Submitted: 13.08.2023
Accepted: 16.08.2023
Early publication date: 23.10.2023

Endokrynologia Polska
DOI: 10.5603/ep.96950
ISSN 0423–104X, e-ISSN 2299–8306
Volume/Tom 74; Number/Numer 5/2023

Management of hypoparathyroidism: a Position Statement of the Expert Group of the Polish Society of Endocrinology

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Abstract

Over the past few years, there have been significant advances in our understanding of hypoparathyroidism (HypoPT) in terms of its epidemiology, clinical presentation, etiology, and skeletal and renal complications. Moreover, the available treatment options for HypoPT have changed. This position statement of the Expert Group of the Polish Society of Endocrinology summarizes the current state of knowledge and provides recommendations for optimal management to assist clinicians in the diagnosis, treatment, and monitoring of HypoPT in Poland. The specific aspects of HypoPT management in children, pregnant and lactating women, and patients with chronic kidney disease are also discussed.

HypoPT is a rare disorder characterized by hypocalcemia and the lack or deficiency of parathyroid hormone (PTH). Hypoparathyroidism can be associated with complications, including nephrocalcinosis, nephrolithiasis, renal insufficiency, cataract, seizures, cardiac arrhythmia, depression, and an increased risk of infection. Minimizing complications of HypoPT requires careful evaluation and close monitoring of laboratory parameters. Conventional management of HypoPT has focused on maintaining serum calcium levels using oral calcium and active vitamin D. However, this approach is limited because it does not restore normal PTH function, is often associated with inadequate biochemical control, and raises concerns as to long-term side effects. HypoPT is the only classic endocrine insufficiency that is not commonly treated with the substitution of the missing hormone. Recently, recombinant human PTH(1-84) has become available, offering hope that the use of the missing hormone in the treatment of HypoPT will help achieve better control and reduce the risk of complications. However, this treatment is currently unavailable in Poland. **(Endokrynol Pol 2023; 74 (5): 447–467)**

Key words: *calcium; disorders of calcium/phosphate metabolism; hypoparathyroidism; parathyroid hormone; parathyroid-related disorders; phosphates*

Recommendations in brief

— Hypoparathyroidism (HypoPT) is a rare disorder characterized by an insufficient production of parathyroid hormone (PTH), resulting in hypocalcemia and hyperphosphatemia. HypoPT may occur in the form of PTH resistance known as pseudohypoparathyroidism.
— Most symptoms of HypoPT are due to hypocalcemia. However, some chronic complications may result from PTH deficiency, inadequate phosphate control or develop as adverse effects of treatment.
— Approximately 75% of HypoPT cases in adults are iatrogenic and develop after extensive neck surgery, including thyroid and parathyroid surgery, or after radiotherapy to the neck.
— Vitamin D deficiency before surgery and the level of surgical experience are among the most important risk factors for surgical HypoPT.
— Serum PTH levels measured 12–24 hours after surgery appear to be the most important predictor of hypocalcemia and permanent HypoPT. At PTH levels higher than 10 pg/mL (1.05 pmol/L), permanent HypoPT is highly unlikely and there is no indication for long-term calcium and vitamin D supplementation.
— Chronic HypoPT can be diagnosed if symptoms persist for at least 12 months after anterior neck surgery.

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— Spontaneous HypoPT may be of genetic, autoimmune, or metabolic origin and may be caused by abnormalities in parathyroid gland formation, disorders in PTH secretion, or parathyroid injury or lesions.
— The diagnosis of HypoPT requires confirmed hypocalcemia (low serum calcium adjusted for albumin or low ionized calcium) in the presence of undetectable or inappropriately low levels of intact PTH on at least 2 occasions at least 2 weeks apart.
— Symptoms of acute hypocalcemia range from mild paresthesias to severe tetany, and in extreme cases, life-threatening laryngospasm or seizures.
— The management of symptomatic hypocalcemia requires urgent intravenous calcium administration, and in most cases, continued treatment with calcium by slow intravenous infusion. Once the severe symptoms of tetany resolve, oral calcium preparations should be introduced in previously untreated patients, and calcitriol or any other active vitamin D metabolite should be considered. In previously treated patients, the causes of acute hypocalcemia should be assessed and existing therapy should be modified accordingly.
— The conventional treatment of HypoPT includes oral calcium supplementation and a judicious use of active vitamin D (i.e., calcitriol or another active analogue) at individualized doses, depending on clinical assessment. In patients with hypercalciuria, thiazide diuretics may be helpful. The need for independent vitamin D3 supplementation is also emphasized.
— The frequency of monitoring of serum calcium, phosphate, and other parameters such as magnesium is very much a function of the extent to which a patient is stable on a given dosing regimen. Patients who are well controlled can be assessed for these parameters once or twice a year, while in the remaining patients, the monitoring should be much more frequent (often several times a year).
— Patients in the process of establishing calcium and calcitriol dosing may require biochemical monitoring once a week and sometimes several times a week until stable serum calcium levels are achieved.
— In 2015, recombinant human PTH(1-84) [rhPTH(1-84)] was registered by the US Food and Drug Administration for the treatment of selected cases of HypoPT. One preparation of rhPTH(1-84) was registered in the European Union in 2017 and was granted conditional marketing authorization by the European Medicines Agency in March 2022, but it is currently unavailable in Poland. Teriparatide [rhPTH(1-34)] has not yet been approved for the treatment of HypoPT.
— In pregnant women with HypoPT, it is crucial to maintain corrected serum calcium concentrations in the lower or middle range of their reference values. Therefore, serum albumin-corrected calcium should be closely monitored every 3 to 4 weeks during pregnancy and lactation, and more frequently in the months preceding and following childbirth, and also if symptoms of hypercalcemia or hypocalcemia occur, because the demand for calcium and calcitriol may increase, remain stable, or decrease during pregnancy.
— The demand for calcium and calcitriol in lactating women with HypoPT is generally significantly reduced; therefore, it is necessary to monitor serum corrected calcium concentrations and adjust calcitriol doses in line with the reduced requirement.
— In children, HypoPT most often has a genetic etiology and manifests itself either as an isolated condition or as part of multisystem or polyglandular syndromes. Owing to the predominant genetic background and a congenital nature of the condition, a phenotypic assessment, dysmorphological analysis, and molecular genetic testing are crucial in addition to a differential diagnosis based on hormonal and biochemical testing. In children, much more often than in adults, acute hypocalcemia can manifest as seizures or tetany, sometimes leading to a misdiagnosis of epilepsy. The first-line treatment includes oral calcium supplementation and active vitamin D (e.g., calcitriol) administered at individualized doses based on clinical and laboratory assessment. As there are no official recommendations that apply to children, we propose that monitoring follows the same guidelines as in the adult population.

1. Introduction

Over the past few years, there have been significant advances in our understanding of hypoparathyroidism (HypoPT) in terms of its epidemiology, clinical presentation, etiology, and skeletal and renal complications. Moreover, new treatment options for HypoPT have emerged. This position statement was developed by the Expert Group of the Polish Society of Endocrinology to summarize the current state of knowledge and provide recommendations for optimal management to assist clinicians in the diagnosis, treatment, and monitoring of HypoPT in Poland. Moreover, it discusses the specific aspects of managing HypoPT in children, pregnant and lactating women, and patients with chronic kidney disease (CKD).

In 2015, the first preparation of recombinant human parathyroid hormone(1-84) [rhPTH(1-84)] was intro-

duced in the United States for the treatment of selected cases of HypoPT, and HypoPT was classified as a rare (orphan) disease. This led to significant breakthroughs over the subsequent 5 years in our understanding of calcium homeostasis as well as of the pathophysiology of HypoPT with multiorgan complications resulting from chronic hypocalcemia but also developing as direct effects of absent or deficient parathyroid hormone (PTH), inadequate phosphate[1] control, and treatment side effects. In August 2022, the situation of Polish patients with HypoPT became complicated following the manufacturer's decision to discontinue the production of alfacalcidol, which was the only active vitamin D metabolite available in Poland at the time. An emergency import and subsequent registration of calcitriol, another active vitamin D metabolite, enabled treatment continuation in patients with HypoPT. However, as the new drug had a different activity and pharmacokinetics than alfacalcidol, physicians had to learn the principles of the drug switch.

In November 2022, a series of articles were published by a panel of experts in HypoPT after 2 years of activity as part of the Second International Workshop on the Evaluation and Management of Hypoparathyroidism [1–9]. The task force was convened to summarize the significant advances in knowledge and clinical practice, to define optimal management strategies, and to set new directions for future research on HypoPT. Considering these important advances, we recognized a need to present the current state of the art in the diagnosis, treatment, and monitoring of HypoPT and to update the Polish guidelines for the management of this disorder.

2. Clinical features of hypoparathyroidism

HypoPT (International Classification of Diseases, Tenth Revision code E20) is a complex endocrine disorder characterized by the underproduction of PTH, resulting in hypocalcemia and hyperphosphatemia. HypoPT may also occur in the form of PTH resistance known as pseudohypoparathyroidism (PHP) [9–11].

Most symptoms of HypoPT are caused by acute and chronic hypocalcemia. However, a number of chronic complications, including the inhibition of bone metabolism, nephrolithiasis or nephrocalcinosis, kidney failure, basal ganglia calcifications, cataract, and mental disorders, may be caused by PTH deficiency, inadequate phosphate control, or develop as side effects of treatment.

[1] The term "phosphate" is used throughout the paper in a general (physiological) sense but is also used to refer to measurable serum concentrations of inorganic phosphorus (Pi).

3. Epidemiology

HypoPT is a rare condition with an estimated prevalence of 6.4 to 37/100,000 person-years and an incidence of 0.8 to 2.3/100,000 person-years, although the exact incidence rates remain unknown (they are higher in iodine-deficient countries) [2, 10, 12–17]. Differences in the reported prevalence may be explained by the varying timing and scope of biochemical monitoring and the different definitions of chronic postoperative HypoPT. The number of patients with HypoPT in the United States is estimated at approximately 77 000 [9, 12]. Based on publicly available data from the Polish National Health Fund regarding patients with a principal or secondary diagnosis of HypoPT who received at least one inpatient or outpatient service between 2018 and 2020, the prevalence of HypoPT in Poland (before the coronavirus disease — 2019 pandemic) can be estimated at 8.34/100,000 person-years, including 5.35/100,000 insured persons per year in the group of 20-year-olds and 10.01/100,000 insured persons per year in the group of patients older than 20 years of age. Although these data are not fully reliable because they refer only to insured persons, there are significant differences in reports for individual years, and individual patients may have received benefits with different diagnosis codes, they remain in line with the estimated data for other countries [18]. In January 2014, HypoPT was listed as an orphan disease both by the National Institutes of Health in the United States and by the European Commission.

4. The etiology of hypoparathyroidism

In adults, approximately 75% of HypoPT cases are iatrogenic and develop as a result of extensive neck surgery, including thyroid and parathyroid surgery, or after radiotherapy to the neck area [2, 3, 10, 11, 14]. Postoperative HypoPT is most often classified as a surgical complication. However, in some cases, especially after total thyroid resection in patients with cancer, postoperative HypoPT — like hypothyroidism — is a rather predictable and inevitable consequence of the surgical treatment of the underlying disease.

4.1. Postoperative hypoparathyroidism

The most common cause of acquired HypoPT is a volumetric reduction of the hormonally active parathyroid parenchyma resulting from an inadvertent or unavoidable excision of the glands, a mechanical or thermal injury, and ischemia or the cut-off of blood flow during surgical procedures in the anterior neck region [3, 19–22]. The reported incidence rates of postoperative hypocalcemia depend on the extent of surgery

and the applied diagnostic criteria for hypocalcemia and HypoPT [20].

Depending on the duration of hypocalcemia, postoperative HypoPT is described as transient or permanent. Permanent HypoPT is defined as a condition that persists for more than 12 months after surgery [9]. However, some authors additionally use the concept of prolonged (protracted) HypoPT, defined as abnormally low PTH levels (< 13 pg/mL) and/or the need for calcium substitution with or without active vitamin D after 4 to 6 weeks from surgery [21]. According to literature data, hypocalcemia diagnosed in the early postoperative period after total thyroid resection is a complication in 5.4% to 83% of cases [22–24], while permanent HypoPT occurs in 0.12% to 12.1% of cases [10, 14, 19–24].

Risk factors for hypocalcemia in the early postoperative period can be divided into patient-related factors (vitamin D deficiency, female sex, young age), factors related to the disease that constituted an indication for surgery (giant goiter, advanced malignancy, hyperthyroidism), and surgery-related factors (the extent of surgical intervention, reoperations, the surgeon's experience, and postoperative hemodilution) [25–31].

Recently, the importance of vitamin D deficiency in the preoperative period and the associated hypertrophy and increased blood supply to the parathyroid glands have been emphasized [31-35]. Therefore, we recommend preoperative vitamin D supplementation to obtain the recommended values (serum 25(OH) D > 30 ng/mL), where possible.

To reduce the risk of HypoPT, we recommend intraoperative visualization and sparing of at least 2 parathyroid glands [3, 36–41]. Recently, new imaging methods have been described to aid the assessment of the parathyroid glands: near-infrared autofluorescence (wavelength, 700–900 nm; infrared spectrum, 700 nm–1 mm) and the intravenous administration of indocyanine green [42–50]. These methods appear to be promising for reducing the rate of postoperative HypoPT.

A meta-analysis of 25 studies showed an increased risk of postoperative HypoPT in patients who underwent parathyroid autotransplantation during thyroid surgery [51]. We recommend that all parathyroid glands are left in situ, that elective parathyroid autotransplantation is not performed, and that indications for parathyroid autotransplantation are limited only to cases of unintentional parathyroid resection [9, 52, 53]. In such situations, parathyroid autotransplantation may effectively prevent permanent HypoPT, even though it is associated with an increased incidence of hypocalcemia in the early postoperative period.

Serum PTH levels measured 12 to 24 hours after surgery appear to be the most important predictor of hypocalcemia and permanent HypoPT [5, 10, 29, 54–63]. If the PTH level is higher than 10 pg/mL (1.05 pmol/L), permanent HypoPT is highly unlikely and there are no indications for long-term calcium and vitamin D supplementation. In contrast, serum PTH levels lower than 10 pg/mL are associated with a significantly higher risk of permanent HypoPT (> 50%), although a large number of patients may still recover from transient HypoPT [5, 10]. Therefore, we recommend that serum PTH levels are measured 12 to 24 hours after anterior neck surgery to identify patients who are unlikely to develop persistent hypocalcemia and who thus do not require prolonged monitoring.

4.2. Spontaneous hypoparathyroidism

The etiology of nonsurgical HypoPT is rather complex and requires careful evaluation with the identification of the underlying cause or causes, including genetic, autoimmune, and metabolic factors [4, 10, 11, 64, 65].

Genetically determined HypoPT may be isolated or part of a syndrome. It may be caused by abnormal parathyroid gland formation, anomalous PTH secretion, or parathyroid damage [4, 65]. The diagnostic assessment includes a thorough family history, with a particular attention to the presence of other clinical features characteristic of the syndromic forms of HypoPT.

Autoimmune HypoPT may occur either alone or as part of autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy (APECED), also known as autoimmune polyglandular syndrome type 1 (APS-1). The syndrome is caused by mutations in the autoimmune regulator gene, *AIRE* [65–68], while HypoPT in APECED results from parathyroid damage due to autoantibodies and lymphocytic infiltrations. Apart from HypoPT, the typical major components of APECED are chronic mucocutaneous candidiasis and adrenal insufficiency. HypoPT occurs in more than 80% of patients with APECED and may be the only endocrinopathy present. Patients may also reveal other ("minor") components of APS-1. The diagnosis of APS-1 is likely when at least one of the main features is present with the presence of antibodies to type 1 interferon (observed in > 95% of patients) [4]. The diagnosis can be established if mutation in the *AIRE* gene is confirmed.

Activating antibodies against calcium-sensing receptor (CaSR) and the inhibition of PTH secretion were reported in individuals with autoimmune HypoPT, mainly in those with APS-1 but also in those with an isolated form [69–73]. Some patients showed recovery over time. Unfortunately, there are currently no commercially available tests for antibodies against CaSR.

The rare causes of spontaneous HypoPT include copper deposition (Wilson disease), iron or aluminum in parathyroid tissue [74–77], and infiltration of

the parathyroid glands by tumors [78, 79], granulomatous or inflammatory cells, or amyloid protein [80]. The immune checkpoint inhibitors used in cancer immunotherapy may also induce HypoPT by activating autoantibodies against CaSR [81].

5. The pathogenesis of hypoparathyroidism

Parathyroid hormone is the main regulator of calcium and phosphate homeostasis. It shows direct activity in the bones and kidneys, while in the gastrointestinal tract, it acts indirectly by regulating renal 1α-hydroxylase activity and calcitriol synthesis [82–85]. An inverse steep sigmoidal relationship between serum calcium concentrations (Ca^{++}) and PTH secretion is mediated by the CaSR located on the surface of parathyroid cells [84]. In cases of insufficient PTH production, there is a decrease in the tubular maximum for calcium reabsorption with a concomitant increase in tubular maximum phosphate reabsorption [3, 84]. These 2 pathophysiological processes are, at least in part, responsible for the characteristic biochemical abnormalities of HypoPT: hypocalcemia and hyperphosphatemia [3, 84–86]. Neuromuscular irritability, one of the cardinal clinical features of HypoPT, is caused by hypocalcemia. Ectopic deposition of insoluble calcium phosphate complexes in soft tissues is primarily due to hyperphosphatemia and increased levels of the calcium–phosphate product. Ectopic calcification can also occur in chronic hyperphosphatemia, even if the levels of the calcium-phosphate product are not elevated. [9,84-86].

6. The clinical picture of hypoparathyroidism

The complete clinical picture of HypoPT (signs, symptoms, and complications) is a direct consequence of parathyroid gland damage or dysfunction and, in particular, of deficient PTH secretion or receptor resistance to PTH, resulting in the lack of PTH signaling in the classic target tissues (bone and kidney) as well as in other tissues demonstrating the expression of PTH receptors [84–86]. Therefore, HypoPT is a disease caused by the lack of PTH secretion or PTH signaling [85]. Over a person's lifetime, the consequences of HypoPT can involve almost every organ in the body. In addition, the standard management of hypocalcemia, consisting of oral calcium agents and calcitriol or other active vitamin D analogues, can alleviate disease symptoms, while at the same time causing a number of side effects [9–11, 83, 85].

6.1. Symptoms of hypocalcemia

Most symptoms of HypoPT result from hypocalcemia [11, 12, 84–87]. In the past, physicians focused mainly on symptoms of acute hypocalcemia. Acute hypocalcemia associated with HypoPT may occur immediately after anterior neck surgery. It may also occur in patients who receive treatment for HypoPT in whom the demand for calcium and active vitamin D is altered (e.g., as a result of gastrointestinal dysfunction or interactions with drugs affecting calcium homeostasis) or (more commonly) in patients who do not adhere to medical recommendations. The most common symptom of acute hypocalcemia is tetany. Patients may also develop seizures and laryngospasm, which are life-threatening signs [84–87]. However, it is worth noting that the clinical manifestation of hypocalcemia depends more on how rapidly serum calcium levels decrease rather than on absolute serum calcium levels [85, 86]. This means that even a small decrease in serum calcium levels after neck surgery can manifest as a full-blown tetany attack, whereas patients with autoimmune HypoPT, which develops over years, may present with extremely low serum calcium levels without any tetany symptoms.

There is currently an increasing focus on the consequences of chronic hypocalcemia and hyperphosphatemia. Mild and usually nonspecific neuromuscular symptoms such as numbness and tingling of the face, hands, or feet, paresthesias, and myoclonic spasms of single muscle groups are often the initial clinical signs that warrant a medical consultation. In a less likely scenario, HypoPT is identified on the basis of an incidental finding of hypocalcemia on routine laboratory screening rather than on the basis of symptoms but based on an incidental finding of hypocalcemia on [84].

Chronic hypocalcemia can significantly affect tissues and organs, including the brain, muscles, heart, and kidneys. Disorders in divalent cation homeostasis can cause mild dysfunction, such as paresthesias, latent tetany symptoms, "brain fog", corrected QT interval prolongation on electrocardiography, but also life-threatening conditions [9, 11, 84, 87].

Chronic hypocalcemia and hyperphosphatemia, with elevated levels of serum calcium-phosphate product, observed in untreated or inadequately treated patients, may lead to the development of soft tissue calcification many years later, especially in the brain (particularly in the basal ganglia), mimicking Fahr syndrome, and in the kidneys (nephrolithiasis and nephrocalcinosis). Calcifications may also occur in the joints, skin, blood vessels of the eye, and other organs [9, 86, 87].

6.2. Skeletal manifestations

Bone mineral density (BMD), as determined by dual-energy X-ray absorptiometry (DXA), tends to be higher in

patients with HypoPT compared with controls matched for age, sex, and body mass index [88–92]. Abnormal microstructure of the skeleton involves both the cortical and trabecular bone. Findings from peripheral quantitative computed tomography, high-resolution computed tomography, and histomorphometric analyses of bone biopsies indicate an increased volumetric BMD of the cortical bone, increased volume of the trabecular bone, and reduced porosity of the cortical bone, reflecting a significant slowing (or "freezing") of metabolic turnover, directly related to PTH deficiency [93–99]. Abnormally low bone remodeling and elevated BMD in patients with HypoPT suggest the accumulation of old bone that may be more susceptible to fracture. However, the impact of these changes on bone strength, or the effect of HypoPT on fracture risk, has not been fully elucidated. Available studies are limited by a small number of participants, and reported results are inconsistent [90,100,101].

6.3. Renal symptoms

Considering the absence of PTH action on the renal tubules, it would be natural to expect hypercalciuria and reduced urinary phosphate excretion in untreated patients with HypoPT. However, this is generally not observed, because filtered calcium load is usually much lower than that in patients with normal calcium levels. Similarly, hyperphosphatemia leads to increased filtered phosphate load. Therefore, urinary calcium and phosphate excretion in untreated individuals may be normal [10, 11, 14, 84, 85]. However, this changes radically once therapy is initiated: most patients show hypercalciuria (sometimes significant), reflecting the high demand for calcium and/or active vitamin D to maintain normal serum calcium levels. Because of the high levels of calcium-phosphate product, these patients are at risk of calcium deposition in the kidneys: either manifesting as nephrolithiasis in the pyelocalyceal system or as nephrocalcinosis in the renal parenchyma [6, 10, 11, 101–104]. On the other hand, ectopic calcium deposition does not require an elevated level of calcium-phosphate product [84, 85]. Over time, kidney function in patients with HypoPT becomes impaired. The prevalence of CKD in this population ranges from 2.5% to 41%, depending on the definition and methodology used in the study [101–109]. According to a population-based Danish study, the risk factors for CKD include longer disease duration, higher mean levels of calcium-phosphate product (2.80 $mmol^2/l^2$), and a higher frequency of hypercalcemic episodes [101]. Patients with spontaneous HypoPT are at greater risk of CKD, including CKD stages 4 and 5 [9, 106].

7. The course of the disease and complications

Biochemical abnormalities and target organ changes in patients with HypoPT described above are part of the natural history of the disease and reflect complications that result from the need to use high doses of calcium and active vitamin D metabolites over many years [102, 110, 111]. The various sequelae of the disease and its treatment may develop insidiously over decades [112, 113]. Calcifications of the basal ganglia and other brain regions may lead to complex neurological abnormalities, mainly pyramidal and extrapyramidal disorders [114–118]. They can also form epileptogenic foci, resulting in tonic-clonic (80%), petit mal, partial, or atonic seizures [119]. This is further complicated by the fact that hypocalcemia leads to the lowering of the membrane depolarization threshold, resulting in increased neuronal excitability and lower seizure threshold [120, 121].

Several studies showed that patients with HypoPT are at increased risk of major cardiovascular disease, infections, cataract, and bipolar affective disorder, as described in detail below [112]. The incidence rates of the most common complications are shown in Table 1.

HypoPT may affect the cardiovascular system [102]. Hypocalcemia can result in electrocardiographic abnormalities, including corrected QT interval prolongation. Patients with HypoPT were shown to be at increased risk of ischemic heart disease, cardiac arrhythmias, and stroke [122–124]. However, increased cardiovascular mortality rates were not reported. Although hypocalcemia is a putative etiological factor in a number of these cardiac complications, it was postulated that the lack of direct action of PTH on arterial smooth muscles, endothelial cells, cardiomyocytes, and the cardiac conduction system may also play a role [125].

A higher incidence of all types of infections was reported in patients with both spontaneous and post-

Table 1. ***Incidence of the most common complications of chronic hypoparathyroidism reported in the literature***

Complication	Median incidence rate (%)
Cataract	17
Infections	11
Nephrocalcinosis/nephrolithiasis	15
Kidney failure	12
Convulsions	11
Depression	9
Ischemic heart disease	7
Arrhythmia	7

operative HypoPT [113, 126]. In particular, urinary and respiratory infections were more common in those patients than in the general population. The risk factors for infections seem to be longer disease duration, a higher incidence of hyperphosphatemia, and a higher number of hypercalcemic episodes, but the mechanisms underlying these links remain unclear. As calcium signaling plays an important role in immune function (including cytokine production by mast cells, T cells, and natural killer cells, T-cell cytotoxic effects, and lymphocyte differentiation), immune dysfunction may be directly caused by abnormally low serum calcium levels [126].

The risk of cataract in patients with chronic HypoPT is 2- to 4-fold higher than in the general population, and surgical treatment may be required earlier, at around the age of 35 years old on average. The mechanisms leading to cataract are not well understood, and the risk factors for cataract include spontaneous HypoPT and prolonged disease duration [127, 128].

One of the most common complaints in patients with HypoPT is significantly worse quality of life, mainly due to neuropsychiatric symptoms, including brain fog [129–133]. Quality-of-life studies based on standardized questionnaires, including the 36-Item Short Form Survey (SF-36) for chronically ill patients or the Hypoparathyroid Patient Experience Scale-Symptom (HPES-Symptom) designed specifically for patients with HypoPT [134], reported significantly lower scores in patients with HypoPT *vs* the general population in both cognitive and emotional domains as well as in self-assessment of physical and mental health. The lower quality of life appears to be independent of the etiology of HypoPT, duration of the disease, or the degree of biochemical compensation with calcium preparations and active vitamin D metabolites.

The relationship between HypoPT and mortality is not clear. Data from 5 registries are inconclusive, with mortality rates reported to be increased in some studies but not in others [14, 135, 136].

HypoPT imposes a heavy financial burden on the healthcare system, mainly because of increased use of health services. The management of symptoms and comorbidities in patients with HypoPT results in increased costs and resource utilization, with an increased number of outpatient consultations and emergency department admissions. This refers particularly to patients with inadequately controlled disease [137–141].

8. The diagnosis of hypoparathyroidism

The diagnosis of HypoPT is confirmed by the finding of hypocalcemia (low serum calcium adjusted for albumin or low ionized calcium) in the presence of undetectable or inappropriately low intact PTH levels on at least 2 occasions separated by at least 2 weeks [4, 9–11, 83, 142–144]. In theory, the measurement of ionized serum calcium levels should be more physiologically accurate than that of albumin-corrected total serum calcium levels. However, this test is not widely used in clinical practice owing to several limitations including the ion-selectivity of the electrodes, the type of material tested (serum, plasma, heparinized whole blood), and, most importantly, the need to carry out assays under anaerobic conditions, within a maximum of 15 minutes of collection [4, 143]. Most clinicians assess serum calcium levels in relation to the albumin concentration and make the standard adjustment as mentioned above [4].

HypoPT is further confirmed by additional abnormalities caused by PTH deficiency, although their presence is not required to establish the diagnosis. These abnormalities include elevated serum phosphate levels, reduced 1,25-dihydroxyvitamin D [1,25(OH)2D], and low urinary calcium excretion. Postsurgical HypoPT can be defined as permanent if it persists for 12 months or longer after neck surgery [9]. Diagnostic criteria for HypoPT are summarized in Table 2.

Once the diagnosis of HypoPT is established, the following further steps are recommended (Tab. 3):

— medical history: family history; history of anterior neck surgery or irradiation; assessment for kidney stones and fractures based on reported renal and skeletal symptoms; assessment of the general quality of life as well as medications and supplements used;
— physical examination: evaluation of the Chvostek sign and Trousseau sign of tetany (neuromuscular hyperactivity); examination of the anterior neck for signs of previous surgery, nails and mucous membranes for fungal infection (candidiasis), the skin for signs of vitiligo; examination for cataract, calcifications, and joint mobility.
— Imaging: skull X-ray for basal ganglia and other intracerebral calcifications; abdominal ultrasound, X-ray, or computed tomography for renal stones and calcifications;

Table 2. ***Diagnostic criteria for hypoparathyroidism***

- Hypocalcemia (corrected for albumin concentration) confirmed on at least 2 occasions separated by at least 2 weeks
- Undetectable or abnormally low PTH levels (i.e., < 20 pg/mL), as measured by second- or third-generation immunoassay, in addition to hypocalcemia identified by at least 2 measurements
- Phosphate levels at or above the upper range of normal (helpful to confirm the diagnosis but not required)
- Permanent postsurgical hypoparathyroidism diagnosed if it persists for 12 months or longer after neck surgery

PTH — parathyroid hormone

Table 3. *Recommended diagnostic steps after confirming hypoparathyroidism in adults*

Family history	Family history of hypoparathyroidism or other endocrine disorders
Medical history	History of anterior neck surgery or irradiation, other endocrine diseases
	Neurological disorders, seizure disorders/convulsions;
	Visual disturbances
	Mental disorders
	History of long bone fractures
	Cardiovascular diseases and events
	Multiple recurrent infections or conditions suggesting immune deficiencies
	Abnormal laboratory findings
Physical examination	Ectopic calcifications (e.g., the organ of vision)
	Signs of previous neck surgeries (including scars from strumectomy)
	Tetanic symptoms: Chvostek sign, Trousseau sign, Vitiligo
	Nail beds for fungal infection
	Candidiasis of the mucous membranes
	Musculoskeletal examination: the range of joint mobility, joint contours
Additional laboratory tests	Serum magnesium levels
	Serum 25-hydroxyvitamin D, 1,25-dihydroxyvitamin D
	Serum creatinine
	Daily calcium and creatinine excretion in a 24-hour urine collection, creatinine clearance or eGFR
Imaging of target organs	X-ray (skull X-ray in PA and lateral projection)
	Ultrasound or computed tomography of the kidneys
	Bone mineral density by densitometric analysis
Genetic and molecular testing	Recommended if genetic or hereditary background is suspected (young age, facial dysmorphic features and body disproportion, strong family history, polyglandular failure)

eGFR — estimated glomerular filtration rate; PA — posterior-anterior

— genetic studies: if the clinical picture suggests a genetic background (e.g., family history, young age, signs of another autoimmune disease), germline mutation testing should be considered to assess the risk of the disease in other family members (siblings, children). In patients who reveal other clinical features of autoimmune polyendocrinopathy (APECED), we recommend genetic testing for the pathogenic variants of the autoimmune regulator gene *AIRE* gene. The term "autoimmune HypoPT" should be avoided when referring to patients without APECED, as there is no definitive diagnostic test for polygenic autoimmune HypoPT.

9. Differential diagnosis of hypoparathyroidism

Hypocalcemia is characteristic of PHP and may accompany rickets or osteomalacia in the setting of hypovitaminosis or vitamin D metabolic disorders. In both these situations, serum PTH levels are elevated [144]. In PHP, there is resistance of target organs to PTH, resulting in low serum calcium and high phosphate levels, even though PTH secretion may be significantly increased (see below) [4, 14, 84, 144]. In the case of vitamin D deficiency, intestinal absorption and bioavailability of calcium and phosphate are impaired, while PTH is secondarily elevated.

10. Treatment of acute hypocalcemia

Acute hypocalcemia may be an early consequence of anterior neck surgery. It may also reflect sudden changes in calcium and vitamin D requirement or result from inadequate compliance with treatment. Symptoms of acute hypocalcemia may range from mild paresthesias to severe tetany and, in extreme cases, laryngospasm or seizures [9, 10, 14, 84].

Symptomatic hypocalcemia requires an intravenous administration of 1 to 2 (10–20 ml) ampoules of calcium chloride (184 mg/10 mL), corresponding to elemental calcium at a dose of 184 to 368 mg (4.6–9.2 mmol), preferably in 50 mL of 5% glucose over 10 to 20 minutes. Most often, treatment should be continued with a slower intravenous calcium infusion (0.5–1.5 mg Ca/kg/h), for example, 5 ampoules of calcium chloride (920 mg Ca^{++}) in 500 mL of 0.9% sodium chloride (NaCl) or 5% glucose, starting at 50 mL/h, under control of serum calcium levels. Alternatively, calcium gluconate (10%) can be used, but allowing for the fact that the elemental calcium content in this case is approximately twice as low (2.23 mmol; 89 mg/10 mL). The aim is to reduce symptoms of hypocalcemia, which usually means achieving serum calcium levels slightly below the reference range [8, 9, 83, 145, 146].

After resolution of acute tetany symptoms, oral calcium preparations (e.g., calcium carbonate, 3 × 1000 mg) should be introduced in treatment-naive patients, and active vitamin D (e.g., calcitriol, 0.25 μg to 0.5 μg once or twice daily) should be considered. In previously treated patients, the causes of acute hypocalcemia should be assessed and the existing therapy modified accordingly.

Recommendations on acute treatment are presented in detail in Table 4.

Table 4. *Treatment of hypoparathyroidism*

Acute hypocalcemia	
Calcium chloride, 1 ampoule of 10 mL = 184 mg Ca^{++} (4.6 mmol)	Intravenous 1–2 ampoules of 10–20 ml followed by *i.v.* infusion of 5 ampoules of calcium chloride (920 mg Ca^{++}) in 500 mL of 0.9% NaCl or 5% glucose, starting at 50 ml/h, under control of serum calcium levels In children: 3.68 mg (0.092 mmol) = 0.2 mL/kg body weight by slow *i.v.* infusion
Calcium gluconate (10%), 1 ampoule of 10 mL = 89 mg Ca^{++} (2.23 mmol)	The number of ampoules should be increased accordingly
The treatment should be continued until resolution of hypocalcemia symptoms, which is usually associated with obtaining serum calcium levels just below the reference range	
Chronic treatment	
Oral calcium salts The average demand for elemental calcium for the treatment of hypoparathyroidism is 1.0–3.0 g Ca^{++}/d	**Calcium carbonate**, 40% Ca^{++} 3–6 g/d (1.2–2.4 g Ca^{++}), in 3–4 doses, preferably with meals for better absorption and to act as a phosphate binder **Calcium citrate**, ~20% Ca^{++} Indicated in patients with achlorhydria or in those chronically treated with proton pump inhibitors, as well as in patients with gastrointestinal intolerance to calcium carbonate **Calcium lactogluconate**, 13% Ca^{++}
Active metabolites of vitamin D	**Calcitriol,** capsules of 0.25 μg and 0.5 μg, usually 0.25–2 μg/d, in one or two doses Alternatively: **Alfacalcidol**, capsules of 0.25 μg and 1.0 μg 0.5–6 μg/d, in one or two doses
Vitamin D_3 (cholecalciferol)	In all patients, in line with current recommendations for the general population
Thiazides	If necessary to control hypercalciuria; they may cause hypokalemia, hyponatremia, and exacerbate hypomagnesemia
Phosphate binders	Sevelamer, lanthanum carbonate, and, exceptionally, antacids (only when a low-phosphate diet is not sufficient to control hyperphosphatemia (Pi > 6.5 mg/dL)
Magnesium	250–1000 elemental Mg^{++} in 2 doses between meals (not to be combined with calcium medications)

Ca — calcium; *i.v.* — intravenous; NaCl — sodium chloride; Pi — inorganic phosphate; Mg — magnesium

11. Chronic treatment of hypoparathyroidism

For many years, the conventional approach to HypoPT treatment involved the judicious use of oral calcium and active forms of vitamin D (i.e., calcitriol or another active analogue) in individualized doses, depending on clinical assessment [9, 83, 142, 146, 147]. In patients with hypercalciuria, thiazide diuretics may be helpful. The need for independent vitamin D_3 (cholecalciferol) supplementation is also emphasized due to its nonclassical, extraskeletal (noncalcemic) effects, in line with the current recommendations for the healthy population [148].

The aims of chronic treatment of HypoPT are as follows:

— to prevent symptoms of hypocalcemia;
— to maintain serum calcium levels slightly below normal, i.e., not more than 0.125 mmol/L (0.5 mg/dL) below the reference values or in the low range of normal [2.1–2.6 mmol/L (8.4–10.4 mg/dL)];
— to maintain fasting serum phosphate concentrations within the high normal range or only slightly elevated [in adults: 0.9–1.6 mmol/L (2.8–5.0 mg/dL)];
— to avoid hypercalcemia;
— to avoid hypercalciuria (reference range: women < 250 mg/24 h; men < 300 mg/24 h);
— to maintain the calcium-phosphate product below 55 mg^2/dL^2 (4.4 $mmol^2/L^2$); and
— to avoid renal calcification (nephrocalcinosis/nephrolithiasis) and other soft tissue calcifications [9, 83, 142].

Detailed recommendations on chronic treatment are outlined below and in Table 4.

11.1. Calcium supplementation

The average requirement for elemental calcium in the treatment of HypoPT is 1.0 to 3.0 g/d, although it may be higher in individual cases [146, 149–151]. The optimal preparation for HypoPT treatment is calcium carbonate (40% of elemental calcium). In some cases, calcium citrate (approx. 20% Ca^{++}) is an alternative, for example, in patients with achlorhydria, patients on chronic treatment with proton pump inhibitors, and patients with persistent constipation due to calcium carbonate use [9, 151–153]. Calcium lactogluconate, although well tolerated, contains only 13% of elemental calcium. Medications containing calcium phosphate should be avoided.

11.2. Active metabolites of vitamin D: calcitriol and alfacalcidol

The rationale for using the active forms of vitamin D (e.g., calcitriol) in HypoPT is quite clear, considering that the underproduction of PTH, together with hyperphosphatemia, impairs the renal conversion of 25-hydroxycholecalciferol to its active form [154]. As with calcium supplementation, the range of calcitriol requirements to maintain the target serum calcium concentration is quite wide — generally from 0.25 to 2 μg per day at 1

or 2 doses [9, 146, 155]. Calcitriol is an active vitamin D analogue that is most widely used in the treatment of HypoPT. Alternative analogues that require activation in the liver, such as 1α-hydroxyvitamin D (alfacalcidol) and dihydrotachysterol, are used only in some European countries and in Asia [146, 156–159]. Compared with alfacalcidol, calcitriol is about twice more potent and an increase in serum calcium levels occurs as early as 12 to 24 hours and stabilizes after 2 to 3 days, but the effective duration of action is shorter (about 24–36 hours *vs.* 5–7 days for alfacalcidol). This means that for patients previously treated with alfacalcidol, while switching the therapy from alfacalcidol to calcitriol, the dose of the drug initially needs to be twice reduced, and at least some patients will require at 2 doses every 12 hours [160, 161].

When the amount of supplemental calcium and active vitamin D is adjusted in patients who either start treatment or have switched medications, serum calcium levels should be measured every 1 to 2 weeks, or even several times a week, until stable calcium levels are achieved. It is important to note that an increase in the dose of calcitriol or other active vitamin D not only results in higher serum calcium levels but also increases the intestinal absorption of phosphate and serum phosphate levels.

11.3. Thiazides

Thiazide diuretics increase calcium reabsorption in the distal renal tubules and are used to reduce hypercalciuria. Their potential side effects include hypokalemia, hypomagnesemia, and hyponatremia [162, 163]. In patients with autoimmune polyendocrine syndrome type 1, especially with adrenal insufficiency, thiazides may exacerbate orthostatic hypotonia and hyponatremia, so they should be used with caution and introduced under close monitoring of blood pressure and serum sodium and potassium levels.

11.4. Phosphate binders

In most patients with chronic HypoPT, a low-phosphate diet (e.g., without milk and milk products) helps maintain phosphate levels that are normal or near the upper limit of normal. Only in situations where hyperphosphatemia is significantly above normal (phosphate levels > 6.5 mg/dL), the use of phosphate binders (sevelamer, lanthanum carbonate, or, exceptionally, aluminium containing antacids) should be considered [9, 83].

12. Treatment monitoring

The frequency of monitoring of serum calcium, phosphate, and other parameters such as magnesium is very much a function of the extent to which a patient is stable on a given treatment regimen. Patients with well-controlled disease can be assessed once or twice a year, while in others assessments should be done much more frequently, often several times a year [5, 9, 11, 83, 85, 142].

During the initial adjustment of calcium and calcitriol to the patient's needs, calcium measurement is recommended once a week, and sometimes several times a week, until stable serum calcium levels are achieved. Sometimes it is useful to measure serum calcium levels at different times of the day. Adjusting drug doses to the individual patient's needs can be challenging because daily requirements can be significantly affected by gastrointestinal disorders, infections, and even intense physical exertion as well as anxiety or distress. Dividing the calcium dosage into several doses per day helps prevent fluctuations in serum calcium levels.

Renal function should be assessed once a year by 24-hour urine collection with the measurement of daily calcium and creatinine excretion as well as calculation of creatinine clearance. In patients with a history of nephrolithiasis or calciphylaxis, renal imaging (ultrasound, computed tomography) is recommended every 3 to 5 years in the absence of symptoms, or more frequently if the patient presents with pain or dysuria.

Ophthalmological follow-up examinations for cortical cataract depend on the results of the initial examination and should be repeated every 1 to 2 years and whenever vision deteriorates.

It is not clear whether basal ganglia calcifications and other central nervous system calcifications require regular monitoring, even if detected during initial diagnosis. Although BMD in patients with HypoPT is usually above the reference range, densitometric monitoring is recommended according to current standards [164].

A summary of recommendations for treatment monitoring is presented in Table 5.

Table 5. ***Monitoring of conventional treatment in patients with hypoparathyroidism***

- Calcium, phosphate, magnesium, creatinine/eGFR: once a year or more often if needed
- Daily urinary calcium and creatinine excretion, assessment of creatinine clearance once a year or as clinically indicated
- Renal imaging studies (in the case of nephrolithiasis/nephrocalcinosis)
- Ophthalmological examination (cataract)
- Imaging of the central nervous system (basal ganglia and other sites of calcification)
- BMD: every year or every second year

BMD — bone mineral density; eGFR — estimated glomerular filtration rate

13. Parathyroid hormone in the treatment of hypoparathyroidism

Until recently, of all classic endocrine deficiency disorders, HypoPT has been the last one for which the missing hormone was not available. In 2015, rhPTH(1-84) was registered by the US Food and Drug Administration (FDA) for the treatment of selected cases of HypoPT. In the European Union, the first preparation of rhPTH(1-84) was registered in 2017, and in March 2022, it was granted conditional marketing authorization by the European Medicines Agency. However, the drug is currently unavailable in Poland.

The benefits and risks of PTH therapy, as compared with conventional therapy, were assessed in May 2022 in a systematic review and meta-analysis of randomized trials [7]. The studies confirmed that PTH treatment reduces calcium and active vitamin D metabolites by at least 50% in a significant number of patients, and in some patients even results in complete calcitriol withdrawal. The significant reduction of serum phosphate levels, when compared with conventional therapy, may be beneficial in terms of lowering the risk of ectopic calcifications, but further studies are needed to confirm this [165–170]. A meta-analysis evaluating PTH therapy *vs* conventional therapy reported a small, but significant, improvement in the quality of life [171]. PTH treatment is unlikely to cause significant adverse events, but the quality of evidence is rather low. In randomized trials, PTH treatment was associated with an increase in the number of hypercalcemic episodes, as compared with conventional therapy [7].

Treatment with PTH may be appropriate in patients with HypoPT inadequately controlled by conventional therapy, including individuals with significant fluctuations in serum calcium levels, those requiring repeated emergency interventions or hospitalization for hypocalcemia or hypercalcemia, and patients with hyperphosphatemia, renal insufficiency, significant hypercalciuria, nephrocalcinosis, or nephrolithiasis. Patients with gastrointestinal pathology and malabsorption or gastrointestinal side effects associated with high doses of calcium may also benefit from PTH treatment. Finally, PTH therapy may also be appropriate for individuals with osteoporosis who require pharmacological intervention, as antiresorptive drugs (e.g., denosumab) may significantly exacerbate hypocalcemia [9, 10, 83].

The treatment with rhPTH(1-84) starts at a dose of 50 μg per day subcutaneously; then, the dose is increased by 25 μg every 4 weeks under serum calcium control to a maximum dose of 100 μg per day.

Teriparatide [rhPTH(1-34)] has not yet been approved for the treatment of HypoPT.

Table 6. *Indications for treatment with recombinant human parathyroid hormone (1-84) in hypoparathyroidism*

- Inadequate control of serum calcium (may be caused by a comorbidity or medications used, malabsorption, lack of compliance with treatment)
- Need for high doses of calcium or vitamin D to maintain target serum calcium levels: Ca > 2.5 g elemental calcium/d, calcitriol > 2.0 μg/d (alfacalcidol > 3.0 μg/d)
- Hypercalciuria, nephrolithiasis, nephrocalcinosis, or reduced creatinine clearance/eGFR (> 60 mL/min)
- Hyperphosphatemia > 6.5 mg/dL and/or calcium-phosphate product > 55 mg^2/dL^2 (4.4 mmol^2/l^2)
- Gastrointestinal disorders associated with malabsorption
- Reduced quality of life

Ca —eGFR — estimated glomerular filtration rate

Indications for treatment with rhPTH(1-84) are summarized in Table 6.

14. Hypoparathyroidism in pregnancy and lactation

Pregnancy causes characteristic changes in serum ion and calciotropic hormone concentrations that can be easily misinterpreted as indicating the presence of calcium and bone disorders, especially as calcium, phosphate, and calciotropic hormone assays are not commonly ordered during pregnancy. The increase in extracellular fluid volume already in early pregnancy leads to a decrease in albumin levels along with total serum calcium levels. However, the concentration of ionized calcium (the biologically active fraction) as well as of serum phosphate remains stable. The PTH level is in the lower range of normal (i.e., at 10-30% of the reference values for a nonpregnant woman) and returns to prepregnancy values after delivery. This phenomenon is not observed in women with inadequate calcium supply and vitamin D deficiency, who show elevated PTH levels in late pregnancy, and the increase may be significant. The serum $1,25(OH)_2D$ concentration increases twofold already in very early pregnancy and remains elevated until delivery. This increase in calcitriol synthesis is independent of PTH. The PTH-related peptide (PTHrP) is produced by the placenta and mammary gland tissue, and its serum concentration starts to increase from the third to the thirteenth week of gestation to increase threefold by the end of pregnancy. The increase in PTHrP levels is most likely responsible for the increase in $1,25(OH)_2D$ synthesis and for the suppression of PTH secretion in pregnant women [172, 173].

Due to increased endogenous production of $1,25(OH)_2D$ and PTHrP during pregnancy, pregnant women with HypoPT may have a lower demand for

calcium and active vitamin D. However, the increased demand for calcium by the developing fetal skeleton, as well as increased urinary calcium loss, may result in an increased tendency to hypocalcemia in some women with HypoPT, which may necessitate the use of higher calcitriol doses. This refers particularly to women with inadequate dietary calcium [174–179].

In pregnant women, it is crucial to maintain normal serum calcium levels. Hypocalcemia in pregnancy is associated with an increased uterine contraction activity and an increased risk of either preterm labor or pregnancy loss. Maternal hypocalcemia also leads to secondary hyperparathyroidism in the fetus, which may end in death, and may be associated with fetal skeletal demineralization and in-utero fractures [180, 181]. On the other hand, maternal hypercalcemia may inhibit the development of the fetal parathyroid glands and cause transient hypocalcemia in the newborn. After birth, the newborn should be assessed and closely monitored for normal serum calcium levels. Therefore, because during pregnancy the demands for calcium and calcitriol may increase, remain stable, or decrease, serum albumin-corrected calcium levels should be assessed every 3 to 4 weeks during pregnancy and lactation, with a higher frequency in the months preceding and following childbirth, as well as if symptoms of hypercalcemia or hypocalcemia occur. During pregnancy and lactation, it is recommended to maintain serum calcium adjusted for albumin within the low-to-mid normal reference range. Changes in serum albumin levels during pregnancy warrant the measurement of calcium adjusted for albumin or ionized calcium [9, 177].

In isolated cases, pregnant women with PHP (genetically determined PTH resistance) were found to have normal calcium levels, reduced PTH levels by 50% (or more), and a 2- to 3-fold increase in the serum $1,25(OH)_2D$ concentration. However, due to a defect in the common receptor for PTH and PTHrP, these changes cannot be linked to the action of PTHrP, and the mechanism by which calcium metabolism is improved remains unknown [182–184].

After delivery, $1,25(OH)_2D$ concentrations quickly return to normal; however, the breast tissue of the lactating woman start to produce significant amounts of PTHrP, which enhances maternal bone resorption and increases calcium reabsorption by the mother's kidneys. As a result, the demands for calcium and calcitriol in lactating women with HypoPT are generally significantly reduced [176, 177, 185, 186]. In at least one case, it was confirmed that maternal serum PTHrP levels were sufficient for normal $1,25(OH)_2D$ synthesis and maintenance of normal calcium levels. During lactation, it is necessary to monitor serum-corrected calcium levels and adjust calcitriol according to decreasing demands. The lack of the regular monitoring of serum calcium levels and appropriate adjustment of the calcitriol dose may lead to symptomatic hypercalcemia. Changes in calcitriol dosage should be monitored by repeat measurement of serum calcium levels within 2 to 3 days.

After cessation of breastfeeding, PTHrP production generally ceases and mineral metabolism abnormalities, typical of HypoPT, quickly return. However, a case of a woman was described who showed persistent PTHrP production by the mammary glands after cessation of breastfeeding and normal calcium levels.

In lactating women with PHP, PTHrP resistance is responsible for the lack of a significant increase in endogenous $1,25(OH)_2D$ synthesis and, probably, for a significantly lower mobilization of calcium from the skeleton than in healthy women. As a result, the demands for calcium and calcitriol may be significantly higher [182–184].

Establishing an optimal diet for a pregnant woman with HypoPT remains a challenge. On one hand, it should be appropriate for normal fetal development and should include a balanced supply of protein, carbohydrates, fats, vitamins, and micronutrients. On the other hand, it should limit the supply of phosphates to a necessary minimum.

Calcium, vitamin D_3, and active vitamin D analogues, although formally in category C of the drugs for use in pregnancy, may be safely used in pregnant women with HypoPT (calcitriol does not pass through the placenta) [9, 177]. Thiazide diuretics are not recommended for use during pregnancy (category B). While PTH therapy is potentially very attractive for pregnant women, it is not recommended due to the lack of safety data and is categorized by the FDA as pregnancy risk category C [9, 177]. Changes in calcitriol dosage should be monitored by serum calcium assay after 2 to 3 days.

We recommend an interdisciplinary approach to the care of pregnant and lactating women with HypoPT, with a close collaboration between the endocrinologist, gynecologist or obstetrician, and neonatologist.

15. Hypoparathyroidism in children and adolescents

In contrast to the adult population, HypoPT in children is most often genetic in origin, manifesting either as an isolated condition or as part of multisystem or polyglandular syndromes, with endogenous PTH insufficiency either as a leading or a component feature. Most commonly, congenital HypoPT during the developmental period is caused by agenesis or hypoplasia of the parathyroid glands, usually a component of the DiGeorge syndrome, caused by a microdeletion

of the long arm of chromosome 22 (22q11.2 deletion syndrome). In addition to HypoPT, the syndrome encompasses other anomalies caused by the failure of the third and fourth pharyngeal pouches to develop. These anomalies include thymic aplasia with immune disorders and conotruncal congenital heart and facial defects (velo-cardio-facial syndrome, or Shprintzen syndrome). A diagnosis based on the finding of biochemical abnormalities, typical for HypoPT, and on the phenotype evaluation, can ultimately be confirmed by the detection of the 22q11.2 deletion by fluorescence in situ hybridization or single nucleotide polymorphism microarray [187]. HypoPT may also be a component of a number of other rare genetic syndromes: deletion of the short arm of chromosome 10, isolated congenital HypoPT, resulting from agenesis/hypoplasia of the parathyroid glands, and HypoPT combined with deafness and renal dysplasia (HDR, or Barakat syndrome) [188], as well as autosomally inherited Kenny-Caffey syndrome type 1 and type 2, and Sanjad-Sakati syndrome (HypoPT, retardation and dysmorphism syndrome).

HypoPT during the developmental period may also result from parathyroid damage in the course of an autoimmune process, either as an isolated form or, more often, as part of polyendocrinopathy inherited in an autosomal recessive manner: APS-1/APECED (see section 4.2) [66, 68]. Autosomal dominant hypocalcemia type 1 (familial hypercalciuric hypocalcemia), where the inhibition of PTH secretion is due to mutations in the *CASR* gene, should also be considered in the differentiation of spontaneous HypoPT in children [73, 189–192]. An analogously acquired effect may depend on the action of antibodies against the extracellular domain of CaSR (see section 4.2) [69, 71, 72]. Pediatric patients are likely to gradually recover normal PTH activity along with a decrease in anti-CaSR antibody titers [69, 71].

In children and adolescents, it is much less common for HypoPT to result from parathyroid injury following neck surgery or radiotherapy. Neck surgeries in the neck region (thyroid excision, plastic surgery in 22q11.2 deletion syndrome) are associated with a very high risk of permanent parathyroid damage and perioperative hypocalcemia in children [193–196]. This is highlighted in the guidelines for the management of children with 22q11.2 deletion syndrome, which recommend mandatory calcium monitoring in the perioperative period [197]. HypoPT in children may be a consequence of inflammatory infiltration in infectious or metabolic diseases (Wilson disease), although such cases are extremely rate. Severe chronic magnesium deficiency, although rare, can lead either to suppression of PTH secretion or lack of any biological effects of PTH due to the insensitivity of effector tissues to the hormone.

As in adults, HypoPT in children is characterized by either absent or inadequate PTH secretion, hypocalcemia, and hyperphosphatemia, and is manifested by symptoms resulting from acute or chronic hypocalcemia and by chronic disturbances of bone and mineral metabolism. In children, the risk of nephrolithiasis, basal ganglia calcifications, and neuropsychiatric and seizure disorders is higher than in adults [9, 198], while acute hypocalcemia can be more frequently manifested by seizures or tetany, sometimes leading to a misdiagnosis of epilepsy. The finding of extremely low PTH activity in children presenting with hypocalcemia always requires a thorough examination of an underlying mechanism. Due to the predominant genetic background and a congenital nature of the condition, a phenotypic assessment and dysmorphological analysis, as well as molecular genetic testing, are crucial in addition to differential hormonal and biochemical diagnosis. Children with HypoPT often present with a wide spectrum of dental anomalies, such as hypoplastic teeth, which generally require specialist care. The current data on BMD or fracture risk in children with HypoPT are rather inconclusive. Studies involving small groups of children with 22q11.2 deletion syndrome and pediatric patients after thyroid cancer surgery did not show any significant changes in BMD. However, it is possible that during growth in children with HypoPT, quantitative abnormalities on DXA scan or the microstructural impairment of the skeleton may not yet become apparent owing to the too short duration of the disease process [199].

The treatment of neonates, infants, and children with HypoPT aims to maintain normal calcium and phosphate levels and to prevent severe symptoms associated with hypocalcemia (seizures, tetany, neuropsychiatric disorders) and hyperphosphatemia [190, 197–200]. The first-line treatment includes oral calcium supplementation and active forms of vitamin D (calcitriol) at individualized doses based on clinical and laboratory evaluation [8, 197–200]. Regardless of vitamin D analogues, conventional cholecalciferol supplementation should be used at age-recommended doses [8, 148]. In children with permanent hyperphosphatemia, sevelamer carbonate is used, with cautious dose selection based on individual needs and serial measurements of serum phosphate levels [201]. During the therapy, calcium (total, corrected, and ionized), phosphate and alkaline phosphatase, as well as urinary calcium (calcium/creatinine) and phosphate levels should be monitored regularly using a 24-hour urine collection. In children with HypoPT, DXA may not be the standard of management, but the assessment

of BMD of the whole skeleton (total body less head) and lumbar spine 1-4 can provide valuable information about the skeletal status. In the absence of official recommendations, we suggest following the guidelines on monitoring for adults (see section 11).

When conventional treatment is insufficient, there is a hope in the results of studies on the subcutaneous use of teriparatide [rhPTH(1-34)], which may have the expected metabolic effect [202–204]. However, these observations apply only to small groups of patients with genetic syndromes. The use of rhPTH(1-84) has not been studied yet in the developmental age population with HypoPT [8, 9].

16. Hypoparathyroidism in patients with chronic kidney disease and in patients on dialysis

HypoPT may be associated with CKD, but there are no data on the incidence of these comorbidities. Patients with previously diagnosed HypoPT may develop CKD, and this refers both to patients with spontaneous or postoperative HypoPT, but those with spontaneous HypoPT appear to be at greater risk of CKD. In an alternative scenario, HypoPT develops in patients at various stages of CKD (end-stage renal disease, when on dialysis, or after kidney transplant). HypoPT in these patients will almost always be iatrogenic (e.g., following surgical treatment for secondary or tertiary hyperparathyroidism or other anterior neck surgery, such as for thyroid cancer).

The complexity of calcium-phosphate homeostasis disorders lies in the consequences of PTH deficiency or insufficiency compounded by abnormalities due to CKD: phosphate retention, overproduction of phosphatonins (e.g., fibroblast growth factor 23), impaired renal synthesis of calcitriol [1.25$(OH)_2$D], and reduced gastrointestinal calcium absorption, which cannot be compensated for by a secondary increase in PTH secretion and increased bone resorption [205].

The range of tools available to the physician for the diagnosis and monitoring of treatment in patients with HypoPT and kidney disease is not fundamentally different from those recommended for patients with HypoPT without impaired renal function. However, given the metabolic abnormalities associated with kidney disease and its potential treatment, important differences should be accounted for. For example, in many patients, reliable assessment of urinary calcium, phosphorus, and creatinine excretion is not possible due to oliguria. Moreover, patients with end-stage renal failure may take drugs that affect calcium-phosphate metabolism, and this may include long-term chronic treatment. Calcium and noncalcium phosphate binders that reduce the absorption of phosphate from the gastrointestinal tract and reduce the level of the calcium-phosphate product [206], as well active vitamin D metabolites or analogues (paracalcitol, 19-nor-1,25-$(OH)_2D_2$) [207], are at the same time frequently used for HypoPT treatment. Also some patients with preserved trace parathyroid function and HypoPT with partial PTH deficiency may receive suppressive calcimimetic treatment (e.g., with cinacalcet) [208]. Therefore, a close cooperation between the nephrologist and endocrinologist is vital.

In patients who are not on dialysis, the most important therapeutic issue is a very high phosphate retention, which translates into high calcium-phosphate product levels. Therefore, these patients require a restrictive low-phosphate diet (< 700 mg phosphorus per day), and usually the use of noncalcium (e.g., sevelamer) and calcium (calcium carbonate) phosphate binders [209]. The aim of treatment is to maintain a calcium-phosphate product level of less than 55 mg^2/dL^2. Levels higher than 70 mg^2/dL^2 are associated with a high risk of calcium salt precipitation (e.g., in the walls of small vessels, which may lead to calciphylaxis) [210].

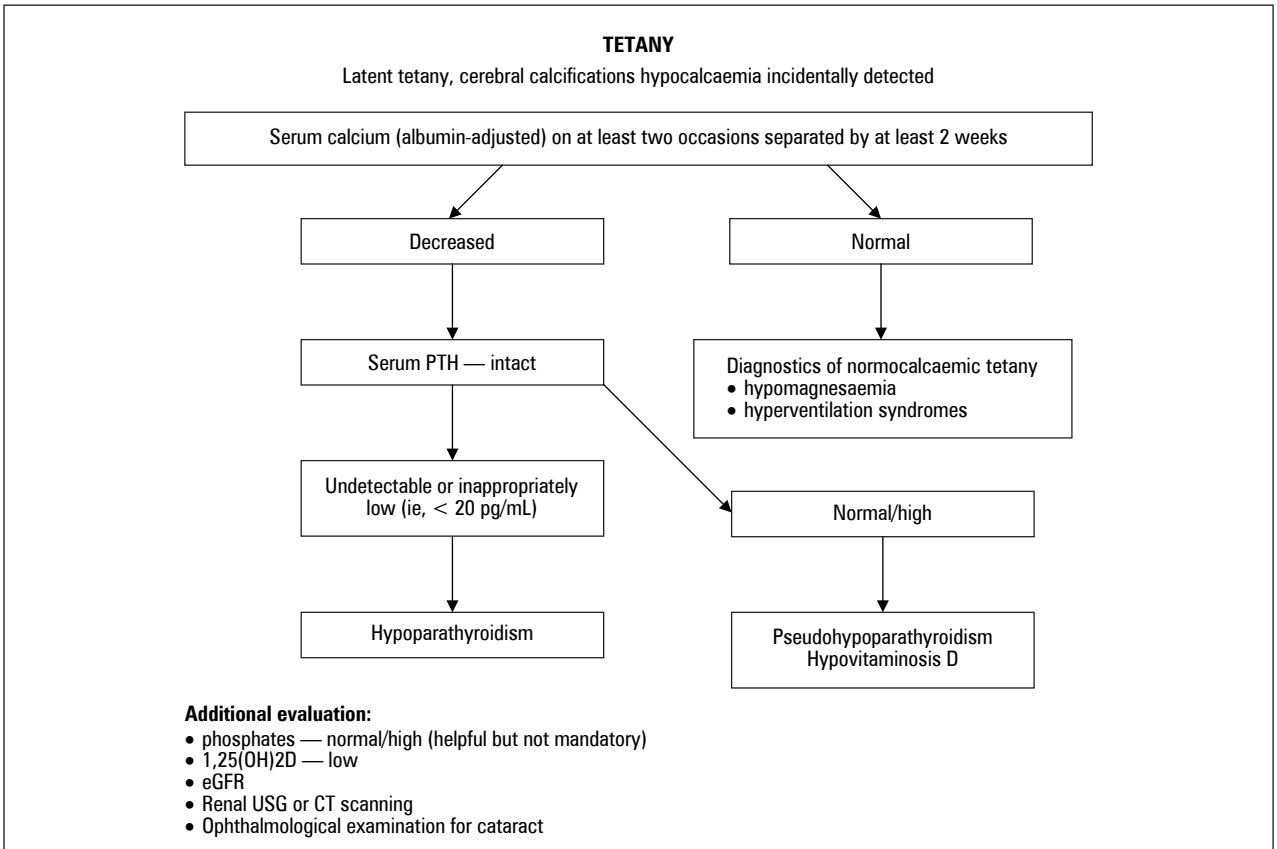
In patients on dialysis, the choice of dialysis fluid is crucial [211]. This should be a high-calcium dialysate, as it reduces the doses of hydroxylated vitamin D derivatives and thus lowers the severity of hyperphosphatemia. It is also necessary to adjust the duration of dialysis to the individual patient's needs. In general, standard dialysis is too short to result in normal serum phosphate levels. Patients are still required to follow a low-phosphate diet.

In patients after kidney transplant, the early post-transplant period is particularly important, because this is when increased renal phosphorus loss is observed, which can lead to varying degrees of hypophosphatemia [212].

In summary, HypoPT treatment in patients with advanced CKD is challenging and requires the involvement of an experienced physician. Therefore, such patients should be transferred to reference centers providing multidisciplinary care.

17. Pseudohypoparathyroidism and pseudopseudohypoparathyroidism

A key element in the pathogenesis of PHP is PTH resistance, which may be caused by various genetic defects [14, 213]. An extreme example of PTH resistance is Blomstrand lethal chondrodysplasia due to mutations of both alleles encoding the PTH receptor type 1. However, this is not *de facto* a form of PHP [214, 215]. Postreceptor defects lead to PHP type 1a (PHP1a; GNAS mutations affecting exons 1–13), PHP type 1b



CONVENTIONAL TREATMENT		MONITORING
Acute hypocalcaemia	**Chronic**	
Ca intravenously *then* Ca orally Calcitriol	Oral calcium supplements Calcitriol or active vitamin D analogs Magnesium Thiazide diuretics if necessary to control hypercalciuria Low-phosphate diet Phosphate-binding drugs if necessary to control hyperphosphatemia)	• Ca, PO4, Mg, creatinine/eGFR: once a year or more often if the clinical situation requires • Ca and creatinine in daily urine once a year or as clinically indicated • Renal USG/CT scanning (nephrolithiasis /nefrocalcinosis) • Ophthalmological exam (cataract) • CNS CT/MRI imagining (basal ganglia calcifications and others) • BMD (by DXA)

Figure 1. *Algorithm for the management of hypoparathyroidism (E20). PTH — parathyroid hormone; 1,25(OH)2D — calcitriol; eGFR — estimated glomerular filtration rate; Ca — calcium; PO4 — phosphate; Mg — magnesium; USG — ultrasonography; CT — computed tomography; CNS — central nervous system; MRI — magnetic resonance imaging; BMD — bone mineral density; DXA — dual energy X-ray absorptiometry*

(PHP1b) (GNAS methylation abnormalities), and PHP type 1c (PHP1c; GNAS mutations affecting exon 13). Reduced expression or activity of the GNAS-encoded Gsα subunit in patients with PHP1 results in resistance to PTH, and often to other hormones requiring Gsα to couple their receptors to adenylyl cyclase, such as thyroid-stimulating hormone or gonadotropins (follicle-stimulating hormone and luteinizing hormone), and to hypothalamic neurotransmitters, leading to neurocognitive defects and obesity [214–219]. The genetic defect that determines PHP type 2 is not fully understood [7, 220].

All of the above mutations lead to PTH resistance and the biochemical features that are typical of PHP such as hypocalcemia, hyperphosphatemia, and elevated serum PTH levels. Patients with PHP1a (and less commonly with PHP1b) also show the phenotype of Albright's hereditary osteodystrophy, which includes short stature, subcutaneous ossifications, varying degrees of intellectual disability, facial dysmorphia, dental hypoplasia and brachydactyly, a defect that is not visible at birth but usually becomes apparent in the second decade of life [7, 215, 219]. In addition to brachydactyly, other long bone formation disorders may also be present.

In patients with PHP, hypocalcemia can be treated with calcium medications and active vitamin D analogues more aggressively than in patients with true HypoPT, as there is a lower risk of hypercalciuria [14, 218, 219]. Calcium and calcitriol should be given at doses that maintain normal calcium levels, so that serum PTH levels are either at the upper limit of normal or only slightly elevated. Failure to reduce PTH to near normal levels will result in the persistence of elevated bone turnover, eventually leading even to tertiary hyperparathyroidism [221]. Because the distal renal tubule generally retains the ability to respond to PTH, so that tubular calcium reabsorption is preserved, patients with PHP1a/c or PHP1b usually do not develop hypercalciuria if PTH levels remain near the upper limit of normal. At the same time, treatment with excessive doses of calcium and calcitriol that reduce PTH levels below normal should be avoided, as this may result in the loss of PTH action in the distal tubules and hypercalciuria, and an increased risk of developing nephrocalcinosis and nephrolithiasis [14, 218, 219].

PHP1 is caused by heterozygous loss-of-function mutations in the maternal GNAS gene.

The same mutation in the father-derived gene does not cause PTH resistance, as paternal GNAS in the renal proximal tubule is always "silenced" because of genetic imprinting [84, 222]. As a result, individuals with pseudopseudohypoparathyroidism show most of the somatic features of Albright's hereditary osteodystrophy, typical of PHP1A, but – what is remarkable — without hormonal resistance.

18. Summary

HypoPT is a rare disease that represents a complex endocrine disorder associated with poor quality of life and increased demand for medical care. In this paper, updated recommendations for the diagnosis and management of HypoPT were presented. Most symptoms of HypoPT are due to acute and chronic hypocalcemia. However, several chronic complications, including the inhibition of bone metabolism, nephrolithiasis or nephrocalcinosis, kidney failure, basal ganglia calcifications, cataract, or psycho-emotional disorders, may be either caused by PTH deficiency or inadequate control of blood phosphate, or may represent the adverse effects of treatment. An early diagnosis of hypoparathyroidism and the initiation of an effective conventional therapy with calcium medications and active vitamin D metabolites are effective measures to control the symptoms of hypocalcaemia. Most patients worldwide are treated with calcium medications and active vitamin D analogues, however such a treatment is not ideal and does not restore normal PTH secretion. Consequently, there is a risk of inadequate biochemical control and complications, particularly renal complications. HypoPT is the only classic endocrine insufficiency that is not commonly treated with the substitution of the missing hormone. In 2015, rhPTH(1-84) was registered for treatment of selected cases of HypoPT by the US Food and Drug Administration. One preparation of rhPTH(1-84) was registered in the European Union in 2017, and the European Medicines Agency granted conditional marketing authorization in March 2022, but the drug is currently unavailable in Poland. The fact that HypoPT is rare constitutes a considerable barrier to optimal management. There is almost no or only very limited experience of practicing endocrinologists who manage patients with HypoPT. As authors and experts of the Polish Society of Endocrinology, we hope that the recommendations presented in this statement will help Polish endocrinologists better understand the disease itself and the important aspects of the current approach to diagnosis and treatment.

Conflict of interest

None declared.

Funding

None declared.

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