HYPOPARATHYROIDISM

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Author contributions

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Abstract | Hypoparathyroidism is a disease characterized by inadequately low circulating concentrations of parathyroid hormone (PTH) resulting in low calcium levels and increased phosphate levels in the blood. Symptoms of the disease result from increased neuromuscular irritability caused by the hypocalcaemia and include tingling, muscle cramps and seizures. The most common cause of the disease is inadvertent removal or injury to the parathyroid glands during neck surgery, followed by genetic, autoimmune, and idiopathic etiologies. Conventional treatment includes activated vitamin D and/or calcium supplements, but this treatment does not fully replace the functions of PTH and can lead to short-term complications (such as hypocalcaemia and hypercalcaemia) and long-term complications, which include increase in urinary calcium excretion, nephrocalcinosis, kidney stones and brain calcifications. PTH replacement has emerged as a new treatment option. Clinical trials using human PTH(1-34) and PTH(1-84) showed that this treatment was safe and effective in studies lasting up to six years. Recombinant human PTH(1-84) has been approved in the United States and Europe for the management of hypoparathyroidism.

However, its effect on long-term complications is being evaluated. Clinical practice guidelines, describing the consensus of experts in the field, have been published and recognize these needs to optimize care. In this Primer, we summarize current knowledge of prevalence, pathophysiology, clinical presentation, and management of hypoparathyroidism.

[H1] **Introduction**

Hypoparathyroidism is a disease characterized by absent or inappropriately low concentrations of circulating parathyroid hormone (PTH), leading to hypocalcaemia, hyperphosphataemia and elevated fractional excretion of calcium in the urine [1,2]. The most common aetiology of the disorder is the removal of or injury to the parathyroid glands during neck surgery, for example total thyroidectomy or radical neck dissection for head and neck malignancies; other aetiologies include autoimmune, genetic and, very rarely, infiltrative disorders (such as haemochromatosis, Wilson disease and metastasis)[3] The discovery of many genetic defects responsible for hypoparathyroidism has enhanced our understanding of the parathyroid gland physiology. These defects include gain-of-function mutations affecting the extracellular calcium-sensing receptor (CaSR) or the guanine nucleotide-binding protein subunit α-11 and loss-of-function mutations affecting essential transcription factors or *PTH* itself[2].

The clinical presentation varies from mild disease with paresthesia (burning or tingling sensations) and muscle cramps to severe symptoms such as laryngospasm (spasm of the voice box) and seizures. [2] Although conventional treatment with activated vitamin D and oral calcium is currently the standard of care, it does not fully replace the functions of PTH and is associated with long-term complications such as extraskeletal calcifications. Of particular concern are the calcium losses in the urine in the absence of PTH, which are associated with nephrocalcinosis (renal parenchymal calcification) and impaired renal function in the long term. Several clinical studies have also reported reductions in quality of life (QOL) of patients with hypoparathyroidism. Novel treatments are therefore needed, and until recently, hypoparathyroidism represented one of the few classic endocrine deficiency states not treated by replacement of the missing hormone. However, clinical trials demonstrating the efficacy

of PTH for the treatment of hypoparathyroidism have led to the approval of recombinant human PTH(1-84) for hypoparathyroidism in the United States and the European Union and stimulated research into new treatment modalities and novel PTH analogues. [4 5] As new therapies become more widely used, evaluation of their effectiveness on disease control, long-term complications, and QOL will be critically important.

[H1] Epidemiology

The available estimates of the prevalence of postsurgical hypoparathyroidism in the United States, Denmark and Italy are relatively close, and in the range of 22-37 per 100,000 persons [3], but the prevalence in some other countries is reported to be lower.[6] The variation between countries might be explained by differences in surgical expertise, since the majority of cases are the consequence of surgery. Further research is needed to define the prevalence and incidence of hypoparathyroidism outside the United States and Europe, as no studies have been performed in South America, Asia, Africa or Australia. Although the prevalence of inherited causes of hypoparathyroidism is similar between men and women[7], postsurgical hypoparathyroidism is more common in women than men[8] because women are more likely to have thyroid cancer and hence undergo thyroidectomy more often than men[9].

[H2] North America

The best estimate of the prevalence of hypoparathyroidism in North America is based on analysis of a large U.S. health plan claims database over a 12-month period from 2007-2008[10].Population prevalence of hypoparathyroidism is estimated at 59,000 adults with health insurance and 77,000 adults in total in the United States. An alternative approach based on the incidence of neck surgeries and the incidence of chronic hypoparathyroidism as a surgical

complication using the same database led to similar estimates[10]. Another estimate of the prevalence of hypoparathyroidism was presented as an abstract[11] and is based on the longitudinal population-based Rochester Epidemiology Project, in which medical records linkage resources were used to identify all individuals residing in Olmsted County (Minnesota, USA; mean age ± 58 ± 20 years and 71% women) in 2009, who were diagnosed with hypoparathyroidism of any cause since 1945[11]. 54 cases of hypoparathyroidism were found, which led to a calculated prevalence of 37 per 100,000 residents. This prevalence projected to an estimated 115,000 individuals with hypoparathyroidism from any cause in the United States. In this database, hypoparathyroidism resulted from neck surgery in 78% of cases, other secondary causes in 9%, familial disorders in 7%, and was idiopathic in 6%.

[H2] Europe

The prevalence of hypoparathyroidism in Denmark was estimated using the Danish National Patient Registry[7,8,12]. This study also assessed mortality and comorbidities by comparing patients with hypoparathyroidism with age-matched and sex-matched population-based controls. A total of 1,849 individuals with postsurgical hypoparathyroidism and 180 individuals with nonsurgical hypoparathyroidism were identified. The estimated prevalence of postsurgical hypoparathyroidism was 22 per 100,000 individuals and nonsurgical hypoparathyroidism was 2.3 per 100,000 individuals. The incidence of postsurgical hypoparathyroidism was estimated to be 0.8 per 100,000 person-years [12]. Of the postsurgical cases, indications for surgery included malignancy (primarily thyroid cancer) in 30%, nontoxic goiter (normally active non-cancerous thyroid hypertrophy) in 37%, toxic goiter (overactive thyroid hypertrophy) in 25%, and primary hyperparathyroidism in 8%[12]. The prevalence of hypoparathyroidism in Norway is about half the other estimates, that is, 10.2

per 100,000 individuals.[4] The mean hospitalization rate for hypoparathyroidism in Italy was 5.9 per 100,000 person per year[13].

[H1] Mechanisms/pathophysiology

Hypoparathyroidism is characterized by absent or inappropriately low levels of circulating PTH, which is involved in mineral homeostasis. The most common cause is surgical destruction or injury to the parathyroid glands; other causes are autoimmune diseases or genetic disorders affecting parathyroid gland development or the biosynthesis or release of PTH.

[H2] PTH and mineral homeostasis

The parathyroid glands control extracellular calcium homeostasis by secreting PTH (FIG 1). PTH is synthesized as a 115-amino acid precursor peptide (pre-proPTH), that later matures into full-length PTH containing 84 amino acids. PTH is stored in secretory granules and released by the parathyroid glands when circulating ionized calcium concentrations are reduced. These changes in serum calcium levels are detected by the CaSR, a G-protein coupled receptor, which is highly expressed on the surface of parathyroid cells[14]. A decrease in extracellular calcium reduces CaSR signalling via the G_{11} and G_q, which induces a marked increase in PTH release from the parathyroid glands. The secreted PTH circulates in the blood stream and acts on the G-protein-coupled PTH1 receptor (PTH1R)[15] in bone and the kidneys to increase serum calcium levels, which leads to feedback inhibition of PTH secretion[14].

PTH also regulates circulating phosphate levels. Indeed, a rise in circulating phosphate stimulates the secretion of PTH, which in turn acts on the kidneys to inhibit tubular phosphate reabsorption[16]. Phosphate homeostasis is further regulated by fibroblast growth factor 23 (FGF23), an osteocyte-derived hormone that inhibits renal tubular phosphate reabsorption and the renal synthesis of 1,25-dihydroxy vitamin D ($1,25(OH)_2D$; also known as calcitriol)[17].

In the setting of hypoparathyroidism, absent or low circulating PTH levels lead to hypocalcaemia by: impairing osteoclast activity, which diminishes the efflux of calcium from bone; enhancing urinary calcium excretion; and by inhibiting the renal synthesis of $1,25(OH)_2D$, which impairs the intestinal absorption of dietary calcium[18]. Deficiency of PTH also causes hyperphosphataemia due to an increase in the renal tubular reabsorption of phosphate, and chronic hyperphosphataemia has been shown to be associated with elevations in serum FGF23 levels in patients with hypoparathyroidism[19].

PTH is also involved in magnesium homeostasis. PTH increases magnesium reabsorption in the kidney[20], whereas severe and prolonged hypomagnesemia results in hypocalcaemia through inhibition of PTH secretion and PTH end-organ resistance[21,22] . Hypermagnesemia may also inhibit PTH release through activation of the CaSR, thus promoting hypocalcaemia[23,24].

[H2] Postsurgical hypoparathyroidism

Neck surgery is the most common cause of acquired hypoparathyroidism and accounts for ~75% of all cases of hypoparathyroidism[3]. Surgeries associated with the development of hypoparathyroidism are total thyroidectomy or radical neck dissection for head and neck

malignancies; the causes of hypoparathyroidism are inadvertent gland removal, intraoperative trauma to the parathyroid glands or gland devascularization. Total parathyroidectomy aimed at removing, for example, one or more parathyroid tumours, can also lead to hypoparathyroidism[1,3,25].

Transient postsurgical hypoparathyroidism, defined as low or absent PTH levels lasting <6 months, affects 25-30% of patients following total thyroidectomy, whereas permanent postsurgical hypoparathyroidism (hypoparathyroidism for >6 months) affects only up to 3% of patients [26]. Low preoperative levels of serum calcium and 25(OH)D, low intraoperative PTH concentrations, autotransplantation (parathyroid gland reimplantation in the neck or forearm following neck surgery) of one or more parathyroid glands and longer duration of surgery have been identified as independent predictors of transient hypoparathyroidism post-thyroidectomy[27]. Risk factors for permanent hypoparathyroidism following thyroid surgery include extent of the surgery; a preoperative diagnosis of Graves' disease (autoimmune disease causing thyroid overactivity); failure to identify ≥2 parathyroid glands during surgery; serum calcium ≤1.88 mmol/l (7.5 mg/dl; (normal range 2.12-2.62 mmol/l or 8.5-10.5 mg/dl) at 24 hours post-surgery; and reoperation for bleeding[27]. Rarely, post-surgical hypoparathyroidism can present years after neck surgery[28]. The mechanism underlying this delayed presentation is unclear, but may be caused by the effects of age-related changes to the vasculature of the marginally functional, residual parathyroid tissue present post-surgery[1].

[H2] Genetic causes of hypoparathyroidism

Hypoparathyroidism has a genetic aetiology in <10% of cases[3]. However, chromosomal microdeletions and monogenic abnormalities represent the major cause of hypoparathyroidism in children[29]. Genetic forms of hypoparathyroidism occur either as a

component of syndromic disorders or as a solitary endocrinopathy, which is referred to as isolated hypoparathyroidism (Table 1). Genetic forms of PTH resistance (Box 1) — a distinct set of diseases that are referred to as pseudohypoparathyroidism —are not covered in this Primer in detail.

1. Syndromic Hypoparathyroidism

[H3] DiGeorge syndrome. DiGeorge syndrome has been reported in ~60% of children with hypoparathyroidism[29]. The syndrome presents with hypoparathyroidism, cardiac outflow tract malformations, facial dysmorphia, psychiatric illness, palatal dysfunction, and thymic hypoplasia[30]. DiGeorge syndrome is mainly caused by a heterozygous 3Mb microdeletion of chromosome 22q11.2[30], which is referred to as DiGeorge syndrome type 1 (also known as 22q11.2 deletion syndrome) (Table 1). The deleted region encompasses *TBX1*, which encodes a T-box transcription factor involved in the development of the parathyroid glands and thymus from the embryonic pharyngeal region (FIGS 2 and 3)[31]. Abnormalities in TBX1 explain all of the main phenotypical features of DiGeorge syndrome type 1[32].

Some patients harbor chromosome 10p deletions[18], referred to as DiGeorge syndrome type 2. Deletion of *NEBL*, encoding the actin-binding protein NEBL (also known as nebulette), is likely responsible for this disorder (TABLE 1)[33], but how deficiency in NEBL causes hypopoparathyroidism is currently unclear.

In addition, some patients with DiGeorge syndrome have features of the CHARGE syndrome, which is characterized by coloboma (hole in one or more ocular structures), heart abnormalities, choanal atresia (congenital nasal airway abnormality), growth retardation, and genitourinary and/or ear anomalies[34]. CHARGE syndrome is caused by heterozygous

mutations in *CHD7* (TABLE 1), encoding for the chromodomain helicase DNA binding protein 7[34], which is expressed within the pharyngeal ectoderm[35] and may play a part in the development of the pharyngeal region.

[H3] Autoimmune polyendocrine syndrome type 1. Autoimmune polyendocrine syndrome type 1, which is also referred to as the autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy syndrome, is an autosomal recessive disorder characterized by immune deficiency and autoimmune destruction of endocrine organs such as the parathyroid glands, adrenal cortex and ovaries (Table 1 and Figure 2)[36]. Autoimmune polyendocrine syndrome type 1 is caused by mutations of *AIRE,* encoding autoimmune regulator. AIRE is expressed in thymic medullary epithelial cells[37] and promotes immunological tolerance to self-antigens by deleting clones of auto-reactive T-cells within the thymus[38]. Autoimmune polyendocrine syndrome type 1 is clinically defined by the presence of at least two components of the triad that consists of mucocutaneous candidiasis (candida infection of the skin, mucous membranes or nails), hypoparathyroidism and adrenal insufficiency[39]. However, the disorder can also be associated with a variety of other autoimmune disorders such as gonadal failure, alopecia, pernicious anemia, vitiligo and type 1 diabetes mellitus, and can also present with isolated hypoparathyroidism[40]. Patients can have ectodermal dystrophies such as hypoplasia of tooth enamel[41] and are at higher risk of developing oral cancer[42].

[H3] Hypoparathyroidism, sensorineural deafness, and renal disease syndrome. Hypoparathyroidism, sensorineural deafness, and renal disease (HDR) syndrome is an autosomal dominant disorder in which patients often have hypocalcaemia and undetectable, low, or inappropriately normal serum PTH concentrations[43,44]. Moreover, HDR is associated with bilateral symmetrical sensorineural deafness and renal abnormalities consisting mainly

of cysts that compress the glomeruli and tubules, thereby leading to renal impairment[44]. HDR is caused by germline heterozygous mutations of *GATA3* (TABLE 1)[45], which encodes GATA-binding factor 3. This dual zinc finger transcription factor mediates *PTH* expression (FIG 2) and is involved in the embryonic development of the common parathyroid-thymus primordia (FIG 3) [46-49].

[H3] Mitochondrial disorders associated with hypoparathyroidism. Hypoparathyroidism has been reported to occur in three disorders associated with mitochondrial dysfunction: the Kearns–Sayre syndrome, the mitochondrial encephalopathy with lactic acidosis and stroke-like episodes (MELAS) syndrome, and the mitochondrial trifunctional protein (MTP) deficiency syndrome (Table 1 and Figure 2)[50-52]. Kearns–Sayre syndrome is characterized by progressive external ophthalmoplegia (paralysis of the eye muscles) and pigmentary retinopathy occurring at <20 years of age[51]. Deletions, duplications and missense substitutions in mitochondrial DNA cause Kearns–Sayre syndrome and MELAS [18,29,50], whereas MTP deficiency syndrome, which is a disorder of fatty acid oxidation in the mitochondria associated with cardiomyopathy, peripheral neuropathy, pigmentary retinopathy and liver dysfunction, is caused by mutations of *HADHB* , which encodes the trifunctional enzyme β-subunit[52]. The mechanism(s) leading to hypoparathyroidism in these mitochondrial disorders is currently not understood.

[H3] Inherited bone dysplasias associated with hypoparathyroidism. Hypoparathyroidism occurs in >50% of patients with Kenny-Caffey syndrome[18], which is also characterized by short stature and osteosclerotic bone dysplasia. Kenny-Caffey syndrome can be inherited as an autosomal recessive (type 1) or dominant (type 2) disorder[18]. The Sanjad-Sakati syndrome, which is also known as the hypoparathyroidism-retardation-dysmorphism

syndrome, affects Middle Eastern populations and has a similar phenotype to Kenny-Caffey syndrome [53]. Sanjad-Sakati syndrome and Kenny-Caffey syndrome type 1 are caused by mutations of *TBCE*[54], which encodes a chaperone protein required for the correct folding of α-tubulin subunits [54] and is postulated to have a role in parathyroid gland migration[55]. Kenny-Caffey syndrome type 2 is caused by heterozygous missense mutations of *FAM111A*, encoding for a protein involved in DNA replication and chromatin maturation, and may be involved in embryonic development[56,57]. A truncating *FAM111A* mutation, Ser342del, has been shown to cause gracile bone dysplasia, which occurs in association with hypoparathyroidism, and represents a perinatally lethal condition (Table 1 and Figure 2)[57].

2. Autosomal dominant hypocalcaemia (ADH)

[H3] Autosomal dominant hypocalcaemia. Autosomal dominant hypocalcaemia comprises two genetically distinct disorders, designated as autosomal dominant hypocalcemia type 1 and type 2, which are caused by germline gain-of-function mutations of the CaSR and G-protein subunit α_{11} ($G\alpha_{11}$ proteins, respectively (FIG 2, TABLE 1)[14,58,59]. Type 1, which is the most common type of autosomal dominant hypocalcemia, is associated with hypocalcaemia, PTH levels ranging from undetectable to normal and elevated fractional excretion of calcium, which can lead to frank hypercalciuria even in the setting of low serum calcium concentrations. [14,59-61]. Ectopic calcifications of the kidneys or basal ganglia affect ~35% of patients with autosomal dominant hypocalcemia type 1[14,59,62]. Some patients with autosomal dominant hypocalcemia type 1, associated with severe gain-of-function mutations of *CASR*, may also have a Bartter-like syndrome characterized by hypokalemic alkalosis, renal salt wasting and hyperreninemic hyperaldosteronism, in addition to hypocalcemia and hypoparathyroidism [14,63]. Autosomal dominant hypocalcemia type 2 has a similar serum biochemical phenotype to type 1[58,64,65], but usually a milder renal phenotype, with

considerably less urinary calcium excretion [66]. Moreover, some patients have short stature caused by postnatal growth insufficiency[66,67].

3. Isolated Hypoparathyroidism

[H3] Autosomal forms of hypoparathyroidism. The glial cells missing homolog 2 (GCM2) is a parathyroid-specific transcription factor (FIG 2) that has a critical role in extracellular calcium homeostasis by promoting development of the parathyroid glands [46,47,68] and by interacting with the GATA3 and MAFB transcription factors to increase PTH expression (FIG 3)[48,49]. Germline *GCM2* mutations are often associated with severe hypocalcaemia and low or undetectable serum PTH concentrations[69]. Homozygous *GCM2* mutations cause an autosomal recessive form of isolated hypoparathyroidism by impairing nuclear localization, DNA binding and/or transactivation activity of the GCM2 transcription factor[69], whereas heterozygous *GCM2* mutations cause autosomal dominant hypoparathyroidism by exerting a dominant-negative effect on GCM2 transactivation activity[70,71].

Germline *PTH* gene abnormalities are a rare cause of autosomal dominant and recessive forms of isolated hypoparathyroidism (TABLE 1). These abnormalities, which comprise missense, nonsense or splice-site mutations, mainly affect exon 2 (encoding the signal peptide region of the pre-proPTH1-115) peptide) and are predicted to impair PTH biosynthesis and secretion (FIG 2)[18,72-74]. A mutation affecting the mature PTH(1-84) peptide has recently been identified in a family with an autosomal recessive form of hypocalcaemia and has been demonstrated to impair binding of the mutant PTH peptide with the PTH1R[74]. Affected family members showed either high or low plasma PTH levels depending on the type of PTH assay used. The mutation (Arg25Cys) was subsequently revealed to interfere with some PTH immunoassays that used antibodies raised against PTH(1-34) and PTH(13-

34) fragments, thus explaining why some assays were unable to detect the mutant PTH peptide[74].

[H3] X-linked recessive hypoparathyroidism

X-linked recessive hypoparathyroidism only affects men and is associated with infantile hypocalcaemic seizures[75]. Molecular deletion-insertions involving chromosome 2p25 and Xq27 have been identified and these structural alterations may alter expression of the nearby gene *SOX3* (TABLE 1)[76,77]. *SOX3* encodes a high-mobility group (HMG) box transcription factor, which is expressed in the parathyroid glands during embryogenesis and may a play a part in the development of the parathyroid glands from the pharyngeal pouches (Figure 3)[76].

[H2] Other causes of hypoparathyroidism

Some cases of isolated hypoparathyroidism, in which no other cause can be identified, are also presumed to be caused by autoimmune destruction of the parathyroid glands. No formal diagnostic criteria and no established laboratory tests are available to confirm this diagnosis.

Severe and prolonged hypomagnesemia can lead to functional hypoparathyroidism.[78,79].

Rarely, infiltrative diseases such as hemochromatosis, Wilson disease and metastasis can cause hypoparathyroidism[2]. The mechanism is thought to involve inhibition of parathyroid cellular function by iron (primary iron excess in hemochromatosis and secondary iron overload due to blood transfusions in thalassemia (inherited blood disorder associated with abnormal haemoglobulin production), copper (in Wilson disease) and replacement of functional parathyroid tissue by tumor cells. Parathyroid tissue is relatively radiation-resistant. Although cases of radiation-induced hypoparathyroidism have been reported, this aetiology is very rare[2].

[H1] Diagnosis, screening and prevention

[H2] Clinical manifestations

The clinical manifestations of hypoparathyroidism are variable and can involve almost any organ system (Figure 4). The classic symptom of hypoparathyroidism is neuromuscular irritabilityowing to hypocalcaemia. Other manifestations can be due to episodes of hypercalcaemia and hyperphosphatemia (for example, extraskeletal calcification), whereas the cause of others (for example, neuropsychiatric symptoms) remains poorly understood.[2]

[H3] Peripheral nervous system. Hypocalcaemia partially depolarizes the neuron's resting membrane potential, thereby increasing the probability of triggering action potentials[80]. This leads to neuromuscular irritability — the hallmark symptom of hypocalcaemia from any cause. Sensory neuron irritability manifests as paresthesia in the extremities and in the peri-oral and oral area. Motor neuron irritability can manifest as muscle spasms or tetany, ranging from the classic carpopedal spasm (spasms in the hand and feet) to life-threatening laryngospasm[81,82]. Increased neuromuscular irritability can be detected using the Chvostek (ipsilateral twitching of facial muscles when tapping on the area of the facial nerve) and Trousseau sign (muscular contraction of the hand when inflating a blood pressure cuff on the arm above systolic blood pressure for three minutes) [83].

[H3] Central nervous system. Severe hypocalcaemia can precipitate seizures which can be focal or generalized (tonic-clonic type). Although seizures were frequently observed in the past, prevalence rates of seizures in patients with hypoparathyroidism were only 4-8% in two more recent studies [12,84]. Possible explanations might be selection bias of the earlier studies or better control of serum calcium levels in the later studies.

Central nervous system calcifications (Figure 5) are a common finding in hypoparathyroidism with prevalence rates of 52-74% in two moderate-size cohorts from the United States and India[84,85]. The calcifications are most commonly seen in the basal ganglia but can also occur in the gray and white matter junction, the cerebellar parenchyma, the thalamus and the dentate nucleus. Although the exact cause of these calcifications is unclear, increased progression of calcifications over time was independently associated with a decreased ratio of calcium to phosphate in serum, which suggests that altered phosphate metabolism may play a key part in ectopic calcifications[85]. Notably, two genes found to be associated with familial idiopathic basal ganglia calcification (also known as Fahr syndrome) encode proteins involved in phosphate transport (that is, PIT2 and XPR1), which supports the hypothesis that abnormal phosphate homeostasis has a role in ectopic calcifications[86,87]. The clinical relevance of the central nervous system calcifications seen in patients with longstanding hypoparathyroidism is unclear. Symptoms including Parkinsonism (neurological movement disorder characterized by tremor, bradykinesia, rigidity and postural instability) and dystonia (neurological movement disorder associated with twisting or abnormal fixed postures) have been reported in hypoparathyroidism, but at a much lower prevalence than basal ganglia calcifications[84,85,88]. In addition, the relationship between the extent and location of calcification with neurological findings is conflicting[89,90].

[H3] Cardiovascular system. Cardiac arrhythmias are rare in hypoparathyroidism. Some patients with chronic hypocalcaemia associated with hypoparathyroidism showed prolongation of the corrected QT interval on electrocardiogram, along with prominent U wave and T wave abnormalities[91]. However, most of these findings resolve promptly after treatment of hypocalcaemia. Hypocalcaemia-associated dilated cardiomyopathy, which can occur during chronic severe hypocalcaemia, is typically reversible with treatment[92].

However, a recent case report of an infant with severe hypocalcemia suggested a non-reversible component in hypocalcaemia-associated dilated cardiomyopathy [93]. Despite the numerous case reports, the prevalence of cardiomyopathy is very low in cohorts of patients with hypoparathyroidism, suggesting that there is a subset of vulnerable patients with as yet undefined risk factors[12,84].

[H3] Renal system. Hypoparathyroidism *per se* is usually not associated with renal disease, even among those with gain-of-function mutations of *CASR* who are most likely to have hypercalciuria without treatment[62,94]. However, conventional treatment of hypoparathyroidism with calcium and activated vitamin D metabolites leads to increased excretion of calcium into the urine because of the lack of PTH-mediated reabsorption in the distal nephron. The resulting hypercalciuria can lead to nephrocalcinosis and kidney stones. The reported prevalence rates of nephrocalcinosis in patients with hypoparathyroidism who are treated with calcium and activated vitamin D is 12-57%[62,95,96]; the hazard ratio of developing kidney stones is 4.82 (95% confidence interval (CI): 2.00–11.64) in a large Danish case-control study of patients with post-surgical hypoparathyroidism[12]. Patients with hypoparathyroidismhave a significantly increased risk of chronic kidney disease. In a US cohort[84], 41% of patients had an estimated glomerular filtration rate (eGFR) of <60 ml/min/1.73 m^2 (with an eGFR of ≥90 ml/min/1.73 m^2 considered normal)**,** which was 2- to 17-fold higher than age-appropriate norms, and in two Danish case-control studies[7,12], the hazard ratios for diagnosed renal insufficiency were 3.10 (95% CI: 1.73–5.55) and 6.01 (95% CI: 2.45–14.75) for patients with surgical and nonsurgical hypoparathyroidism, respectively, compared to age-matched controls.

[H3] Musculoskeletal and dental system. Hypoparathyroidism is associated with low bone turnover (the active process of coupled bone formation and bone resorption) associated with normal or increased bone mineral density and distorted bone microarchitecture[97,98]. The reduction in bone formation is demonstrated by the profound reduction of tetracycline labelling in bone biopsies compared to controls[99-101]. The activation frequency (marker for the number of times per year a specific bone site undergoes bone formation) is decreased by 50-80% in patients with hypoparathyroidism compared with controls. In addition to the overall reduction in bone remodeling, depth and number of resorption pits are reduced, suggesting a reduction in bone resorption. Bone formation rate, osteoid (unmineralized bone matrix) surface and osteoid width are consistently and substantially reduced. The reduction in bone formation is reflected by reductions in mineralizing surface and mineral apposition rate. In hypoparathyroidism, the decrease in bone turnover leads to a situation where more bone is deposited than removed after each remodeling cycle is completed[98]. This observation explains the increase in bone mineral density and cortical thickness that has been reported in some studies. These skeletal abnormalities are detected in trabecular and cortical bone and are confirmed by microcomputed tomography of the bone biopsies[102]. Dentition can be affected in patients with nonsurgical hypoparathyroidism including shortened roots, hypoplastic enamel and hypoplastic or absent teeth[103,104].

The impact of the skeletal abnormalities associated with hypoparathyroidism, if any, on osteoporosis and fracture risk remains unclear. In the Danish case-control studies[7,12], no reported differences in overall fracture rate compared with the general population were detected. Analyses of specific fracture types showed that patients with nonsurgical hypoparathyroidism had an increased hazard ratio for upper extremity fractures (1.94, 95% CI 1.31-2.85) compared with controls, whereas patients with post-surgical

hypoparathyroidism had a lower hazard ratio for the same fracture (0.69, CI 0.49-0.97)[8]. Hypoparathyroidism has also been associated with a spondyloarthropathy in several case reports, characterized by ligament ossification and syndesmophyte formation[105]. One small case series reported the presence of clinically overt spondyloarthropathy in 3 out of 40 patients with hypoparathyroidism with radiologic changes identified in 14 out of 40 [106].

Myopathy of the skeletal muscles, characterized by increased serum levels of creatine phosphokinase and histological abnormalities in muscle biopsies, are also seen in hypoparathyroidism and seems to relate to the severity of hypocalcaemia[107,108]. Compared with age-matched and sex-matched controls, patients with hypoparathyroidism have a significant reduction in muscle strength and maximal force production and also require a longer time to complete tests of physical function [109].

[H3] Ophthalmologic system. Hypoparathyroidism is associated with an increased risk of cataracts with reported prevalence rates of 27-55%[110-112]. In the Danish case-control studies, nonsurgical hypoparathyroidism was associated with an elevated hazard ratio of 4.21 compared with controls, but the risk of cataracts in patients with post-surgical hypoparathyroidism was not significantly different from the general population, suggesting that age of onset and/or duration of hypoparathyroidism are important risk factors [7,12]. In a recent case-control study of patients with cataract, those with hypoparathyroidism were significantly younger than typical patients with cataract who do not have hypoparathyroidism and had evidence of more severe posterior capsule (membrane that surrounds the lens) disease and a higher rate of anterior capsule disease[112]. In addition, hypoparathyroidism is predominantly associated with cortical cataract (gradual clouding starting in the periphery of the lens), whereas typical age-related cataracts are more likely nuclear (gradual clouding of

the central portion of the lens)[111]. The aetiology of the cataract formation is unclear, though preclinical studies suggest that it may be a consequence of chronic hypocalcaemia[113]. Papilledema (swelling of the optic disc caused by increased intracranial pressure) can also be seen in patients with hypoparathyroidism and typically improves with correction of hypocalcaemia[114].

[H3] Dermatologic system. Skin and skin appendages are affected by hypoparathyroidism; dry, scaly skin is commonly reported and nails are often brittle and subject to onycholysis (separation of the nail from the nail bed) [115]. Scalp, axillary and pubic hair can be coarse and thin[115]. A rare and severe type of psoriasis (generalized pustular psoriasis associated with pus-filled blisters) has been described in numerous case reports; in all cases, pustular psoriasis was associated with profound hypocalcaemia and improved with treatment[116,117].

[H3] Neuropsychiatric system. Hypoparathyroidism is associated with an increased risk of neuropsychiatric diseases[118]. In the Danish cohort, the risk of being hospitalized due to neuropsychiatric diseases such as depression or bipolar affective disorders was significantly increased in postsurgical (hazard ratio: 1.99) and non-surgical hypoparathyroidism (hazard ration: 2.45) compared with matched controls[8].

[H2] Diagnosis

Biochemical investigations are required to confirm the clinical diagnosis of hypoparathyroidism. The combination of levels of albumin-corrected or ionized calcium in serum below the laboratory normal range (<8.5 mg/dl or 2.12 mmol/L) respectively and absent, low or inappropriately normal PTH levels at the time of hypocalcaemia is the hallmark of hypoparathyroidism and helps to differentiate hypoparathyroidism from other

disorders associated with hypocalcaemia, such as pseudohypoparathyroidism (Box 1). Hence, a reliable assay for measuring PTH in serum is critical for diagnosis (Box 2).

The biochemical diagnosis of hypoparathyroidism in the right clinical setting is usually straightforward. For example, when a patient with a prior history of neck surgery presents with symptoms of hypocalcaemia and has low PTH levels, hypoparathyroidism can be inferred. However, circulating PTH levels in these patients can also be within the normal range. Similar to diagnosing patients with hyperparathyroidism, the PTH value has to be considered in relationship to the serum calcium value drawn simultaneously. In patients with hypocalcaemia, PTH levels that are within "normal laboratory range" are inappropriate, as they should be elevated if the function of the parathyroid gland was intact. In patients with a positive family history of hypoparathyroidism, and in children with nonsurgical hypoparathyroidism, a search for a possible genetic defect should be considered with appropriate pretest counseling and informed consent.

[H2] Monitoring

At regular intervals, patients should be monitored for potential complications to the disease (Table 2 and 3) [4, 5] In addition to total calcium and albumin, or ionized calcium, biochemical tests should include serum phosphate to detect hyperphosphataemia, creatinine levels in blood with calculation of eGFR to detect renal impairment, and serum magnesium concentrations, particularly in patients with autosomal dominant hypocalcaemia. An upper threshold of the calcium-phosphate product of 55 mg^2/dl^2 is recommended to avoid renal calcifications[1,4]. This target calcium-phosphate product is used by nephrologists in patients with chronic kidney disease to reduce the risk of arterial calcification. However, the value of using the calcium-phosphate product level in hypoparathyroidism to predict the risk of

calcifications that may lead to renal insufficiency remains controversial[119,120] and awaits further evaluation. Nevertheless, most experts are mindful of the calcium-phosphate product in hypoparathyroidism and will endeavor to lower it, particularly if it exceeds the threshold that has been set, however uncertain that threshold may be.

Patients should be asked whether they have experienced symptoms including flank pain or haematuria (to detect kidney stones), blurred vision (to detect cataract), neuropsychiatric symptoms (to detect, for example, depression and anxiety), among others; if symptoms are present, patients should be referred for proper evaluation. Measurement of 24-hour urinary calcium once a year should be considered for monitoring of hypercalciuria. Patients with a greater tendency to hypercalciuria might require more frequent monitoring. In children, 24-hour urine calcium measurements should be adjusted for body surface area or body weight. Renal imaging should be considered periodically [121], or if a patient has symptoms of renal stone disease or if serum creatinine levels start to rise[4]. Renal ultrasonography is a safe modality to detect the presence of early stage nephrocalcinosis and was shown in one study to be superior to CT[122]. As hypoparathyroidism treated by conventional therapy is associated with low bone turnover, patients are not especially prone to developing osteoporosis. Dual energy X-ray absorptiometry (DXA) scans to determine bone mineral density are not needed specifically for hypoparathyroidism, but may be performed according to guidelines for the diagnosis and monitoring of osteoporosis (for example, screening in populations at risk). Due to the uncertain clinical relevance of calcifications in the central nervous system, brain imaging using CT should only be performed in case of unexplained neurologic manifestations[4,121].

[H2] Screening

As most cases of hypoparathyroidism are postsurgical, patients should be evaluated for hypocalcaemia following such neck surgeries. In familial forms of hypoparathyroidism, biochemical screening of first-degree relatives may be offered. In a number of patients with seizures, including children presumed to be suffering from febrile convulsions, lack of measurement of serum calcium concentrations have caused a delay in the diagnosis of hypoparathyroidism[123].

[H2] Prevention

To avoid postsurgical hypoparathyroidism, surgical experience in neck surgery is critical. In non-surgical hypoparathyroidism with a known genetic aetiology, genetic counseling should be offered. To avoid lengthy episodes of hypocalcaemia or hypercalcaemia, patients with hypoparathyroidism should be aware of symptoms of low and high circulating calcium concentrations in order to allow for early detection and adjustment of treatment. Of note, serum calcium levels may fluctuate without obvious reasons in patients on treatment of chronic hypoparathyroidism. Likewise, patients should be familiar with potential complications of their disease to allow for early detection.

[H1] Management

[H2] Conventional therapy

Conventional treatment of adults with hypoparathyroidism involves calcium supplementation or activated vitamin D supplementation (calcitriol or alphacalcidol; box 3) or a combination of both. Treatment is aimed at increasing intestinal calcium absorption to increase serum calcium concentrations (Figure 1). Goals of chronic management include prevention of signs and symptoms of hypocalcemia and reducing the risk of long-term

complications (Table 2 and 3) [4,5]. Treatment is adjusted to achieve low-normal serum calcium and normal urine calcium levels.

Patients often require a minimum of 1g of elemental calcium in doses divided throughout the day. Calcium carbonate (40% calcium by weight) is the least expensive formulation. Since it depends on an acidic gastric pH for efficient absorption, it should be taken with meals. Calcium citrate is recommended forpatients who have achlorhydria (impaired gastric acid secretion) or are on concomitant proton-pump inhibitor therapy. Calcium citrate, calcium gluconate or calcium lactate are alternatives for calcium carbonate, but more tablets are needed due to their relatively low content of elemental calcium. Acute severe hypocalcaemia is treated with intravenous calcium gluconate.[4,5]

A variety of vitamin D metabolites and analogues (Box 3) have been used to treat hypoparathyroidism. Although high-dose of the vitamin D precursors, ergocalciferol (vitamin D2) and cholecalciferol (vitamin D3), can be used[124], such treatment is not commonly used and can lead to prolonged hypercalcaemia due to the long half-life of these precursors. The use of activated vitamin D — calcitriol ($1,25(OH)_2D$) or alphacalcidol ($1\alpha(OH)D_3$) — is favoured, because of their direct action on the gastrointestinal tract to increase intestinal calcium absorption, their shorter onset of action and half-life[125]. Both alphacalcidol and calcitriol are titrated to achieve desired serum calcium concentrations in the low-normal range [~8.0-8.5 mg/dl (2.0-2.12 mM). Infants and young children should receive calcitriol (weight-based dosing, 0.01-0.04 μg/kg/day); some centers will also give calcium carbonate supplements (20-40 mg/kg/day) divided into two or three doses. Older children usually receive adult doses of active vitamin D (alphacalcidol and calcitriol)[126].

[H2] PTH analogues

Although conventional therapy with activated vitamin D and calcium supplements can restore serum calcium levels, it does not restore other actions of PTH, such as bone turnover or renal calcium reabsorption. In addition, conventional treatment is associated with hypercalciuria, which increases the risk of developing nephrocalcinosis and kidney stones. To establish a more physiologic alternative to conventional therapy, studies aimed at PTH replacement were first initiated with synthetic human PTH 1-34 (hPTH 1-34), the biologically active amino terminal fragment of the full-length PTH peptide. Both the active amino terminal fragment and the full-length 84 amino acid peptide, bind to and activate the PTH1R.

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[H3] Human PTH(1-34). Human PTH(1-34) (hPTH(1-34)

Synthetic hPTH was used in the first clinical trials testing hormonal replacement therapy of hypoparathyroidism. In these studies, investigational synthetic human (PTH 1-34) was formulated in the pharmacy at the study site as there was no commercially available hormone when the studies were initiated in 1992. Synthetic hPTH 1-34 was given alone without calcitriol, thiazide diuretics or phosphate binders and titrated to maintain low-normal serum calcium levels and normal urine calcium excretion. Various hPTH(1-34) regimens were evaluated in short- or long-term studies[60,61,127-131]. Initial studies confirmed the advantages of once-daily subcutaneous rhPTH(1-34) injection over conventional therapy[130]. The phosphaturic and calcium-retaining effects on the kidney of rhPTH(1-34) reduced serum phosphate levels and urinary calcium excretion compared with conventional therapy over a period of 10 weeks [130]. hPTH replacement compared with conventional therapy was further investigated in a randomized controlled study over a 3-year period in both adults and children[127,129].

Comparisons of once- and twice-daily rhPTH(1-34) therapy in both adults and children demonstrated that an increased frequency of injections significantly reduced the total daily dose needed [61,128]. Twice-daily injections resulted in lower markers of bone turnover and more physiologic serum calcium and magnesium profiles with less fluctuation in the later portion of the day compared with once-daily rhPTH(1-34) injection. A three-year randomized controlled trial in children compared conventional therapy to twice-daily subcutaneous rhPTH(1-34) injection therapy with doses titrated to specific target serum and urine levels[129]. In both treatment groups, mean serum calcium was slightly below the normal range; mean urine calcium excretion, lumbar spine and whole body bone mineral density, and height and weight percentiles were within normal range and did not differ between groups.[127,129]. Serum $1,25(OH)_2D$ levels were higher in children receiving twice-daily hPTH(1-34) injections compared with those receiving conventional therapy[129].This study shows that treatment with hPTH(1-34) is safe and effective in maintaining stable calcium homeostasis in children with hypoparathyroidism and allowed for linear growth over a 3-year period.

In 27 adults with hypoparathyroidism, twice-daily injections of rhPTH(1-34) was compared to conventional treatment in a three-year randomized open-label trial[127]. Serum calcium levels were maintained slightly below the normal range in both groups. Although mean urinary calcium excretion was consistently within normal range in the rhPTH(1-34) group and above the normal range in the conventional treatment arm, the levels were not statistically different between groups. Bone mineral content and bone mineral density, measured twice yearly, were not different between the groups (reference 109). Treatment with hPTH(1-34) for three years was safe and effective in maintaining serum calcium at the low-normal range without hypercalciuria in adults with hypoparathyroidism.

To further improve metabolic control, pump delivery of hPTH(1-34) was studied in adults and children with various aetiologies of hypoparathyroidism and compared with twice-daily injections[60,131]. hPTH(1-34) microboluses (0.1 μg) were delivered at intervals ranging from 2 to 8 pulses per hour and corresponded to a dose range of 4.8 to 19.2 μg/day, which is one-third of the average daily rhPTH(1-34) dose required during twice-daily injection therapy. Pump delivery of rhPTH(1-34) led to less fluctuation of serum calcium and a more than 50% reduction in urine calcium levels in adults with postsurgical hypoparathyroidism compared with twice-daily delivery[131]. Serum magnesium concentrations were higher and bone resorption markers lower in the pump group[131]. Pump treatment requires a skilled provider with expertise in the management of hypoparathyroidism and in pump devices.] In children with congenital hypoparathyroidism (autoimmune polyendocrine syndrome type 1 or a mutation in the CaSR), pump delivery of hPTH(1-34) compared with twice daily injections resulted in near normalization of mean serum calcium (2.02 ± 0.05 vs. 1.88 ±0.03 mmol/l, $P<0.05$), a nonsignificant reduction of mean urine calcium excretion (5.17 ±1.10 vs. 6.67 ± 0.76 mmol/24 h, $P= 0.3$) and a significant reduction of markers of bone turnover. Pump therapy lowered the urinary magnesium excretion and/or permitted reduction in magnesium supplements[60,131].

Three children with hypoparathyroidism (2 siblings with autoimmune polyendocrine syndrome type 1and one child with idiopathic hypoparathyroidism) refractory to conventional therapy were successfully treated with continuous subcutaneous administration of rhPTH(1-34) over a 3 year period. The two patients with autoimmune polyendocrine syndrome type 1 required substantially higher doses compared to the child with idiopathic hypoparathyroidism[132].

Sudden discontinuation of treatment with rhPTH(1-34) may lead to hypocalcaemia, and patients may require significantly higher than baseline doses of calcium and calcitriol[133].

rhPTH(1-34) (Forteo) was FDA approved in 2002 for treatment of osteoporosis in adults. Restrictions on the length of treatment to two years and the exclusion of its use in children renders this peptide not practicable for use in long-term replacement therapy of hypoparathyroidism as an 'off-label' drug. rhPTH(1-84) (Natpara) was approved in 2015 for the treatment of hypoparathyroidism in adults.

[H3] Recombinant human PTH(1-84). rhPTH(1–84), the full-length hormone, is associated with a longer calcaemic effect when injected into the thigh as compared with the abdomen[134] One single center study tested subcutaneous rhPTH(1-84) injection in the thighin 33 patients over a 6 year period compared with baseline[135]. The initial dose was 100 μg subcutaneously every other day, but most patients transitioned to once-daily injections with a dose ranging from 25-100 μg daily. Compared to baseline, serum calcium was stable over 6 years, and serum phosphate and urinary calcium decreased significantly at several of the measured time-points. Bone mineral density at the spine was mildly increased, whereas it decreased at the hip and the distal radius. The required calcium dose was reduced by 53% and calcitriol dose by 67%, Adverse events included hypercalcaemia (12 episodes in 9 patients), hypocalcaemia (5 episodes), musculoskeletal symptoms, infections, fractures (8 fractures in 6 patients), and renal stones (3 patients). This study concluded that treatment with rhPTH(1-84) is safe and effective for at least 6 years and allows a reduction in the dose of conventional therapy.

In another single-center study, 62 patients with hypoparathyroidism were randomized

(1:1) to either placebo or rhPTH(1-84) (100 μg/day) for 24 weeks as add-on to conventional therapy[136]. Supplements were titrated to achieve normal serum calcium and 24-hour urine calcium excretion. Daily doses of calcium and activated vitamin D decreased by 75% and 73%, respectively, in patients randomized to rhPTH(1-84) compared with placebo. Bone turnover markers increased, and bone mineral density decreased by 1.59% in the hip and by 1.76% in the lumbar spine with rhPTH(1-84) therapy compared with placebo.

In a double-blind, multinational, randomized controlled trial (REPLACE), 134 patients with hypoparathyroidism were randomized (2:1) to rhPTH(1-84) or placebo for 24 weeks[137,138]. When rhPTH(1-84) was initiated at 50 μg/day, activated vitamin D (calcitriol or alphacalcidol) and/or calcium supplements were reduced by ~50%. At subsequent 2-week intervals, doses of rhPTH(1-84) were increased, and supplements were reduced. The primary endpoint was defined as $\geq$50% reductions of activated vitamin D and calcium supplements at 24 weeks, while maintaining serum calcium within the target range (equal to baseline and less than upper limit of normal). This was achieved in 53% of patients treated with rhPTH(1-84) versus 2% of patients treated with placebo ($p<0.001$). Urinary calcium levels did not change with rhPTH(1-84) therapy[138], but serum phosphate levels decreased significantly compared with placebo[137]. Adverse events were similar between both groups and included hypocalcaemia, muscle spasm, paresthesia, headache and nausea. After the end of treatment with rhPTH(1-84), hypocalcaemia was reported in a higher proportion of patients in the rhPTH(1-84) than in the placebo group[138].

Conventional treatment does little to alter the marked static and dynamic abnormalities of bone in hypoparathyroidism[121]. Use of rhPTH(1-84), on the other hand, has shown reversal and recovery of many of these abnormalities. Transiliac crest bone biopsies have

demonstrated a rapid and marked increase in tetracycline-labeled surfaces, representing an increase in bone formation, as early as 3 months after rhPTH(1-84) administration [100]. Within a year of treatment, improvements in both cortical and trabecular bone were observed, including for example a reduction in trabecular width and an increase in trabecular number[100]. In more than half the biopsies, intratrabecular tunneling (bone resorption in trabecular packets) was demonstrated[139]. These microstructural changes demonstrate that one of PTH's actions in bone is to maintain ongoing turnover and repair bone.

The US Food and Drug Administration approved rhPTH(1-84) in 2015 as an adjunct to calcium and vitamin D for the treatment of adults with hypoparathyroidism who cannot be well-controlled on conventional therapy. In 2017, the European Commission has granted Conditional Marketing Authorization for rhPTH(1-84) in Europe.

[H2] Thiazide diuretics

Thiazide diuretics can reduce urinary calcium excretion[140-143] and are prescribed as an adjunct therapy. A study in dogs with hypoparathyroidism treated with chlorothiazide demonstrated a progressive decrease in the fractional clearance of calcium with increased clearance of sodium[144]. Thus, a high salt diet would override any reduction in calciuria associated with thiazides, and dietary restriction of sodium is required. Indeed, a study in 7 patients with mild postsurgical hypoparathyroidism reported that oral chlorthalidone in combination with a low salt diet was effective in lowering urinary calcium levels[145]. Patients with autosomal dominant hypocalcaemia type 1 have been treated with thiazides[146]. Thiazides lead to urinary magnesium losses. Therefore patients with ADH type 1, who have abnormally high urinary magnesium excretion and hypomagnesemia, should avoid thiazide diuretics. Likewise, patients with autoimmune polyendocrine syndrome type 1 and adrenal insufficiency should

generally avoid thiazide diuretics to avoid the resulting increase in urinary sodium excretion[147].

[H2] Diet

Treatment of hypoparathyroidism is facilitated by a diet rich in calcium. To manage hyperphosphatemia, dietary phosphate restriction and phosphate binders are sometimes prescribed in hypoparathyroidism. Simply avoiding foods with phosphate additives and limiting commercially prepared foods, which are often high in sodium and phosphate, effectively limits phosphate intake but allows for dairy intake which provide important nutrients, especially in children. All patients, in particular, if risk factors for kidney stone formation are present, should be counseled regarding adequate fluid intake to decrease the risk of renal calcifications.

[H2] Complications

Conventional therapy is often associated with hypercalciuria even when the serum calcium levels are in the low-normal or below the normal range. Although PTH therapy has the potential to reduce urine calcium excretion compared with conventional therapy, only a few studies demonstrate such a reduction, possibly because of an insufficient duration of action of once-daily PTH injections on the kidneys. [130,135,136] To avoid renal damage from recurrent transient hypercalcaemia and concurrent hypercalciuria, close monitoring of serum calcium should occur after each medication adjustment (Table 2 and 3). [4, 5]

The effects of replacement rhPTH injections on bone depend on the size and frequency of the PTH dose. Once-daily or twice-daily rhPTH(1-34) and alternate day or once-daily rhPTH(1-84) injections produced persistently elevated bone turnover markers with varying long-term

effects on bone mineral density measured with by DXA[61,135]. Pump delivery of PTH(1-34) normalized the levels of bone turnover markers in a 12–week study[60], but further studies of pump delivery of PTH(1-34) are required to determine its long-term effects on bone.

Potential carcinogenic effects underlie the current FDA black box warning on rhPTH(1-34) and rhPTH(1-84) use. In 1998, the Eli Lilly company released its 2-year rat carcinogenicity data in connection with the new drug application of rhPTH(1-34) to the FDA[148-150]. Osteosarcomas developed in these rats exposed to 3-58 times the human equivalent dose over a period of 18-24 months (about 75 years of a human life). The osteosarcomas were dose- and duration-dependent and most evident in animals receiving the highest dose (75 μg/kg). Similar rodent carcinogenicity studies demonstrated an increased osteosarcoma risk associated with pharmacologic doses of subcutaneous PTH(1-84) injections[151]. Subsequent data in nonhuman primates receiving high doses of PTH(1-34) (5 μg/kg) for 18 months showed increased bone mass, but no osteosarcoma or bone proliferative lesions were evident after the therapy was discontinued or during a subsequent 3-year observation period[152]. Despite the rat toxicity data, an important observation in humans is that longstanding hyperparathyroidism is not associated with the development of osteosarcomas despite chronically elevated PTH levels[153]. Furthermore, no increased rate of osteosarcoma has emerged despite extensive use of rhPTH in patients with hypoparathyroidism or osteoporosis over >20 years, but most of the latter were treated for only two years[154,155].

Recently, two guidelines were developed to assist clinicians treating chronic hypoparathyroidism in adults[4,5] (**TABLE 2 and 3**). The data on which these guidelines are based are relatively small trials with mainly biochemical as opposed to clinical endpoints (such as, disease progression, survival). The guideline sponsored by the European Society of

Endocrinology[4] was based on a systematic review of the literature and the guideline from the First International Conference on Hypoparathyroidism was based on both literature review and expert opinion[5]. Both guidelines recommend intervals for monitoring for possible complications of the condition such as renal insufficiency, soft tissue calcifications, hypercalciuria, as detailed in **TABLE 2 and 3**.

[H1] Quality of life

Patients with hypoparathyroidism on conventional therapy with calcium and active vitamin D often have complaints suggestive of reduced quality of life (QoL)[1,2,156]. These complaints include physical symptoms such as fatigue; neuromuscular complaints such as weakness, cramps, paresthesia, and seizures; inability to concentrate or to focus often described as "brain fog"; and emotional difficulties, which are variable but encompass, among others, anxiety, depression, and personality disorders. Recent studies have attempted to define the nature and prevalence of QoL impairments in hypoparathyroidism[6,109,111,118,157]. When compared with healthy controls or with patients who have had thyroid surgery but retained normal parathyroid function, patients with postsurgical hypoparathyroidism had significantly higher global complaint scores[111], lower physical summary scores on Short Form Health Survey (SF36) and decreased muscle function[109]. Lower QoL scores have also been observed in patients with hypoparathyroidism in registries and surveys from Denmark[7,8], Norway[6] and the United States[118]. Finally, patients who developed postsurgical hypoparathyroidism had lower QoL scores than anticipated by either healthy individuals given the description of the disease or by experienced (endocrine) surgeons[157].

When rhPTH(1-34) and rhPTH(1-84) became available, there was a hope that replacing the missing hormone would restore QoL in patients with hypoparathyroidism. Indeed, many

patients treated with rhPTH report improved wellbeing compared with baseline (conventional treatment). However, despite such laudable anecdotal reports, findings from the studies of PTH on QoL have been inconsistent. In an open-label, uncontrolled study from Columbia University, New York, QoL as assessed by SF36 was low in all domains at baseline despite acceptable control of serum calcium through conventional therapy[158,159]. All domains improved significantly in response to rhPTH(1-84) at 1 and 2 years[158]. In individuals who completed 5 years of therapy, QoL improved for the duration of the study[159]. Similar improvements were reported in an Italian study which used twice daily injection of rhPTH(1-34)[160]. However, in this study many patients had hypocalcaemia at baseline which was corrected during the study[160]. Thus, it is possible that improved wellbeing may be at least in part due to better calcaemic control.

In contrast to the strikingly positive results of the open-label studies described above, a Danish double-blind, placebo-controlled study which enrolled relatively well-controlled patients with hypoparathyroidism found that patients had less improvement in SF36 scores compared with placebo and actually had worse performance on at least some muscle function tests[161]. However, many patients treated with rhPTH(1-84) in that study developed hypercalcaemia which may have negatively affected their well-being. Preliminary analysis of the REPLACE study revealed improved QoL scores (SF36) with rhPTH(1-84) treatment but not with placebo. However, the between-group differences were not statistically significant [162].

Further studies are clearly needed to better understand the nature and the degree of QoL impairments, individual differences, and relationship to biochemical variables (if any) and

treatment modalities. Developing better and hypoparathyroidism-specific instruments to assess QoL will be critical in achieving this goal.

[H1] Outlook

In the past 25 years since the first studies of hPTH replacement therapy were initiated, our knowledge of hypoparathyroidism has increased markedly. For a rare disease, the stimulus to conduct further research is due to the fact that hypoparathyroidism was one of the last of the classic endocrine deficiency diseases for which the replacement hormone was not available. This is an ironic historical note as the primary amino acid sequence of PTH was delineated in the late 1960s[163] and it was the second peptide hormone, after insulin, for which a sandwich immunoassay was developed[164]. Almost 50 years later, we now have an approved replacement therapy for hypoparathyroidism.

The recent interest in this disorder has resulted in more information about the incidence, prevalence and natural history of hypoparathyroidism. Our understanding of the underlying genetics of many of the rare variants has been enhanced greatly. Such insights have not only added to our knowledge of rare genetic mutations that cause hypoparathyroidism, but have given us insight into the molecular actions of PTH and its cellular functions under normal circumstances.

The experience with rhPTH(1-84) as a treatment of hypoparathyroidism provides evidence for maintenance of the serum calcium, at doses of supplemental calcium and active vitamin D that are substantially lower than pretreatment values. Only modest effects on urinary calcium excretion, restoration of abnormal skeletal histomorphometric parameters, and QoL have

been observed. Experts have galvanized new knowledge of hypoparathyroidism by offering guidelines for the diagnosis and management of this disease[4,5].

As we look to the future, a number of issues begs for greater insights and knowledge. Highlighting this list are questions related to which patients should be considered for treatment with newly approved replacement therapy, rhPTH(1-84). Although patients with mild disease can often be managed with oral calcium and active vitamin D, patients with more-severe manifestations require higher doses of calcium and active vitamin D, which raises concerns about long-term sequelae such as soft tissue calcifications in the kidneys, brain and joints. Moreover, conventional therapy does not restore the underlying hormonal deficiency. Some experts also consider the reduced QoL, now substantiated in many studies using generic metrics such as the SF-36 QoL scale, as being due, at least in part, to the lack of PTH.

The indications for the use of FDA-approved rhPTH(1-84) target patients with hypoparathyroidism who cannot be well-controlled on conventional therapy. Although the wording of the FDA term, 'well-controlled' is subject to interpretation, the International Conference on the Diagnosis and Management of Hypoparathyroidism considered 6 specific situations, any one of which could lead to rhPTH(1-84) therapy[121] (Box 4). These guidelines will evolve over time and are not meant to be rules but instead guidance for the clinician to help decide the best course of action for an individual patient. Data on the efficacy of rhPTH(1-84) therapy in preventing long-term complications of hypoparathyroidism are sparse, and safety data in large cohorts of patients, especially in children, is missing. The current costs of PTH therapy and the compliance with injectable form are potential hurdles

for its use. Long-term, multicenter controlled trials are necessary to determine the best possible treatment for patients with hypoparathyroidism.

In addition, more detailed analysis of the skeleton with newer technologies, such as High-Resolution peripheral Quantitative Computed Tomography, Trabecular Bone Score and Reference Point Indentation, might yield insights into altered bone quality in hypoparathyroidism. To understand the long-term impact of rhPTH(1-84), insight in the natural history of hypoparathyroidism, skeletal dynamics, bone quality, renal function, QoL, and known complications of the disease is needed. With regard to long-term studies, the idea that rhPTH(1-84) might have an effect to reverse or mitigate ectopic calcifications in soft tissues is worthy of study. Another direction that is likely to be of importance is the feasibility and applicability of new delivery systems (transdermal patch; continuous infusion pump, oral PTH formulations) as well as PTH analogues and mimetics[165,166].

With the advances over the past decade and the marked interest in this orphan disease, we are likely to learn more, not only about the disease itself but also about the many important and varied actions of PTH.

Box 1 | Pseudohypoparathyroidism

Pseudohypoparathyroidism is a disorder associated with PTH resistance. Although it also leads to hypocalcaemia and hyperphosphatemia, circulating PTH concentrations are increased in pseudohypoparathyroidism, which differentiates this condition from hypoparathyroidism. The primary cause of pseudohypoparathyroidism is a mutation in the G_s α-subunit ($G_{s\alpha}$) (FIG 2)[167]. $G_{s\alpha}$, encoded by *GNAS*, is biallelically expressed in most tissues, but imprinting restricts expression to the maternal allele in the proximal renal tubule and thyroid gland. Maternally inherited heterozygous inactivating mutations of *GNAS* cause pseudohypoparathyroidism type 1a. In addition to PTH resistance, patients with pseudohypoparathyroidism type 1a exhibit features of Albright hereditary osteodystrophy (AHO) including short stature, obesity, round facies, subcutaneous calcifications and brachydactyly (shortening of fingers or toes) [167]. Resistance to other hormones that signal through $G_{s\alpha}$ may occur, for example to thyroid-stimulating hormone (TSH) and growth hormone-releasing hormone. Conversely, paternally inherited *GNAS* mutations cause pseudopseudohypoparathyroidism, characterized by the AHO phenotype without PTH resistance. Pseudohypoparathyroidism type 1b is characterized by *GNAS* methylation defects leading to resistance to PTH, and sometimes to TSH[167-169]. Pseudohypoparathyroidism type 1b is caused by autosomal dominant maternal deletions in NESP55 (part of the complex *GNAS* locus) **[Au:OK?]** or the nearby gene *STX16*, but the molecular defect of the more common sporadic form of the disease is still unresolved. Epigenetic or coding-region *GNAS* abnormalities may also cause pseudohypoparathyroidism type 1c, which is clinically similar to type 1a, though $G_{s\alpha}$ activity is not affected *in vitro*[170]. In contrast to type 1a and 1b, in which cAMP responses to PTH are blunted, pseudohypoparathyroidism type 2 patients demonstrate conserved responses; pseudohypoparathyroidism type 2 may in some cases be explained by vitamin D deficiency[171]. As $G_{s\alpha}$ is expressed from both alleles in the distal renal

tubule and is not imprinted, urinary calcium reabsorption is normal in the distal tubule, and patients with $G_{s\alpha}$ mutations are not at increased risk for nephrocalcinosis. Treatment of PTH resistance in pseudohypoparathyroidism consists of activated vitamin D and calcium but therapeutic goals differ from those of hypoparathyroidism, that is, normalization of blood calcium levels and maintenance of PTH levels in the normal to mildly elevated range. Blood chemistries should be monitored frequently and urinary calcium excretion occasionally.

Box 2 | Measurement of serum PTH levels.

Circulating PTH peptides include full-length, active PTH(1-84) peptides and several forms of truncated, mostly carboxyl-terminal fragments, the majority being PTH(34-84) and PTH(37-84)[172,173]. These truncated fragments cannot bind and activate the classic PTH1R. Although the plasma half-life of intact PTH(1-84) is only a few minutes, renal clearance of PTH fragments is slower. Thus, under normocalcaemic conditions, only about 20% of the PTH peptides are intact, biologically active PTH[174].

To improve the clinical performance of the first generation PTH assay[175], which detected not only intact PTH but also truncated fragments, the two-site immunoradiometric (IRMA) assay was introduced in 1987[164]. This sandwich assay uses a carboxyl-terminal capture antibody linked to a solid phase and an amino-terminal detection antibody, making the measurement of PTH(1-84) more accurate. This 'second-generation' IRMA, which does not detect the majority of carboxyl-terminal fragments, is the most widely used intact PTH assay to date. In 1999, a 'third generation' PTH assay was introduced[176] called 'whole PTH' or 'biointact PTH' assay. This assay uses a similar C-terminal capture antibody as the second-generation test but an amino-terminal detection antibody which only detects the extreme amino-terminal region of PTH (that is, PTH(1-6)). Interestingly, although this test is theoretically better, it has not been proven to be superior in clinical practice, but studies are limited[177,178].

Box 3 | Vitamin D metabolism.

Vitamin D precursors are derived from the conversion of cholesterol to cholecalciferol (vitamin D3) through a chemical reaction that takes place in the skin and requires UVB radiation. Cholecalciferol or ergocalciferol (vitamin D2) can be ingested through the diet, but only very few foods (such as, fatty fish) contain adequate levels. The biologically inactive cholecalciferol or ergocalciferol are activated by two hydroxylation steps. Hydroxylation in the liver to either calcifediol (25(OH)cholecalciferol) or to 25(OH)ergocalciferol – together known as 25(OH)D - produces the stable precursor of the active hormone which is typically measured in clinical practice to assess vitamin D status. Further hydroxylation of 25(OH)D in the kidney to calcitriol ($1,25(OH)_2D$) – the active form of vitamin D - is the rate-limiting step that is enhanced by PTH and blocked by FGF23. Treatment of hypoparathyroidism often involves calcitriol, or alphacalcidol ($1\alpha(OH)D_3$), the latter which requires hepatic 25-hydroxylation for bioactivation.

Box 4 | Indication for considering the use of rhPTH(1-84) therapy

Expert opinion of International Conference on the Diagnosis and Management of Hypoparathyroidism to guide the use of rhPTH(1-84)[5]

Inadequate control of the serum calcium with hypocalcemia, or erratic swings to hypocalcaemia or hypercalcaemia on conventional therapy

- Doses of supplemental calcium that exceeds 2.5 gram or of active vitamin D of > 1.5 μg calcitriol or >3.0 μg alphacalcidol per day
- Evidence for renal involvement with hypercalciuria, nephrocalcinosis, nephrolithiasis or reduced creatinine clearance on conventional therapy
- Hyperphosphatemia or a calcium-phosphate product of > 55 mg^2/dl^2 (or 4.4 $mmol^2/L^2$) on conventional therapy
- A gastrointestinal disorder or post-bariatric surgery, associated with malabsorption
- Reduced quality of life on conventional therapy

Figure legends

Figure 1 | Regulation of extracellular calcium homeostasis. Activation of the extracellular calcium-sensing receptor (CaSR) owing to a reduction in extracellular calcium (Ca^{2+}) levels results in a rapid increase in PTH secretion. PTH acts on the PTH1 receptor (PTH1R) in the kidneys and bone. In bone, PTH1R activation in osteoblasts (bone forming cells) and osteocytes (differentiated osteoblasts that have become embedded in the bone matrix and that are involved in regulation of osteoblast and osteoclast activity and phosphate homeostasis, among others) results in the release of cytokines that stimulate osteoclast (bone resorbing cell) activity, thereby enhancing bone resorption and the release of calcium from the skeleton.[15] In the kidney, PTH increases tubular calcium reabsorption and stimulates the 25-hydroxyvitamin D 1-α-hydroxylase (CYP27B1) enzyme, which promotes the conversion of the active 1,25-dihydroxyvitamin D ($1,25(OH)_2D$) metabolite from its precursor (25-(OH)D). $1,25(OH)_2D$ acts on the intestine to increase absorption of dietary calcium via the vitamin D receptor (VDR).[18] The rise in Ca^{2+} and $1,25(OH)_2D$ levels mediated by PTH act on the parathyroid glands to induce feedback inhibition of further PTH secretion[14].

Figure 2 Components involved in the parathyroid regulation of calcium homeostasis. Variations in extracellular calcium (Ca^{2+}) are detected by the calcium-sensing receptor (CaSR), which is expressed by cells in the parathyroid gland, kidney and bone. The CaSR signals via the $G_{q/11}\alpha$ proteins to stimulate phospholipase C (PLC), which catalyses the hydrolysis of phosphoinositide (PIP_2) to inositol triphosphate (IP_3), thereby increasing intracellular calcium, and diacylglycerol (DAG). The CaSR also signals via the $G_i\alpha$ protein, which inhibits adenylate cyclase (AC), thereby leading to a reduction in the formation of cAMP from ATP. In parathyroid cells, these proximal signals modulate downstream pathways, which lead to alterations in the synthesis and secretion of PTH. Secreted PTH acts on the PTH1 receptor (PTH1R), which mediates signalling via the Gsα and $G_{q/11}\alpha$ proteins and cAMP activation. Abnormalities in several genes and encoded proteins in these pathways involved in calcium-sensing and G-protein function, mitochondrial activity, tubulin formation; and gene

transcription and chromatin remodelling have been identified in patients with genetic hypoparathyroid disorders[18].

Figure 3 Transcription factors involved in parathyroid gland development and function. The parathyroid glands in humans are derived from the endoderm of the third and fourth pharyngeal pouches[47], whereas the glands develop together with the thymus from the third pharyngeal pouch endoderm in mice[47,49]. Studies using mouse models have shown that a network of transcription factors mediate patterning of the third pharyngeal pouch and formation of the common parathyroid-thymus primordia[47,49]. These transcription factors act in a spatiotemporal manner. For example, TBX1, expressed in the pharyngeal endoderm, is required for the development of the third pharyngeal pouch[31], whereas GATA3, expressed later than TBX1 in the common parathyroid-thymus primordial, mediates the differentiation and survival of parathyroid and thymus progenitor cells[46,47]. Moreover, GATA3 regulates the expression of GCM2, which is expressed in the parathyroid domain of the common primordia and mediates the initial stages of parathyroid organogenesis[46,47]. MAFB is also expressed in the parathyroid domain and facilitates the separation of the parathyroid glands from the thymus and the migration of the parathyroids towards the thymus[49]. GATA3, GCM2 and MAFB act synergistically to upregulate *PTH* expression[48]. Since the expression of GATA3, GCM2 and MAFB persists into adulthood, these transcription factors are likely required for the postnatal expression of *PTH*[48].

Figure 4 | Clinical manifestations of hypoparathyroidism. Common and rare manifestations are shown. *Manifestations are mostly the result of treatment with calcium and activated vitamin D rather than the disorder itself.

Figure 5. Central nervous system calcifications. Coronal (part a) and sagittal (part b) MRI scan showing calcifications in XXXX

Winer, K. K., Yanovski, J. A. & Cutler, G. B., Jr. Synthetic human parathyroid hormone 1-34 vs calcitriol and calcium in the treatment of hypoparathyroidism. *JAMA* **276**, 631-636 (1996).
This is the first controlled study in patients with hypoparathyroidism using a PTH analogue, demonstrating that it is a safe and effective treatment.

Winer, K. K. *et al.* Synthetic human parathyroid hormone 1-34 replacement therapy: a randomized crossover trial comparing pump versus injections in the treatment of chronic hypoparathyroidism. *J Clin Endocrinol Metab* **97**, 391-399, doi:10.1210/jc.2011-1908 (2012)
This trial of adults with postsurgical hypoparathyroidism demonstrated that continuous subcutaneous infusion of a PTH analogue when compared to twice-daily injection resulted in less fluctuation in serum calcium, normalized urinary calcium excretion, normalized bone turnover markers, and a decreased overall medication dose.

Rubin, M. R. *et al.* Therapy of Hypoparathyroidism With PTH(1-84): A Prospective Six Year Investigation of Efficacy and Safety. *J Clin Endocrinol Metab* **101**, 2742-2750, doi:10.1210/jc.2015-4135 (2016)
This report describes a cohort of 33 patients treated with PTH(1-84) demonstrating persistent efficacy and apparent safety of this treatment regimen over a relatively long time.

Mannstadt, M. *et al.* Efficacy and safety of recombinant human parathyroid hormone (1-84) in hypoparathyroidism (REPLACE): a double-blind, placebo-controlled, randomised, phase 3 study. *Lancet Diabetes Endocrinol* **1**, 275-283, doi:10.1016/S2213-8587(13)70106-2 (2013)
This phase 3 randomized controlled trial, using flexible dosing of PTH(1-84) in hypoparathyroidism demonstrated efficacy in reducing calcitriol and calcium needs and served as the basis for drug approval in the United States.

Arlt, W. *et al.* Well-being, mood and calcium homeostasis in patients with hypoparathyroidism receiving standard treatment with calcium and vitamin D. *European journal of endocrinology / European Federation of Endocrine Societies* **146**, 215-222, doi:146215 [pii] (2002)
The authors investigated mood and well-being in 25 women with postsurgical hypoparathyroidism compared to a control group of women with a history of thyroid surgery alone and found decreased well-being, with specific increases in anxiety in the hypoparathyroid women despite generally good control of serum calcium.

Mitchell, D. M. *et al.* Long-term follow-up of patients with hypoparathyroidism. *J Clin Endocrinol Metab* **97**, 4507-4514, doi:10.1210/jc.2012-1808 (2012).
The first large long-term follow-up of patients with hypoparathyroidism revealed that rates of complications including renal disease are high.

Underbjerg, L., Sikjaer, T., Mosekilde, L. & Rejnmark, L. Cardiovascular and renal complications to postsurgical hypoparathyroidism: a Danish nationwide controlled historic follow-up study. *J Bone Miner Res* **28**, 2277-2285, doi:10.1002/jbmr.1979 (2013)
This analysis of a national patient registry in Denmark confirmed elevated risks of renal disease and seizures in patients with hypoparathyroidism.

Brandi, M. L. *et al.* Management of Hypoparathyroidism: Summary Statement and Guidelines. *J Clin Endocrinol Metab* **101**, 2273-2283, doi:10.1210/jc.2015-3907 (2016).
Guidelines produced by experts in the field.

Bollerslev, J. *et al.* European Society of Endocrinology Clinical Guideline: Treatment of chronic hypoparathyroidism in adults. *European journal of endocrinology / European Federation of Endocrine Societies* **173**, G1-20, doi:10.1530/EJE-15-0628 (2015)

Guidelines developed by panel representating the European Society of Endocrinology.

Boyce, A.M. *et al*. Ultrasound is superior to computed tomography for assessment of medullary nephrocalcinosis in hypoparathyroidism. *J Clin Endocrinol Metab* **98**, 989-94 (2013)
This study demonstrated that ultrasound had substantially higher sensitivity for detection of nephrocalcinosis, particularly mild-to-moderate disease, among patients with hypoparathyroidism when compared to CT.

Goswami R *et al*. Prevalence and progression of basal ganglia calcification and its pathogenic mechanism in patients with idiopathic hypoparathyroidism. *Clin Endocrinol* **77**(2):200-6, (2012)
This study of a large Indian cohort of patients with idiopathic hypoaprathyroidism reported a very high prevalence of basal ganglia calcifications (73.8%) and that the risk of progression over time was associated with a lower serum calcium/phosphorus ratio.

Pearce S. H. et al. A familial syndrome of hypocalcemia with hypercalciuria due to mutations in the calcium-sensing receptor. *N Engl J Med* **335**:1115-22 (1996).
Building on previous case reports, this paper reported activating mutations of the calcium-sensing receptor in 5 out of 6 kindreds with autosomal dominant hypocalcemia.

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Table 1. Inherited types of hypoparathyroidism

Disorder	Inheritance	Chromosomal location	Gene
Syndromic hypoparathyroidism			
DiGeorge syndrome type 1 (also known as 22q11.2 deletion syndrome)	AD	22q11.2	*TBX1*
DiGeorge syndrome type 2	AD	10p13-14	*NEBL*
CHARGE syndrome	AD	8q12.2	*CHD7*
Autoimmune polyendocrine syndrome type 1	AR	21q22.3	*AIRE*
Hypoparathyroidism, sensorineural deafness, and renal disease (HDR) syndrome	AD	10p15	*GATA3*
Kearns-Sayre syndrome*	Mat	-	Mitochondrial DNA
Mitochondrial encephalopathy, lactic acidosis, and stroke-like episodes (MELAS) syndrome*	Mat	-	Mitochondrial DNA
Mitochondrial trifunctional protein (MTP) deficiency syndrome*	AR	2p23	*HADHB*
Kenny-Caffey syndrome type 1**	AR	1q42.3	*TBCE*
Sanjad-Sakati syndrome**	AR	1q42.3	*TBCE*
Kenny-Caffey syndrome type 2 (KCS2)**	AD	11q12.1	*FAM111A*
Gracile bone dysplasia **	AD	11q12.1	*FAM111A*
Autosomal dominant hypocalcemia (ADH)			
ADH type 1 (ADH1)	AD	3q21.1	*CASR*
Bartter syndrome type 5	AD	3q21.1	*CASR*
ADH type 2	AD	19p13.3	*GNA11*
Isolated hypoparathyroidism			
Autosomal hypoparathyroidism	AD or AR	11p15, 6p24.2	*PTH, GCM2*
X-linked hypoparathyroidism	XR	Xq26-27	*SOX3?*
AD, autosomal dominant; AR, autosomal recessive; XR, X-linked recessive; *, Mitochondrial disorder; ** Bone dysplasia and short stature			

Table 2. Goals of management of hypoparathyroidism according to the European Society of Endocrinology

Therapeutic goal	Parameter to monitor	Complication(s) to be prevented	Frequency of monitoring	Level of recommendation for the goal of management; quality of evidence[1]	Level of recommendation for the frequency of monitoring, (quality of evidence[1])	Comment
Serum calcium in the low-normal range	Albumin-corrected total serum calcium levels 8.0-8.5 mg/dl or 2.0-2.12 mM Ionized serum calcium levels 1.00 mM)	Hypocalcaemia: for example, symptomatic tetany and mental status changes. Hypercalcemia: for example dehydration, renal dysfunction, and mental status changes	Every 3 to 6 months	Suggested, +	Recommended; evidence not graded	During active adjustments of treatment with calcium and vitamin D analogues, clinical assessments and serum biochemistry should be done frequently (weekly or every other week)
Prevent hypercalciuria	Urinary calcium levels below the sex-specified normal range (<250 mg/d for women; <300 mg/d for men, or <4 mg/kg/day for both sexes)	Hypercalciuria, nephrocalcinosis, kidney stones and renal insufficiency	Once a year or every second year	Suggested; +	Suggested; evidence not graded	NA
Serum phosphate levels within reference range	Serum phosphate levels within or close to age-adjusted reference range	Ectopic soft tissue calcifications (brain, kidney, vascular system and other tissues)	Every 3 to 6 months	Suggested, (+)	Recommended (evidence not graded)	After a change in therapy monitor weekly or every other week
Control calcium-phosphate product levels	Serum calcium-phosphate levels <55 mg^2/dL^2 (product < 4.4 $mmol^2/l^2$)	Ectopic soft tissue calcifications in the brain, kidneys, vascular system and brain	Every 3 to 6 months	Suggested; +	Recommended (evidence not graded)	Monitor weekly or every other week after a change in treatment
Serum magnesium levels within reference range	Serum magnesium levels within reference range	Hypomagnesemia	Every 3 to 6 months	Suggested; +	Recommended; evidence not graded	NA
eGFR within	Creatinine	Renal insufficiency	Every 3 to 6	NA	Recommende	Monitor

reference range	levels in serum and urine; eGFR between 90 and 120 mL/min/1.73 m^2 should be aimed for		months		d; evidence not graded	weekly or every other week after a change in treatment
Vitamin D adequacy	Serum 25(OH)D of >50 nmol/L or >20 ng/mL	Non-skeletal effects of vitamin D deficiency including myopathy	Yearly	Suggested; +	NA	Vitamin D levels should be maintained within the normal range
Prevention of the formation of kidney stones or nephrocalcinosis	Urine levels of kidney stone risk markers and renal imaging (mainly ultrasonography)	Flank pain, infection, renal insufficiency, among others	With all clinical monitoring and as a co-morbidity at regular intervals (e.g., yearly)	Recommended; evidence not graded	Recommended; evidence not graded	Renal imaging is also recommended if symptoms of renal stone disease present or serum creatinine starts to rise
Improved quality of life, absence of symptoms of hypocalcaemia	Quality of life, well-being, symptoms	Impaired quality of life	Every 3 to 6 months	Recommended; evidence not graded	Personalised treatment recommended	No specific instrument used to assess quality of life
Maintain bone mass	Bone mineral density by dual energy X-ray absorptiometry	Osteoporosis or fractures	Not routinely recommended	NA	NA	NA
Recommendations are graded as recommended (strong recommendation) and suggested (weak recommendation) with grading of evidence as strong (++++), moderate (+++), low (++), and very low (+) according to the GRADE (Grading of Recommendations Assessment, Development and Evaluation) principles ([4]). **NA, not applicable**						

Table 3. Goals of management according to the First International Conference on the Management of Hypoparathyroidism

Therapeutic goal	Parameters to monitor	Complications to be prevented	Frequency of monitoring	Comment
Prevention of hypocalcaemia	Clinical symptoms and signs of hypocalcaemia using patient history and physical examination Laboratory tests (serum calcium and albumin)	Tetany, seizures, muscle cramps, paresthesias, and other neuromuscular complications, fatigue, poor concentration, memory, cognitive function, impaired quality of life, and congestive heart failure (if severe and chronic)	Every 6 months (once stable dosing has been achieved) Twice a year (yearly if very stable)	During active adjustments of treatment with calcium and vitamin D analogues, clinical assessments and serum biochemistry should be done frequently (several times per week, weekly or monthly) depending on the circumstances.
Maintain serum calcium, level slightly below the normal range	Total serum calcium levels no more than 0.5 mg/dL below the lower limit of normal (with normal being 8.5 mg/dl) Serum phosphate, magnesium, creatinine, eGFR and electrolytes			
Prevent or minimize hypercalciuria	24-hour urine calcium excretion and creatinine levels and eGFR	Kidney stones, nephrocalcinosis , renal dysfunction and end-stage renal disease	At least once yearly, consider remeasuring with dose adjustments	If thiazide diuretics are used, monitor serum K and Mg. Volume status should be monitored clinically and by physical examination. If patients have normal urinary calcium levels for several years without renal complications, physicians may opt not to measure urinary calcium.
Keep the calcium-phosphate product <55 mg^2/dL^2 or 4.4 $mmol^2/L^2$	Serum calcium, and phosphate	Ectopic calcifications in the brain, kidneys, vascular system and soft	Every 6 months (yearly if very stable)	Consider reassessing with dose changes
			Once yearly	
Avoid hypercalcemia	Serum calcium phosphate, urea nitrogen, creatinine, electrolytes	Symptomatic hypercalcemia (weakness, altered mental status, nausea, abdominal pain), increased risk of renal calcification	Twice a year (yearly if very stable)	During active adjustments of calcium and vitamin D analogues, clinical assessments and serum biochemistry should be done frequently (several times per week, weekly or monthly).
Decrease potential for renal and other extraskeletal	Renal imaging (ultrasonography or	Renal dysfunction and progression to	Every 5 years (if history of kidney	It is unclear if basal ganglia or other

calcifications	CT), brain calcifications (CT) and cataracts (slit lamp examination)	dialysis or transplantation. Central nervous system calcifications and possible dysfunction (for example, seizures, altered mental activity and movement disorder). Visual loss.	stones or nephrocalcinosis and if currently asymptomatic); more frequently if signs of renal stones or renal dysfunction develop.	CNS calcifications should be monitored and at what frequency if detected at the baseline or interval examination. The frequency of cataract monitoring will depend on results of baseline ophthalmologic exam and current status of the patient.
eGFR, estimated glomerular filtration rate. Guidelines from First International Conference on the Management of Hypoparathyroidism[5] NA, not applicable				