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Current and Emerging Treatments For the Management of Hypoparathyroidism

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Abstract

Chronic hypoparathyroidism is a rare endocrine disorder marked by parathyroid hormone (PTH) deficiency, leading to hypocalcemia and its associated complications. Conventional therapy with oral calcium and active vitamin D fails to address the hormonal deficit and poses risks such as hypercalciuria and nephrocalcinosis. Recent advances in PTH replacement therapy have shifted the treatment paradigm. Palopegteriparatide, a long-acting prodrug of PTH (1–34), is now U.S. Food and Drug Administration (FDA) and European Medicines Agency (EMA)-approved, demonstrating effective calcium homeostasis, reduced reliance on conventional therapy, and potential renal benefits. Discontinuation of rhPTH (1–84) has accelerated interest in emerging alternatives such as eneboparatide, calcilytics (e.g., encaleret), MBX2109, and oral PTH1 receptor agonists. These novel therapies target PTH signalling through diverse mechanisms—offering injectable and oral options with improved safety, efficacy, and quality-of-life outcomes. This review synthesizes current evidence on approved and investigational treatments, underscoring their mechanisms, clinical impacts, and roles in personalized care for chronic hypoparathyroidism.

Introduction

Hypoparathyroidism is a rare endocrine disorder characterized by insufficient secretion of PTH, leading to hypocalcemia, hyperphosphatemia, and impaired calcium homeostasis. Conventional therapy with oral calcium salts and activated vitamin D does not address the underlying hormonal deficiency and is associated with complications such as hypercalciuria, nephrocalcinosis, and ectopic calcification. Studies have shown that patients receiving PTH replacement therapies, including PTH (1–34) and recombinant human (rh) PTH (1–84) have demonstrated improvements in biochemical control, urinary calcium excretion, bone turnover, and quality-of-life. However, PTH (1–34) is not approved for the indication of treating hypoparathyroidism and the discontinuation of rhPTH (1–84) manufacturing has created an urgent need for alternative PTH replacement therapies. Palopegteriparatide is a once daily PTH injectable that has received FDA and EMA approval for the treatment of hypoparathyroidism. Patients treated with palopegteriparatide have demonstrated eucalcaemia, decreased requirements for conventional therapy, and improvements in renal function. Other emerging therapies for hypoparathyroidism include eneboparatide, MBX 2109, oral PTH1 receptor agonists, and calcilytics. This paper reviews current evidence and evolving therapies for the treatment of chronic hypoparathyroidism, highlighting their mechanisms of action, clinical efficacy, and potential to address unmet therapeutic needs.

Conventional Treatment

Conventional treatment for hypoparathyroidism includes oral calcium salts and activated vitamin D to maintain serum calcium levels at or just below the lower limit of normal in nonpregnant individuals.[1] The aim is to alleviate hypocalcemia symptoms without overtreatment, as excess calcium and activated vitamin D can increase urinary calcium loss and raise phosphate levels, raising the risk of ectopic calcification.[1] Recommended calcium supplements include calcium carbonate (40% elemental calcium), which requires food for absorption, and calcium citrate (21% elemental calcium), which can be taken without meals.[2]

Activated forms of vitamin D, such as calcitriol or alfacalcidol, are used to enhance

calcium and phosphate absorption from the gastrointestinal tract.[1,2] Calcitriol is the more potent of the two, and both require close monitoring. Regular assessments of serum calcium, phosphate, urinary calcium, and 25-hydroxyvitamin D are essential to avoid complications such as hyperphosphatemia or hypercalciuria. The target 25-hydroxyvitamin D level is 75–125 nmol/L, with supplementation using ergocalciferol or cholecalciferol if needed.[1,2]

Magnesium levels should be normalized since hypomagnesemia as well as hypermagnesemia may cause hypoparathyroidism. Thiazide diuretics may reduce urinary calcium in select patient populations, though they should be avoided in those with autosomal dominant hypocalcemia types 1 and 2 (ADH1, ADH2), or adrenal insufficiency.[1,2] Patients initiated on thiazides need to be counselled on their associated increased risk of skin cancer.[1,2]

PTH replacement therapy offers an alternative to conventional therapy–its indications are listed in **Table 1**.

Intolerance to conventional therapy
Malabsorption issues impeding absorption of conventional therapy
Persistent electrolyte disturbances despite conventional therapy
Complications (e.g., nephrocalcinosis, renal impairment) to conventional therapy
Impaired quality-of-life on conventional therapy
Cognitive symptoms related to hypoparathyroidism

Table 1. Indications for Parathyroid Hormone Replacement Therapy in Hypoparathyroidism[2]*; courtesy of Sarah Khan, MD, FRCPC and Aliya Khan, MD, FRCPC, FACP, FACE, FASBMR*

PTH (1–34) and rhPTH(1–84)

PTH replacement was first explored in 1929 and has since evolved into a potential therapy for chronic hypoparathyroidism.[2] PTH (1–34) consists of 34-amino acids and is the biologically active peptide fragment of the full-length PTH (1–84) molecule. Both PTH (1–34) and rhPTH (1–84) have been studied as treatments for hypoparathyroidism.[2] PTH (1–34) normalizes serum calcium, lowers urinary calcium, and enhances phosphate excretion, with administration via infusion pump delivery offering more stable calcium levels and reduced dosing compared to injections. Currently, PTH (1–34) is used off-label and is not approved for the indication of hypoparathyroidism, despite its demonstrated effectiveness. rhPTH (1–84), with a 3-hour half-life, can be administered as a once daily injection.[2] The REPLACE study, a phase 3 trial, randomized patients with chronic hypoparathyroidism to receive rhPTH (1–84) or placebo for 24 weeks. The study showed that patients receiving rhPTH (1–84) exhibited reductions in calcium and calcitriol supplementation, improved serum calcium and phosphate balance, and enhanced quality-of-life.[2] Although the REPLACE study did not demonstrate a significant decline in renal calcium excretion among patients receiving rhPTH (1–84), a subsequent open-label study spanning over 8 years demonstrated reductions in urinary calcium excretion. Long-term studies showed increases in bone mineral density (BMD) at the lumbar spine and hip, with stable values at the femoral neck and decreased values at the one-third radial site, which were consistent with the known PTH effects to increase cortical porosity and endosteal resorption.[2] Despite its FDA approval, rhPTH (1–84) was globally discontinued in 2024 due to manufacturing issues.

Palopegteriparatide (TransCon PTH, Yorvipath)

Palopegteriparatide, also known as TransCon PTH, has received regulatory approval in both North America and Europe for treating chronic hypoparathyroidism.[2] It is a modified version of PTH (1–34) that is bound to a polyethylene glycol (PEG) molecule through a cleavable linker. This structural design prolongs its half-life to approximately 60 hours, allowing sustained PTH activity.[3] Once administered, the linker is cleaved at physiological pH and temperature conditions, releasing active PTH (1–34), while the PEG fragment is eliminated through the kidneys.[3]

Data from phase II and III studies has demonstrated that palopegteriparatide is effective in achieving normal calcium levels and in reducing both urinary calcium excretion and serum phosphate levels compared to placebo.[4-6] The phase III PaTHway trial enrolled 84 participants with chronic hypoparathyroidism who were on stable doses of conventional therapy. At week 26,

93% of individuals receiving palopegteriparatide achieved stable calcium levels without the need for conventional therapy.[6] Patients in the palopegteriparatide group also had significant improvements in quality-of-life as well as normalized urinary calcium.[6] Additionally, a post hoc analysis demonstrated that patients on palopegteriparatide for one year had an estimated glomerular filtration rate (eGFR) improvement of 9.3 mL/min/1.73 m^2.[2,7] While these results suggest the possibility of renal benefits, further studies are needed to confirm these outcomes.[7]

The 3-year results from the phase II PaTH Forward trial were recently published.[8] This trial began with a 4-week randomized double-blind placebo-controlled study followed by an ongoing 210-week open-label extension period.[8] During the initial 4-week double-blind phase, the primary end point was the percentage of participants who met all the following criteria: normal serum calcium levels, achieved independence from active vitamin D supplementation, required less than or equal to 1000 mg of oral calcium per day, and either normal urinary calcium excretion or a 50% decrease from baseline.[8] By week 162 of the trial, 91% of patients on palopegteriparatide achieved the above stated criteria. At week 62, patients on treatment maintained 24-hour urinary calcium excretion within the normal range. Palopegteriparatide treatment was associated with an initial rise in serum levels of bone turnover markers, with serum c-terminal telopeptide of type 1 collagen (CTX) levels peaking at week 12 and P1NP levels peaking at week 26.[8] These markers then declined and stabilized above baseline, establishing a new steady state that persisted through week 162. BMD T-scores remained within normal limits throughout the study period and stabilized after

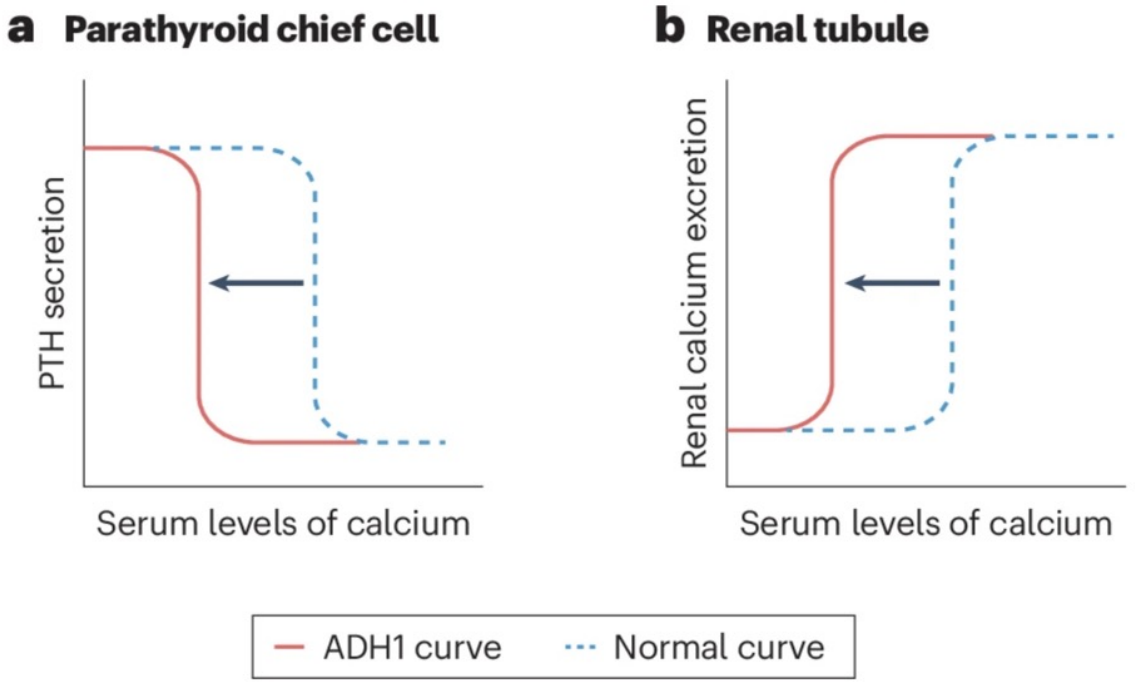

Figure 1. The Effect of ADH1 on PTH Secretion*; reproduced with permission from Khan et al.*[2]

The calcium–parathyroid hormone (PTH) secretion curve shows how PTH secretion changes as calcium levels in the blood vary. Normally, elevated calcium levels activate the calcium-sensing receptor (CaSR), leading to decreases in PTH secretion, and vice versa. In autosomal dominant hypocalcaemia type 1 (ADH1), activating mutations in the CaSR-encoding gene (CASR) leads to increased calcium sensitivity in CaSR. As a result, PTH secretion is suppressed even when calcium levels are within the normal range. This leads to a leftward shift in the serum calcium–PTH secretion curve. This means that lower concentrations of calcium are 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. Calcilytic agents work by normalizing CaSR sensitivity to calcium, leading to a shift of the curve toward normal. Through this mechanism, calcilytics increase serum PTH levels and decrease urinary calcium losses in patients with ADH1.

the initial 26 weeks of treatment. Z-scores, which were elevated at baseline due to chronic hypoparathyroidism, gradually trended toward values consistent with age- and sex-matched norms and remained above zero at week 162.[8]

Results from the phase 3 PaTHway trial up to week 52 have now been published.[9] The study assessed a multi-component efficacy endpoint, which measured the proportion of participants who maintained eucalcaemia while simultaneously achieving independence from calcium and active vitamin D supplementation. Among those receiving TransCon PTH, 81% met this composite endpoint, with 95% attaining independence from standard therapy.[9] At baseline, all participants exhibited elevated T-scores and Z-scores, indicating increased bone density secondary to hypoparathyroidism. In the palopegteriparatide group, BMD decreased relative to baseline over the initial 26 weeks but subsequently stabilized between weeks 26 and 52.[9] This early BMD decline paralleled increases in bone turnover markers. After 26 weeks, these markers gradually decreased toward normal reference values for sex and menopausal status, aligning with attenuated BMD losses through week 52.[9] These findings are consistent with observations reported at week 110 in the phase II PaTH Forward trial. Collectively, the 52-week data suggest a temporal progression toward a new skeletal equilibrium that more closely resembles age-appropriate bone turnover with ongoing palopegteriparatide therapy in patients with hypoparathyroidism.

Ongoing studies are evaluating the long-term efficacy and skeletal effects of palopegteriparatide. The recommended initial dose of palopegteriparatide is 18 mcg once daily, with subsequent uptitration to achieve eucalcaemia, accompanied by a gradual reduction in conventional therapy. Phase III clinical trials investigating the long-term impact of palopegteriparatide are ongoing.

Emerging Therapies

i) Long-acting PTH/ PTHrP (1–36) Analogue (Eneboparatide, AZP-3601)

Eneboparatide is a synthetic novel 36-amino acid analogue of PTH/PTHrP, designed to bind with a strong affinity to the PTH1 receptor in its R0 conformation. This receptor interaction enables multiple cycles of G-protein mediated signalling and a sustained pharmacodynamic profile despite a short pharmacokinetic profile.[2] Administered as a once-daily injection, eneboparatide has demonstrated in animal studies the ability to maintain prolonged G-protein mediated signalling and improved serum calcium levels over a 24 hour period despite its short half-life of less than 1 hour.[10,11] The phase II open-label study of eneboparatide enrolled 28 patients who were divided into two cohorts: Cohort 1 (n=12) received a starting dose of 20 µg/day, titrated up to 60 µg/day and Cohort 2 (n=16) received a starting dose of 10 µg/day, titrated up to 80 µg/day.[12] Both cohorts received eneboparatide for 3 months, during which conventional therapy was gradually reduced as eneboparatide doses were increased. After 3 months of treatment, 88% of patients achieved independence from conventional therapy while maintaining albumin-adjusted serum calcium within the target range. Patients on treatment experienced a significant reduction in urinary calcium, a benefit that was maintained during the extension phase. Additionally, a mean increase in eGFR of 6 mL/min/1.73 m^2 from baseline was noted.[12] Bone health indicators, including mean BMD, T-scores, Z-scores, and trabecular bone scores remained stable during the treatment period. No serious adverse effects were reported.[12] Eneboparatide is currently in the phase III clinical trial stage, with its optimal dose yet to be determined.

ii) Calcilytics

Individuals with autosomal hypocalcemia type 1 have a gain of function mutation in the calcium-sensing receptor gene (CaSR) which leads to an increase in the sensitivity of CaSR to serum calcium in both the parathyroid gland and kidneys.[2] The increased sensitivity in the parathyroid gland leads to decreased PTH secretion at low-normal serum calcium concentrations leading to hypocalcemia. At the renal level, increased sensitivity of the CaSR leads to increased renal calcium excretion.[2] Calcilytics, which are CaSR antagonists, work by decreasing the receptor's sensitivity to serum calcium. They restore the CaSR's sensitivity to calcium, thereby helping to normalize PTH synthesis and secretion, as well as urine calcium excretion in ADH.[2] **See Figure 1 for further details on the effect of ADH1 on PTH secretion.**

A phase IIb open-label trial evaluated the efficacy of encaleret, an oral calcilytic agent, in 13 individuals diagnosed with ADH1.[13] Encaleret was administered twice daily, with the dosage

adjusted to maintain albumin-corrected serum calcium within the normal range.[13] Over the 24-week treatment period, participants achieved normalized serum calcium levels, reduced 24-hour urinary calcium excretion, and exhibited increases in circulating PTH and 1,25-dihydroxyvitamin D levels[13]. Concurrently, serum phosphate levels declined relative to baseline.[13] As expected with elevated PTH, bone turnover markers showed an upward trend. While changes in BMD over this short duration were minimal, extended follow-up is necessary to determine encaleret's long-term skeletal impact. The eGFR remained stable and within normal limits, and there were no observed changes in the frequency or severity of nephrocalcinosis or nephrolithiasis on renal ultrasound.[13] Importantly, no serious adverse events were reported.[13] Encaleret is currently undergoing evaluation in a phase III clinical trial for the treatment of ADH1.

NPSP795, also referred to as SHP635, is a calcilytic compound assessed in a small proof-of-concept study involving five participants. Treatment with NPSP795 led to elevated PTH levels while maintaining stable ionized calcium concentrations, even as conventional therapy was gradually withdrawn, relative to baseline measurements prior to initiation. To mitigate the risk of fasting-related hypocalcemia, all participants received bedtime calcium supplementation throughout the study. The physiological response to NPSP795 was found to be dose-dependent.[14]

Quinazolinone-based calcilytics (ATF936 and AXT914) have been investigated in animal studies for the treatment of ADH1.[15] They offer an alternative to amino alcohol based calcilytics (i.e., encaleret, NPSP795) which are not effective for all ADH-1 causing mutations. In vitro and in vivo experiments using murine models demonstrated that ATF936 and AXT914 bind to the CaSR transmembrane domain, overlapping with the binding site used by amino alcohol calcilytics. In vivo, AXT914 significantly increased plasma PTH and albumin-adjusted calcium levels. No adverse effects or changes in phosphate, magnesium, or renal function were observed.[15] These findings support AXT914 as a promising targeted therapy for ADH1.

iii) MBX 2109: PTH Peptide Prodrug

MBX 2109 is a novel PTH peptide long-acting prodrug designed for once-weekly dosing due to its extended half-life of 184–213 hours.[16] Structurally, it is a 35-amino acid peptide incorporating the first 32 amino acids of human PTH with three modifications: two amino acids (Sar0, D-Lys–1) at the N-terminus and one (Lys33) at the C-terminus.[16] Both termini are bound to fatty acids that inactivate the molecule and promote albumin binding. Under physiological conditions, the fatty acid–linked N-terminal dipeptide is gradually cleaved, converting the prodrug into active PTH (1–32).[16]

A phase 1 randomized, double-blind, placebo-controlled study assessed the safety and tolerability of MBX 2109 in 40 healthy adults aged 21–60.[16] Participants discontinued calcium and vitamin D supplementation and received either MBX 2109 or placebo once weekly for 4 weeks. Treatment-emergent adverse events (TEAEs) were reported in 50–88% of MBX 2109 recipients versus 25% in the placebo group, with injection site reactions being the most common. No serious TEAEs occurred.[16] MBX 2109 produced dose-dependent increases in serum calcium and CTx levels, while reducing endogenous PTH. P1NP and bone-specific alkaline phosphatase (BSAP) initially declined but returned to baseline by week 4.[16] However, the study's limitations include a small sample size of healthy participants, necessitating further trials in hypoparathyroid populations.[16]

iv) Oral PTH-1 Receptor Agonist

Oral small molecule therapies may offer an alternative to both conventional treatments and injectable PTH replacement.[17] Activation of the PTH1 receptor (PTH1R) promotes calcium reabsorption and phosphate excretion from the kidneys and stimulates bone turnover by mobilizing calcium from the skeleton. SP-1462 is a selective oral PTH1R agonist that activates these pathways.[17] In vitro studies using human renal proximal epithelial cells and osteoblast-like cells (Saos-2) showed that SP-1462, similar to PTH, modulates gene expression related to transport, immunity, matrix remodelling, Wnt signalling, and bone metabolism.[17] In a rat model of surgical thyroparathyroidectomy, a single dose of SP-1805 (a related compound) increased serum calcium in a dose-dependent manner, with effects comparable to injectable PTH.[17] These findings suggest that oral PTH1R agonists can mimic the biological actions of PTH and may serve as a non-injectable option for hypoparathyroidism.[17] SP-1462 has now progressed to phase 1 clinical trials in healthy volunteers in Australia.

Conclusion

Management of chronic hypoparathyroidism is advancing beyond conventional therapies due to their inability to correct the underlying PTH deficiency and their association with long-term complications such as hypercalciuria and nephrocalcinosis. Palopegteriparatide, now approved by both the FDA and EMA for the indication of treating hypoparathyroidism, offers a long-acting, physiologic PTH replacement. It has demonstrated efficacy in normalizing calcium levels, improving renal outcomes, and reducing treatment burden. Eneboparatide is showing promising results as an emerging treatment for hypoparathyroidism and is currently in phase 3 clinical trials. Calcilytics, particularly encaleret, are being actively investigated as treatment options for ADH1, with encaleret having advanced to the phase 3 clinical trial stage. MBX2109 provides a once-weekly alternative for PTH replacement injectables, while oral PTH receptor agonists support the development of oral replacement strategies. As long-term data mature, these therapies may support more personalized, effective, and safer management strategies, ultimately improving outcomes and quality-of-life for individuals living with hypoparathyroidism.

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