



Unveiling the complexities of hypoparathyroidism: a comprehensive review of clinical manifestations, diagnosis, and novel therapies

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Abstract

Background Hypoparathyroidism (HypoPT) is a rare endocrine disorder characterized by insufficient or absent secretion of parathyroid hormone (PTH), which results in hypocalcemia, hyperphosphatemia, and disruption of calcium phosphate homeostasis. Despite advances in understanding its pathophysiology and management, HypoPT remains a complex and impactful condition associated with significant morbidity, impaired quality of life, and long-term complications affecting the skeletal, renal, and neurological systems.

Methods A literature search was performed on PubMed. Articles were selected based on their relevance to the main topic of the review, with particular attention to recent studies.

Results This review provides a comprehensive synthesis of the current knowledge on HypoPT, addressing its epidemiology, underlying pathophysiological mechanisms, genetic and acquired etiologies, clinical manifestations, diagnostic strategies, and chronic disease-related complications. Emphasis is placed on the genetic spectrum of the disease, challenges of postsurgical management, and burden of conventional therapy, which often fails to fully restore mineral homeostasis and patient well-being. The evolving therapeutic landscape is detailed, highlighting advances from traditional calcium and active vitamin D supplementation to innovative PTH replacement strategies. Among these, palopegteriparatide and eneboparatide (phase 3 clinical trial ongoing) are reshaping treatment paradigms by enabling more physiological restoration of calcium-phosphate balance, reducing complications, and improving patient-centered outcomes, including renal function and quality of life.

Conclusions By integrating clinical expertise with the latest research developments, this review offers an updated and holistic perspective on HypoPT management, aiming to support clinicians in delivering effective and individualized care to patients across the spectrum of disease severity.

Keywords Hypoparathyroidism · Postsurgical HypoPT · Nonsurgical HypoPT · HypoPT diagnosis · PTH replacement therapy · PTH analogues

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Introduction

Hypoparathyroidism (HypoPT) is a rare endocrine disorder defined by the absence or inappropriately low concentration of parathyroid hormone (PTH), resulting in hypocalcemia and hyperphosphatemia due to disrupted calcium-phosphate homeostasis. Clinically, it may manifest as neuromuscular irritability, paresthesia, tetany, and, in severe cases, seizures or cardiac arrhythmias. Chronic hypocalcemia, particularly when inadequately managed, is associated with a significant disease burden, including basal ganglia calcification, nephrolithiasis, nephrocalcinosis, and neurocognitive disturbances [1, 2].

HypoPT significantly affects patients' health-related quality of life (HRQoL). Patients with HypoPT often face chronic fatigue, cognitive dysfunction (often called "brain fog"), anxiety, depression, and reduced physical functioning, even when biochemical levels are normal [2–4]. These issues create considerable emotional, social, and occupational challenges, emphasizing the importance of management strategies that focus on both biochemical control and patient-centered outcomes.

The most frequent cause is postsurgical HypoPT, typically after anterior neck surgery like thyroidectomy or parathyroidectomy [2]. Less common causes include autoimmune polyglandular syndrome (APS) type 1 (APS-1), also known as autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy (APECED); infiltrative disorders; hereditary syndromes, such as autosomal dominant hypocalcemia (ADH) type 1 (ADH1) from activating mutations in the calcium sensing receptor (*CASR*) gene; and isolated or syndromic parathyroid agenesis, including DiGeorge syndrome [5, 6]. Although rare, these genetic forms have critical implications for diagnosis and management, especially in the pediatric population.

Over the past decade, growing interest has focused not only on acute management but also on the long-term sequelae of chronic HypoPT. Despite conventional therapy, many patients remain symptomatic or develop complications due to poor biochemical control or overtreatment [5, 7]. The advent of PTH replacement therapy has introduced new paradigms in disease management, which now require long-term and real-world evidence [5, 7].

To date, comprehensive reviews have mainly focused on the biochemical and clinical aspects of the disease. However, integrative reviews that cover the genetic spectrum of HypoPT, postsurgical management challenges, and treatment strategies are lacking. This review seeks to fill this gap by offering a structured overview of HypoPT, emphasizing its pathophysiology, classification, and clinical management, while also highlighting new insights into genetic

causes and the evolving role of replacement therapy in the management of chronic disease.

Epidemiology

The prevalence of chronic HypoPT has been estimated to range between 6.4 and 37 per 100,000 individuals worldwide [8, 9]. Data were gleaned from national and, in some cases, regional databases of in- and/or outpatients and collectively registered different prevalence according to countries and cause of HypoPT (surgical vs. nonsurgical) [8, 9]. In the United States, health plan claims databases reported 65,000 and 43,000 cases in 2007–2008 and 2014–2019, respectively [10, 11]. Extrapolation from the 2007 to 2008 health insurance database suggested a national prevalence of 77,000 cases (25 per 100,000 inhabitants), with 90% classified as chronic HypoPT [10]. A 2010 online survey conducted as part of this study further indicated that 73% of these cases were postsurgical [10]. The Rochester Epidemiology Project, analyzing data from Olmsted County, Minnesota, reported a prevalence of 37 per 100,000 individuals [12].

In South Korea, an analysis of the national health insurance database (2007–2016) identified 19,063 cases of postsurgical HypoPT, with a prevalence ranging from 2.6 to 7.3 per 100,000, while the prevalence of nonsurgical HypoPT was 0.2 and 1.1 per 100,000 in 2005 and 2015 [13]. In Taiwan, the National Health Insurance database (1998–2011) documented 314 postsurgical HypoPT cases among 9,316 patients who underwent thyroid surgery [14]. In Japan, a study using a large employee health insurance database (2015–2018) reported an overall prevalence of 38.3 per 100,000, with 37 per 100,000 postsurgical cases and 1.2 per 100,000 nonsurgical cases [15]. These data align with a report by Takatani et al., who performed a nationwide survey in the major hospitals in Japan in 2017 and illustrated a 1.8/100,000 inpatient prevalence of nonsurgical hypoparathyroidism [16]. In India, a retrospective study (1990–2015) of military healthcare personnel (>50,000 individuals) identified 16 cases of sporadic and idiopathic HypoPT, yielding an incidence of 2.6 per 100,000 person-years [17].

European studies have reported considerable variations in the prevalence of HypoPT, largely influenced by healthcare system coverage and population demographics. In Denmark, national health data from 1988 to 2011 identified 1,568 HypoPT patients, with an estimated prevalence of 22 per 100,000 [17]. The annual incidence of postsurgical HypoPT was 0.8 per 100,000, whereas nonsurgical cases were reported in 2.3 per 100,000 (180 patients) [17]. In Norway, a nationwide study (2010–2013) covering 80% of the population reported 511 cases (321 postsurgical and 148

nonsurgical HypoPT) with a prevalence of 10.2 per 100,000 [4]. A study conducted in Scotland (1988–2015) using the Tayside Health Informatics Centre database identified 280 HypoPT patients, corresponding to a prevalence of 40 per 100,000 [18]. Among these, 41% were postsurgical, 38% were idiopathic, and 21% were hypomagnesemia-related [18]. In Spain, a 2022–2023 retrospective study across 16 hospitals identified 337 patients with postsurgical HypoPT attending follow-up visits ≥ 3 years post-thyroidectomy [19].

Italian inpatient data from 2006 to 2013 identified 27,692 patients with HypoPT, with a mean hospitalization rate of

5.3 per 100,000 inhabitants per year [20]. Of these cases, 23% were postsurgical, corresponding to an annual incidence of 1.3 per 100,000, while autoimmune and genetic forms of HypoPT had a similar incidence of 1.3 per 100,000 [20]. Data from the Tuscany Region’s electronic health records (EHRs), including inpatient and outpatient cases, estimated a prevalence of 27 per 100,000 individuals during the same period [21].

In terms of demographics, HypoPT is more frequent in young women than in men [9]; female sex and age < 40 years were also listed among factors predisposing to postsurgical HypoPT, together with the extent of neck dissection and eventual lymph node dissection, type of surgery, and the presence of thyroid malignancy [9, 22].

The evaluation of mortality rates associated with various forms of HypoPT was performed in several epidemiological studies that showed inconsistent results, as increased, equal, and decreased mortality risks have been reported [8, 17, 18, 23, 24]. The lack of homogeneity between studies in terms of population studied, the exclusive inclusion of inpatients, outpatients, or both, and the different data sources may be considered when analyzing these results.

Box 1 - Key takeaways - Epidemiology

National administrative databases may underestimate nonsurgical HypoPT, which remains under-recognized in both epidemiologic and clinical settings.
Younger age and female sex are consistent risk factors for postsurgical HypoPT, particularly after extensive thyroid surgery or malignancy.
Mortality data in HypoPT are heterogeneous; conflicting outcomes likely reflect differences in study design and population characteristics.

Table 1 Evaluation of hypoparathyroidism

Family history	• Parathyroid disorders • Endocrine diseases • Autoimmune disease • Consanguinity
Personal history	• Prior anterior neck surgery • Other endocrine diseases (Addison’s disease, gonadal failure, thyroid disease, diabetes mellitus, hypercalciuria) • Non-endocrine or metabolic abnormalities: congenital abnormalities (cleft palate, heart disease, deafness, immunodeficiency, stroke, urogenital dysplasia, lactic acidosis, etc.) • Kidney stones, nephrocalcinosis, or fractures • Seizures • Arrhythmias • Dietary and supplemental intake of calcium, phosphate, and vitamin D
Physical examination	• Neck: scars of previous surgery • Eyes: cataracts • Skin: mucocutaneous candidiasis, other fungal infection, vitiligo • Chvostek or Trousseau sign to evoke hypocalcemic signs • EKG: prolonged QTc • Joints: arthritis
Laboratory	• PTH • Total calcium • Albumin • Creatinine • Magnesium • Ionized calcium • Serum phosphate • Estimated glomerular filtration rate (eGFR) • 24-hour urine for creatinine, calcium, and biochemical stone risk profile
Screening for end-organ damage	• Abdomen: ultrasound or computed tomography • Bone density test by DXA and VFA, at least in patients with high risk of fragility fractures • Skull (optional): MR or CT for basal ganglia calcification screening • ECG for QT prolongation or other arrhythmias
Genetic evaluation	Dependent on family or personal history

PTH, parathyroid hormone; QTc, corrected QT interval; ECG, electrocardiogram; eGFR, estimated glomerular filtration rate; DXA, dual-energy X-ray absorptiometry; VFA, vertebral fracture assessment; MR, magnetic resonance; CT, computed tomography

Etiology

The etiology of HypoPT can be categorized as nonsurgical or postsurgical [6].

Nonsurgical HypoPT

It accounts for only 25% of all cases and includes genetic, autoimmune, infiltrative, and metabolic disorders [6, 25, 26]. Suspicion of nonsurgical HypoPT is usually based on a positive family history, coexisting syndromic features, on lack of history of neck surgery, or onset in patients younger than 40 years, prompting consideration of genetic testing (Table 1) [6, 25, 26]. Additionally, *AIRE* gene variants should be investigated in patients with clinical features of autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy syndrome (APECED). The term ‘autoimmune’ HypoPT is discouraged in patients, mostly adults, without

any clear etiology, because of the lack of definitive diagnostic tests. Rare etiologies include deposition of iron (e.g., in patients with thalassaemia major, primary iron overload in hemochromatosis, and inherited disorders marked by abnormal hemoglobin production), copper (in Wilson disease), or aluminum in parathyroid cells [27, 28]. The proposed mechanisms involve suppression of parathyroid cell function. Other causes include infiltration of parathyroid tissue by invasive neoplastic cells, amyloid protein, or inflammatory cells. Severe and prolonged hypomagnesemia can lead to functional HypoPT [29]. Parathyroid tissue shows a high resistance to radiation. Although, there have been reports of radiation-induced HypoPT, this cause is exceedingly rare [2]. Immune checkpoint inhibitors have been associated with HypoPT owing to the activation of autoantibodies that stimulate the *CASR* gene [30, 31].

Genetic etiologies represent a significant subset of HypoPT and are more commonly observed in children. However, subtle manifestations of HypoPT may remain undetected until adulthood, particularly in cases of mild or intermittent hypocalcemia [32, 33].

Table 2 summarizes the primary genetic causes of HypoPT, which can arise from mutations in several key genes that are essential for parathyroid development and function [34–43].

DiGeorge syndrome, also known as 22q11.2 deletion syndrome, velocardiofacial syndrome, and conotruncal anomaly face syndrome, is the most common genetic cause of HypoPT in pediatric populations, accounting for approximately 60% of cases. Microdeletion leads to loss of the *TBX1* gene, which encodes a critical transcription factor for the development of thymic and parathyroid glands [34].

APS-1 is a rare autosomal recessive disorder characterized by autoimmune destruction of various endocrine glands, including the parathyroid glands. Loss of AIRE function results in the autoimmune-mediated destruction of endocrine glands. In patients with HypoPT, APS-1 typically co-presents with additional endocrinopathies such as adrenal insufficiency and hypothyroidism and commonly features chronic mucocutaneous candidiasis [35].

HypoPT-deafness-renal (HDR) syndrome, also known as Barakat syndrome, is a rare, autosomal dominant disorder. The clinical presentation of HDR syndrome is notably heterogeneous, with some individuals presenting with all three cardinal features, whereas others may exhibit only one or two. The age of onset and symptom severity were also highly variable among the affected individuals [36].

Familial Isolated Hypoparathyroidism (FIH) is a rare genetic form of HypoPT occurring without other associated clinical manifestations. It is characterized by hypocalcemia and low or undetectable levels of PTH. Subtle manifestations of FIH may go undetected until adulthood, especially

in cases of mild or intermittent hypocalcemia. This condition exhibits diverse inheritance patterns, including autosomal dominant, autosomal recessive, and X-linked recessive forms. Several genes have been implicated, notably *GCM2*, which encodes a transcription factor that is essential for parathyroid gland development. Mutations in both copies of the *GCM2* gene (homozygous) lead to an autosomal recessive form of FIH by disrupting the *GCM2* transcription factor's ability to enter the nucleus, bind DNA, or activate transcription. In contrast, mutations in a single copy of *GCM2* (heterozygous) result in an autosomal dominant form of FIH, as they interfere with *GCM2*'s transcription activity through a dominant-negative effect [38]. Germline mutations in the *PTH* gene are a rare cause of autosomal dominant and recessive forms of FIH. These defects primarily occur in exon 2, which encodes the signal peptide region of the pre-proPTH (1–115) peptide [26]. These genetic variants cause congenital HypoPT through impaired hormone synthesis, endoplasmic reticulum stress leading to apoptosis of parathyroid cells, or secretion of inactive hormones. Specific *PTH* mutations can mimic pseudohypoparathyroidism clinically, complicating the diagnosis due to elevated but biologically ineffective PTH levels [44].

Mutations in the *CASR* gene, which encodes the calcium-sensing receptor, a G protein-coupled receptor central to calcium homeostasis, can cause ADH1 [45]. ADH1 is clinically characterized by hypocalcemia, PTH levels ranging from undetectable to normal, and elevated excretion of calcium which leads to marked hypercalciuria even in the setting of low serum calcium concentrations [38]. Around 35% of individuals with ADH1 develop ectopic calcifications in the kidney or basal ganglia [45]. Some individuals with ADH1 caused by severe gain-of-function mutations in *CASR* may also present with Bartter-like syndrome (Bartter syndrome type 5) [46]. The *GNAT1* gene encodes the alpha subunit of the G11 protein, which is involved in intracellular calcium signaling. Mutations in the *GNAT1* gene are associated with ADH type 2 (ADH2), similarly presenting with hypocalcemia and inadequately low or normal PTH levels [39]. Individuals with ADH2 usually have a milder renal phenotype and show less urinary calcium excretion. In addition, some patients present with short stature due to postnatal growth failure [47].

Beyond the primary genetic causes, HypoPT can also be a feature of broader genetic conditions, emphasizing the complexity and heterogeneity underlying its genetic etiology. For example, mutations in *SOX3*, a transcription factor involved in developing multiple tissues, including the parathyroid glands, have been implicated in X-linked recessive HypoPT, which is often accompanied by hypopituitarism [48]. Additionally, rare genetic syndromes and mitochondrial disorders, such as MELAS syndrome [43], may include

Table 2 Primary genetic causes of hypoparathyroidism

Syndrome/Condition	Genetic abnormality	Inheritance	Clinical manifestations	Source
DiGeorge Syndrome (22q11.2 deletion syndrome)	Microdeletion on chromosome 22q11.2 and loss of <i>TBX1</i> gene	Autosomal dominant	HypoPT; Congenital heart defects; Characteristic facial features: small jaw, low-set ears, and a wide nose	Funato N. et al. [31]
Autoimmune Poly-endocrine Syndrome Type 1 (APS-1)	Loss of <i>AIRE</i> function and deregulation of immune self-tolerance	Autosomal recessive	HypoPT; Adrenal insufficiency (Addison's disease); Chronic mucocutaneous candidiasis	Cranston T et al. [32]
HypoPT -Deafness-Renal Syndrome (HDR) or Barakat syndrome	Loss-of-function in the <i>GATA3</i> , a transcription factor crucial for the development of the parathyroid glands, inner ear, and kidneys	Autosomal dominant	HypoPT; Sensorineural deafness; Renal dysplasia. Possible additional features related to developmental abnormalities of the face, urinary tract, and genitals	Gaynor KU et al. [33]
Familial Isolated Hypoparathyroidism (FIH)	Loss-of-function in the <i>GCM2</i> , a transcription factor essential for parathyroid gland development	Autosomal dominant/autosomal recessive/ X-linked recessive	Isolated HypoPT, without other associated features	Cinque L et al. [34]
Autosomal Dominant Hypocalcaemia type 1 (ADH1)	Gain-of-function of <i>CASR</i> , encoding the calcium-sensing receptor, which regulates PTH secretion and renal calcium handling	Autosomal dominant	Hypocalcemia with inappropriately low or normal PTH levels and hypercalciuria; Renal complications, such as nephrocalcinosis and nephrolithiasis	Roszkowski KL et al. [35]
Autosomal Dominant Hypocalcaemia type 2 (ADH2)	Gain-of-function in the <i>GNA11</i> encoding a protein involved in CaSR signaling	Autosomal dominant	Hypocalcemia with low or inappropriately normal PTH levels; Similar to ADH1 but with less prominent renal complications	Howles SA et al. [36]
Kenny-Caffey Syndrome (KCS)	Putative loss-of-function in the <i>FAM111A</i> gene, the function of which is not fully understood	Autosomal recessive	HypoPT; Skeletal dysplasia; Dwarfism; Dysmorphism	Eren E et al. [37]
			Kenny-Caffey Syndrome Type 2 (KCS2) à HypoPT; Short stature; Skeletal abnormalities (e.g., thickening of the long bones); Eye abnormalities (e.g., microphthalmia)	Chen X et al. [38]
Mitochondrial disorders	Group of genetic mutations (loss-of-function) on <i>HADHB</i> , encoding the beta-subunit of mitochondrial trifunctional protein	Mitochondrial	HypoPT as part of a multisystem disorder; Muscle weakness; Neurological problems; Developmental delays	Romo L. et al. [39] Gordon RJ et al. [40]

HypoPT, hypoparathyroidism; PTH, parathyroid hormone; CASR, calcium-sensing receptor; GATA3, GATA binding protein 3; GCM2, glial cells missing homolog 2; GNA11, guanine nucleotide-binding protein subunit alpha-11; AIRE, autoimmune regulator; FAM111A, family with sequence similarity 111 member A; HADHB, hydroxyacyl-CoA dehydrogenase trifunctional multienzyme complex subunit beta.

HypoPT as part of their clinical spectrum, underscoring the complexity of its genetic etiology and the need for comprehensive genetic evaluation in affected individuals.

Postsurgical HypoPT

It is the most common etiology, accounting for approximately 75% of cases [6, 49, 50]. Postsurgical HypoPT is

a common complication following neck surgery, particularly total thyroidectomy or reoperations (Table 1) [49, 50]. The risk of developing chronic HypoPT after neck surgery was calculated at 1.5% [21]. It is considered permanent if it persists for 12 months after surgery rather than 6 months previously [50]. Postsurgical HypoPT can be caused by several factors, mainly related to surgical technique and to the localization of the parathyroid glands during the procedure.

Direct physical damage to the parathyroid glands during surgery is a common cause, including (i) the accidental removal of one or more glands, which may be unintentionally excised along with the thyroid, particularly if they are not clearly visible or are in an atypical position, and (ii) the interruption of their blood supply, since the parathyroid glands have a terminal type of vascularization and damage to their blood vessels can lead to functional failure [51].

For patients who are likely to recover parathyroid function after neck surgery involving inadvertent damage to the parathyroid glands, the II International Workshop provides strong supporting evidence [50]. PTH should be measured on the first post-operative day (ideally within 12–24 h), as a PTH level above 10 pg/mL makes permanent HypoPT unlikely, suggesting that prolonged calcium and active vitamin D supplementation may not be necessary. In other words, this cut-off likely excludes chronic HypoPT. Nevertheless, many patients with PTH levels < 10 pg/mL may recover from transient HypoPT [50]. Caution is still advised even when PTH is above 10 pg/mL, since a single measurement does not provide absolute certainty that the patient will not develop hypocalcemia in the following days or weeks. PTH levels are influenced by several biochemical factors—including magnesium status, pre-surgical PTH levels, and renal insufficiency—which should all be considered when evaluating the 10 pg/mL PTH cut-off [6, 52].

Moreover, recent evidence suggests that preoperative chronic hypovitaminosis D may also represent a potential risk factor for the development of postoperative HypoPT, although this association remains debated [53].

A recent meta-analysis evaluated the risk factors for post-thyroidectomy HypoPT, including those for permanent HypoPT, as:

- type of surgery (total thyroidectomy *versus* lobectomy or subtotal thyroidectomy);
- accidental parathyroidectomy (finding parathyroid tissue in the histological specimen);
- malignant pathology;
- presence of lymph node metastases;
- extent of lymph node dissection (central/lateral cervical).
- preoperative hyperthyroidism [49].

To reduce the incidence of post-operative HypoPT, it is crucial to minimize accidental parathyroidectomy during surgery. Parathyroid auto-transplantation is associated with a higher rate of HypoPT, although it is likely a temporary condition, and patients are less likely to develop permanent HypoPT [54]. However, it does not always restore

PTH to adequate or preoperative levels, and the functional recovery of transplanted glands may take a long time [55, 56]. Therefore, this practice should only be performed in cases of accidental gland removal [49, 57]. The prevention of postsurgical HypoPT begins with proper preoperative planning and meticulous surgical techniques. To reduce the risk of developing this complication, the primary goal is to identify and preserve the parathyroid gland during surgery. It is crucial for the surgeon to clearly identify the parathyroid glands and carefully dissect them from the thyroid with minimal manipulation of the glands to reduce the incidence of intracapsular hemorrhages, which should be treated by releasing the capsule. Additionally, devascularization must be avoided and gland ischemia should be assessed. In recent years, intraoperative parathyroid visual identification has been enhanced using innovative tools. Using these intraoperative strategies to aid parathyroid identification and preservation is particularly advantageous, especially for less experienced surgeons [58]. However, these procedures are reserved for highly experienced surgeons and performed at specialized centers. A recent meta-analysis revealed that indocyanine green fluorescence, autofluorescence, and carbon nanoparticles are more effective in identifying parathyroid glands than direct visual inspection alone [59]. The first two imaging techniques require a fluorescent system. Indocyanine green fluorescence, applied via intravenous injection, exploits the molecule's fluorescence stimulated by near-infrared light [60]. Although initially received with enthusiasm, this technique, while improving intraoperative parathyroid identification, has not demonstrated a significant reduction in post-operative HypoPT rates. Parathyroid near-infrared autofluorescence relies on the differing fluorescence intensity of parathyroid tissue compared to the surrounding tissues (thyroid, trachea, adipose tissue, and muscle). It is the most efficient technique in reducing post-operative HypoPT, particularly transient cases, though its impact on persistent HypoPT requires further validation [61, 62]. Autofluorescence has shown the most significant benefit in increasing the identification rate of parathyroid glands, reducing post-operative hypocalcemia, and decreasing the rates of unintentional parathyroid resection and auto-transplantation. When injected into the thyroid tissue, carbon nanoparticles do not penetrate the blood vessels but are absorbed by lymphatic vessels or capillaries through macrophages, becoming trapped in the lymph nodes. During surgery, the thyroid and lymph nodes in the drainage areas appeared black, whereas the parathyroid glands remained unaffected by this staining. This contrast allows for easier intraoperative identification. Using carbon nanoparticles has significantly reduced the rate of accidental parathyroid resection and the incidence of post-operative hypocalcemia and HypoPT [63]. However, among the

three imaging strategies, it showed the least advantage in identifying parathyroid glands. This may be because of the difficulty in recognizing them in a darkened surgical field caused by suboptimal injection. Nevertheless, considering the advantages and availability of carbon nanoparticles, this technique can be a valid option in centers without using intraoperative fluorescence imaging systems [59].

Box 2 - Key takeaways - Etiology

Nonsurgical HypoPT is suspected in hypocalcemic patients <40 years, especially with syndromic features, family history, or unexplained hypocalcemia.

In nonsurgical forms, an inappropriately normal PTH in hypocalcemia is diagnostic: actively pursuing genetic testing, particularly *CASR* and *GCM2* mutations.

Postsurgical HypoPT risk increases with total thyroidectomy, reoperative surgery, malignancy, and extent of lymph node dissection.

Autofluorescence techniques improve identification but not fully prevention of post-surgical HypoPT; meticulous parathyroid preservation remains the cornerstone.

Parathyroid auto-transplantation is restricted to visibly devascularized or excised glands to avoid unnecessary manipulation and delayed recovery.

Clinical evaluation and overview of patients with hypoparathyroidism

Physical examination, symptoms, and clinical manifestations

Neuromuscular irritability is assessed using the Chvostek or Trousseau sign when appropriate. The Chvostek sign is elicited by tapping the facial nerve anterior to the ear and observing an ipsilateral twitch in the facial muscles [64]. This sign can be helpful but is seen in up to 25% of normal subjects and is absent in up to 30% of hypercalcemic individuals [65]. The Trousseau sign is more sensitive and specific, appearing in over 90% of hypercalcemic individuals and only approximately 1% of normocalcemic individuals [64]. A positive Trousseau sign is indicated by a carpal spasm occurring after a 3-minute inflation of the blood pressure cuff to slightly above the systolic pressure. The eyes should be examined for cataracts, the neck evaluated for signs of previous surgery or enlargement, and the skin and mucosa inspected for candidiasis or lack of pigmentation (vitiligo), which may be associated with autoimmune etiologies [64, 65].

Symptoms of hypocalcemia result from neuromuscular excitability and may include paresthesia of the upper and lower extremities and perioral area, laryngospasm, and seizures. These manifestations are highly variable, often unpredictable, and are based solely on serum calcium levels. Hypomagnesaemia can exacerbate these symptoms.

Alkalosis may also precipitate symptoms as ionized calcium decreases further. HypoPT is associated with several complications as recently described [50]. The most common complications were cataracts (17%), infections (11%), nephrolithiasis/nephrocalcinosis (15%), renal insufficiency (12%), seizures (11%), depression (12%), ischemic heart disease (7%), and arrhythmia (7%). Basal ganglia calcification is also a common complication, affecting over two-thirds of patients with nonsurgical HypoPT [66, 67].

Diagnosis

According to the II International Workshop on HypoPT, chronic HypoPT should be diagnosed in the presence of hypocalcemia when PTH is undetectable, low, or inappropriately normal [50]. As PTH secretion is normally elevated in hypocalcemia, the coexistence of normal PTH and low serum calcium levels should not be overlooked, as it may indicate impaired parathyroid function. Hypocalcemia, defined as low-ionized calcium or albumin-adjusted serum calcium, should be confirmed on two separate occasions, at least two weeks apart. Additional biochemical markers that support the diagnosis include elevated serum phosphate, reduced 1,25-dihydroxyvitamin D ($1,25(\text{OH})_2\text{D}$), and increased fractional excretion of urinary calcium [12]. If HypoPT is suspected, the condition should not be classified as chronic until at least 12 months after the surgery.

The II International Workshop on HypoPT further subclassifies permanent postsurgical HypoPT into the following three categories:

- HypoPT: characterized by hypocalcemia with low/undetectable PTH and high-normal or elevated phosphorus levels.
- Parathyroid insufficiency: low PTH level, elevated serum phosphate level, and normal or slightly reduced serum calcium level.
- Relative parathyroid insufficiency: normal PTH, but inadequate to maintain calcium and phosphate homeostasis under specific conditions (e.g., impaired gut absorption) [50].

Before confirming the diagnosis, the panel also recommended excluding any magnesium abnormalities, as hypomagnesaemia and hypermagnesaemia can impair PTH secretion and function [50].

Biochemical investigations play a critical role in the diagnosis of HypoPT and differentiating HypoPT from other diseases characterized by hypocalcemia. At the time of initial diagnosis, biochemical evaluation should include serum

creatinine, estimated glomerular filtration rate (eGFR), calcium (either ionized or albumin-adjusted), 25-hydroxyvitamin D, and a 24-hour urine collection for creatinine and calcium. Phosphorus, 1,25(OH)₂D and magnesium should also be checked.

The essential biochemical assessment for the diagnosis of HypoPT is the consensual finding of hypocalcemia with reduced or inappropriately normal serum PTH levels. This is easily distinguishable from pseudohypoparathyroidism and secondary causes of hypocalcemia (e.g. vitamin D deficiency), in which the PTH level is high. Other biochemical manifestations of HypoPT include serum phosphate levels in the high-to-normal or high range. Phosphate is helpful, but not mandatory, for diagnosing HypoPT. Serum phosphate levels can contribute to diagnosis mainly in secondary conditions of hypocalcemia (e.g. vitamin D deficiency) in which it will be below the normal values, while it will not be useful in pseudohypoparathyroidism. Serum calcium may be measured as ionized calcium or corrected for serum albumin, according to the following formula: corrected serum total Ca = measured total Ca + $[0.8 \times (4.0 - \text{measured serum albumin})]$ even if there is debate about which equation is the best to define correct serum calcium [68, 69].

A reliable assay to measure serum PTH is crucial for diagnosing HypoPT. To date, the most widely used intact PTH assay is the two-site immunoradiometric assay (IRMA), which detects the carboxy- and amino-terminal ends of the molecule at the same time. Third-generation assays of PTH differ from the former in their amino-terminal recognition sites, with the third-generation assay measuring PTH (1–84) rather exclusively [70, 71]. There is no substantial evidence regarding which test is the most specific and preferable. In addition, for all patients who have performed more than one PTH measurement, the measurements should be performed with the same test and possibly in the same laboratory with a specific test reference value.

Hypocalcemia may develop after thyroid surgery or parathyroidectomy. However, assessing serum levels of second or third generation PTH after surgery provides higher sensitivity and specificity than measuring serum calcium levels in predicting permanent HypoPT. The American Thyroid Association Surgical Affair Committee states that there is no need for intensive calcium monitoring when the PTH concentration is >1.6 pmol/L (15 pg/ml) measured more than 20 min after surgery [72, 73]. Recent guidelines recommend the assessment of PTH within 12–24 h after surgery to exclude patients who will not develop permanent HypoPT [44]. A serum level of PTH <1.05 pmol/l (<10 pg/ml) after 1 month after surgery is associated with an increased risk of permanent HypoPT and requires monitoring and treatment for hypocalcaemia [74, 75]. Although most patients with postsurgical HypoPT recover, hypocalcaemia and low

or inappropriate normal PTH should persist for more than 12 months after surgery to establish the diagnosis of postsurgical HypoPT [7, 50, 76–79]. Other biochemical manifestations of HypoPT include serum phosphate levels in the high-to-normal or high range, low levels of 25-hydroxyvitamin D [25(OH)D], 1,25-dihydroxyvitamin D [1,25(OH)₂D], and hypercalciuria. Assessing these biochemical parameters in the diagnostic process is helpful, but not mandatory, for diagnosing HypoPT [7].

Special caution is required when establishing the biochemical diagnosis of ADH1. These patients show low levels of serum calcium with inappropriately low but detectable or normal PTH levels, high normal or elevated phosphate, normal or low levels of magnesium, and relative hypercalciuria [45]. Patients carrying severe gain-of-function variants in *CASR* may have renal waste of sodium, chloride, and magnesium, leading to hypokalemic alkalosis, and hyperreninemia [45]. The combination of these biochemical findings is referred to as Bartter-like syndrome.

Box 3 - Key takeaways – Diagnosis

Inappropriately normal PTH values in hypocalcemia are the hallmark of HypoPT and are not indicative of normal function.

Phosphate levels, often overlooked, provide critical support to suspect HypoPT even when calcium and PTH levels are borderline.

Early postoperative PTH <10 pg/mL identifies patients at risk of HypoPT although it does not always predict a permanent disease. Caution and follow-up are needed even when PTH is >10 pg/ml. Persistent low calcium alone is insufficient: confirming the diagnosis requires understanding the interplay among calcium, PTH, phosphate, and magnesium.

Renal function and 24-hour urinary calcium are essential to anticipate and prevent complications early in the course.

Low serum calcium with inappropriately low but detectable or normal PTH levels, high normal or elevated phosphate, normal or low levels of magnesium, and relative hypercalciuria may suggest the diagnosis of ADH1.

Bone, kidney, neurological, and cardiovascular complications

Both postsurgical and nonsurgical HypoPT can have long-term chronic consequences; the major ones occur in the bone, kidney, and nervous system. Biochemical control of the disease may help delay the onset of some complications.

In a retrospective nested case-control study, HypoPT patients with serum phosphate above the reference range (>1.45 mmol/l or >4.5 mg/dl) had 3.3-fold higher odds [confidence interval (CI): 1.24–8.58] of cardiovascular event. Hypercalciuria evaluation usually includes 24-h urine creatinine excretion to ensure complete 24-h collection. There is still debate regarding the value of measuring the calcium/creatinine ratio rather than the 24-h urine excretion [76].

The 24-h urine calcium level may be inappropriately (for serum calcium levels) low-normal before calcium and vitamin D supplementation is started [80]. Renal complications are assessed by regularly monitoring renal function (eGFR and serum creatinine level) [76]. In HypoPT, 25(OH)D and 1,25(OH)₂D are low or in the lower normal range, and in the diagnostic workup, assessment of both active 25(OH)D and 1,25(OH)₂D is recommended [50]. Although a position paper from The International Federation of Clinical Chemistry and Laboratory Medicine Committee on bone metabolism does not include HypoPT in the indication for 1,25(OH)₂D assessment [81], 25(OH)D level definition is also recommended also in perioperative management of patients at risk of post-operative HypoPT [76]. Magnesium plays a key role in calcium homeostasis, impairing PTH function, and serum magnesium levels needs to be evaluated mainly in cases of hypocalcemia without a known etiology [82, 83]. Bone turnover markers in chronic HypoPT are usually in the lower half of the normal range [84]. Still, their assessment does not play a role in defining the diagnosis of HypoPT.

Regarding imaging studies, guidelines recommend a complete baseline assessment of renal calcification or nephrolithiasis via renal ultrasound or computed tomography. There is less consensus on the necessity of three-site (forearm included) dual-energy X-ray absorptiometry (DXA) or skull imaging to assess the basal ganglia or other intracerebral calcifications [65].

Skeletal abnormalities are mostly related to a reduction in bone turnover and an increase in bone mineral density (BMD) compared to healthy subjects of the same sex and age as detected by DXA [85, 86]. Histological findings of dynamic histomorphometry studies of iliac crest bone biopsies highlight a reduction in the mineralizing surface and bone formation rate [87]. Assessment of bone quality using peripheral quantitative computed tomography (pQCT) and high-resolution pQCT (HRpQCT) showed greater trabecular and cortical volumetric BMD (vBMD) and lower cortical porosity at the radius and tibia in hypoparathyroid patients [88]. Despite the higher bone mass and these structural changes in HypoPT, its effect on fractures is still debated. This is also due to the rarity of the disease, since data evaluate populations with different numbers and etiologies and considers either clinical fractures or morphometric vertebral fractures [89]. Trabecular bone score (TBS) does not currently provide reliable information on the bone quality of HypoPT patients since it has limitations in detecting abnormal bone microarchitecture in nonsurgical HypoPT [90]. Studies using HR-pQCT scans to assess bone microarchitecture, as well as measuring cortical material bone strength by micro-indentation and hip structural analysis, have provided evidence of an altered bone microstructure

and strength in HypoPT [91]. Epidemiological studies suggest a decreased risk of fractures at the humerus in postsurgical HypoPT [92]. In contrast, an increased risk of fractures in the upper arm has been shown in nonsurgical HypoPT, probably because of an increased risk of falls as a consequence of seizures and cataracts [93]. Emerging data highlight an increased risk of vertebral fractures (VF), mostly in nonsurgical HypoPT patients [94]. Recent data from the Swedish national cohort of patients with chronic HypoPT of any cause show an increased risk of vertebral fractures compared to controls (2.6% vs. 1.7%, HR 1.55; 95% CI: 1.12–2.14), and a reduced risk of hip fractures (2.0% vs. 2.9%, 0.70; 95% CI: 0.50–0.98) [94]. Use of anticonvulsants and menopause were significantly associated with VF ($P < 0.05$). In this series, both postsurgical and nonsurgical HypoPT are conventionally treated [23, 94–97].

All these findings highlight the need to screen these patients for vertebral fracture assessment (VFA), especially those with long-standing conditions or with elevated risk of fragility fractures due to the presence of other risk factors such as those undergoing levothyroxine suppressive treatment [98].

HypoPT per se is usually not associated with renal diseases, even among those with gain-of-function mutations in *CASR*, who are most likely to have hypercalciuria without treatment. The conventional treatment of HypoPT leads to increased urinary calcium excretion. The resulting hypercalciuria can lead to nephrocalcinosis, kidney stones, and a prevalence of chronic kidney disease (CKD) [99–101]. The CKD ranges from 2.5% to 41%, depending on the definition: eGFR < 60 mL/min/1.73 m², International Classification of Diseases (ICD) codes, or self-report. Patients with nonsurgical HypoPT had an increased risk of CKD stages 4 (eGFR = 15–29 mL/minute) and 5 (eGFR < 15 mL/minute) compared to matched controls [102]. A population study from Denmark suggested that a longer disease duration, higher median calcium-phosphate product (>2.80 mmol²/L²), and a higher frequency of episodes of hypercalcemia were associated with an increased risk of CKD [103, 104]. Patients with nonsurgical HypoPT had an increased risk of CKD stage 4 compared with matched controls [102]. Meola et al. found that 30% of the study population treated with conventional therapy had nephrolithiasis detected by renal ultrasound, and that most were asymptomatic [101]. The same authors, in a case-control, cross-sectional study, confirmed a similar rate (29.2%) of nephrolithiasis [105]. In a systematic literature review, Gosmanova et al. reported that the percentage of patients with nephrolithiasis ranged from 0% to 35.5% [99]. The lowest rates were detected in studies reporting a shorter disease duration and in pediatric populations. Nephrocalcinosis varied from 0% to 38%. Patient type and assessment methods used to detect renal

complications, including diagnostic codes, ultrasound, and patient self-reporting, can explain these discrepancies. Hadker et al. used a self-reported cross-sectional survey of adult patients. They found that those who indicated severe disease on the questionnaire reported a significantly higher occurrence of nephrocalcinosis than patients who reported mild disease (22% vs. 6%; $P \leq 0.05$) [3]. Some studies have reported a combined nephrolithiasis/nephrocalcinosis outcome of 19–31% [100]. In a recent study, 418 patients developed HypoPT after thyroidectomy (12.9%). Postsurgical-HypoPT patients, after an average follow-up of 11.6 years, sustained an estimated glomerular filtration rate decline of $\geq 50\%$ (adjusted hazard ratio 2.77, $P < 0.001$) compared to the controls. Permanent HypoPT was an independent risk factor in determining the worsening of renal function [106].

New insights on the potential metabolic role of renal impairment in patients with HypoPTH highlight that obesity could serve as an independent adverse factor, contributing to worsening renal function (AUROC 7%, $P=0.008$), suggesting more attention to obese subjects. Another important question to consider is the role of FGF23 (fibroblast growth factor 23) in HypoPT, particularly given its upregulation in hyperphosphatemic conditions. FGF23 is primarily produced by osteocytes and osteoblasts in bone and plays a crucial role in phosphate and calcium metabolism, by regulating their concentrations in the blood. Both FGF23 and PTH aim to reduce blood phosphate levels through renal excretion. FGF23 acts directly, whereas PTH increases renal excretion partly by stimulating FGF23. In renal failure, FGF23 increases early before hyperphosphatemia occurs, but at present there are few literature data on its role in HypoPT. Current evidence suggests that in renal impairment associated with HypoPT, the effect of FGF23 may be attenuated, potentially due to the absence of PTH. However, measuring FGF23 levels is not yet routinely recommended in clinical practice.

Seizures, tetany, and muscle stiffness are common features in 40%–60% of patients with HypoPT, with the former being more common in younger patients with nonsurgical HypoPT [107]. Data from national registers and population-based cohort studies have highlighted a higher incidence of neuropsychiatric disorders, including anxiety, depression, and bipolar affective disorders, in patients with HypoPT [23, 92, 93, 102]. Both postsurgical HypoPT and nonsurgical HypoPT report poor QoL due to muscle weakness, fatigue, and mildly impaired cognitive function, often described as brain fog, even under normalization of calcemia [105]. Given the relevance of this aspect, a disease-specific instrument, the Hypoparathyroid Patient Experience Scale-Symptom (HPES-Symptom), has been developed and validated for HypoPT [108]. In a recent cross-sectional study,

including thirty-six well-treated postsurgical HypoPT, magnetic resonance imaging (MRI) showed a difference in brain structure, with a reduced volume of the hippocampus area, especially in the more symptomatic group, suggesting a possible association between cognitive impairment and brain changes [109]. These features worsen in HypoPT with disease duration and higher calcium $\times$ phosphate product or increased serum calcium due to high-dose calcium supplementation [110]. Basal ganglia calcification is a common complication, and it has been postulated that it may affect the quality of life or symptoms. According to previous studies, the prevalence of basal ganglia calcification ranges from 60% to 90% [66, 111, 112]. Basal ganglia calcification was most common in the globus pallidus (69%), followed by the putamen (56%), caudate nucleus (55%), grey-white junction (40%), cerebellar parenchyma (31%), thalamus (29%), and dentate nucleus (25%) [66]. The cortical grey surface of the brain is spared from calcification. The prevalence varies according to the etiology: in postsurgical HypoPT the cases and the duration of the disease are lower, leading to discordant results. In the case-control retrospective study, which considered medical records over 20 years, Zavatta and colleagues found basal ganglia calcification in 25.4% of 142 patients with chronic HypoPT treated with conventional therapy. Basal ganglia calcification was 5.1 times more common in nonsurgical HypoPT than in postsurgical HypoPT, and patients were younger than the controls [67]. One possible explanation for the existence of basal ganglia calcification is the significantly higher expression of osteogenic molecules such as osteonectin, osteopontin, and CA-II in the caudate nucleus than in the gray matter ($P = 0.01$, 0.001, and 0.04, respectively), suggesting that basal ganglia calcification would probably be the outcome of an active process. The molecular biology of BGC is likely to be different in hypoparathyroidism when compared to the ectopic calcification in chronic kidney disease, where PTH is increased, but BGC is not common. Both type 1 and type 2 parathyroid hormone receptors (PTHr1 and PTHr2) are present in the central nervous system, with type 2 being particularly well represented. PTHr2 is responsive to TIP39 (tuberoinfundibular peptides of 39 residues, a small PTH-related peptide family) but it is also responsive to PTH. It has been found that in the basal ganglia its expression is 8 times reduced compared to the grey matter: this, combined with the lack of PTH, could contribute to the worsening of BGC. Beyond that there was a 3-fold reduced mRNA expression of the PiT1 (phosphate transporter) and similar increased expression of osteonectin in the caudate nucleus as compared with the grey matter. It is possible that reduced expression of PiT1 would not allow phosphate to enter the neuronal cells of the basal ganglia, pericytes, thus a quantity of phosphorus remains available for calcium hydroxyapatite

deposition in the matrix of the vessels around basal ganglia [113–115]. Nonsurgical HypoPT revealed that the progression of basal ganglia calcification is related to the calcium/phosphorus ratio during follow-up. This brings forth the importance of adequate phosphorus control in managing HypoPT [66].

Recent emerging, but not yet conclusive, data suggest that cardiovascular risk may also be increased. In the Swedish National Patient Registry, an increased risk was found for valvular heart disease, peripheral artery disease, acute myocardial infarction, and fatal events compared to matched controls, especially in women [116]. Arrhythmia has been reported in several studies [117, 118]. A cardiac risk assessment is suggested to be included in the follow-up of patients to obtain more conclusive data, especially in those with long-standing hypoparathyroidism.

Box 4 - Key takeaways - Bone, kidney, and neurological complications

Despite increased bone mineral density, bone quality in HypoPT is compromised, with reduced remodeling and altered microarchitecture; high BMD does not equal lower fracture risk.

Screen the patients for vertebral fracture assessment (VFA), especially those with long-standing conditions or with high risk of fragility fractures.

Hypercalciuria induced by conventional therapy, not HypoPT itself, is the main driver of nephrolithiasis and renal impairment over time.

Non-surgical HypoPT carries a higher burden of basal ganglia calcifications and neurocognitive decline compared to postsurgical forms, emphasizing the role of phosphorus control.

Poor QoL and neurocognitive symptoms persist in many patients despite normalized calcium levels, indicating that biochemical targets alone are insufficient markers of disease control.

Treatment of hypoparathyroidism

Acute scenario

When symptoms of hypocalcemia are present, they can be life-threatening and require rapid intervention using intravenous administration of calcium, with calcium gluconate preferred [65]. The first step is to resolve symptoms, which can be achieved by intravenous infusion of 1 to 2 ampules of calcium gluconate (93 mg of elemental calcium/10 mL) in 50 mL of 5% dextrose for 15–30 min. The second step involves a slower infusion of calcium gluconate at 0.5–1.5 mg/kg body weight per hour over an 8 to 10-hour period [65]. If calcium gluconate is not an option, calcium chloride can be used as an alternative, but it is more irritating to veins and should only be given via a central line [119].

Table 3 Conventional therapy for hypoparathyroidism

Therapeutic agent	Typical dose range	Notes
Calcium Supplements	500–3000 mg/day of elemental calcium, into divided doses	Use calcium carbonate or calcium citrate Take with meals to enhance phosphate binding effects
Active Vitamin D metabolites	Calcitriol: 0.25–3 mcg/day, divided into doses Alfacalcidol: 0.5–6 mcg/day	Start at lower doses and titrate based on serum calcium and phosphate levels.
Vitamin D3	Colecalciferol: 1000 IU/day to 100,000 IU/day	Based on 25-hydroxy-vitamin D level
Vitamin D2	Ergocalciferol: 50,000 IU/week	Based on 25-hydroxy-vitamin D level
Magnesium Supplements	300–600 mg/day (magnesium oxide, magnesium citrate, or magnesium gluconate)	Dose depends on the severity of hypomagnesemia. Monitor to avoid diarrhea as a side effect.
Thiazide Diuretics	Hydrochlorothiazide: 25–100 mg/day	Often combined with a low-sodium diet to enhance calcium retention and reduce hypercalciuria

Conventional therapy and monitoring

Conventional treatment for patients with HypoPT typically includes calcium supplements and active vitamin D metabolites, such as calcitriol or alfacalcidol, administered in adjustable doses (Table 3) [50, 120]. The primary goal of therapy is symptom management, prevention of complications associated with chronic hypocalcemia and hyperphosphatemia, and improvement in the patient's QoL [1, 50]. Treatment should also aim to: (i) maintain serum calcium levels within the lower range or just below the normal reference interval; (ii) keep serum phosphorus levels within the high normal range or slightly elevated; (iii) prevent hypercalciuria; (iv) maintain a calcium-phosphate product well below the upper limit of normal ($55 \text{ mg}^2/\text{dL}^2$ or $4.4 \text{ mmol}^2/\text{L}^2$); and (v) avoid calcifications in the kidney and other tissues Table 4.

Calcium supplementation

Oral calcium supplements contain various proportions of elemental calcium: calcium carbonate provides 40%, calcium citrate 21%, calcium gluconate 9%, and calcium lactate 13%. Calcium carbonate and calcium citrate are the most frequently used in routine practice. These calcium salts are efficiently absorbed and serve as phosphate binders, helping reduce serum phosphorus levels when consumed with meals. Calcium carbonate is absorbed more

Table 4 Comparison of PTH treatments

Therapy	Main characteristics	Regulatory approvals	Advantages (pros)	Limitations/disadvantages (cons)
PTH (1–34)	• Contains only the N-terminal fragment of the PTH molecule, essential for the hormone's biological action • Requires daily multiple subcutaneous injection to maintain normocalcemia • Half-life about 1 h	• Approved for osteoporosis • Off-label use for HypoPT in some countries	• Rapid control of serum calcium • Good efficacy in maintaining normocalcaemia	• Not specifically approved for HypoPT • Need for multiple daily injections or infusion pump • Conflicting evidence regarding impact on QoL • Inconsistent results on urinary calcium excretion
rhPTH (1–84) – Natpara	• Full 84-amino-acid recombinant human PTH • Once-daily subcutaneous injection (thigh preferred for slower absorption and longer calcemic response) • Half-life 2–3 h • Reduces calcium and active vitamin D requirements	• FDA approved (2015) and EMA approved (2017) for chronic HypoPT not adequately controlled by standard therapy as add-on treatment • Recalled in 2019 due to device-related contamination • Global production discontinued in 2024	• Effective at maintaining serum calcium and reducing supplementation needs • Favorable effect on serum phosphate and calcium-phosphate product • Improves bone turnover and QoL in long-term studies	• Extremely limited availability • Risk of hypercalcaemia, especially with fixed dosing • Inconsistent results on urinary calcium excretion • Contrasting results in QoL changes
Palopegteriparatide (TransCon PTH 1–34)	• PTH (1–34) conjugated to methoxy polyethylene glycol (mPEG) via a TransCon linker for gradual release • Once daily subcutaneous injection with sustained PTH release over 24 h • Half-life about 60 h • Provides continuous PTH receptor type 1 activation	• Approved by FDA and EMA as the first PTH replacement therapy specifically for adults with chronic HypoPT	• Maintains stable calcium and phosphate levels with complete discontinuation of calcium and vitamin D supplements • Significant and clinically meaningful QoL improvement (PaTH-way and PaTH Forward trials) • Potential renal benefit (↑ eGFR at 52 weeks) • Safe for skeletal health with normalized BTMs and BMD remaining within normal range	• Long-term data still limited • Renal benefits need confirmation in further studies
Eneboparatide (LA-PTH, AZP-3601)	• Synthetic 36-amino acid peptide selectively binding the R0 conformation of the PTH receptor type 1 • Very short terminal half-life (<1 h) but prolonged biological effect (>24 h) due to sustained receptor signalling • Once-daily subcutaneous injection (under investigation)	• Phase 2 trial successfully completed • Phase 3 CALYPSO trial ongoing	• Maintains normocalcemia and normalizes urinary calcium without increasing bone turnover • Allows discontinuation of standard therapy • Favorable pharmacological profile with stable calcium and balanced bone remodeling	• Not yet approved for clinical use • Long-term efficacy and safety data still pending • Limited real-world clinical experience

HypoPT, Hypoparathyroidism; FDA, Food and Drug Administration; EMA, European Medicines Agency; QoL, Quality of life; eGFR, estimated glomerular filtration rate; BTMs, bone turnover markers; BMD, bone mineral density

effectively when taken with food to improve its absorption. In contrast, calcium citrate can be absorbed effectively, regardless of food intake, as absorption is not dependent on gastric pH [121]. Therefore, calcium citrate may be more effective in patients with achlorhydria or in those using proton pump inhibitors. It can also be used in patients who complain of worsening constipation as well as in patients who prefer to take supplements outside mealtimes [1, 122]. Only one randomized, double-blind, crossover trial has compared the efficacy of calcium citrate *and* calcium carbonate in HypoPT subjects [123]. The authors found that serum calcium and phosphorus concentrations did not differ

between the two calcium preparations; however, calcium citrate was associated with less constipation and a reduction in urinary oxalate excretion, which could have a potential beneficial effect on nephrolithiasis risk. The amount of elemental calcium supplementation required by patients with HypoPT varies, typically 500–1000 mg two to three times daily, although more frequent dosing may be necessary (Table 3). The intestinal absorptive capacity was likely saturated by a single dose of 500 mg of calcium. Therefore, a higher dose is unlikely to provide additional benefits to the patients [121, 124]. Patients with mild hypocalcemia should receive oral therapy, even if they present with nonspecific

symptoms, such as fatigue, brain fog, and anxiety, which may improve with treatment [120]. For symptomatic severe hypocalcemia, intravenous calcium gluconate may be used for a short period [1, 7]. Intravenous calcium transiently increases serum calcium levels; however, continuous infusion is often required until the patient is stabilized, and oral calcium and vitamin D supplementation have beneficial effects. Intravenous calcium must be infused slowly, as rapid administration can shorten the myocardial action potential and precipitate arrhythmias; in patients on digoxin the synergistic rise in intracellular calcium may trigger severe cardiotoxicity (“stone heart”). Therefore, continuous ECG monitoring is recommended during intravenous calcium replacement [119].

Vitamin D metabolites

Active vitamin D metabolite therapy plays a key role in the management of HypoPT [1, 120, 124]. Calcitriol (1,25-dihydroxy vitamin D₃) enhances intestinal calcium absorption and stimulates bone remodeling through the RANKL signaling pathway. Calcitriol reaches peak serum concentrations within 3–6 h of administration, while serum calcium levels typically begin to rise within 1 to 3 days. In adults, its elimination half-life ranges from 5 to 8 h. The standard daily dose of calcitriol is between 0.25 and 2 µg, covering the normal daily production of calcitriol [1, 6–8, 120, 124]. In some patients, higher doses may be necessary, and when exceeding 0.75 µg, calcitriol is typically administered in divided doses (Table 3) [125]. Alfacalcidol (1α-hydroxyvitamin D₃) can also be administered although it is less potent than calcitriol. Calcitriol is approximately twice as potent as alfacalcidol in terms of its calcemic effect. Alfacalcidol is rapidly activated in the liver by 1,25(OH)₂D. The onset of action of alfacalcidol is similar to that of calcitriol, occurring within 1–3 days, with a longer offset of 5–7 days [1, 126]. The typical daily dose of alfacalcidol ranges from 0.5 to 6 µg. Vitamin D₂ (ergocalciferol) or vitamin D₃ (cholecalciferol) could be used where active vitamin D metabolites are unavailable and/or too expensive [1, 50, 120]. At high concentrations, 25(OH)D may bind to the vitamin D receptors and exhibit activity [50, 120]. Cholecalciferol or ergocalciferol is often required to maintain 25(OH)D levels within the normal range [50, 120].

Additional therapies

Magnesium supplementation may be required because it plays a crucial role in PTH secretion and function [1, 50, 120]. Persistent hypomagnesemia can worsen hypocalcemia and may require correction before other treatments are effective. In some cases, thiazide diuretics are prescribed to

reduce urinary calcium excretion, helping maintain higher serum calcium levels while minimizing the risk of kidney stones or nephrocalcinosis [7, 50, 120]. A low-salt diet with a daily dose range of 25–100 mg may also be advised. Thiazide treatment may lead to adverse effects such as hypokalemia, hypomagnesemia, and hyponatremia. Consequently, it is important to regularly monitor electrolyte levels during therapy. Thiazide diuretics may be limited by hypotension and are contraindicated in adrenal insufficiency. Additionally, caution is necessary when prescribing thiazide diuretics to patients with ADH because they can exacerbate urinary magnesium loss [83]. The risk of hypomagnesemia may be reduced if a combination of thiazide diuretics with a potassium-sparing agent is used [127]. Additionally, potassium or sodium phosphate binders may be used to manage hyperphosphatemia if dietary measures alone are insufficient to lower phosphate levels. According to the guidelines for the general population, patients should be advised to maintain an adequate calcium intake [128, 129]. A diet low in phosphorus and avoiding high-phosphorus foods such as processed meats, dairy products, and certain soft drinks should also be considered. Therefore, adequate hydration is recommended to reduce the risk of kidney complications.

Doses are tailored for each patient based on the laboratory results, symptoms, and tolerance. It is important for patients to be educated on the significance of treatment adherence and to recognize signs of hypo- or hypercalcemia. The current management of HypoPT with calcium and vitamin D metabolite therapy remains suboptimal, as most patients continue to experience fluctuations in serum calcium levels, negatively affecting their QoL.

PTH replacement therapy overview

PTH 1–34

PTH (1–34) has been officially approved for the management of osteoporosis but, in some countries, it is used off-label for the treatment of HypoPT in addition to conventional therapy with calcium and active vitamin D. PTH (1–34) contains the N-terminal portion of the PTH molecule, which is critical for the physiological effects of the hormone. However, PTH (1–34) has a shorter plasma half-life than PTH (1–84). Studies have reported that PTH (1–34) must be injected twice daily in both children and adults to maintain normocalcemia in patients with HypoPT [130, 131]. In a 6-month, open-label, randomized crossover trial, continuous infusion of PTH (1–34) via an insulin pump provided more stable plasma calcium levels, reduced urinary calcium excretion, and further decreased the total PTH (1–34) dose required to maintain normokalaemia [132]. However, evidence

regarding its impact on QoL remains mixed, with some studies reporting contrasting outcomes [133–135].

PTH 1–84

Recombinant human PTH (1–84), or rhPTH (1–84), marketed as Natpara, is a synthetic protein replicating the full 84-amino-acid sequence of human parathyroid hormone. Approved by the FDA in 2015 and the EMA in 2017, Natpara was designed as a once-daily treatment for chronic HypoPT in patients inadequately managed with standard therapies [136]. However, this was recalled in 2019 because of device-related contamination issues. Despite limited availability in Europe and the U.S. under special-use programs, Takeda announced plans to cease global production by 2024, owing to unresolved safety concerns. The therapeutic goal of rhPTH (1–84) in HypoPT management is to mimic the natural secretion of PTH to support calcium and phosphate homeostasis. Pharmacokinetic studies revealed a biphasic absorption pattern following subcutaneous injection with an initial peak within 30 min and a secondary peak at two hours. The half-life is approximately 2–3 h, but its effects on calcium levels can last over 24 h. Initially available only in fixed 100 µg doses, introducing lower doses has allowed for individualized treatment, enabling better dose adjustments and a more tailored approach [137, 138]. Subcutaneous injection in the thigh is preferred over abdominal administration because of its slower absorption, leading to a prolonged calcemic response [136]. Clinical trials, including the pivotal REPLACE study, have demonstrated that rhPTH (1–84) reduces the need for high-dose calcium and vitamin D supplementation while maintaining stable biochemical parameters [139]. In the REPLACE trial, 53% of patients achieved the primary endpoint of calcium stability with reduced supplementation compared with only 2% in the placebo group. Similar findings have been reported in long-term open-label studies, showing sustained efficacy in stabilizing calcium levels and decreasing supplemental calcium requirements [139]. While rhPTH (1–84) effectively reduces serum phosphate and calcium-phosphate products, its impact on urinary calcium excretion has been heterogeneous, with contrasting results [139, 140]. Long-term studies have indicated a reduction in urinary calcium levels, while in a randomized controlled trial with a fixed 100 µg dose of rhPTH (1–84), urinary calcium did not significantly decrease [138, 141]. However, overall renal function remains stable with extended PTH therapy [139, 141, 142]. In bone health, rhPTH (1–84) reverses the low bone turnover state of HypoPT and restores skeletal properties to near-normal levels [143]. While cortical bone mineral density may decrease slightly, the clinical significance of these findings remains unclear owing to a lack of fracture data.

Long-term open-label studies using rhPTH (1–84) reported improved QoL scores, particularly in patients with lower baseline scores [144–146]. However, short-term trials have not consistently demonstrated significant QoL improvements, likely due to hypercalcemic episodes from fixed dosing [147, 148]. Safety data highlight hypercalcemia as a notable adverse event, particularly at fixed doses. Dose adjustments significantly reduce this risk and most episodes are asymptomatic or mild. Recently, it has been shown in a randomized, double-blind, placebo-controlled, phase 3b-4 study that rhPTH(1–84) alongside conventional therapy improved symptoms and health-related quality of life to a greater extent than conventional therapy alone in patients with symptomatic HypoPT [149]. Overall, rhPTH (1–84) offers effective management of HypoPT, reducing dependence on supplementation, and improving biochemical stability. The longest follow-up experience of rhPTH (1–84) therapy in chronic hypoparathyroidism has been provided by Agarwal S et al. [150]. The authors demonstrated that over the 12-year period the drug sustained biochemical stability but overall decreases in bone mass [150]. However, the primary challenge to its use is its limited availability, in addition to the contrasting effects on urinary calcium and QoL.

Palopegteriparatide

Palopegteriparatide, also known as TransCon PTH (1–34), has recently received marketing authorization from both the European Medicines Agency (EMA) and the U.S. Food and Drug Administration as the first PTH replacement therapy in adults with chronic HypoPT. This innovative therapy is designed to deliver a sustained release of active PTH through once-daily injection, maintaining physiological levels over a 24-hour period. The unique drug formulation combines PTH (1–34) with a methoxy polyethylene glycol (mPEG) carrier via a TransCon linker. Under physiological conditions, the linker cleaves automatically, releasing active PTH gradually, which avoids the sharp fluctuations in plasma PTH levels observed with short-acting PTH agonists. This sustained action provides stable activation of the PTHR1 receptor and its associated signaling pathways, ensuring a consistent therapeutic effect [151]. In both phase II and phase III clinical trials, TransCon PTH maintained normokalemia and stabilized phosphate levels while permitting complete independence from conventional therapy. This drug has a significant and noteworthy impact on patients' QoL [152–154]. In the PaTHway and PathForward studies, QoL was rigorously evaluated using a hierarchical approach and a disease-specific scale (HPES questionnaire) [152, 153]. Once-daily subcutaneous administration of palopegteriparatide resulted in both statistically and clinically

meaningful improvements in QoL for patients with chronic HypoPT compared to conventional treatment. The potential effect of this drug on kidney function is remarkable. Indeed, in this post hoc analysis of the PaTHway trial, palopegteriparatide treatment was associated with a significantly improved eGFR at week 52, in addition to the previously reported maintenance and normalization of serum and urine biochemistry [155]. To the best of our knowledge, this is the first study that a PTH analogue report improvement in renal function. However, further investigation is required to confirm these findings. The drug demonstrated a good tolerability profile with no reports of treatment-related serious adverse events (SAEs) or adverse events (AEs) resulting in treatment discontinuation or fatalities. Furthermore, it appears to be safe for skeletal health. The latest update from the Phase 2 PaTH Forward Trial showed that bone turnover markers (BTMs) increased from baseline and gradually decreased toward age- and sex-adjusted normal levels, remaining stable and below the upper normal limit throughout the study period. The mean bone mineral density (BMD) Z-scores moved closer to age- and sex-matched norms and remained above zero in all regions of interest throughout the study. Participants with lower baseline BMD T- and Z-scores exhibited smaller BMD reductions over time [136].

Data from Week 214 of Phase 2 PaTH Forward Trial showed that long-term treatment with Palopegteriparatide continued to provide a durable response in adults with hypoparathyroidism: nearly all patients (98%) continued to have normal albumin-adjusted serum calcium levels and 93% remained independent from conventional therapy [156].

Eneboparatide

Eneboparatide, also known as LA-PTH or AZP-3601, is a novel synthetic peptide consisting of 36 amino acids that is specifically engineered to selectively bind the R0 conformation of the parathyroid hormone 1 (PTH1) receptor. This targeted binding leads to sustained intracellular signaling and extended biological activity, despite the peptide's brief presence in circulation due to its short terminal half-life [157]. Preclinical studies in animal models have shown that eneboparatide delivers a favorable pharmacological profile, producing sustained increases in serum calcium (sCa) without elevating urinary calcium (uCa) or affecting the bone structure [158, 159]. In healthy human volunteers, a single subcutaneous dose of 40–60 µg prompted a rapid, dose-dependent increase in sCa that persisted for over 24 h, even though the drug's terminal half-life remained under one

hour. This prolonged effect is attributed to extended receptor signaling. Furthermore, when administered daily over a 14-day period at doses of 20 µg or higher, eneboparatide achieved steady sCa levels without increasing uCa excretion or altering bone turnover marker levels. In a phase 2 clinical trial, eneboparatide enabled patients to discontinue standard treatment regimens, while effectively maintaining serum calcium within the desired range, normalizing uCa excretion, and supporting balanced bone remodeling [160]. A phase 3 clinical trial (CALYPSO) is currently ongoing. The FDA granted a fast-track designation in May 2024 for accelerated approval and priority review [161].

Biochemical investigation for the treatment monitoring

For the therapeutic monitoring of HypoPT, the same blood tests for diagnosis are used but with different priorities and weights [153]. The main parameter used to monitor treatment in patients with HypoPT is serum calcium. The therapeutic objective is to maintain the blood calcium level in the lower half of the reference range to avoid hyperphosphatemia and hypercalciuria [153, 162, 163]. Conventional therapy with calcium and active vitamin D (calcitriol or calcidiol) is recommended as first-line therapy for patients with HypoPT [7, 120, 153]. However, conventional therapy poses several challenges, including fluctuating serum calcium levels and further exacerbation of hyperphosphatemia and hypercalciuria. Serum phosphate concentrations should be kept in the lower part of the reference interval (0.75–1.45 mmol/l (2.3–4.5 mg/dl), similar to the calcium-phosphate product (i.e. less than 55 mg²/dL² (4.4 mmol² L²), as they contribute to extra-skeletal calcifications and other complications when elevated [83, 100, 120, 163]. Hypercalciuria (urine calcium level higher than 250 mg/day in women and higher than 300 mg/day in men) is an independent risk factor for renal calculi (OR 21.27; 95% CI 2.31–195.91) and impairment of renal function. Hypercalciuria is present in about 51% of HypoPT patients, even if treated with thiazide [164]. All guidelines recommend considering the risk of renal complications and monitoring the renal function (eGFR) [7, 120, 153]. Vitamin D status needs to be assessed to ensure that vitamin D levels remain within the normal range (75–125 nmol/l) [7, 153]. Patients with persistent hypercalciuria taking thiazide diuretics require close monitoring of serum potassium and magnesium levels.

Biochemical measurements of bone turnover do not change significantly with calcium and vitamin D supplementation, and their assessment is of limited clinical use

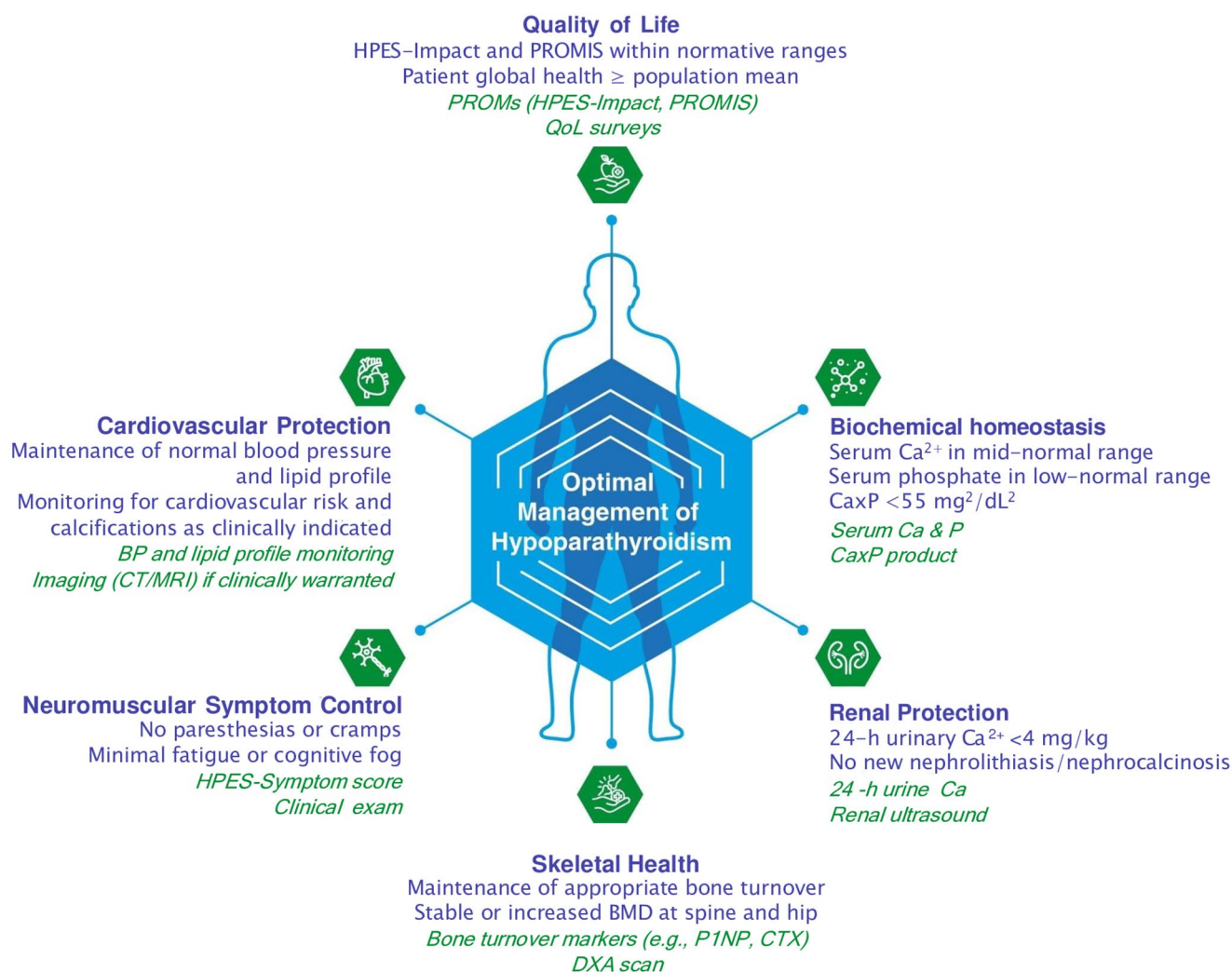


Fig. 1 Multidimensional goals for the optimal management of hypoparathyroidism. A comprehensive framework encompassing six key domains—quality of life, biochemical homeostasis, renal protection, skeletal health, neuromuscular symptom control, and cardiovascular

protection. Each domain is associated with specific clinical targets and monitoring strategies, supporting a holistic approach to long-term management of patients with chronic hypoparathyroidism

during standard therapy courses [84]. PTH replacement therapy is based on the administration of either PTH (1–84) or its active fragment PTH (1–34) (i.e. rhPTH (1–84), palopegteriparatide, and teriparatide. Palopegteriparatide, besides normalizing serum calcium and phosphate in most patients, is the only medication able to consistently reduce hypercalciuria and improve renal function [134, 152, 164]. Despite better control of the biochemical profile in HypoPT treated with palopegteriparatide, replacement therapy, and the substantial suspension of calcium and vitamin D supplementation, the guidelines do not provide for different monitoring in patients treated with palopegteriparatide.

Box 5 - Key takeaways - Treatment

Conventional therapy with calcium and active vitamin D stabilizes serum calcium but does not fully replicate PTH's protective effects on kidneys, bone, and neurocognitive function.

The risk of hypercalciuria and progressive renal damage is driven more by treatment side effects than by HypoPT itself; proactive monitoring of urinary calcium and eGFR is mandatory.

Persistent symptoms despite corrected calcium levels reflect unmet needs in tissue-level mineral balance and should prompt reconsideration of management strategies.

PTH replacement therapies, particularly sustained-release analogs like palopegteriparatide, redefine therapeutic targets: not just normocalcemia, but stabilization of renal function, bone remodeling, and QoL.

Long-term management should prioritize minimizing calcium-phosphate product, protecting renal function, preserving cognitive performance, and individualizing therapy beyond biochemical thresholds.

Future directions

HypoPT is a complex and impactful endocrine disorder that extends beyond simple biochemical abnormalities, significantly affecting patients' skeletal, renal, and neurological health, as well as their quality of life. Although conventional therapy with calcium and active vitamin D supplementation has historically been the cornerstone of management, it does not fully replicate the physiological actions of parathyroid hormone nor prevent long-term complications.

The emergence of PTH replacement therapies marks a paradigm shift in the treatment landscape. Agents such as palopegteriparatide and eneboparatide offer the potential for more physiological restoration of calcium-phosphate homeostasis, reducing reliance on high doses of supplements, stabilizing renal function, and improving patient-reported outcomes. These advances reinforce the concept that optimal management of HypoPT should aim not only for biochemical control but also to preserve organ health and enhance quality of life. This multidimensional perspective is summarized in Fig. 1, which illustrates the key domains and targets for optimal hypoparathyroidism management, reflecting the need for an integrated and individualized treatment strategy.

Looking ahead, several areas warrant further attention. First, the implementation of personalized treatment strategies based on patient-specific risk profiles and comorbidities is critical. Second, long-term real-world data are needed to confirm the benefits of new therapeutic approaches on significant clinical outcomes, including fracture risk, chronic kidney disease progression, and neurocognitive decline. Third, advances in the genetic characterization of nonsurgical HypoPT could open new avenues for early diagnosis, risk stratification, and targeted intervention. Integrating clinical experience with translational research will be the key to fully unlocking the potential of new therapies and improving the standard of care for patients with HypoPT.

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Data availability Data sharing is not applicable to this article, as no datasets were generated or analyzed.

Declarations

Conflict of interest The first and Corresponding Author of this paper is an associate Editor of JENI. All other authors declare that they have no conflicts of interest regarding material presented in this review.

Ethical approval No approval needed for this study.

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