteriparatide).

In addition to stabilising calcium concentrations, clinical trials on the treatment of chronic HypoPT with palopegteriparatide have shown improvement in QoL, reductions in renal calcium excretion, increased eGFR, and normalisation of phosphate levels and the calcium-phosphate product[82,83] (see **Clinical Question II**).

For the purposes of the above, frequent fluctuations in calcium levels are considered if 3 or more adjustments per year are needed in doses of activated vitamin D and/or calcium supplements to maintain a calcium concentration in the target range. Such patients are considered inadequately controlled by conventional therapy and usually suffer from a significant disease burden with likewise frequent and costly demands on healthcare resources[175,176]. These patients might benefit from PTH replacement therapy.

Impaired QoL attributable to chronic HypoPT is multifaceted[177], including a high pill burden, lack of energy with reduced psychological well-being, and impairment of physical - (frequent symptoms of hypo-/hypercalcaemia including neuromuscular irritability with muscle spasms and pain) and cognitive- (brain fog, reduced memory, difficulties in concentrating/focusing) function. The parameters, measures, and extent to which reduced QoL is attributed to HypoPT that justifies PTH replacement therapy are currently not specifically defined and require individual decision-making. Certain disease-specific questionnaires may aid in the assessment of QoL in HypoPT patients and inform treatment decisions regarding PTH replacement therapy[124].

HypoPT is associated with an increased risk of renal complications[8,25,54,125]. Kidney function (creatinine-based eGFR) decreases in patients with HypoPT on conventional treatment[81,178], but improves in response to treatment of chronic HypoPT with palopegteriparatide. This effect was more pronounced if eGFR at the start of treatment was below 60 mL/min per 1.73 m^2; e.g., 52 weeks of treatment with palopegteriparatide in HypoPT patients with a baseline eGFR below 60 mL/min per 1.73 m^2 resulted in a mean (standard deviation) increase of 11.5 (11.3) mL/min per 1.73 m^2[179]. Accordingly, it seems reasonable to offer this treatment to patients with impaired kidney function. However, it must be acknowledged that an effect of palopegteriparatide on tubular creatinine secretion rather than filtration has not been ruled out.

Effects of replacement with palopegteriparatide should be evaluated 6-12 months after starting the treatment.

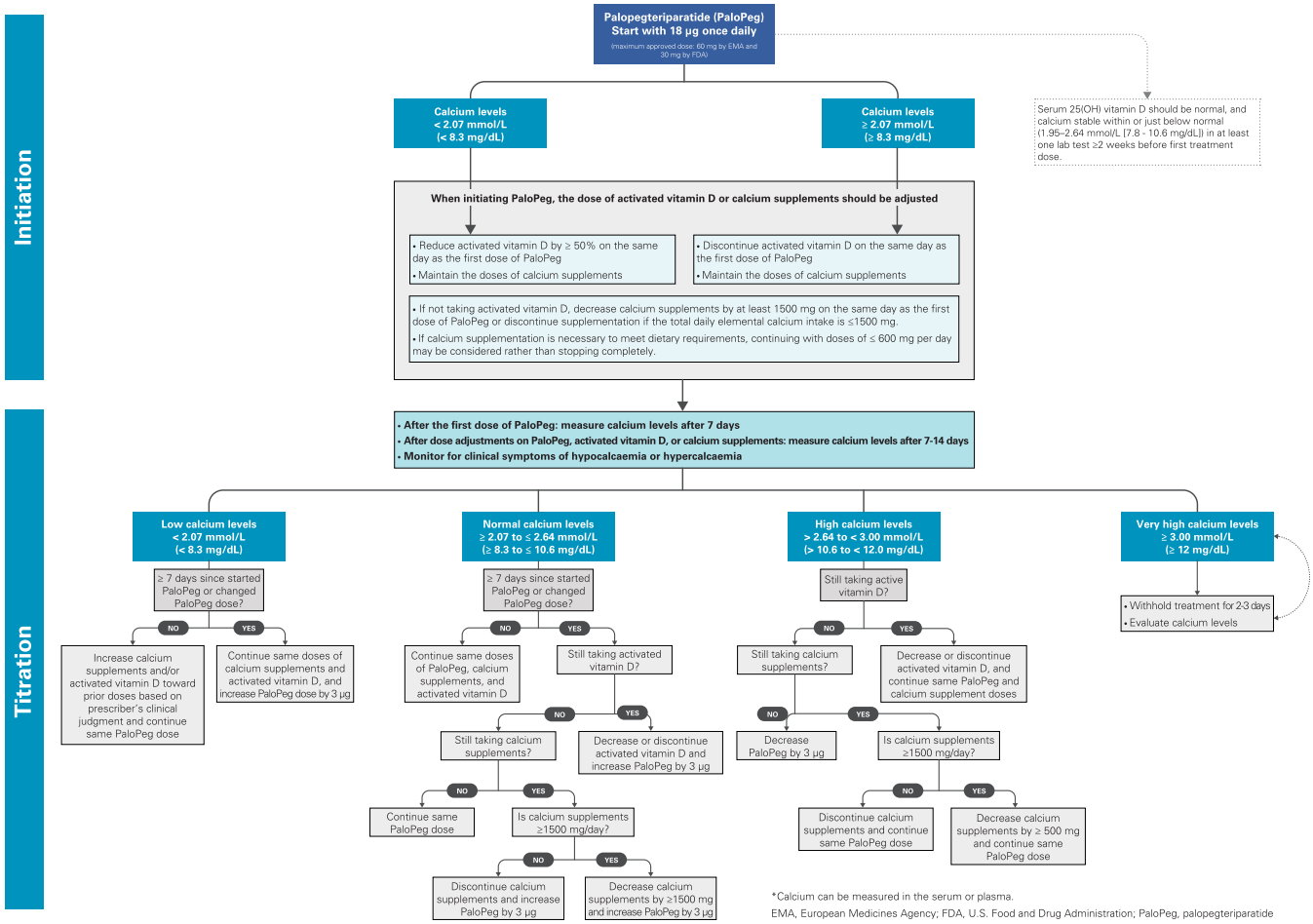

Figure 3. Palopegteriparatide treatment algorithm.

However, if the circumstances that led to the start of treatment (**R.3.5.2**) did not improve, it should be considered whether the new treatment is of value for the patient.

If palopegteriparatide must be discontinued, frequent monitoring of calcium levels (e.g., every 2 to 3 days) is recommended until disease control is re-established with conventional therapy. Due to its prolonged half-life, calcium levels may remain relatively stable for several days. However, the pharmacologic effect of a single dose diminishes gradually, with no meaningful biological activity expected beyond 10 to 14 days. To minimise the risk of hypocalcaemia following discontinuation, conventional therapy should be reinstated promptly. Patients can be advised to resume calcium and activated vitamin D in the same dose as prior to starting palopegteriparatide. At present, no studies have evaluated the optimal strategy for discontinuing palopegteriparatide. It remains unclear whether abrupt cessation or a gradual tapering approach (e.g., reducing the dose by 3 µg every 2-3 days until cessation) is preferable.

Apart from palopegteriparatide, a sustained PTH effect can be achieved by pump-therapy or through several daily subcutaneous injections with PTH(1-34) or PTH(1-84). As PTH(1-84) therapy has recently been withdrawn from the market, only PTH(1-34) is available, but it has not been marketed for the treatment of HypoPT. However, PTH(1-34) is used off-label in some countries, and clinical studies have shown a beneficial effect compared to conventional treatment[68,69,79]. In an open-label phase 2 study, eneboparatide, an agonist of the PTHR1 receptor, has been effective and safe for disease control in chronic HypoPT[85]. Eneboparatide is thus a potential new treatment for patients with chronic HypoPT that still requires further study results and approval by regulatory authorities before use in patient care[85].

R.3.6 In the presence of hypercalciuria, we suggest measures to lower urinary calcium excretion, which may include decreased doses of calcium supplements and/or activated vitamin D analogues, a low sodium chloride intake (< 6 g NaCl or < 2.4 g sodium/day) and/or addition of treatment with a thiazide diuretic. If these measures are not effective in normalising hypercalciuria, while maintaining calcium levels within the target range, we suggest PTH replacement therapy. (⊕OOO)

Reasoning: In the general population, high renal calcium excretion is associated with an increased risk of renal calcifications. In HypoPT, the risk of renal complications is increased[8,63,125,180], but only insufficient data are available on whether a high urinary calcium excretion in HypoPT is associated with this increased risk. However, it seems reasonable to aim to normalise the 24-hour urinary calcium (Figure 2), even though formal scientific proof is lacking. Replacement therapy with a sustained PTH effect has demonstrated lowering urinary calcium in HypoPT[174].

No data exist on whether dietary recommendations are useful in reducing urinary calcium in HypoPT. In patients with intact parathyroid function, urinary calcium is positively associated with the intake of calcium and sodium chloride[181,182]. Accordingly, it may be helpful to reduce the intake of sodium chloride to < 6 g/day[183,184]. See also the European Association of Urology 2024 Guidelines on Urolithiasis: EAU Guidelines on Urolithiasis - Uroweb, and **Figure 2.** If patients are receiving treatment with a high daily dose of calcium supplements, the daily dose of activated vitamin D may be increased to allow for reducing the dose of calcium supplements. If dietary recommendations or changes in the daily dose of calcium supplements and/or activated vitamin D analogues do not sufficiently reduce urinary calcium excretion, treatment with a thiazide diuretic may be considered (**Figure 2**). Treatment with a thiazide diuretic is associated with a lowering of urinary calcium in patients with HypoPT[63,185-188] and can be considered in patients with hypercalciuria. Pharmacological management of urolithiasis includes treatment with a thiazide diuretic in case of hypercalciuria[189]. A calcium-sparing effect of thiazides may also allow for reduced doses of calcium supplements. The addition of amiloride to a thiazide may further lower urinary calcium losses and decrease the risk of hypokalaemia. Moreover, amiloride may lower renal magnesium excretion[46,190]. However, no data are available on whether thiazides reduce the risk of renal complications in HypoPT. If a thiazide diuretic is prescribed, it should be noted that the hypocalciuric effect is dose-dependent, and treatment should preferably be combined with sodium restriction (85). A relatively high dose administered twice daily is often needed to lower 24-hour urinary calcium, i.e., hydrochlorothiazide 50 mg twice daily or bendroflumethiazide 5 mg twice daily. Thiazide-like diuretics (e.g., chlorthalidone and indapamide) may, however, be administered only once daily as they have a longer duration of action. Risks of adverse effects increase with dose, and potential adverse effects should be monitored early (1-2 weeks) and closely during treatment, including blood electrolyte disturbances, decrease in eGFR and potentially reduced blood pressure. In case of calcium nephrolithiasis, the other metabolic risk factors (volume, oxalate, citrate, animal protein consumption) must be assessed and corrected, (see EAU Guidelines on Urolithiasis - Uroweb). HypoPT patients with nephrolithiasis and hypercalciuria despite optimised conventional therapy are candidates for PTH replacement therapy.

R.3.7 In the presence of hyperphosphataemia, we suggest dietary interventions and/or adjustment of treatment with calcium supplements and vitamin D analogues. If these measures are not effective in normalising hyperphosphataemia while maintaining calcium levels within the target range, we suggest PTH replacement therapy. (⊕OOO)

Reasoning: High phosphate levels and/or a high calcium-phosphate product are presumed to increase the risk of extra-skeletal calcifications, interventions aiming at normalising these biochemical indices should be considered[191] (**Figure 2**), although evidence from trials is lacking. Patients may be advised to reduce their intake of dietary sources rich in phosphate. As calcium binds phosphate in the intestine and calcitriol increases intestinal absorption of phosphorous, it may be considered to titrate therapy so that the daily intake of calcium supplements (together with a meal) is increased, which may allow for a decrease in daily dose of activated vitamin D analogues. Following such changes, 24-hour urinary calcium should be measured to ensure that patients have not developed severe hypercalciuria. No data exist on the use of phosphate binders in HypoPT. Of note, studies in patients with chronic kidney disease (mostly not on dialysis) have suggested increased mortality and risk of vascular calcifications in patients on treatment with calcium-containing versus calcium-free phosphate binders[192]. It is unknown whether lowering phosphate levels in HypoPT by increasing calcium intake is of benefit or harm to patients.

R.3.8 In a patient with hypomagnesaemia, we suggest measures to increase magnesium levels. (⊕OOO)

Reasoning: Low magnesium levels are often reported in HypoPT, and marked magnesium deficiency may cause symptoms like hypocalcaemia[141]. In addition to HypoPT, other causes of hypomagnesaemia must be considered, including treatment with certain diuretics and PPIs[193]. To normalise magnesium levels, a diet rich in magnesium (e.g., leafy greens, nuts, and whole grains) and/or treatment with magnesium supplements or amiloride can be considered[190,194]. Magnesium supplements are not always well tolerated due to gastrointestinal adverse events. Various magnesium salts can be prescribed, based on the tolerance of the individual patient. Amiloride has been shown (in patients with an intact parathyroid function) to act as a magnesium-sparing diuretic[190,195].

Of note, magnesium is mainly present in the intracellular compartment, distributed in soft tissue (19%), muscle (27%), and bone (53%). Only 0.8% of magnesium is found in the circulation, with 0.3% in serum and 0.5% in erythrocytes[196]. As mentioned above, circulating magnesium levels do not provide an accurate proxy of magnesium status. If magnesium levels are chronically low, a magnesium retention test may be considered. This involves administering 0.5 mmol of magnesium per kg of body weight in 500 mL of saline as an intravenous infusion over 6 hours. The test should be avoided in cases of severe renal impairment, and the dose should be reduced in patients with mild renal dysfunction. This test helps determine whether the patient has intracellular magnesium depletion. If 24-hour urinary magnesium excretion is < 50% of the infused amount, magnesium deficiency is likely present, and the infusion itself will serve as treatment[197-199].

R.3.9 Ensure replete levels of vitamin D by using a daily vitamin D supplement (cholecalciferol or ergocalciferol; vitamin D_3 or D_2) of 800-2000 IU (20–50 µg).

Reasoning: Vitamin D is of importance for many physiological processes, including calcium homeostasis. In otherwise healthy individuals, PTH secretion starts to rise if concentrations of 25(OH)D, the accepted marker of vitamin D status, decrease. Vitamin D deficiency may thus increase the requirement for PTH in mineral metabolism. There is no clear threshold for vitamin D sufficiency, but at a circulating 25(OH)D level ≥ 75 nmol/L (30 ng/mL), PTH secretion to compensate for a poor vitamin D status is considered minimal, if at all present[200-202]. The vast majority of patients will effectively

and safely achieve levels of 25(OH)D ≥ 75 nmol/L (30 ng/mL) if vitamin D (cholecalciferol or ergocalciferol; vitamin D_3 or D_2) is supplemented at a dose of 800-2000IU/day (20 -50 µg/day)[203-208]. A reasonable target range for vitamin D status in chronic HypoPT patients may be 25(OH)D of 75 to 125 nmol/L (30 to 50 ng/mL)[122].

5.4. Monitoring

R.4.1 We suggest measuring PTH levels once a year, as appropriate, to assess endogenous function for potential recovery.

Reasoning: Recovery of chronic postsurgical HypoPT following years after the initial diagnosis, although rare, has been reported[35,94,209-211]. In a case series of four individuals, recovery of parathyroid function was documented up to 8 and 16 years after the initial diagnosis following treatment with PTH(1-84) for 36 to 63 months[209]. Underlying mechanisms may involve the potential effects of PTH in enhancing vascularisation of the remaining parathyroid tissue or the reduction of calcium and vitamin D supplements that are well-known negative regulators of parathyroid function[212-215]. A few patients may regain sufficient parathyroid function even after several years. This possibility should be tested periodically by lowering treatment doses (including PTH analogues if used), measurement of PTH and calcium, and assessment of related symptoms. Of importance, in certain types of non-surgical HypoPT, PTH secretion may also be reestablished (e.g., autoimmune HypoPT).

R.4.2 We recommend routine biochemical monitoring of circulating levels of ionised, or albumin-adjusted total calcium, phosphate, magnesium, and creatinine (estimated glomerular filtration rate [eGFR]), as well as assessment of symptoms of hypocalcaemia and hypercalcaemia at regular time intervals (e.g., every 3-6 months).

Reasoning: In a patient with HypoPT on stable therapy, calcium levels and renal function may change without an obvious cause and without causing noticeable symptoms. On the other hand, hypocalcaemia-related symptomatology may be present, yet unrecognised despite maintaining calcium levels within the normal range, imposing a significant negative impact on the patient's QoL[216]. Although there are currently no data defining optimal monitoring of patients with HypoPT, it seems reasonable to offer biochemical screening and clinical assessment of related symptomatology to patients at regular time intervals (Figure 2).

As no straightforward relationship exists between calcium levels and hypocalcaemic symptoms, the occurrence of hypocalcaemic symptoms should be evaluated at regular time intervals to ensure that the treatment provides relief of symptoms without causing adverse effects.

R.4.3 Following changes in therapy, we recommend biochemical monitoring every 1-2 weeks.

Reasoning: If the daily dose of activated vitamin D or calcium is changed, or if a new treatment is introduced (such as thiazide diuretics), circulating levels of calcium, phosphate, magnesium, and creatinine (together with eGFR) should be closely monitored for the first weeks (Figure 2). This also applies to the change from conventional to PTH replacement therapy. In case of severe hypo- or hypercalcaemia, more frequent monitoring (e.g., several times a week) may be needed, but not earlier than 2 to 3 days after adjusting conventional therapy.

R.4.4 When receiving conventional treatment, we suggest monitoring of 24-hour urinary calcium at regular time intervals (e.g., every 1-2 years).

Reasoning: Hypercalciuria is a well-known risk factor for renal calcifications[126,134-136], and although currently no data exist on patients with HypoPT, assessment of 24-hour urinary calcium, sodium, and creatinine at regular time intervals may allow for early intervention, in case hypercalciuria is present.

Vitamin D status should be normal when measuring 24-hour urinary calcium[217]. In addition, high dietary sodium and increased urinary sodium excretion are known to significantly increase calcium excretion. Therefore, a low-sodium diet should be advised, especially in the presence of hypercalciuria[218-221].

No data, however, are available on whether these measures will help to reduce long-term morbidity. Monitoring of urinary calcium at shorter time intervals may be considered in cases where specific treatment targeting lowering urinary calcium is advised (e.g., thiazide diuretics) and in patients requiring higher than generally recommended calcium levels.

As stated in **R.3.5**, PTH replacement therapy decreases renal excretion of calcium, wherefore we do not suggest monitoring 24-hour urinary calcium routinely during treatment with PTH analogues.

R.4.5 We recommend against routine renal imaging but perform renal imaging (ultrasound or CT) if there are clinical or laboratory features suggestive of nephrolithiasis, nephrocalcinosis, or unexplained decline in renal function.

Reasoning:. Renal imaging upon diagnosis or during monitoring is generally not recommended but may be considered in patients with additional risk factors of nephrolithiasis, such as positive family history, type of hypoparathyroidism (e.g., ADH1), duration of treatment for HypoPT, arterial hypertension, diabetes, obesity, or gout[222-224]. For people with CKD, a change in eGFR of > 20% and/or a doubling of the urinary albumin-over-creatinine ratio on a subsequent test exceeds the expected variability and warrants further evaluation[225]. eGFR and albuminuria should be assessed at least annually.

R.4.6 We suggest monitoring for the development of signs or symptoms of co-morbidities at regular time intervals (e.g., yearly).

Reasoning: HypoPT is associated with multiple co-morbidities (Table 2). While the risk for renal complications is well-established, particularly for chronic kidney failure, hypercalciuria, nephrolithiasis, and nephrocalcinosis, the causality with other complications is less well-understood. Increased cardiovascular risk has been reported in patients with HypoPT, and the risk for cardiovascular events appears to

increase with the duration of the disease[8,48,226]. Increased risk of basal ganglia calcifications is also associated with HypoPT and varies with the severity of the disease, its aetiology, or the duration of treatment[227,228]. However, patients with basal ganglia calcifications do not appear to have an increased risk of neurological conditions or musculoskeletal symptoms. Patients with HypoPT are also at increased risk of neuropsychiatric disorders (i.e., depression, bipolar affective disorder, anxiety)[10,44,229], and infections[44,48,230], but the underlying mechanisms and whether both surgical and non-surgical forms are equally affected remain to be elucidated.

Early detection of complications may be of importance, which is why it seems reasonable to assess whether patients are experiencing symptoms, which may indicate emerging complications. However, so far, screening for comorbidities in chronic HypoPT has not shown a beneficial effect in terms of a favourable cost-benefit outcome.

As certain drugs/diseases and conditions may interfere with the treatment of HypoPT, awareness of concomitant medication is relevant (Table 6).

R.4.7 We suggest assessing fracture risk as recommended for the general population.

Reasoning: The relationship between HypoPT and bone health is complex. The absence of parathyroid hormone leads to low bone turnover, thereby increasing bone mineral density (BMD) by up to around 30%, and reducing the loss of BMD during the ageing process, despite having risk factors for osteoporosis[231-233]. Data on the risk of fragility fractures, however, is limited, and an increase in the overall risk of fractures has not been consistently reported[44,51,234]. A recent meta-analysis reported an increased risk of vertebral fractures in patients with nonsurgical HypoPT[235], but an increased risk of vertebral fractures has also been reported in postsurgical HypoPT[236]. Furthermore, high BMD readings on DXA may not accurately represent the risk of fractures or the true state of bone health in patients with HypoPT[237,238]. In addition, the female preponderance in postsurgical hypoparathyroidism and certain presurgical conditions, such as Graves' disease or corticosteroid use, may affect the baseline risk for bone disease and should be taken into consideration when evaluating the individual patient. A recent cross-sectional study based on the Canadian National Hypoparathyroidism Registry reported that 35% of postmenopausal women had osteoporosis by BMD or prior fragility fracture, and three men ≥ 50 had osteoporosis by BMD or fragility fracture (33.3%; n = 3/9)[239]. A large registry study from Sweden, published after our systematic reviews were conducted, reported no difference in major osteoporotic fractures of patients with HypoPT versus matched controls (HR 0.93; 95% CI 0.69-1.26)[240]. However, patients with HypoPT had a higher risk of vertebral fractures (HR 1.55; 95% CI 1.12-2.14) and a lower risk of femur fractures (HR 0.70; 95% CI 0.50-0.98) compared to controls. Despite being more often diagnosed with osteoporosis (HR 1.54; 95% CI 1.21-1.95), HypoPT patients were less frequently prescribed osteoporosis medication (HR 0.69; 95% CI 0.54-0.88) compared to controls[240].

Therefore, patients with chronic HypoPT should be screened for risk factors for fragility fractures (including measurement of BMD by dual-energy X-ray absorptiometry (DXA), as in the general population, and a closer follow-up may be required for postmenopausal women and men > 50 years. For patients treated with PTH analogues, an initial decrease in BMD has been reported, and as the long-term effects of this treatment are unknown, more frequent monitoring of fracture risk factors with or without BMD may be considered[174]. Patients with osteoporosis or low-energy fractures should be considered for pharmacological therapy as per general population guidelines, bearing in mind the potential risk of (aggravation) of hypocalcaemia when antiresorptive treatment is initiated.

5.5 Special circumstances

Autosomal dominant hypocalcaemia

R.5.1 We recommend close monitoring of patients with autosomal dominant hypocalcaemia (ADH), who are being treated with calcium and/or activated vitamin D, as such patients may be at greater risk of hypercalciuria and renal complications.

Reasoning: ADH is classified into two subtypes based on the gene involved: ADH1, caused by activating variants in the calcium-sensing receptor (*CASR*) gene[241,242], and ADH2, caused by activating variants in the alpha subunit (Gα11) of the associated G-protein (*GNA11*)[243,244], see Table 1. A diagnosis of ADH can be established through genetic testing[241,242,244]. The gain-of-function mutations cause a lowering of the calcium set-point in the parathyroid glands. At equivalent calcium levels, patients with ADH have lower PTH levels than normal individuals. In a strict sense, this is not a state of HypoPT, as the parathyroid glands are well preserved, although less responsive to a hypocalcaemic challenge[245]. The CaSR and GNA11 are also expressed in the renal tubule, and renal calcium excretion is often markedly increased in patients with ADH who are at increased risk of renal complications[241,246,247]. Asymptomatic patients should, in general, not be treated unless calcium levels are very low and there is no hypercalciuria[138]. Because of enhanced CaSR sensing, increasing calcium levels may further suppress PTH secretion and exacerbate urinary calcium excretion. Therefore, target serum calcium levels may be lower in ADH than in other forms of hypoparathyroidism where renal calcium handling is less affected[248]. Besides conventional treatment, thiazide diuretics are prescribed in some patients with ADH to reduce urinary calcium excretion[63,186,241,249]. Calcilytics, which act as antagonists to the CaSR and increase PTH levels, are promising new therapies for ADH1[86]. Encaleret, an oral calcilytic, has shown efficacy and safety in a phase 2b trial in 13 patients with ADH1 and is currently being evaluated in a multinational phase 3 trial[86].

In general, the frequency of monitoring will be dependent on the clinical situation and whether any change in treatment is introduced, see Figure 2.

Pregnancy and breastfeeding

R.5.2 We suggest treatment with activated vitamin D analogues and calcium supplements as in non-pregnant women.

Reasoning: Case series and registry data indicate an increased risk of pregnancy complications in women with chronic HypoPT, including higher rates of induced labour, preterm

birth, lower birth weight, blood transfusions, and congenital anomalies[55,58,250]. However, robust data from cohort studies or randomised controlled trial data are lacking, but most women with chronic HypoPT have uncomplicated pregnancies and give birth to healthy babies[55,58,250].

Activated vitamin D treatment and calcium supplements are the mainstay of HypoPT treatment during pregnancy and lactation. This conventional treatment should remain unchanged when a sufficiently well-controlled woman with HypoPT becomes pregnant, unless initial evaluation after conception reveals the need for adjustment[57,59,251]. PTH replacement therapy is currently not recommended for use during pregnancy outside of clinical studies. However, case reports of women treated with either subcutaneous PTH(1-84) injections or continuous subcutaneous PTH(1-34) infusions throughout pregnancy have been described with favourable outcomes and no teratogenic effects[252-255]. While we currently do not recommend PTH replacement therapy during pregnancy, it might be considered for individual patients who are inadequately controlled by conventional therapy. This position may evolve as additional evidence on safety becomes available. Thiazides should be discontinued before conception or once pregnancy is confirmed due to potential risks but could be used with caution in the second and third trimesters after careful risk-benefit assessment[57].

Although group comparisons of women with HypoPT indicate no significant changes in calcium levels from pre-pregnancy to pregnancy, there is notable inter-individual variability[256-258]. While many women do not require a change in their conventional treatment during pregnancy, a substantial proportion requires adjustments, with either increased or decreased doses of activated vitamin D and/or calcium supplements[256-261]. These treatment changes are, however, not predictable and may vary throughout pregnancy with a tendency towards higher dosage requirements in the third trimester[256-258]. Therefore, pre-pregnancy counselling is essential, with optimisation of calcium and vitamin D status prior to conception, and ongoing shared care between endocrinology and obstetrics to ensure maternal and foetal safety.

Towards the end of pregnancy and during lactation, rising PTHrP levels may cause hypercalcaemia unless calcium and activated vitamin D dosages are significantly reduced in the days after, and sometimes even in the days up to, delivery. In some cases, conventional treatment can be temporarily discontinued during lactation[256-258,262]. After weaning, maternal hormone changes gradually subside, leading to increased dosage requirements for activated vitamin D and calcium. Generally, women with HypoPT stabilise on a similar, if not the same, medical regimen as pre-pregnancy, but careful adjustment and monitoring are essential to ensure smooth transitions.

R.5.3 We recommend monitoring ionised calcium and/or albumin-adjusted calcium levels regularly (e.g., every 3 - 4 weeks) throughout pregnancy and lactation and even more frequently (e.g., weekly) during the 4 weeks before and after delivery, aiming to keep calcium levels at the lower end of the normal range.

Reasoning: Calcium falls in normal pregnancy due to haemodilution-induced reductions in serum albumin levels, whereas ionised calcium and albumin-adjusted calcium remain stable[263,264]. Thus, in pregnant women with HypoPT, ionised calcium and/or albumin-adjusted calcium levels are the preferred parameters for monitoring. Frequent monitoring (e.g., every 3 - 4 weeks) is essential because of the common and unpredictable changes in dosage requirements of activated vitamin D and calcium supplements[57,251,265]. Levels of calcium are recommended to be kept at the lower end or lower half of the normal range in pregnant women with chronic HypoPT[57]. Maternal hypo- and hypercalcaemia should be avoided during pregnancy.

During lactation, there are high rates of bone resorption due to mammary tissue production of PTHrP[266]. The onset of the PTHrP-induced rise in calcium levels during lactation usually occurs in the first few days after delivery, but the timing may vary. Hypercalcaemia is commonly encountered in nursing women with HypoPT, if activated vitamin D therapy is not reduced quickly after delivery[259,266-270]. Hypercalcaemia after delivery has even been reported in women who did not breastfeed[271]. Therefore, activated vitamin D and calcium supplements are generally reduced immediately postpartum with close biochemical monitoring indicated to detect rapid and unpredictable change in calcium levels. Some women, however, may develop hypocalcaemia immediately postpartum before the further physiologic effects of PTHrP become evident, underscoring the need for more frequent monitoring of calcium levels (e.g., weekly) in the four weeks before and after delivery[57,262,266]. After weaning, activated vitamin D and calcium supplements should be gradually re-escalated with close follow-up as maternal hormones return to pre-pregnancy levels and a new steady state is achieved. In the rare event that PTH replacement therapy is required during lactation, it may be (re-)started a few weeks after delivery, though clinical data are insufficient.

R.5.4 We recommend that a paediatrician and/or neonatologist be informed of maternal HypoPT and be involved in the immediate care and monitoring of the infant for potential consequences related to both maternal treatment and the underlying maternal disorder.

Reasoning: Depending on the ease and degree of control of the maternal calcium and phosphate levels during pregnancy, the neonate may be at greater risk of disordered parathyroid function and calcium levels postnatally. The neonate is at risk for suppressed PTH secretion, manifested as neonatal hypocalcaemia, if the mother has been hypercalcaemic during pregnancy. Alternatively, the infant may demonstrate secondary hyperparathyroidism with bone demineralisation and its consequences, if the mother has been significantly hypocalcaemic during pregnancy. The intensity of monitoring of the newborn may depend on maternal calcium levels during pregnancy and on underlying disease in case of maternal non-surgical HypoPT. A rough guidance for newborn monitoring is to undertake serial ionised calcium monitoring, starting on day two of life and typically repeating every 48 hours during the first week[57]. Routine newborn vitamin D supplementation, according to local or national guidelines, should be ensured[57,272].

Acknowledgments

The authors of the guideline would like to thank and acknowledge Sigridur Björnsdottir, Michael Mannstadt and Salvatore Minisola for their expert review. We are also grateful for all the valuable and critical comments of members of the European Society of Endocrinology. The comments of the reviewers, as well as our responses, are available in Supplementary Table 10.

In addition, the authors would like to thank J.W. Schoones for his help in conducting the literature searches.

Funding

This work is supported by the European Society of Endocrinology.

Conflict of interest: Conflicts of interest are stated in Supplementary Table 1.

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