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Review article

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Hypoparathyroidism: diagnosis, management and emerging therapies

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Abstract

Hypoparathyroidism is characterized by inadequate parathyroid hormone (PTH) secretion or action and results in hypocalcaemia, and can lead to hyperphosphataemia and hypercalciuria. Most cases of hypoparathyroidism occur as a complication of surgery, with the remainder due to causes including autoimmune disease, genetic causes, infiltrative diseases, mineral deposition or due to abnormalities in serum levels of magnesium. Hypoparathyroidism can cause multisystem disease, with long-term complications resulting from ectopic calcification as well as renal complications with nephrocalcinosis, nephrolithiasis and renal impairment in addition to respiratory, cardiac or neurological manifestations. Conventional therapy consists of oral calcium salts and active vitamin D but it has limitations, including fluctuations in serum levels of calcium and a high pill burden, and can increase the risk of long-term complications. By contrast, PTH replacement therapy can effectively achieve normal serum levels of calcium, and lower serum levels of phosphate. The long-acting PTH analogue, palopegteriparatide, has been shown to normalize urine levels of calcium. In addition, PTH replacement therapy reduces the pill burden. Palopegteriparatide is also associated with improved quality of life in comparison to conventional therapy. This Review summarizes current recommendations regarding the pathophysiology, evaluation and management of hypoparathyroidism and also references the 2022 international hypoparathyroidism guidelines. Palopegteriparatide has now been approved as PTH replacement therapy for hypoparathyroidism. Emerging therapies will also be presented in this Review.

Sections

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Key points

- Hypoparathyroidism is a complex disease characterized by inadequate secretion or action of parathyroid hormone (PTH), which leads to hypocalcaemia and can lead to hyperphosphataemia and hypercalciuria.
- Hypoparathyroidism is a biochemical diagnosis based on the confirmation of hypocalcaemia in association with a low or inappropriately normal PTH level.
- The aetiology of hypoparathyroidism can be divided into surgical causes (75–80% of cases) and non-surgical causes (20–25% of cases).
- Hypoparathyroidism affects multiple organ systems, including the renal, skeletal, cardiovascular, ophthalmological and neurological systems.
- Conventional treatment of hypoparathyroidism with oral calcium salts and active vitamin D can cause fluctuating serum levels of calcium and can exacerbate hyperphosphataemia and hypercalciuria. Conventional therapy has not consistently been shown to improve quality of life.
- PTH replacement therapy is now possible with palopegteriparatide, which provides a valuable management option for addressing symptomatic hypocalcaemia and might also reduce the long-term complications of hypoparathyroidism.

Introduction

Hypoparathyroidism is defined as impaired or inadequate parathyroid hormone (PTH) secretion or action resulting in various complications due to hypocalcaemia, hyperphosphataemia and hypercalciuria[1]. The prevalence of chronic hypoparathyroidism ranges between 6.4 and 37 per 100,000 people worldwide. The incidence of chronic hypoparathyroidism is approximately 0.8–2.3 per 100,000 people per year[2]. Hypoparathyroidism greatly affects the quality of life of patients living with hypoparathyroidism. The health-care costs of treating patients with hypoparathyroidism and its complications are substantial, as these patients often require hospitalizations and frequent emergency room visits for the management of hypocalcaemia or hypercalcaemia as well as complications of hypoparathyroidism[3]. An International Task Force on Hypoparathyroidism was convened in 2020 to develop updated guidelines on the diagnosis, evaluation and management of patients living with this condition. These new guidelines from the Second International Workshop on the Evaluation and Management of Hypoparathyroidism, published in 2022, provide a framework to standardize the diagnosis and management of hypoparathyroidism.

Hypoparathyroidism has been conventionally treated with calcium and active vitamin D. These treatments correct hypocalcaemia; however, they can exacerbate hypercalciuria and hyperphosphataemia. This might potentially increase the long-term complications of nephrocalcinosis, nephrolithiasis and chronic kidney disease in addition to other complications of hypoparathyroidism[4,5]. PTH replacement therapy is now possible with palopegteriparatide as an alternative to conventional therapy. Studies evaluating PTH (1–34) (teriparatide), the active fragment of PTH that contains the first 34 amino acids of the full molecule, has demonstrated that it can achieve eucalcaemia. However, multiple daily doses or a subcutaneous infusion is required to lower urine levels of calcium, as teriparatide has a half-life of only 1 h[6–12]. PTH (1–84) has a longer half-life of 3 h and is able to acheive eucalcaemia and lower the pill burden in patients with hypoparathyroidism. However, PTH (1–84) has not been demonstrated to reduce urine levels of calcium in comparison to conventional therapy[13–15]. Palopegteriparatide has a half-life of 60 h and has been demonstrated to acheive eucalcaemia, lower serum levels of phosphate and lower urine levels of calcium with once-daily dosing in patients with hypoparathyroidism[16]. Emerging therapies include a long-acting PTH receptor analogue (eneboparatide), currently in phase III clinical trials, and calcilytic therapy (encaleret) for autosomal dominant hypocalcaemia type 1 (ADH1), also in phase III clinical trials[17,18]. A long-acting once-weekly PTH peptide pro-drug is being evaluated in phase II clinical trials[19] and, in addition, a novel oral small molecule PTH1 receptor agonist is being evaluated in phase I clinical trials[20]; an oral PTH molecule is also being evaluated[21].

This Review aims to provide an updated summary of the pathophysiology, evaluation and management of hypoparathyroidism including reference to the 2022 international guidelines. We present the current approved PTH replacement therapy palopegteriparatide, and discuss emerging treatments that are currently under clinical investigation. Furthermore, we address the challenges in managing hypoparathyroidism during pregnancy and lactation, where physiological changes affect calcium homeostasis and require careful monitoring and adjustment of treatment. This Review aims to provide clinicians with a comprehensive overview of current and emerging therapies as well as practical guidance based on the available evidence and the clinical expertise of the authors for managing this complex condition.

Aetiology

Hypocalcaemia is the presenting feature in most individuals with hypoparathyroidism, which is defined as low serum levels of calcium (ionized or total serum levels of calcium, adjusted for albumin) in the presence of an undetectable, low or inappropriately normal serum level of intact PTH[3]. The underlying aetiology of hypoparathyroidism is divided into two major categories: postsurgical and non-surgical. Postsurgical causes of hypoparathyroidism comprise up to 75–80% of all hypoparathyroid cases and non-surgical causes account for approximately 20–25% of all cases of the disease[1,22,23].

Most patients with postsurgical hypoparathyroidism will recover[24]. Patients are considered to have immediate postsurgical hypoparathyroidism if their total serum levels of calcium adjusted for albumin and levels of PTH recover within 1 month after surgery[1]. Patients who require supplementation for ongoing hypocalcaemia beyond 1 month are considered to have protracted hypoparathyroidism[1]. Chronic hypoparathyroidism is diagnosed if the hypocalcaemia persists beyond 1 year after surgery[3].

Postsurgical hypoparathyroidism

There is substantial variation in the prevalence of temporary and permanent disease in the literature due to varying definitions of hypoparathyroidism and practices around the monitoring parameters and treatment goals of hypoparathyroidism[25–28]. For this Review, we have used the definitions of immediate postsurgical hypoparathyroidism, protracted hypoparathyroidism and chronic hypoparathyroidism based on the

2022 international guidelines on hypoparathyroidism[1,3]. Surgery is the most common cause of hypoparathyroidism, particularly surgery involving the thyroid, parathyroid or other extensive neck dissection[1]. Risk factors for developing postsurgical hypoparathyroidism include pre-operative vitamin D deficiency, Graves disease and inadvertent parathyroidectomy[29]. Incidental parathyroidectomy significantly increases the risk of both transient and chronic hypoparathyroidism compared with those without incidental parathyroidectomy. Risk factors for incidental parathyroidectomy include central neck dissection, reoperation, malignancy and total thyroidectomy[30]. In a 2021 study performed in the USA, surgeons with greater experience in performing thyroidectomy procedures had a lower rate of incidental parathyroidectomy[31]. Further risk factors for postsurgical hypoparathyroidism are presented in Box 1.

Non-surgical causes of hypoparathyroidism

There are several causes of non-surgical hypoparathyroidism, including autoimmune disease, genetic causes, infiltrative diseases, mineral deposition or disorders due to abnormalities in serum levels of magnesium, with either magnesium excess or deficiency resulting in hypoparathyroidism.

Autoimmune dysfunction leading to hypoparathyroidism

Among the various causes of non-surgical hypoparathyroidism, autoimmune causes are the most common[32]. Autoimmune causes of hypoparathyroidism can occur in isolation or as part of a syndrome. Mutations in the *AIRE* gene result in autoimmune polyendocrine syndrome type 1 (APS1; also known as autoimmune polyendocrinopathy–candidiasis–ectodermal dystrophy (APECED))[33–36]. The cardinal features of APS1 include adrenal insufficiency, hypoparathyroidism and mucocutaneous candidiasis. At least 80% of patients with APS1 have hypoparathyroidism[36]. Other characteristics of APS1 that are less frequent than hypoparathyroidism are noted in refs. 1,24,37 (Supplementary Box 1). In APS1, antibodies against the parathyroid-expressed antigen NALP5 (NACHT leucine-rich-repeat protein 5) are present and are associated with hypoparathyroidism[36,38]. Autoantibodies to type I interferons, namely IFNω and IFNα subtypes, are present in almost all patients[36]. Genetic testing for mutations in the *AIRE* gene is recommended if patients exhibit at least two cardinal features of APS1: chronic mucocutaneous candidiasis, adrenal insufficiency or hypoparathyroidism. If patients present with at least one of the other features of disease (Supplementary Box 1), testing for type I interferon autoantibodies is the first step. If interferon testing is unavailable, then clinicians should proceed with genetic testing. *AIRE* gene sequencing confirming biallelic mutations indicates APS1, and a dominant negative mutation indicates non-classic APS1. Patients with type I interferon antibodies but no evidence of an *AIRE* gene mutation require imaging to exclude thymomas and gene sequencing for potential *RAG* mutations as these conditions are also associated with the presence of these antibodies. Patients negative for both antibodies and *AIRE* mutations are classified as having an 'APS1-like' syndrome[36].

Autoimmune causes of hypoparathyroidism that occur in isolation include the presence of activating antibodies directed towards the calcium-sensing receptor (CaSR), resulting in decreased PTH secretion[39–41]. Currently, there is no gold standard test for CaSR antibodies, which has made it challenging to address their prevalence in autoimmune cases of hypoparathyroidism[24].

Genetic causes of hypoparathyroidism

Genetic causes can be divided into two main categories, syndromic and non-syndromic[42] (Table 1). Syndromic forms of hypoparathyroidism include DiGeorge syndrome (DGS), coloboma–heart anomaly–choanal atresia–retardation–genital–ear anomalies syndrome (CHARGE), hypoparathyroidism–deafness–renal dysplasia (HDR) syndrome and Kenny–Caffey syndrome.

Deletion at the site of chromosome 22q11.2 leads to a developmental defect of the pharyngeal pouches and results in DGS, which is associated with hypoparathyroidism in addition to several immunological, cardiac, renal and developmental anomalies[24,42–45]. Approximately 60% of patients with DGS develop hypoparathyroidism during their lifetime[46]. Hypocalcaemia can be the first presenting symptom leading to the diagnosis of DGS[47]. Heterozygous deletions at the 22q11.2 chromosome account for more than 80% of instances of DGS – the majority of these are due to de novo deletion mutations[48]. The *TBX1* gene, located in the DGS region on chromosome 22q11.2, has a pivotal role in the development of the pharyngeal apparatus during embryogenesis[49]. Mutations in the *TBX1* gene have been implicated in the developmental anomalies noted in patients with DGS[50,51]. Variable expression of deletions and mutations in the 22q11.2 region, which includes *TBX1*, explain the variance in phenotypes observed in these patients[50,51].

CHARGE is an autosomal dominant disorder due to genetic mutations at the chromosomal locations 7q21.11 (*SEMA3E*) and 8q12.2 (*CHD7*) and has been associated with hypocalcaemia and hypoparathyroidism[24,52,53]. HDR syndrome is secondary to heterozygous mutations in the *GATA3* gene[54]. *GATA3* belongs to a family of six transcription factors and is expressed in the ear, parathyroid and kidney. Hence, mutations in this gene lead to the classic triad of sensorineural hearing loss, hypoparathyroidism and renal dysplasia of HDR syndrome[54–56]. Kenny–Caffey syndrome has two distinct phenotypes: type 1, also known as Sanjad–Sakati syndrome, and type 2.

Box 1 | Risk factors for postsurgical hypoparathyroidism[1]

Patient factors
- Obesity
- BMI >40
- Vitamin D deficiency
- Paediatric patients

Disease factors
- Graves disease
- Malignancy
- Concomitant thyroid and/or parathyroid surgery

Operative factors
- Central lymph node level VI dissection
- Reoperative surgery
- Trans-oral approach
- Surgical time >3 h
- Low surgical volume
- Incidental parathyroidectomy.

Box 1 was adapted from ref. 1.

Table 1 | Important genetic causes of hypoparathyroidism

Condition	Clinical features	Inheritance pattern	Genetic mutation
Syndromic			
DiGeorge syndrome type 1	Cardiac anomalies (ventricular septal defect, tetralogy of Fallot), neurocognitive abnormalities, immune deficiency	Autosomal dominant	*TBX1*
DiGeorge syndrome type 2	Recurrent infections, cleft palate, renal anomalies, ocular and skeletal anomalies, hearing loss	Autosomal dominant	*NEBL*
Coloboma–heart anomaly–choanal atresia–retardation–genital–ear anomalies syndrome	Choanal atresia and malformations of the heart, inner ear (deafness) and retina (coloboma)	Autosomal dominant	*SEMA3*
	Poor growth, genital hypoplasia	Autosomal dominant	*CHD7*
Hypoparathyroidism, deafness, renal dysplasia syndrome	Sensorineural deafness, renal conditions (that is, renal dysplasia, renal failure, renal agenesis)	Autosomal dominant	*GATA3*
Type 1 Kenny–Caffey syndrome (Sanjad–Sakati syndrome)	Short stature, dysmorphic features, growth retardation, small hands and feet	Autosomal recessive	*TBCE*
Type 2 Kenny–Caffey syndrome	Short stature, cortical thickening of tubular bones, gracile bone dysplasia	Autosomal dominant	*FAM111A*
Kearns–Sayre syndrome	Ophthalmoplegia, retinal pigmentation, cardiac conduction defects, bulbar weakness	Autosomal recessive	mtDNA
Mitochondrial trifunctional protein deficiency syndrome	Neuropathy, retinopathy, fatty liver	Autosomal recessive	mtDNA
Mitochondrial encephalomyopathy, lactic acidosis and stroke-like episodes	Lactic acidosis, stroke-like symptoms, external ophthalmoplegia, diabetes mellitus, hearing loss	Autosomal recessive	mtDNA
Non-syndromic			
Autosomal dominant hypocalcaemia with hypercalciuria type 1	Hypomagnesaemia, hypercalciuria	Autosomal dominant	*CASR*
Autosomal dominant hypocalcaemia with hypercalciuria type 2	Hypomagnesaemia, hypercalciuria	Autosomal dominant	*GNA11*
Familial isolated hypoparathyroidism type 1	Hypoparathyroidism, hypocalcaemia	Autosomal dominant, autosomal recessive	*PTH*
Familial isolated hypoparathyroidism type 2	Hypoparathyroidism, hypocalcaemia	Autosomal dominant, autosomal recessive	*GCM2*

Data in Table 1 were derived from Mannstaadt et al.[24] and Ali et al.[137]. mtDNA, mitochondrial DNA.

Kenny–Caffey syndrome type 1 is an autosomal recessive condition that leads to variations in the gene coding for TBCE, which is a protein that probably has a role in parathyroid function[57,58]. ADH1 is another genetic cause of hypoparathyroidism. This condition occurs due to an activating (gain-of-function) mutation of *CASR*, the gene encoding CaSR, and affects CaSRs, which are most prominently expressed in the kidney and the parathyroid glands[59]. An activating mutation of the *CASR* gene results in an increase in the sensitivity of CaSR to calcium both in the parathyroid gland and in the kidney[59]. In the parathyroid gland this increased sensitivity results in a shift of the calcium–PTH curve, which leads to decreased PTH secretion at lower calcium concentrations and results in hypocalcaemia and low levels of PTH compared with individuals without ADH1 (refs. 59–62). Figure 1 summarizes normal CaSR physiology. Figure 2 shows the effect of ADH1 on PTH secretion relative to serum levels of calcium as reflected by the calcium–PTH curve. As CaSR is also hypersensitive in the kidney, urinary calcium losses increase at lower serum levels of calcium, further contributing to hypocalcaemia[59–61]. In ADH1, renal magnesium wasting is also increased, and hypomagnesaemia is usually also present in addition to hypocalcaemia with low or inappropriately normal PTH levels, hyperphosphataemia, and hypercalciuria[24,59,61]. Other genetic aetiologies of hypoparathyroidism are summarized in Table 1.

Other causes of hypoparathyroidism

Rarely, infiltrative disorders can lead to hypoparathyroidism. These disorders include iron deposition, as seen in haemochromatosis[5]. Haemochromatosis is an inherited disorder characterized by increased iron deposits in various organs, including the parathyroid glands, and subsequent parathyroid gland dysfunction. Wilson disease causes hypoparathyroidism due to copper infiltration and destruction of parathyroid tissue. Metastatic cancer can cause hypoparathyroidism through infiltration of tumour cells in the parathyroid gland[5]. Furthermore, granulomatous diseases, such as sarcoidosis, amyloidosis and the invasion of parathyroid glands by inflammatory cells in patients with HIV, can also lead to hypoparathyroidism[1].

Medications associated with hypoparathyroidism include anti-PD1 immune-checkpoint inhibitors, such as nivolumab, which can lead to the development of activating autoantibodies to CaSR[63,64]. L-Asparaginase is used in the treatment of leukaemia and can lead to parathyroid damage. High-dose external beam radiation and radioactive iodine have also been associated with parathyroid destruction and hypoparathyroidism, although this is a rare occurrence[1,65,66].

Magnesium can affect PTH synthesis and secretion and calcium homeostasis through various mechanisms. As magnesium is a cofactor for adenylate cyclase, low serum levels of magnesium can result in tissue resistance to the effects of PTH[67]. High serum levels

of magnesium can activate CaSR and decrease the synthesis and secretion of PTH[66,68].

Functional hypoparathyroidism refers to hypoparathyroidism in association with magnesium excess or deficiency. Hypomagnesaemia can occur secondary to decreased intake, decreased intestinal absorption, increased losses or redistribution of magnesium. At the level of the gastrointestinal system, hypomagnesaemia can occur in patients with poor oral intake of magnesium, pancreatitis or on proton pump inhibitors[67,69]. At the renal level, drugs that cause renal magnesium wasting include thiazide diuretics, antibiotics (aminoglycosides, amphotericin B, foscarnet and pentamidine), and several chemotherapy and immunosuppressive medications[67,69].

Inherited disorders of magnesium homeostasis can lead to hypoparathyroidism and hypocalcaemia. Hypomagnesaemia with secondary hypocalcaemia is an autosomal recessive condition that occurs due to a mutation in the *TRPM6* gene, which is involved in the formation of the magnesium-permeable ion channels in the intestine and kidney[67]. This mutation leads to decreased absorption of magnesium from the intestine and impaired renal reabsorption of magnesium. This condition is associated with hypocalcaemia and hypoparathyroidism. Hypomagnesaemia with secondary hypocalcaemia can result in neurological complications of seizures, tetany or muscle spasms in patients[67]. A detailed list of other inherited causes of hypomagnesaemia is provided in ref. 67. A common acquired form of hypomagnesaemia occurs with the use of long-term proton pump inhibitors, which can lead to inhibition of magnesium absorption in the gastrointestinal tract[67].

Paediatric patients with burn-related injuries can have a strong inflammatory response that leads to an upregulation of the parathyroid CaSR through an unknown mechanism, resulting in hypoparathyroidism[70]. Calcium levels in these patients are often low on admission but improve to within the normal range at 6 months after the burn injury. These children can also develop severe magnesium depletion[70].

Infants exposed in utero to maternal hypercalcaemia (for example, in the context of maternal primary hyperparathyroidism) are at risk of developing hypoparathyroidism and postnatal hypocalcaemia[37,71–74]. Transient hypoparathyroidism in infants can occur due to maternal diabetes mellitus. Mothers with diabetes mellitus have increased glucosuria, compared with mothers without diabetes mellitus, which can lead to hypomagnesaemia and subsequent functional hypoparathyroidism in the mother and infant[74]. Permanent forms of hypoparathyroidism in infants can also occur in the presence of inherited magnesium disorders[67] or genetic causes of hypoparathyroidism[74,75] (Table 1).

In patients with hypoparathyroidism who do not have a history of neck surgery, a careful review of the possible non-surgical causes of hypoparathyroidism should be considered. A detailed family history should be undertaken, recognizing that a positive family history of hypoparathyroidism might not be present as de novo genetic mutations can lead to hypoparathyroidism. A comprehensive history and physical examination are of paramount importance to determine whether the hypoparathyroidism is syndromic or non-syndromic, with subsequent evaluation of the appropriate gene panels to determine the underlying genetic cause[3]. Patients and family members should undergo genetic testing if a genetic cause is suspected.

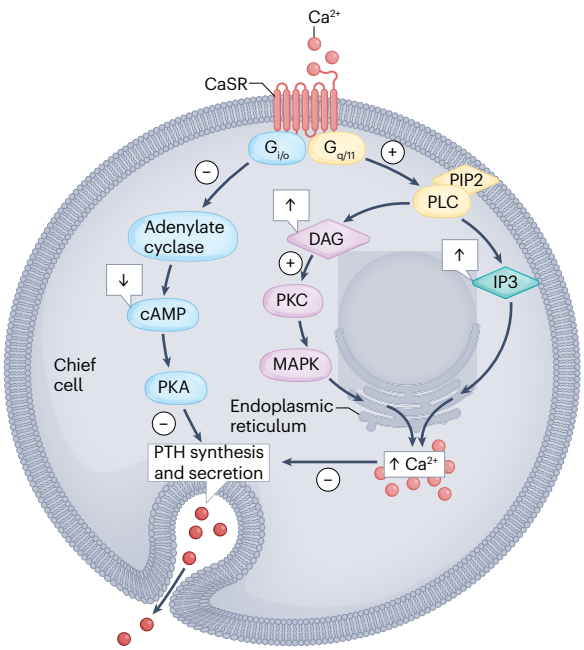

Fig. 1 | Parathyroid chief cell physiology. Calcium binds to the calcium-sensing receptor (CaSR), which is a G-protein-coupled receptor bound to the heterotrimeric guanine nucleotide-binding proteins (G-proteins) $G_{q/11}$ and $G_{i/o}$ (refs. 149,150). Calcium bound to CaSR activates $G_{i/o}$, which leads to inhibition of adenylate cyclase. This binding decreases cAMP production and prevents activation of protein kinase A (PKA), leading to reduced parathyroid hormone (PTH) synthesis and secretion[149,150]. Activation of CaSR also activates $G_{q/11}$, through which phospholipase C (PLC) cleaves phosphatidylinositol 4,5-bisphosphate (PIP2) into diacylglycerol (DAG) and inositol 1,4,5-trisphosphate (IP3)[150]. IP3 binds to receptors on the endoplasmic reticulum, resulting in increased intracellular calcium concentrations, which subsequently inhibit PTH synthesis and secretion[149,150]. DAG activates protein kinase C (PKC), which leads to activation of the mitogen-activated protein kinases (MAPK) signalling pathways. Activation of MAPK pathways also results in increased intracellular concentrations of calcium and inhibition of PTH synthesis and secretion[150].

Diagnosis

Hypoparathyroidism is diagnosed based on the confirmation of hypocalcaemia on two separate occasions at least 2 weeks apart in association with an undetectable, low or inappropriately normal PTH level as based on expert consensus of the Second International Taskforce[3]. Based on their clinical expertise, the authors of this Review recommend that patients presenting with severe symptoms of hypoparathyroidism that require emergency treatment (for example, seizures or cardiac arrhythmias), in association with hypocalcaemia and low levels of PTH, should be treated for presumed hypoparathyroidism. Once the patient has stabilized, serum levels of calcium and PTH can be tested again on two separate occasions at least 2 weeks apart to confirm the diagnosis. Figure 3 provides an algorithm for identifying the underlying genetic aetiologies of hypoparathyroidism.

Other biochemical manifestations of hypoparathyroidism include serum phosphate levels in the high-to-normal or high range, low levels of 1,25-dihydroxyvitamin D and hypercalciuria. Hypocalcaemia is confirmed in the presence of low levels of ionized calcium or calcium adjusted for albumin below the normal reference range[24].

In patients after surgery, the diagnosis of hypoparathyroidism is confirmed in the presence of hypocalcaemia and a low or inappropriately normal PTH level[3,24]. Most patients with postsurgical hypoparathyroidism will recover and not develop chronic hypoparathyroidism[24].

Patients are considered to have chronic hypoparathyroidism if their diagnosis persists beyond 12 months after surgery[3]. Differentiating between transient versus chronic hypoparathyroidism is important to prevent the complications associated with over-treating patients with transient disease and to identify those patients who are likely to require long-term treatment in the presence of chronic disease[24,29].

The International Task Force on Hypoparathyroidism recommends confirming a diagnosis of postsurgical chronic hypoparathyroidism 12 months following neck surgery[1]. Immediate postsurgical hypoparathyroidism was defined by the Task Force as a serum level of calcium corrected for albumin that is <2 mmol/d (8.0 mg/dl) with or without symptoms occuring within 1 month of surgery. Approximately 70–80% of patients recover parathyroid function 1 month after surgery[76–78]. A systematic review and meta-analysis of studies evaluating the use of PTH and/or calcium after total thyroidectomy to predict chronic hypoparathyroidism was undertaken by the international taskforce[24]. Measuring serum levels of PTH 12–24 h after total thyroidectomy provides higher sensitivity and specificity than measuring serum levels of calcium in predicting permanent hypoparathyroidism. A serum level of PTH >10 pg/ml (1.05 pmol/l) almost certainly excludes the risk of developing permanent hypoparathyroidism[24], whereas a serum level of PTH <10 pg/ml (1.05 pmol/l) is associated with a higher likelihood of permanent hypoparathyroidism, although this risk is still lower than 50%. Individuals with serum levels of PTH <10 pg/ml will require ongoing monitoring and treatment to prevent hypocalcaemia[3,76,78–83]. Patients who require supplemental therapy due to persistently low or absent levels of intact PTH 1 month after surgery are considered to have protracted postsurgical hypoparathyroidism[1]. Their chance of parathyroid function recovery at 1 year after surgery is 75%. The likelihood of parathyroid function recovery after this 1-year point is 10–15%[1,26,76].

Complications of hypoparathyroidism

The effect of inadequate PTH levels results in multisystem complications affecting the renal, skeletal, cardiovascular, ophthalmological and neurological systems as well as an increased risk of infections[3]. Patients with non-surgical hypoparathyroidism are more likely to have renal disease that progresses to chronic kidney disease stages 4 and 5 compared with those who do not have hypoparathyroidism[84]. A Danish study noted the risk of kidney disease was increased in patients with hypoparathyroidism when the serum calcium and phosphate product was elevated[85]. This finding was also noted in the Canadian National Hypoparathyhroidism Registry[86]. The International Task Force on Hypoparathyroidism conducted a systematic review confirming that patients with hypoparathyroidism are at three to four times increased risk of renal insufficiency compared to patients with normal parathyroid function[83]. They also estimated the prevalence of nephrocalcinosis and/or nephrolithiasis to be 15% and renal insufficiency to be 12% in patients with chronic hypoparathyroidism. A German study reported an increased prevalence of impaired renal function in patients with chronic hypoparathyroidism compared with the general population, which was independent of the presence of visible renal calcifications[87]. Renal complications can still occur in patients with hypoparathyroidism despite adequate metabolic control, albeit to a lesser degree compared with those with poor metabolic control. Hypercalciuria is a risk factor for nephrocalcinosis, nephrolithiasis and chronic kidney disease.

In the skeleton, low serum levels of PTH led to abnormal skeletal microstructure in cortical and cancellous bone[88–91]. Bone remodelling and bone formation rates are decreased in patients with hypoparathyroidism[92]. There are currently no prospective data confirming the effect of hypoparathyroidism on fracture risk[2,93]. Case–control studies show no difference in the overall fracture rates in comparison to the general population in patients with hypoparathyroidism on conventional therapy[93,94]. In patients with non-surgical hypoparathyroidism on conventional therapy, upper extremity fractures were increased, with a hazard ratio of 1.94 (95% CI 1.31–2.85) in comparison to control individuals[94]. In individuals with postsurgical hypoparathyroidism on conventional therapy, upper extremity fractures had a decreased hazard ratio of 0.69 (95% CI 0.49–0.97) compared with the general population[93]. A meta-analysis reported an increased risk of vertebral fractures in patients with non-surgical hypoparathyroidism but not in those with postsurgical hypoparathyroidism[95].

The Canadian National Hypoparathyroidism Registry is a prospective study that enrolled 101 adults with hypoparathyroidism, of whom 83 (82%) were women and 18 (18%) were men[86]. Of the women in this study, 42% (n = 35) were premenopausal and 58% (n = 48) were postmenopausal. Skeletal health data from this study population has been presented as a conference abstract, although these findings have not yet been published in a peer-reviewed journal article[96]. Osteoporosis is defined by a T-score of −2.5 or less at any of the three skeletal sites (lumbar spine, total hip and femoral neck or 1/3 radial site), which was noted in 15 of the 48 postmenopausal women (31.3%, n = 48) and in 2 of the 9 men (22.2%, n = 9) aged 50 years or older in this study[96]. A T-score is the number of standard deviations the patient's bone mineral density (BMD) is above or below the average BMD of a healthy young adult reference population. In the study, 35% of postmenopausal women were found to have osteoporosis by either BMD criteria or the presence of a prior fragility

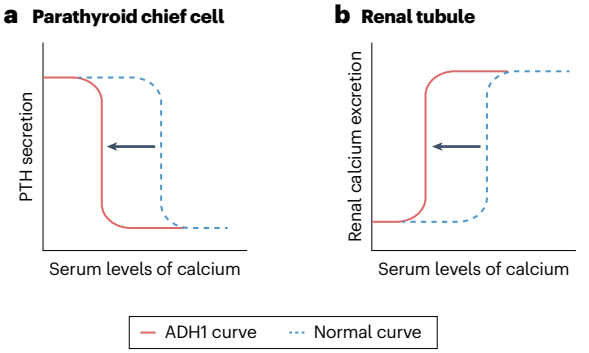

Fig. 2 | The effect of ADH1 on PTH secretion. The calcium–parathyroid hormone (PTH) secretion curve shows how PTH secretion changes as calcium levels in the blood vary. Normally, when calcium levels are elevated, activation of the calcium-sensing receptor (CaSR) decreases PTH secretion, and vice versa. In autosomal dominant hypocalcaemia type 1 (ADH1), an activating mutation in the CaSR-encoding gene (*CASR*) leads to increased calcium sensitivity in CaSR, which causes suppression of PTH secretion even when calcium levels are within normal range. This leads to a leftward shift in the serum calcium–PTH secretion curve, with lower concentrations of calcium required to trigger a reduction in PTH secretion in patients with ADH1 compared with healthy individuals. In the kidney, the curve is also shifted to the left, as CaSR is more sensitive to the effects of serum concentrations of calcium, and urine calcium losses are increased compared with individuals without ADH1. Calcilytics normalize CaSR sensitivity to calcium, leading to a shift of the curve towards normal. Through this mechanism, calcilytics increase serum levels of PTH and decrease urinary calcium losses in patients with ADH1.

fracture[96]. In this study 33.3% of the men over 50 years old had osteoporosis as determined by BMD criteria or the presence of fragility fracture. The baseline results of this prospective cohort study demonstrate substantial skeletal fragility in postmenopausal women with chronic hypoparathyroidism as noted by a higher-than-expected proportion of low BMD, osteoporosis and fractures. Similarly, a large percentage of men over the age of 50 had osteoporosis by BMD criteria or prior fragility fracture. These findings suggest that a close follow-up of bone health is necessary in postmenopausal women and men over the age of 50 with chronic hypoparathyroidism[96]. Prior studies conducted in Italy and Brazil have indicated a higher risk of vertebral fractures in postmenopausal women with postsurgical hypoparathyroidism compared with healthy age-matched control individuals[97–99]. Further research is required to assess the effects of hypoparathyroidism on bone strength and skeletal fragility.

Hypocalcaemia can also result in cardiac conduction abnormalities and arrhythmias by causing an acquired long QT syndrome, which refers to the prolonged ventricular action potential duration that can lead to arrhythmias such as ventricular tachycardia[100]. Hypocalcaemia can also lead to cardiomyopathy and heart failure[101–103]. Data from the Danish registry study reported that patients with non-surgical hypoparathyroidism are at an increased risk of any cardiovascular disease, including ischaemic heart disease, arrhythmias and stroke. Similarly, a study in Korea reported that patients with non-surgical hypoparathyroidism are at an increased risk of cardiovascular disease secondary to underlying arrhythmias and heart failure compared with the general population; however, this study did not note an increased risk of stroke in these patients[104]. Patients with chronic hypoparathyroidism are at a twofold to fourfold increased risk of developing cataracts[84,104] compared with eucalcaemic control individuals. Higher reported rates of neuropsychiatric conditions, such as anxiety, depression and bipolar disease, have also been reported for patients with hypoparathyroidism compared with those without the disease[2]. Hypocalcaemia leads to increased neuronal excitability, which can cause an increased risk of seizures and muscle spasms[3]. The Canadian registry of patients with hypoparathyroidism reported that basal ganglia calcifications are present in 15% of patients with postsurgical hypoparathyroidism and 37% of patients with non-surgical hypoparathyroidism[86]. The clinical importance of basal ganglia calcifications requires further evaluation. Lastly, the risk of infections is increased in patients with chronic hypoparathyroidism in both non-surgical and postsurgical patients compared with individuals with normal parathyroid function[6,93]. The underlying aetiology is thought to be secondary to a lack of calcium signalling, which is necessary for key immune cell populations to function, including mast cells, T cells and natural killer cells[6]. The risk of malignancy in patients with postsurgical hypoparathyroidism did not differ compared with their matched control individuals; however, the risk of gastrointestinal cancers was lower in the hypoparathyroid group[93]. A nationwide case-finding study in Denmark reported that hospitalized patients with non-surgical hypoparathyroidism were at a reduced risk

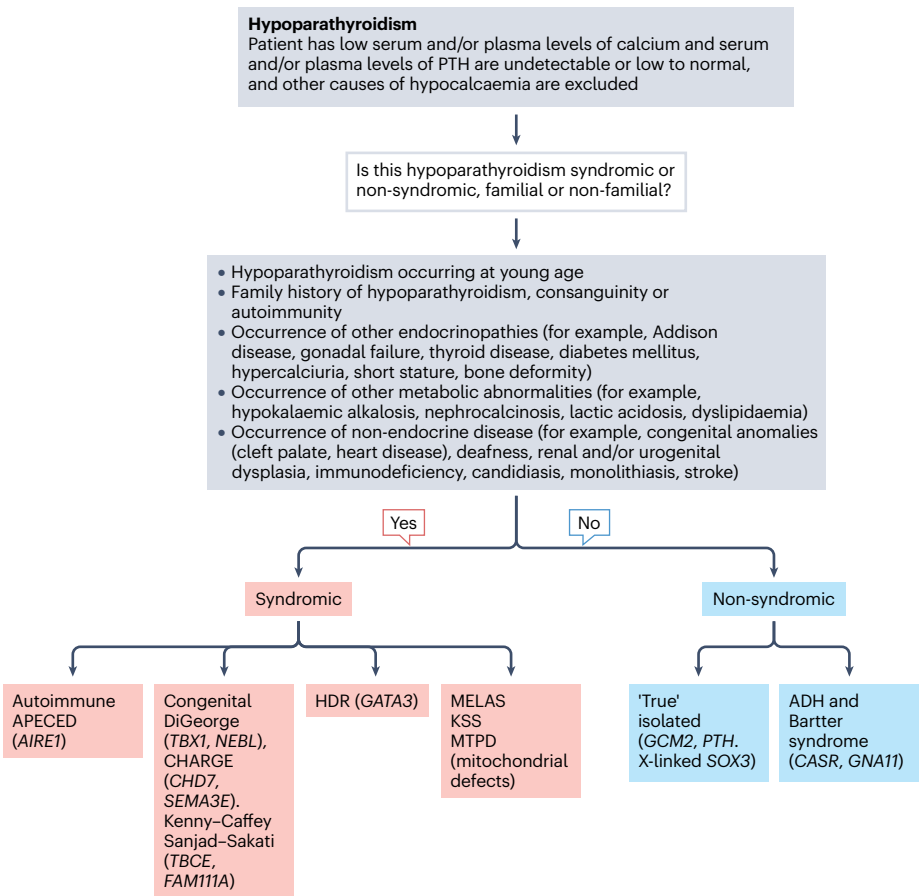

Fig. 3 | Algorithm to determine the genetic aetiology of hypoparathyroidism. If a genetic cause is considered for the hypoparathyroidism, then clinicians should determine whether the hypoparathyroidism is syndromic or non-syndromic. An accurate history and physical examination will help to differentiate between these two forms of genetic causes of hypoparathyroidism and further guide the clinician towards the specific genetic abnormality through the appropriate genetic panel testing (such as autoimmune polyendocrinopathy–candidiasis–ectodermal dystrophy (APECED)). ADH, autosomal dominant hypocalcaemia; CHARGE, coloboma–heart anomaly–choanal atresia–retardation–genital–ear anomalies; HDR, hypoparathyroidism–deafness–renal dysplasia; KSS, Kearns–Sayre syndrome; MELAS, mitochondrial encephalomyopathy, lactic acidosis and stroke-like episodes; MTPD, mitochondrial trifunctional protein deficiency syndrome; PTH, parathyroid hormone. Reproduced with permission from ref. 151, Elsevier.

of malignancy compared with their matched control individuals in the general population[94].

Monitoring

Practices regarding monitoring of laboratory values and imaging for patients with hypoparathyroidism vary substantially amongst physicians. The International Task Force on Hypoparathyroidism conducted a systematic current practice survey to suggest monitoring guidelines for these patients[105]. Of note, at this time, strong evidence is limited, and their monitoring recommendations were graded as low quality. For patients with relatively stable chronic hypoparathyroidism (as determined by clinical judgement), the Task Force suggests assessment of serum levels of creatinine, estimated glomerular filtration rate (eGFR), levels of calcium (ionized or calcium corrected for albumin), magnesium and phosphate every 3–12 months. Levels of 25-hydroxyvitamin D can be evaluated every 6–12 months and 24-h urine levels of creatinine and calcium can be evaluated every 6–24 months[3,105]. More frequent monitoring of these tests is recommended for patients with unstable disease (that is, symptomatic hypocalcaemia and/or hypercalcaemia, varying laboratory values and treatment regimens)[3,105]. With regards to imaging studies, baseline assessment for the presence of nephrolithiasis and/or nephrocalcinosis is recommended with renal imaging[3,105].

Management of hypoparathyroidism

Conventional therapy

Conventional therapy in the treatment of hypoparathyroidism consists of supplementation with oral calcium salts and active vitamin D. Conventional therapy is recommended as first-line therapy for patients with hypoparathyroidism[106]. However, conventional therapy poses several challenges, including fluctuating serum levels of calcium, further exacerbation of hyperphosphataemia and hypercalciuria, increased pill burden, and cumbersome pill regimens. Also, conventional therapy has not been associated with improved quality of life[106].

Oral calcium supplementation can be given in the form of calcium carbonate, which contains 40% elemental calcium, or calcium citrate containing 21% elemental calcium. The elemental calcium content is only 13% in calcium lactate and 9% in calcium gluconate, and these forms of calcium supplements are not recommended as treatment of chronic hypoparathyroidism due to their lower calcium content[107]. Oral calcium also acts as a phosphate binder and is useful for reducing hyperphosphataemia. It is advised that oral calcium carbonate supplements are taken with meals to optimize intestinal calcium absorption, as calcium carbonate requires an acidic pH for absorption. Calcium citrate does not require gastric acid for absorption and can be taken without meals[107–109]. Active vitamin D in the form of calcitriol or alfacalcidol, enhances calcium and phosphate absorption in the intestinal system[110]. Calcium salts and active vitamin D are of value in improving symptomatic hypocalcaemia. The goal of conventional therapy is to improve symptomatic hypocalcaemia and achieve a serum level of calcium just below the normal reference range or in the low–normal reference range. More-aggressive conventional therapy will increase serum levels of calcium but will also increase levels of urinary calcium and serum phosphate, which can lead to an increased risk of long-term complications of hypoparathyroidism[106]. Careful monitoring of levels of calcium (ionized or corrected for albumin), phosphate, urinary calcium and vitamin D is important to ensure calcium and active vitamin D therapy is titrated appropriately to minimize long-term complications. It is recommended to measure 25-hydroxyvitamin D levels to assess vitamin D status and to ensure that vitamin D levels are maintained within the normal range (75–125 nmol/l)[111,112]. Further ungraded panel recommendations by the International Task Force on Hypoparathyroidism include normalizing serum magnesium levels[106]. Ergocalciferol (vitamin D_2) or cholecalciferol (vitamin D_3) can be used to correct 25-hydroxyvitamin D inadequacy[113].

Patients with persistent hypercalciuria can benefit from the introduction of thiazide diuretics with a low salt diet and close monitoring of serum levels of potassium and magnesium[106,114]. Evidence for the benefit of thiazides in patients with hypoparathyroidism is obtained from a small pilot study conducted in 1978 (ref. 114). However, a 2012 chart review of patients with permanent hypoparathyroidism demonstrated that patients on thiazides had higher urinary calcium levels compared with patients not on thiazides[115]. In 2024, data from an observational study presented at the European Congress of Endocrinology showed that thiazide diuretics significantly reduce calciuria in patients with hypoparathyroidism compared with patients with hypoparathyroidism who were not treated with thiazides[116]. As the data pertaining to the benefit of thiazide diuretics is conflicting, physicians should use clinical judgement to assess the utility of thiazides for their individual patients. Patients started on thiazides should have careful monitoring of blood pressure, serum levels of magnesium, serum levels of potassium and renal function. These patients should also be cautioned about the increased risk of certain types of skin cancers associated with thiazide use[117,118]. Thiazides should be avoided in patients with ADH1 or autosomal dominant hypocalcaemia type 2 (ADH2) as they can further exacerbate hypomagnesaemia[37]. Thiazides are also contraindicated in patients with adrenal insufficiency, which is a cardinal feature in APS1 (ref. 3).

As mentioned earlier in this Review, hypomagnesaemia can lead to PTH resistance. The underlying cause of hypomagnesaemia should be corrected. Based on their clinical expertise, the authors of a 2023 review on hypomagnesaemia disorders determined that patients with severe symptomatic hypomagnesemia require intravenous magnesium replacement[119]. Asymptomatic hypomagnesaemia can be corrected with oral therapy. Sustained release preparations (which are designed to release the drug of interest at a consistent and gradual rate over a long period of time) of oral magnesium are preferred over other preparations as they allow magnesium to be slowly absorbed, preventing abrupt rises in serum levels of magnesium[119]. Magnesium oxide is a non-sustained release preparation that can cause more diarrhoea than its sustained release counterparts. Oral formulations should always be started at the lowest dose and gradually titrated to prevent diarrhoea, which is the major adverse effect of magnesium replacement[119].

Conventional therapy is recommended as first-line therapy for patients with hypoparathyroidism[106]. Patients with persistent symptomatic hypocalcaemia, hyperphosphataemia, hypercalciuria, complications of hypoparathyroidism or poor quality of life as well as those unable to tolerate large doses of calcium and active vitamin D should be considered for PTH replacement therapy as advised by the International Task Force on Hypoparathyroidism in their graded recommendation[106].

PTH replacement

Owing to the challenges associated with conventional therapy of hypoparathyroidism, several studies have now evaluated the use of intact recombinant human PTH (1–84) and PTH (1–34) in patients with hypoparathyroidism. PTH (1–34) refers to the biologically active

peptide fragment (34 amino acids) of PTH. PTH (1–84) refers to the full-length PTH protein molecule (84 amino acids).

PTH (1–34) has been studied extensively with differing modes of administration. In a 2021 study, synthetic human PTH (1–34) could maintain normal serum levels of calcium and was able to decrease urinary calcium excretion while increasing urinary phosphate excretion[120]. Once-daily administration required statistically significantly higher PTH daily doses in comparison to twice-daily injections. The twice-daily injections were more effective in maintaining eucalcaemia over 24-h compared with once-daily injections[10,11].

In the long-term observational study of 14 children with severe hypoparathyroidism secondary to APECED or ADH1, PTH (1–34) was administered twice daily or thrice daily subcutaneously. Study participants were observed to have normal mean height velocity and lumbar spine, whole body, and femoral neck bone accretion velocities, which refers to the rate at which new bone mass is accumulated, during this period[9]. The study participants had decreased urinary calcium excretion compared with their baseline treatment with conventional therapy[9]. Continuous PTH (1–34) delivery through a subcutaneous insulin pump was compared with twice-daily injections in children and young adults with non-surgical hypoparathyroidism. Patients receiving continuous PTH (1–34) therapy experienced decreased fluctuations in serum and urinary levels of calcium compared with those receiving twice-daily injections. Patients receiving PTH (1–34) through an infusion pump required lower doses of PTH (1–34) compared with those receiving subcutaneous injections[8]. Similar results were observed in a study of adult patients with postsurgical hypoparathyroidism who received PTH (1–34) through a continuous pump versus twice-daily injections[12]. PTH (1–34) has a half-life of only 1 h and the greatest benefit of PTH (1–34) was observed with continual infusion or multiple daily doses[3]. PTH (1–34) is approved by the FDA for the treatment of osteoporosis but not for the treatment of hypoparathyroidism[121].

The full-length molecule, PTH (1–84), has a longer half-life than PTH (1–34) of 3 h and has been administered as a once-daily dose[13]. The REPLACE study was a prospective randomized double-blind, placebo-controlled, phase III trial conducted in adults with hypoparathyroidism[13]. Eucalcaemia was achieved as conventional therapy was titrated down, and discontinued if possible, with upward titration of PTH (1–84). Approximately 53% of patients who received PTH (1–84) reached the primary end point of at least a 50% reduction in oral calcium and calcitriol while ensuring eucalcaemia was maintained. An observational study evaluated PTH (1–84) use in a cohort of 24 patients with hypoparathyroidism over a period of 8 years and noted similar reductions in the requirements for oral calcium and active vitamin D analogues[14]. Patients receiving PTH (1–84) had stable renal function and the calcium–phosphate product decreased on therapy. A decrease in urinary calcium was not noted in patients who received PTH (1–84), as compared with conventional therapy. Long-term observational data have demonstrated that the lumbar spine BMD increased in the early years of therapy and then stabilized after 4 years of treatment. Total hip BMD increased after a few years of treatment and femoral neck BMD remained stable while one-third radial BMD declined. These findings were consistent with the effect of PTH administration at trabecular and cortical bone sites[14].

A 2011 randomized, placebo-controlled trial added PTH (1–84) therapy to conventional therapy and significantly decreased the median doses of calcium and active vitamin D supplementation required by the study participants without compromising eucalcaemia. This study did not demonstrate a statistically significant reduction in serum levels of phosphate or urinary calcium excretion[15]. A phase IV open-label trial concluded that prolonged use of PTH (1–84) maintained serum levels of calcium, phosphate, calcium–phosphate product and urinary levels of calcium within the normal reference range[122]. No statistically significant bone loss was noted in the 3-year extension study of the phase III study. Four out of 39 patients had treatment-related adverse events, which included upper limb fracture, hypercalcaemia, renal disorder and ureterolithiasis[122]. PTH (1–84) was approved by the FDA to control hypocalcaemia in patients with hypoparathyroidism but, due to issues regarding rubber particles in the solution, manufacturing has been halted and the drug will be discontinued globally at the end of 2024 (refs. 7,122).

A 2022 meta-analysis compared the safety and efficacy of PTH (1–34) versus PTH (1–84) therapy in patients with chronic hypoparathyroidism[123]. This study reported no statistically significant difference between PTH (1–34) and PTH (1–84) on most outcomes (biochemical parameters, bone turnover markers, BMD, use of conventional therapy and quality of life) except that PTH (1–84) was more effective at reducing total calcium–phosphate product[123]. Treatment-related adverse events were minimal in both groups and these included hypercalcaemia, nausea, constipation, headache, injection site reactions and bone pain.

The PTH (1–84) trials consistently demonstrated its beneficial effect in reducing the dose or in discontinuation of calcium and active vitamin D supplements in patients with hypoparathyroidism while maintaining biochemical homeostasis. There is no randomized controlled trial evidence that documents reductions in levels of urinary calcium with PTH (1–84) in comparison with conventional therapy.

Palopegteriparatide

Palopegteriparatide, also known as TransCon™ PTH, consists of PTH (1–34) linked to a polyethylene glycol moiety[124]. With exposure to physiological temperature and pH, the linker is cleaved; this releases the PTH molecule and the polyethylene glycol moiety is cleared renally[125]. This modification of PTH (1–34) allows it to have a longer half-life of approximately 60 h and provides a sustained release of active PTH[125].

In both phase II and phase III trials, palopegteriparatide resulted in achievement of eucalcaemia: more than 90% of participants were able to achieve independence from conventional therapy and demonstrated reductions in urinary calcium excretion and serum levels of phosphate compared to placebo[3,124,126]. The PaTHway trial was a phase III trial with a 26-week, double-blind placebo-controlled phase in which 84 patients were randomized to receive once-daily palopegteriparatide (18 µg daily) or placebo co-administered with conventional therapy. This was followed by a 182-week open-label extension phase[126]. Doses of palopegteriparatide and conventional therapy were titrated to achieve eucalcaemia and independence from conventional therapy. In this study, at week 26, 79% (48 out of 61 patients) of participants treated with palopegteriparatide versus 5% (1 out of 21 patients) treated with placebo met the composite primary efficacy end point of achieving a normal serum level of calcium adjusted for albumin, independence from conventional therapy and stable study drug dose for at least 4 weeks before week 26. At week 26, 93% (57 out of 61 patients) of patients receiving palopegteriparatide therapy were able to achieve independence from conventional therapy. Patients on palopegteriparatide normalized urinary calcium excretion and had greater reductions in urinary calcium excretion than those on placebo from baseline to week 26. Patients on palopegteriparatide demonstrated significantly improved quality of life, a key secondary end point, as measured by

both the Hypoparathyroidism Patient Experience Scale (HPES) domain scores (all $P < 0.01$) and the 36-Item Short Form Survey Physical Functioning subscale score ($P = 0.0347$) compared with placebo. Overall, palopegteriparatide was well tolerated, although some patients did experience mild or moderate adverse events[126]. Treatment-related adverse events in the palopegteriparatide group included injection site reactions (31.1%), hypercalcaemia (9.8%) and headache (9.8%). No study drug-related withdrawals occurred. The post hoc analysis from the week-104 data from the phase III PaTHway trial demonstrated that treatment with palopegteriparatide was associated with a statistically significant mean increase in eGFR from baseline of 9.3 ml/min/1.73 m^2, suggesting that palopegteriparatide and cessation of conventional therapy (active vitamin D and calcium) improves renal function in patients with chronic hyparathyroidism[127]. The underlying mechanism for the increase in renal function requires further study.

The 3-year results from the phase II PaTH Forward trial were presented at the European Calcified Tissue Society's annual conference in 2024 (ref. 128). This trial was a 4-week randomized, double-blind, placebo-controlled study followed by an ongoing open-label extension period. Results up to week 162 of the open-label extension phase were presented.

The primary end point for the study during the 4-week blinded portion was the proportion of participants who achieved all of the following: normal serum levels of calcium, independence from active vitamin D, requiring less than or equal to 1,000 mg of oral calcium supplementation per day, and normal urinary calcium excretion (or 50% decrease from baseline). At week 162, of the 57 participants, 52 (91%) achieved independence from conventional therapy. Treatment with palopegteriparatide over 162 weeks maintained mean serum levels of calcium within the normal range. The mean 24-h urinary calcium excretion normalized within 26 weeks and was maintained within the normal range through week 162 with palopegteriparatide treatment[128]. Serum levels of bone turnover markers initially increased with palopegteriparatide treatment as remodelling was activated, with peaks at weeks 12 for mean C-terminal telopeptide of type 1 collagen (CTX) and weeks 26 for procollagen type 1 N-terminal propeptide (P1NP), after which point they declined and remained stable at a new steady state above the baseline through week 162 (ref. 128). BMD T-scores remained within the normal range over 162 weeks and stabilized after 26 weeks of treatment. Mean *Z*-scores declined from the high baseline levels characteristic of chronic hypoparathyroidism towards age-matched and sex-matched norms and remained above zero through week 162. Higher baseline BMD T-scores and *Z*-scores were associated with greater declines in BMD over time[128].

The 1-year data from the phase III PaTHway trial discussing skeletal end points was presented at the European Calcified Tissue Society's annual conference in 2024 (ref. 128). Of the participants treated with palopegteriparatide, 81% met the multi-component efficacy end point and 95% achieved independence from conventional therapy. All patients had elevated T-scores and *Z*-scores at baseline, demonstrating high bone density in association with hypoparathyroidism. BMD did decline compared with baseline in the first 26 weeks in patients treated with palopegteriparatide but stabilized between weeks 26 and 52. Increases in bone turnover markers in these patients correlated with these declines in BMD. After week 26, bone turnover markers declined towards the normal reference ranges for sex and menopausal status and corresponded to lower declines in BMD through week 52, similar to the results seen through week 110 in the phase II PaTH Forward trial. These 52-week results reflect temporal changes trending towards a new skeletal steady state closer to age-appropriate norms with continued use of palopegteriparatide in hypoparathyroidism[128].

Palopegteriparatide has been demonstrated to be efficacious and well tolerated, and evaluation of long-term efficacy and safety is ongoing. The recommended starting dose for palopegteriparatide is 18 µg daily and is titrated to achieve eucalcaemia. A systematic review and meta-analysis of the completed randomized controlled trials evaluating PTH therapy (all forms) in comparison to conventional therapy was conducted by the International Task Force on Hypoparathyroidism[83]. Palopegteriparatide has now been approved by the FDA in North America and by the EMA in Europe. Long-term data with palopegteriparatide continue to be evaluated in phase II and III clinical trials.

Emerging therapies for hypoparathyroidism

Eneboparatide

A long-acting PTH–PTH-related peptide (PTHrP) analogue, AZP-3601 (eneboparatide), has demonstrated efficacy in maintaining normal serum levels of calcium while enabling reductions in calcium and active vitamin D therapy. Eneboparatide is a 36-amino acid PTH–PTHrP(1–36) analogue designed to have a strong affinity for the PTH1 receptor. As has been noted in animal studies and in healthy volunteers, eneboparatide has a short pharmacokinetic profile but a long pharmacodynamic profile, which results in a long tissue half life and improved serum levels of calcium compared with PTH (1–34) and PTH (1–84) for 24 h after administration[129,130]. By targeting the R0 conformation of the PTH receptor, eneboparatide remains bound to the PTH receptor following G-protein-mediated signalling and this allows multiple cycles of G-protein-mediated signalling and a sustained pharmacodynamic effect on serum levels of calcium[130,131]. This mechanism contrasts with PTH (1–34), which primarily targets the RG conformation of the PTH 1 receptor[132]. Eneboparatide is administered as a once-daily injection. Data have been presented on a phase I, double-blind, placebo-controlled trial that demonstrate that eneboparatide increased serum levels of calcium compared with placebo and that this calcaemic effect was sustained over a period of 24 h. The effect of the drug on serum levels of calcium was dose dependent[130]. An open-label phase II study of eneboparatide assessed 28 patients who received the drug[17]. After 3 months, 88% of patients were independent from conventional therapy while maintaining serum levels of calcium within the target range. These patients also demonstrated a reduction in the mean 24-h urinary calcium excretion by about 50% during the treatment period and these changes were maintained during the extension phase. A mean increase in eGFR by 6 ml/min/1.73 m^2 from baseline was noted in patients[17]. Bone turnover markers were increased compared with baseline but remained within the age-adjusted and sex-adjusted normal range for healthy individuals, suggesting a resumption of physiological bone turnover. Mean BMD, T-scores, *Z*-scores and trabecular bone scores remained stable up to day 84. No serious adverse effects were reported[17]. Eneboparatide is currently in the phase III clinical trial stage and its optimal dose is being evaluated.

Calcilytics

Calcilytics are molecules that function as negative allosteric modulators of CaSR and decrease the sensitivity of CaSR to extracellular calcium. This decreased sensitivity shifts the calcium–PTH curve to the right and can correct for the underlying activating mutation in CaSR that is present in individuals with ADH1 (ref. 133). Calcilytics restore PTH synthesis and secretion in patients with ADH1 by inhibiting the activity of CaSR and ultimately increasing the calcium concentrations

required to suppress PTH secretion. Shifting the calcium–PTH curve to the right will normalize the synthesis and secretion of PTH, and it will require a higher serum concentration of calcium to decrease PTH synthesis and secretion.

A calcilytic molecule NPSP795 (also known as SHP635) was evaluated in a proof-of-principle study in five patients. NPSP795 treatment resulted in increased levels of PTH and stable ionized calcium levels throughout the time that conventional therapy was titrated off compared with baseline levels pre-treatment with NPS795. In this study, all patients received supplemental calcium at bedtime to avoid symptomatic hypocalcaemia while fasting. The effects of NPSP795 were dose dependent[134].

An open-label phase IIb study conducted in 2023 investigated the effect of encaleret, an orally administered calcilytic, in 13 patients with a known diagnosis of ADH1 (ref. 18). Encaleret, an oral drug, was administered twice daily and the dose was further adjusted to achieve normal values of calcium corrected for albumin. Patients were not on active vitamin D or calcium supplements while on encaleret. Patients were instructed to consume at least 1,000 mg of dietary calcium daily and were provided supplements if they did not meet this requirement. They also received cholecalciferol (vitamin D_3) supplements. Over a 24-week period, patients who received encaleret demonstrated normal calcium levels, reduced hypercalciuria, and increased PTH and 1,25-dihydroxyvitamin D levels while phosphate levels decreased compared with baseline. No adverse effects were noted among participants. The short-term effects of encaleret on bone density were minimal; however, longer studies are required to fully assess the effect of cincalcet on skeletal health. Mean eGFR remained unchanged and within normal range. The prevalence and severity of nephrocalcinosis or nephrolithiasis on ultrasound did not change during the study[18]. Encalcaret is now in phase III clinical trials and is being evaluated as a treatment option for individuals with ADH1.

Other emerging PTH molecules, PTH analogues and PTH1 receptor agonists

A novel oral orthosteric PTH1 receptor agonist small molecule is being developed for the treatment of hypoparathyroidism. This molecule has demonstrated the ability to normalize serum levels of calcium in the rat thyroparathyroidectomy (TPTx) model and is now in a phase I study in healthy human volunteers[20]. Another oral PTH molecule, consisting of PTH (1–34) complexed with the excipients salcaprozate sodium and soybean trypsin, is being evaluated. This biochemical structure prevents PTH (1–34) destruction by the digestive system and increases its absorption through intestinal pathways[21]. An open-label pilot study investigated the effect of oral PTH administered four times daily over a 16-week period. The study enrolled 19 patients and 15 completed the trial. Results showed a 42% reduction across the overall study population in the requirements for supplementary calcium compared with baseline. Serum levels of calcium remained above the lower limit of the normal target (>7.5 mg/dl) for patients with hypoparathyroidism and serum levels of phosphate were within the normal range during the study. Urinary levels of calcium were reduced over the course of the study in participants but this finding was not statistically significant[21]. MBX 2109 is a PTH peptide prodrug with a long half life. The prodrug has fatty acyl groups attached to it at both termini, which extend PTH (1–32) by 2 amino acids at the N terminus and 1 amino acid at the C terminus (which results in a 35-amino-acid molecule). This prodrug with fatty acylation has a half life of 184–213 h, which supports once-weekly administration, and is entering phase II clinical trials[19].

Table 2 | Maternal and fetal adverse outcomes in hypoparathyroidism

Maternal serum levels of calcium	Adverse outcomes	
	Fetus	Mother
High	Hypoparathyroidism Polyhydramnios Neonatal seizures	Hypercalciuria Kidney stones
Low	Hyperparathyroidism Increased bone resorption Intrauterine fragility fractures Subperiosteal bone resorption Osteitis fibrosa cystica Respiratory distress	Miscarriage Preterm labour Seizure Arrhythmia

The data in Table 2 were derived from Ali et al.[137].

Hypoparathyroidism in pregnancy and lactation

Hypoparathyroidism can be challenging to diagnose and manage in pregnant patients due to the physiological changes in calcium and phosphorus homeostasis that accompany pregnancy[135]. These physiological changes can lead to altered requirements for doses of active vitamin D and calcium supplements in pregnancy in individuals with hypoparathyroidism[136]. Pregnancy is associated with intravascular blood volume expansion, which results in reductions in serum albumin concentrations. The decline in serum albumin concentrations is associated with reductions in total serum levels of calcium[135,136]. For this reason, levels of ionized calcium or calcium corrected for albumin need to be evaluated and monitored during pregnancy instead of total serum levels of calcium[106,135–137]. Levels of ionized calcium remain within the normal reference range for the general population during pregnancy[137]. Phosphate and 25-hydroxyvitamin D levels are not altered in pregnancy[106,135,136]. PTHrP levels increase throughout pregnancy, reaching triple the normal prepregnancy level at term[136]. Sources of PTHrP in healthy pregnant individuals include the placenta and breast tissue. These changes in PTHrP levels cause an upregulation in the levels of 1,25-dihydroxyvitamin D[135,136]. Increased oestradiol levels in pregnancy further increase levels of 1,25-dihydroxyvitamin D[136]. Levels of 1,25-dihydroxyvitamin D increase by twofold to threefold as early as the first trimester and these increased levels are maintained until term, enabling increased absorption of calcium and phosphate from the gastrointestinal tract. The increased serum levels of calcium lead to a rise in renal-filtered calcium and urinary calcium excretion. In patients with normal parathyroid function, serum levels of PTH are suppressed during early pregnancy and rise within the mid-to-normal range by term[138–140]. In individuals with hypoparathyroidism, the increased production of endogenous 1,25-vitamin D and PTHrP can result in reductions in the doses of active vitamin D and calcium supplements required during pregnancy. However, as the fetal skeleton is also developing, these changes in calcium homeostasis might not be sufficient to meet the calcium requirements during pregnancy in women with hypoparathyroidism and an increase in the dose of calcium and active vitamin D might be required[3,136,137]. Close monitoring of levels of ionized calcium or serum levels of calcium corrected for albumin is of paramount importance in these patients, as advised by recommendations for management of hypoparathyroidism during pregnancy[37,136]. Serum levels of ionized calcium or calcium corrected for albumin should be assessed every 3–4 weeks[3,136,141]. Adjustments to drug therapy should

be made to target a serum level of ionized calcium or calcium corrected for albumin in the lower limit of the normal reference range[136].

A retrospective study of 17 pregnancies in women with hypoparathyroidism demonstrated that more than half of the pregnancies required a 20% or greater increase or decrease in the dose of active vitamin D in order to maintain normocalcaemia[142]. This finding reaffirms the need for close monitoring of calcium levels in pregnant women with hypoparathyroidism as their requirements for calcium and active vitamin D can change rapidly.

It is essential to maintain eucalcaemia during pregnancy to prevent both maternal and fetal complications (Table 2). Maternal hypocalcaemia can cause fetal hypocalcaemia and the development of secondary hyperparathyroidism in the fetus[74,143–145]. These changes can lead to the demineralization of the fetal skeleton and can be associated with intrauterine rib and limb fractures[136]. Increased risk of intrauterine fetal death and low birth weight are reported in patients with hypocalcaemia in pregnancy. On the other hand, hypercalcaemia in the mother can lead to suppression of the fetal parathyroid glands and the development of hypoparathyroidism in the baby and result in neonatal seizures[146,147].

During lactation in healthy individuals, serum levels of ionized calcium or calcium corrected for albumin remain within normal range or perhaps slightly higher[135,137]. Breast tissue produces PTHrP during lactation, resulting in increased systemic levels of PTHrP (Fig. 4). Levels of 1,25-dihydroxyvitamin D normalize postpartum as a result of a decline in serum oestradiol levels and placental levels of lactogen. Oestradiol and placental lactogen are the main activators of 1α-hydroxylase in pregnancy, which is the cause of elevated 1,25-dihydroxyvitamin D levels throughout pregnancy[135,148].

Postpartum women with hypoparathyroidism should have their levels of ionized calcium or calcium corrected for albumin assessed every 3–4 weeks[3,136]. During lactation serum PTHrP levels are increased and can lower the requirements for calcium and/or active vitamin D. Serum levels of calcium should be maintained in the mid-to-low normal range[3,136]. During the weaning phase, PTHrP levels will decline and might cause hypocalcaemia in patients who choose to wean abruptly rather than gradually[3,136].

The use of PTH replacement therapy in pregnant or lactating patients has not been adequately evaluated and is not recommended at this time[37]. Thiazide diuretics are not recommended for use in pregnant or lactating women[106]. Multidisciplinary care by a team consisting of an endocrinologist, obstetrician and paediatrician is advised for the optimal management in pregnant and lactating women with hypoparathyroidism[3,136].

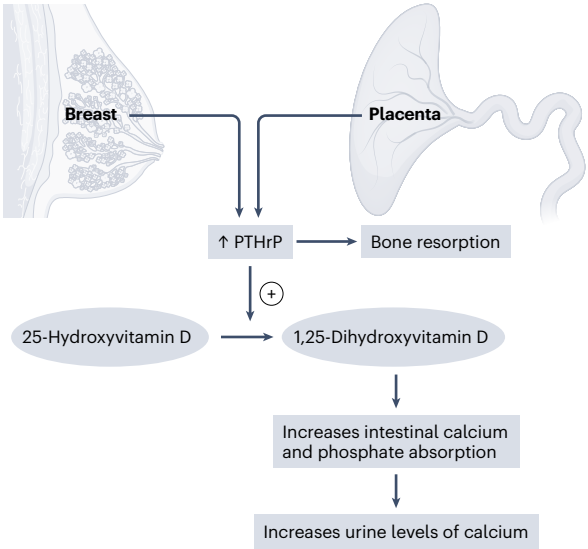

Fig. 4 | The role of PTHrP in pregnancy. Increased levels of parathyroid hormone-related protein (PTHrP) arising from the breast and placenta in pregnancy lead to increased bone resorption and production of 1,25-dihydroxyvitamin D. This increased level of 1,25-dihydroxyvitamin D leads to increased intestinal calcium and phosphate reabsorption, which increases urinary levels of calcium. Reproduced with permission from Khan et al.[136], OUP.

Conclusions

Hypoparathyroidism is a rare condition associated with substantial morbidity, reduced quality of life and a high burden on health-care financial resources. This Review has summarized the latest recommendations regarding the evaluation and management of hypoparathyroidism and has highlighted key recommendations from the international 2022 guidelines from the second international workshop on hypoparathyroidism. Advances in therapy with the availability of long-acting PTH and PTH analogues has been summarized. Novel emerging therapies being developed for hypoparathyroidism have also been presented, including eneboparatide and encaleret, which are showing promising results and are currently in phase III clinical trials.

Further research into understanding the mechanisms that lead to complications associated with hypoparathyroidism, including renal impairment, cardiovascular disease and neuropsychiatric symptoms, are critical in developing strategies that will mitigate these complications. The effect of hypoparathyroidism on the skeleton requires further study, as we currently have limited data regarding fracture risk in patients with hypoparathyroidism. PTH replacement therapy offers a physiological approach to therapy in hypoparathyroidism, as compared with conventional therapy. It also addresses the hypercalciuria and hyperphosphataemia that can result in long-term complications of this condition and are exacerbated by conventional therapy. The lack of PTH on the brain and other organs also undoubtedly results in symptoms and complications, and replacing the missing hormone is now possible with palopegteriparatide. PTH replacement therapy with palopegteriparatide is now available and has been demonstrated to achieve eucalcaemia, reduce the need for conventional therapy as well as reduce serum levels of phosphate and urinary calcium excretion. Improvements in renal function have also been observed. Palopegteriparatide has been shown to improve quality of life and is well tolerated. At present, knowledge regarding the long-term effects of palopegteriparatide on skeletal health is limited and there are no fracture data. Further long-term study will increase our understanding of its effects on bone. Long-term studies of PTH replacement therapies will also further increase our understanding of their safety profile and effect on possibly mitigating other non-skeletal complications of the disease (such as cataracts or neuropsychiatric complications).

The management of hypoparathyroidism in pregnant and nursing patients requires vigilant monitoring of serum levels of calcium and phosphate, and of renal function. The recent 2022 guidelines provided consensus recommendations for the monitoring and management of pregnant and lactating women with hypoparathyroidism. Larger and longer studies that evaluate hypoparathyroidism during pregnancy and lactation will increase our understanding of calcium homeostasis and our ability to improve maternal and fetal outcomes. In addition,

studies are needed to assess the efficacy and safety of PTH replacement therapies in patients who are pregnant and/or lactating. Research in all of these areas will lead to better understanding and management of this rare disease.

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