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Review

Hypoparathyroidism: Clinical definition and news on management

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ABSTRACT

Hypoparathyroidism (HP), a group of heterogeneous disorders characterized by hypocalcemia and hyperphosphatemia due to inadequate PTH secretion or signaling, is a relatively rare endocrine disease, with the exception of postsurgical HP, which is a relatively common condition. The availability of genetic tools and the characterization of specific antibodies against the calcium sensing receptor (CaSR) has helped to classify the different forms of congenital or acquired, non-surgically determined forms of HP, so that few cases can be defined as idiopathic today. Still, precise genetic workup protocols and epidemiological studies on the prevalence and incidence of the various etiologies of HP are needed in order to better classify patients with HP. Bone quality assessment in HP along with a better characterization of the skeletal disturbances, due to the missing action of PTH on bone cells, are advisable. Guidelines on the management of HP are still lacking. HP is the only endocrine condition for which a proper replacement therapy with the missing hormone is not still available. Conventional treatment with calcium and 1α-hydroxylated vitamin D metabolites relieves symptoms of hypocalcemia but it fails in restoring a physiologic calcium and phosphate homeostasis and a normal bone metabolism, since PTH action on kidney and bone is lost. Several trials have tested the effect of teriparatide (PTH1-34) and full length PTH(PTH1-84) on mineral and skeletal homeostasis. PTH replacement therapy, alone or in combination with calcitriol, may restore a more physiological bone metabolism and dynamics, as demonstrated by bone quality studies. Larger and longer randomized intervention trials are needed in order to test PTH toxicity and long-term benefits on bone, kidney, quality of life, and other systems not directly related to mineral homeostasis.

KEYWORDS: hypoparathyroidism, genetics, hypocalcemia, hypercalciuria, bone, parathyroid hormone, calcitriol, PTH1-34, PTH1-84

ABBREVIATIONS

aBMD	-	areal BMD
ADHH	-	autosomal dominant hypercalciuric hypocalcemia
APECED	-	Autoimmune Polyendocrinopathy Candidiasis Ectodermal Dystrophy
CaSR	-	calcium sensing receptor
DEXA	-	dual energy X-ray absorptiometry
DGS	-	DiGeorge sequence
HDR	-	Hypoparathyroidism Deafness Renal Dysplasia
HP	-	hypoparathyroidism
KSS	-	Kearns Sayre Syndrome
MELAS	-	Mitochondrial Encephalopathy Lactic Acidosis Stroke-like episodes
MTPDS	-	Mitochondrial Trifunctional Protein Deficiency Syndrome
μCT	-	micro-computed tomography
PHP	-	pseudohypoparathyroidism
pQCT	-	peripheral quantitative computed tomography
PTHR1	-	PTH receptor 1
vBMD	-	volumetric BMD

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1. INTRODUCTION

The term hypoparathyroidism (HP) refers to a group of heterogeneous disorders characterized by hypocalcemia and hyperphosphatemia resulting from inadequate PTH secretion or receptor activation. Levels of serum PTH are undetectable or inappropriately low so that calcium homeostasis is impaired. The inadequate PTH levels lead to deficient mobilization of calcium from skeletal tissue, insufficient calcium reabsorption from the renal distal tubule and decreased renal production of the biologically active vitamin D [1,25$(OH)_2$ vitamin D] necessary for effective active intestinal calcium absorption [1]. HP can be either a rare congenital endocrine disorder or a relatively common acquired endocrine disorder mostly occurring after neck surgery. The onset and severity of clinical manifestations will depend on the cause and on the extent of parathyroid impairment. Besides the classical symptoms of hypocalcemia due to latent or overt neuromuscolar hyperexcitability, non-classical symptoms are often present in congenital forms, in which HP could also be associated with other abnormalities [2]. Acute HP is often an endocrine emergency and is usually treated with oral calcium and calcitriol associated with intravenous calcium therapy in the most severe cases. Conventional therapy with calcium and calcitriol is still the therapy of choice in chronic HP as well, so far. However, mineral is not fully restored by this treatment, which leads to side effects such as hypercalciuria, nephrocalcinosis and renal failure. In addition, bone metabolism is altered with peculiar changes not reverted by conventional therapy. Therapy with the missing hormone, either as teriparatide (PTH1-34) or full length PTH (PTH1-84), has been successfully tested in randomized controlled trials alone or in combination with conventional therapy in order to decrease or withdraw calcitriol thus decreasing the risk of hypercalciuria, maintain a more physiologic and stable serum calcium levels and restore bone abnormalities [3]. These new therapeutic advances will be extensively discussed in this review.

2. Classification

A classification for hypoparathyroid states based on different etiologies is proposed in Table 1.

HP can be either acquired or congenital, isolated or associated with a variety of syndromes or complex disorders [2]. In the latter case it is usually genetically determined, while the term *idiopathic* HP refers to a chronic hypoparathyroid condition for which the specific pathogenesis is not found or remains to be investigated [3].

2.1. Acquired HP

Postoperative HP is the most common form of HP in adults. It occurs when the parathyroids and/or their blood supply are unintentionally or unavoidably removed or damaged during neck surgery, generally thyroid and parathyroid surgery. Parathyroid reserve is ample so that HP manifests when less than one fully functional parathyroid is left. The prevalence of postsurgical HP is 0.5-6.6% in different case series, depending on the experience of the surgeon based on the annual performed surgical procedures, extent of neck resection and underlying thyroid/ parathyroid pathology [1, 4-7]. Patients undergoing sub-total, total or near-total thyroidectomy and parathyroidectomy, radical lymphnode dissection, re-interventions and/or receiving surgery for retrosternal goiters, Graves' disease, parathyroid hyperplasia, thyroid and parathyroid cancer are at major risk of developing postoperative HP. It usually develops within few days after the surgical procedure in an acute setting and requires prompt therapy (see below). The majority of patients experiencing transient HP due to temporary parathyroid functional abnormality, spontaneously recover within weeks or months and do not develop permanent disease. Postsurgical HP is usually transient, resolving within 6 months after surgery and it is relatively common. Postoperative HP is permanent or chronic when it persists over 6 months.

Autoimmunity is the second cause of acquired HP in adults. Antibodies directed against the parathyroid tissue were found in up to 38% of patients with idiopathic HP and 12-26% of patients with other autoimmune endocrinopathies such as Addison's disease or autoimmune thyroiditis, respectively [8]. Later on, antibodies directed against the calcium sensing receptor (CaSR) have been identified in many cases (29-49% according to different case series and tested with different techniques) of idiopathic/sporadic HP [9]. It is not established

Table 1. Classification of acquired and congenital hypoparathyroidism (the genetic characterization is indicated for the congenital-genetically determined forms only).

Type of hypoparathyroidism	Genetic locus
Acquired	
Postsurgical	
Autoimmune	
Hypo- or hypermagnesemia	
Radiation therapy and infiltration	
Heavy-metal storage disorders	
Post burn	
Maternal hyperparathyroidism	
Congenital (primary)	
Isolated (familial)	
Autosomal dominant	
PTH gene mutation (dominant negative)	*PTH*/11p15
CaSR activating mutation (ADHH)	*CaSR*/3q21.1
GCMB mutation (dominant negative)	*GCM2*/6p24.2
Autosomal recessive	
PTH gene mutation	*PTH*/11p15
GCMB mutation	*GCMB*/6p24.2
X-linked	*SOX3*/Xq26-27
Multisystem syndromes	
Autoimmune polyendocrine syndrome type 1 (APS-1 or APECED)	*AIRE*/21q22.3
DiGeorge sequence (DGS or CATCH-22)	*TBX1*/22q11
Hypoparathyroidism-deafness-renal dysplasia syndrome (HDR)	*GATA3*/10p13-14
Hypoparathyroidism-retardation-dysmorphism (Sanjad-Sakati) syndrome	*TBCE*/1q42-43
Hypoparathyroidism-dwarfism-medullary stenosis of long bones-eye abnormalities (Kenny-Caffey) syndrome	*TBCE*/1q42-43
Parathyroid resistance syndromes	
Pseudohypoparathyroidism	GNAS/20q13.3
Type Ia	
Type Ib	STX16, NESP55 DMR or *not known*
Blomstrand chondrodysplasia	*PTHR1*/3p22-p21.1
Metabolic disorders	
Kearns Sayre syndrome (KSS)	Mitochondrial tRNA mutations
Mitochondrial encephalopathy lactic acidosis stroke like episodes (MELAS)	Mitochondrial tRNA mutations
Mitochondrial trifunctional protein deficiency (MTPDS)	Mitochondrial tRNA mutations
Idiopathic	*not known*

whether the CaSR antibodies play a causal role in the disease or represent a marker of a parathyroid damage by other insults [10]. CaSR antibodies activating the CaSR have been documented in two patients with autoimmune HP, demonstrating that a functional modulation of the CaSR can cause the disease also in the absence of a parathyroid damage [11].

Magnesium deficiency caused by insufficient intestinal absorption or renal reabsorption of magnesium may lead to functional HP, either by decreasing PTH secretion via CaSR activation and increasing PTH resistance in target organs by impairing PTH receptor activity. Hypermagnesemia (i.e. magnesium infusions during tocolytic therapy or hypermagnesemia developing during renal failure) can also inhibit PTH secretion. HP due to magnesium disturbances is usually transient and reversible, and represents the only type of HP fully resolvable after correction of the underlying mineral abnormality [1].

Other forms of acquired HP are more rare and include infiltrative disorders of the parathyroids (such as hemochromatosis, Wilson's disease, neoplastic and granulomatous infiltration, iron overload in thalassemia by frequent blood transfusions) or can result after massive neck irradiation or after severe burns because of an upregulation of the CaSR.

Neonatal HP can be the result of a maternal primary hyperparathyroidism since PTH excess crosses the placental barrier inhibiting fetal parathyroids *via* the CaSR. Symptomatic hypocalcemia is evident at birth and resolves within few days or weeks, depending on the degree of functional suppression of the parathyroids in uterus.

2.2. Congenital HP

Congenital or primary HP is due to functional or developmental abnormalities of the parathyroid glands and is often genetically determined (Figure 1) (for an extensive review see ref. 2). Primary HP can present either as isolated disorder or associated

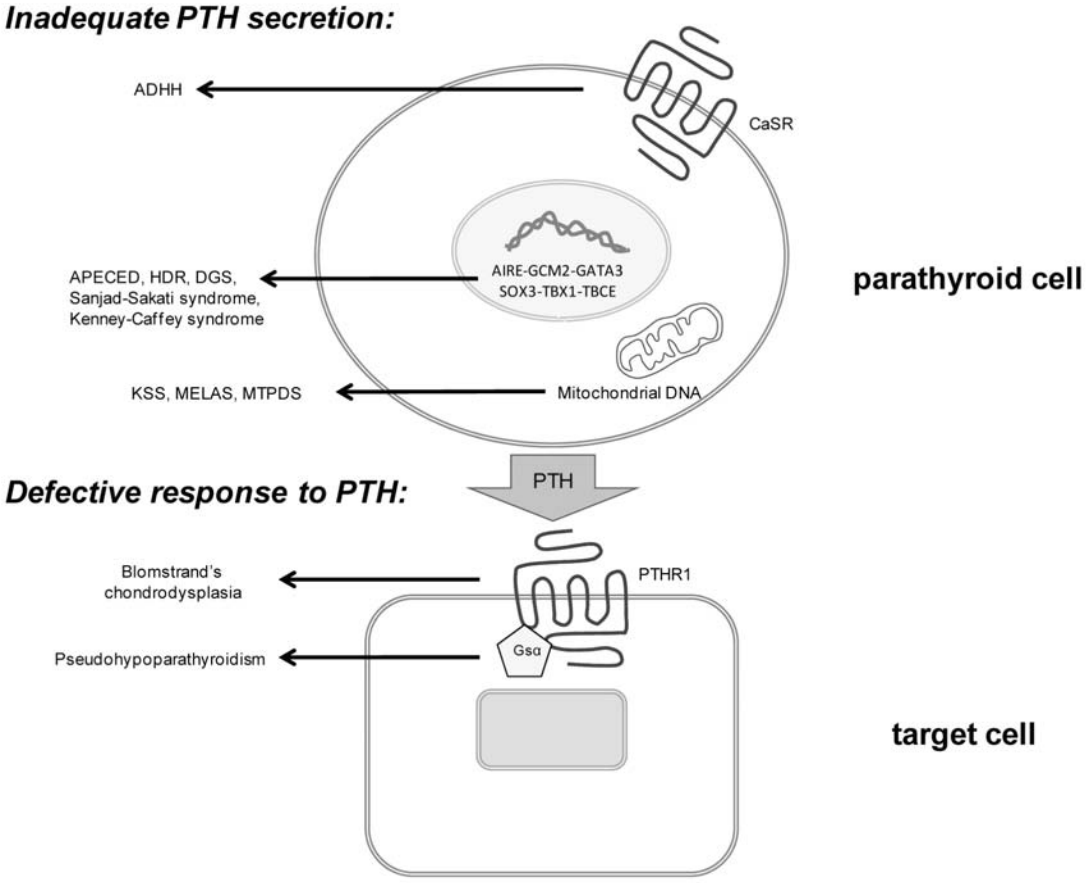

Figure 1. Congenital forms of HP due to genetic defects affecting PTH secretion (i.e. abnormalities in the development or function of the parathyroid cell) or affecting PTH-response in the target cell (i.e. abnormalities in signal transduction).

with other abnormalities in the setting of multisystem syndromes. The genetic defect remains to be defined in about 90% of the sporadic forms and 30% of the familial forms. The penetrance and expressivity may vary according to the different genetic pathogenesis and individual variability. Primary HP may be due to abnormalities of PTH biosynthesis or secretion, of parathyroid gland development, of destruction of parathyroid tissue and of resistance to PTH action.

The only available nationwide survey of primary HP has been conducted in Japan and it has revealed a prevalence of 7.2 per million population for isolated HP and 3.4 per million population for pseudohypoparathyroidism (PHP) in the study period [12].

Epidemiological data on the relative prevalences of the various forms of primary HP in the general population is lacking since no longitudinal studies have been carried out with this specific endpoint. Many of the different forms of HP are considered rare diseases, since the prevalence is lower than 5 cases in 10000 people, according to the definition adopted in the Orphanet database. The available estimated prevalences of some of the different forms of primary HP are shown in Figure 2 (according to Orphanet Report Series- November 2011 and OMIM database) [13]. However, the exact prevalence rate of each of the different forms of primary HP is difficult to assess from the available data sources and maybe they are overestimated because of selected subsets of the study population.

Among the different genetic forms, DiGeorge syndrome or sequence (DGS or CATCH-22 = Cardiac abnormality, Abnormal facies, Thymic hypoplasiam Cleft palate, Hypocalcemia with deletion of chromosome 22q11, MIM 188400) is relatively frequent with a prevalence of 10-50/100000 [14]. DGS is the result of a dysembriogenesis of the third and fourth pharyngeal pouches. The complete sequence is characterized by parathyroid aplasia or hypoplasia (with HP present in up to 6% of patients), thymic aplasia or hypoplasia, congenital heart defects, renal abnormalities with impaired renal function, cleft palate and dismorphic facies, with high phenotypic, penetrance and expressivity variability. The syndrome is commonly due to hemizygous microdeletions within a 250-Kb region of chromosome 22q11.21-q11.23 which includes TBX1 gene codifying for a T-box transcription factor, which has been shown to carry inactivating mutations in some DiGeorge patients [14]. The syndrome is usually caused by *de novo* mutations but rare familial cases with an autosomal dominant pattern of inheritance have been described.

HP associated with sensorineural deafness and renal dysplasia (MIM 146255) is a rare syndrome similar to DiGeorge syndrome but without

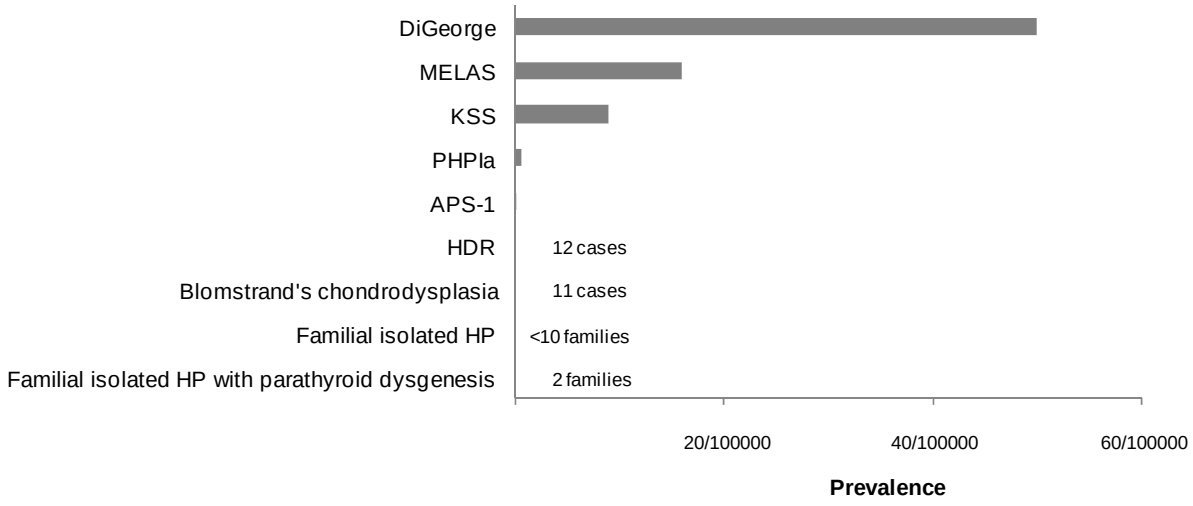

Figure 2. Reported prevalences/number of cases for different genetically-determined forms of HP (drawn according to data belonging to Orphanet and OMIM databases).

immunological and facial abnormalities, caused by mutation in *GATA3* (*GATA binding protein-3*) gene, encoding a protein critical for parathyroid, otic-vescicle and kidney development [15]. HP-retardation-dysmorphism, also known as Sanjad-Sakati syndrome (MIM 241410), and HP-dwarfism-medullary stenosis of long bones-eye abnormalities, also known as Kenny-Caffey syndrome (MIM 244460), are infrequent disorders due to mutations in the tubulin-specific chaperone E (TBCE) gene on chromosome 1q42-43, encoding a protein required for microtubules assembly, although a second genetic locus for variants of these syndromes is possible [16].

Familial isolated HP due to mutations in the PTH gene leading to altered processing of the *pre-pro-PTH* molecule and/or to mRNA translation [17] or mutations in GCMB (human homologue of the Drosophila gene *Gcm, glial cell missing*) is a rare disorder usually inherited as autosomal recessive trait (MIM 146200) [18]. When the mutant protein has a dominant negative effect, this disorder is inherited as an autosomal dominant trait [19].

Activating mutations in the calcium sensing receptor gene (*CaSR*) leading to a left-shifted set point for PTH secretion (defined as the extracellular calcium level required for half-maximal suppression of secretion) cause familial hypercalciuric hypocalcemia (MIM 146200) [20]. The mode of inheritance is autosomal dominant and hypocalcemia is usually mild and asymptomatic, with inappropriately normal or low PTH levels. Although the prevalence in the general population has not been estimated, in a case series up to 48% of patients with congenital HP have been show to harbor activating CaSR mutations, so that mutational analysis of the CaSR gene should be considered as first line molecular diagnostic tool in characterizing HP [21].

X-linked recessive HP (MIM 307700) has been originally identified in two families where only males were affected. Autopsy of an affected subject showed a complete agenesis of the parathyroids. This disorder has been mapped to a 1.5 Mb region on Xq26-q27 [22]. Additional genetic studies have shown that an insertion of genetic material from chromosome 2p25.3 into Xq27.1 might disregulate SOX3 gene transcription thus impairing parathyroid development [23].

Autoimmune destruction of the parathyroids is a main component of a complex of immune-mediated disorders referred to as Autoimmune Poly Endocrinopathy-Candidias-Ectodermal Dystrophy (APECED, MIM 240300) syndrome, also known as APS1 (autoimmune polyglandular syndrome type 1) [24]. This disease (prevalence 0.1:100000 in the general population, higher in some genetically isolated groups) is usually inherited as an autosomal recessive trait and due to mutation of the *autoimmune regulator (AIRE)* gene on chromosome 21q22.3 encoding a transcription factor critical for tolerogenesis in the thymus [25]. In this syndrome parathyroids can be damaged and destroyed by cytotoxic antibodies but in a minority of cases may be only functionally and temporarily inhibited by antibodies against CaSR [26] or other intracellular signaling molecules (such as NALP5) [27]. The classic triad of the syndrome includes mucocutaneous candidiasis, HP (present in up to 80% of cases), adrenal insufficiency, usually appearing in this order. Other abnormalities can be associated such as insulin-dependent diabetes, autoimmune thyroid disease, celiac disease, alopecia, vitiligo.

HP can also be present in 3 disorders characterized by mitochondrial dysfunction (Kearns-Sayre syndrome, the mitochondrial encephalopathy, lactic acidosis, stroke-like episodes syndrome and the mitochondrial trifunctional protein deficiency syndrome) caused by mitochondrial DNA alterations, relatively frequent in the general population (prevalence 9-16/100000).

Hypocalcemia resulting from defective PTH action is present in a group of genetically heterogeneous disorders collectively termed PHP [28]. They are characterized by end-organ (renal) resistance to PTH with hypocalcemia, hyperphosphatemia and inappropriately high PTH levels. The administration of biologically active PTH fails to increase urinary cAMP and phosphate excretion. PHPIa (MIM 103580), in which hypocalcemia is usually associated with Albright hereditary osteodystrophy (round face, mental retardation, brachydactyly, frontal bossing, short stature, obesity and ectopic ossification), is caused by maternally inherited, heterozygous mutations in the *GNAS* locus, encoding the stimulatory G protein (Gsα) [29]. The prevalence of PHPIa is estimated to be 0.72/100000. The PHPIb (MIM 603233) is caused

by maternally inherited microdeletions in the promoter region of GNAS, affecting GNAS methylation [29]. Most cases of PHPIa are familial while the majority of PHPIb is sporadic.

Blomstrand's chondrodystrophy (MIM 215045) is a rare, lethal, autosomal recessive disorder due to mutations in the PTH/PTHrP receptor determining end-organ resistance to PTH and it is characterized by impaired endochondral bone formation with premature ossification of the cartilaginous growth plate.

3. Clinical evaluation

In the presence of hypocalcemic signs and symptoms (as described below), assessment of serum calcium and albumin = [corrected serum calcium (mg/dl) = serum calcium + 0.8 * (4 - serum albumin)] or ionized calcium, serum phosphate and PTH is necessary in order to both confirm hypocalcemia and distinguish between PTH-dependent and PTH-independent forms of hypocalcemia. In PTH-independent hypocalcemia, serum phosphate is low and PTH elevated. Conversely, in PTH-dependent hypocalcemia, PTH is undetectable or in the low normal range, while phosphate is in the upper normal range or mildly elevated because of the missing phosphaturic action of PTH. In the setting of postoperative hypocalcemia, PTH in the low-normal range does not exclude HP. This points to a state of parathyroid insufficiency in which the residual functioning parathyroid tissue is unable to secrete sufficient PTH to restore calcium homeostasis [30].

3.1. Physiopathology and differential diagnosis

All the different forms of HP are characterized by hypocalcemia and hyperphosphatemia [3]. PTH levels, determined by immunoradiometric assays (IRMA), are low or undetectable in HP or markedly elevated in the case of resistance to PTH in the proximal renal tubule (PHP). Phosphatemia is in the upper normal range or frankly elevated because of the missing phosphaturic action of PTH leading to increased tubular phosphate reabsorption. Levels of $1,25(OH)_2$ vitamin D are usually low due to the deficient renal PTH-dependent 1α-hydroxylation, thus contributing to impaired intestinal calcium absorption [1]. In HP fractional extraction of calcium is increased. However, since a lower amount of calcium is filtered because of hypocalcemia, calciuria may be reduced or inappropriately normal. In the case of mutations of the CaSR, calciuria is high for the defective calcium-sensing in the kidney. In PHP calciuria is generally low since the high PTH level promotes calcium reabsorption in the distal renal tubule not affected by PTH resistance.

Urinary cAMP excretion and phosphate excretion are low in HP and PHP, but while they markedly increase after parenteral administration of biologically active PTH in HP, they fail to increase in PHP (*Ellsworth-Howard test*), confirming proximal tubular resistance to PTH [28].

Magnesemia has always to be determined. If magnesium deficiency is detected, a proper magnesium replacement therapy must be initiated before taking into consideration other putative causes of HP. Measurement of 25OH vitamin D levels is important in order to exclude a concomitant vitamin D deficiency contributing to the development of hypocalcemia. When a severe prolonged vitamin D deficiency is the cause of hypocalcemia, serum phosphate is generally low.

Beyond postsurgical HP, for which the cause is easily ascertained, autoimmune HP and hypercalciuric hypocalcemia due to CaSR are by far the most common forms of isolated HP in the adult [3]. A proper collection of the family history is essential for differential diagnosis of HP. A family history of hypocalcemia suggests a genetic cause. In the case of autosomal dominant hypocalcemia due to CaSR activating mutations other family members usually display mild hypocalcemia. The presence of other autoimmune diseases points toward an autoimmune cause of HP. While most forms of congenital HP are exceedingly rare, DiGeorge syndrome must be ruled out in the differential diagnosis, especially when hypoparathyroid patients display also congenital defects and/or immunodeficiencies.

3.2. Signs and symptoms

The extent of clinical manifestations will depend on the degree and speed of onset of hypocalcemia [1]. Chronic forms of HP may also appear as mild forms of asymptomatic hypocalcemia detected in routine examinations or can become unmasked in

particular situations such as vitamin D or magnesium deficiency.

Hypocalcemia causes neuromuscular irritability, neurological and electrocardiographic abnormalities [31]. They vary from numbness and tingling in the perioral region, toes, fingertips in mild hypocalcemia to paresthesias of the upper and lower extremities in moderate hypocalcemia. EKG abnormalities such as a prolonged QT interval can be present. In severe-acute hypocalcemia, carpal spasms, diffuse tetany with epileptic seizures, cardiac rhythm abnormalities, bronchospasm and laryngospasm with acute respiratory insufficiency can be experienced. In mild forms, Chvostek and Trousseau signs can unveil latent tetany. In congenital HP, basal ganglia or soft tissue calcifications may be present in radiological scans.

A recent study suggests that quality of life is compromised in chronic hypoparathyroidism [32]. As a matter of fact, scores for depression, anxiety and somatization are significantly higher in affected individuals relative to age- and sex-matched controls with intact parathyroid function, despite correction of hypocalcemia with calcium and calcitriol.

3.3. Skeletal features

PTH signaling is essential to sustain bone development and maintain a physiologic bone metabolism in adult bone. In chronic HP bone remodeling is markedly altered. Chronic HP is a state of low bone turnover and high BMD, as assessed at cortical skeletal sites by DEXA [33-35]. More accurate techniques such as pQCT have been employed to analyze vBMD and bone geometry. An initial study has applied this technique to compare the different effects of a defect or an excess of endogenous PTH on trabecular and cortical bone comparing postmenopausal women with postoperative or idiopathic HP, primary hyperparathyroidism (PHPT) or without parathyroid pathologies [36]. Either at the level of ultradistal radius, mainly composed of cancellous bone, and at the level of midradius, enriched in cortical bone, vBMD was higher in subjects with HP compared to controls and subjects with PHPT in the order: HP>controls>PHPT. These differences were, at least in part, explained by differences in bone geometry, since periosteal and endosteal surfaces were greater in patients with PHPT, while cortical thickness and area were greater in the order HP>controls>PHPT. Bone strength was similar in the three groups.

Histomorphometric analyses of iliac crest bone biopsies in subjects with HP treated with vitamin D had revealed that, although structural parameters did not change significantly, dynamic indices were markedly altered [37]. Remodeling activation frequency was significantly reduced in hypo-parathyroid patients compared to controls (0.16 *vs* 0.6). Bone formation rate and resorption depth were markedly reduced, with an increased resorption (80 days in patients with HP *vs* controls). This demonstrates that treatment with vitamin D alone is not capable to normalize bone metabolism in HP. A recent similar study performed in a larger cohort has found an increased trabecular bone volume due to an increased trabecular width in HP, in contrast to the previous study [38]. Dynamic parameters such as mineralizing surface and bone formation rate were significantly reduced in the trabecular, endocortical and intracortical bone envelopes, reflecting an overall reduction in bone turnover and an increased BMD in HP. The increase in cancellous bone and trabecular thinckness in HP has recently been confirmed in a three-dimensional analysis by means of μCT [39). Preliminar studies using backscattered electron imaging suggest that the higher BMD in hypoparathyroidism is the direct consequence of the increased bone tissue volume since bones of hypoparathyroid subjects are not overmineralized [3].

These skeletal abnormalities seem to be reversible, at least in part, since therapy with the missing hormone can restore bone metabolism (see below).

4. Conventional therapy of HP

Although formal guidelines in the treatment of HP are still lacking, some common procedures exist in clinical practice relying upon the severity and rapidity of onset of hypocalcemia and/or the presence of related symptoms [1, 31].

Acute HP is an endocrine emergency and requires prompt therapy with active vitamin D metabolites and calcium. Severe hypocalcemia and/or overt hypocalcemic manifestations require intravenous

calcium therapy, which quickly relieves symptoms. In the case of hypocalcemic crisis, calcium gluconate (1 or 2 10% ml ampules, containing 93 mg of elemental calcium each, in 50-100 ml of 5% dextrose) can be infused in a period of 10-20 minutes. Since the effect of this initial infusion is transient lasting 2-4 hours, this can be followed by a slower continuous infusion (usually administered over several hours, at a rate of 1-3 mg of elemental calcium/Kg of body weight/hour), which can be maintained up to 24-48 hours depending on the degree of hypocalcemia and/or presence of symptoms. ECG monitoring is required since arrhythmias can occur during rapid calcium infusion. Meanwhile, an oral therapy with calcium salts (carbonate or citrate, 1-2 g/d) and active vitamin D metabolites (1-1.5 μg/d) should be initiated. In the case of mild or moderate hypocalcemia with minor symptoms or latent tetany, oral calcium and calcitriol can be the first-line treatment [40].

In chronic HP, in addition to oral calcium, active or partially active vitamin D metabolites not requiring the PTH-dependent 1α-hydroxylation (calcitriol, alfacacalcidiol, dihydrotachysterol) are still the therapy of choice to increase active calcium absorption. Calcitriol [1,25$(OH)_2$ vitamin D] is widely used since it displays a rapid effect and the relatively short half-life (2-3 days) helps dosing-adjustment [41].

4.1. Monitoring, toxicity and limits of conventional therapy

The goal of conventional therapy in HP is to control symptoms, maintaining serum calcium within or slightly below the low-normal range (8-8.5 mg/dl), along with a calcium-phosphate product below 55 and urinary calcium below 250-300 mg/24 hours, in order to avoid hypercalciuria, nephrocalcinosis, soft tissue calcifications and renal impairment in the long-term [1, 41]. This can be particularly challenging in hypoparathyroid subjects, which are prone to develop hypercalciuria since PTH-mediated calcium reabsorption in the distal tubule is missing.

Thus, a careful monitoring of therapy is mandatory. Once a stable regimen is established, albumin-corrected serum calcium, phosphate, creatinine and urinary calcium excretion should be checked periodically (every 6-12 months), even in asymptomatic patients. Moreover, calcitriol often requires an adjustment over time, since mechanisms of passive intestinal transport are elicited in the long-term. If urinary calcium is greater than 250-300 mg/24 hours, a thiazide diuretic can be administered in order to decrease hypercalciuria, while maintaining normocalcemia. Excessive sodium intake should be avoided since it increases urinary calcium excretion. Since the risk for soft tissue calcification is high when calcium-phosphate product is >55, hyperphosphatemia should be corrected by means of a low-phosphorus diet and/or a phosphate binder.

Although conventional treatment with calcium and calcitriol is effective in controlling hypocalcemic symptoms in HP, it does not restore a physiological mineral homeostasis and bone metabolism [3].

Under current treatment, normal mineral homeostasis is not restored since the PTH-action on kidney proximal tubule (i.e. calcium reabsorption) is lost and not replaced by conventional therapy. Moreover, the phosphaturic action of PTH is also missing, so that phosphate can be retained, calcium-phosphate product can be high and increases the risk of calcium-phosphate depositions in soft tissues and vessels. Therefore, conventional treatment is often not able to prevent large fluctuations in serum and urinary calcium.

Chronic hypoparathyroid patients under calcium and calcitriol therapy display a high rate of cataract and nephrolithiasis (44% and 8%, respectively) and an overall altered quality of life as compared to control subjects with intact parathyroid function. Moreover, low bone turnover and alteration of microstructural static and dynamic parameters are not corrected by conventional therapy.

4.2. Refractory HP

Few cases of HP are resistant to calcium and calcitriol therapy. Refractory HP is defined as a chronic form of HP where conventional treatment with calcium and calcitriol fails to restore normocalcemia. It is characterized by episodes of symptomatic hypocalcemia alternated with hypercalcemia and hypercalciuria.

In hypercalciuric hypocalcemia due to activating mutations in the CaSR, serum calcium is usually only slightly below the normal range and hypocalcemic symptoms are absent. In rare severe cases requiring treatment, however, therapy with calcium and calcitriol may worsen the constitutive hypercalciuria leading to nephrocalcinosis and deterioration of renal function. Aim of the treatment with active vitamin D metabolites in these subjects is to obtain and maintain serum calcium level only in the low normal range to avoid episodes of severe hypercalciuria. In this setting, alternative therapies not yet approved by the Food and Drug Administration for treatment in HP, such as PTH1-34 and PTH1-84 (see below) and allosteric modulators of the CaSR (calcilytic agents, which are under development) could be successfully employed.

HP in the context of APECED is similarly difficult to manage. Retuximab, a therapeutic agent directed against the B-cells, which are supposed to be the main mediators of parathyroid toxicity in this multi-system disorder, has been proven to prevent the development of the multi-organ inflammation in animals. This pharmacological approach could be used in AIRE-mutations carriers to prevent or modulate major clinical manifestations [42].

4.3. Parathyroid autotransplantation

Intraoperative parathyroid autotransplantation into the sternocleidomastoid muscle, the forearm muscles or the subcutaneous tissue in the anterior chest wall, is a technique employed in a few surgical centers in patients at high risk to develop postoperative HP, in order to prevent hypocalcemia. Delayed autotransplantation with cryopreservation is performed in patients with persistent or recurrent hyperparathyroidism receiving multiple neck interventions [43]. In a large prospective study of 5846 patients who underwent total thyroidectomy by experienced surgeons, those who received parathyroid graft (7.6%) did not develop HP [5]. In a recent retrospective multicenter study on the efficacy of parathyroid autotransplantation, only 1.6% of the total cryopreserved glands had been reimplanted and just a minority (10%) of the successfully reimplanted glands were fully functional at 2 year-follow up. The success rate clearly depended upon the experience of the surgical center [44]. Thus the success rate of parathyroid auto-transplantation is highly variable and cannot still be recommended as a routine procedure in preventing postoperative HP. However, in particular settings, such as subtotal para-thyroidectomy for parathyroid hyperplasia it is advisable to take advantage of parathyroid autotransplantation in the forearm muscles in order to treat possible relapses of the disease avoiding repeated neck interventions.

5. Therapeutic advances in the management of chronic HP

HP is the only endocrine disease for which substitutive therapy with the lacking hormone is not currently employed but it appears as the most physiological option to restore a normal mineral and skeletal homeostasis in these patients. If used in addition to conventional therapy, it may help to reduce calcium and calcitriol requirements thus decreasing the prevalence of side effects. PTH *per se* directly decreases calciuria since it reabsorbs calcium in the distal tubule and at the same time decreases phosphate reabsorption thus reducing the risk of soft tissue calcification due to high calcium-phosphate product. Moreover, it can be the therapy of choice in cases where conventional therapy fails to restore normocalcemia (i.e. refractory HP) and can be potentially useful to control non-classical symptoms of HP.

Over the past few years, subcutaneous daily injections with synthetic human recombinant PTH1-34 or PTH1-84, differently administered according to their peculiar pharmacokinetics, have been tested in the management of chronic HP, but are still not approved by the Food and Drug Administration for this indication.

Replacement therapy with PTH1-34

The effectiveness of PTH1-34 (teriparatide) in HP was initially tested in a pilot short-term randomized crossover trial in 10 adults with HP [45]. PTH1-34 administered subcutaneously once daily for 10 weeks proved to be as effective as $1,25(OH)_2$ vitamin D (calcitriol) in maintaining normocalcemia in the face of a lower urinary calcium level for a given value of attained serum calcium and higher markers of bone turnover.

After this initial study, a 28-week, randomized, crossover, dose-finding study performed in 17 subjects showed that teriparatide administered twice daily was as effective as the once-daily administration in maintaining normocalcemia, but the total daily dose, serum markers of bone turnover and bone pain were lower compared to the daily mono-administration, attaining a more stable serum calcium levels with fewer drops into the hypocalcemic range [46]. These two studies had been followed by a 3-year randomized, open-label study comparing calcitriol and PTH1-34, both administered twice daily together with calcium in 27 adults with HP [47]. The dose of calcitriol and PTH1-34 was adjusted to maintain serum calcium levels in the low-normal range or slightly below the normal range. In the teriparatide-treated group urinary calcium excretion remained within the normal range in the long-term while hypercalciuria was documented in the calcitriol-treated group in the face of the same levels of attained serum calcium. Renal function (creatinine clearance) remained normal in both groups. In PTH1-34 treated group, markers of bone turnover steadily increased up to 2-3 fold, but this was not paralleled by significant changes in regional or total-body BMD or BMC. A similar 3-year randomized trial testing teriparatide twice daily against calcitriol was performed in hypoparathyroid children [48]. There were no significant differences between the two groups in the serum and urinary calcium neither in the attained BMD and BMC, with the exception of the distal radius BMD which decreased significantly in the PTH1-34 treated-group.

Nonetheless, therapy with daily injections of PTH1-34 still produces nonphysiological fluctuations in serum calcium levels. For this reason it was first hypothesized that a continuous administration of teriparatide by means of pump-infusion could solve this issue.

Teriparatide multipulse pump infusion has been successfully employed for the first time in children with HP, in the context of APS-1 or idiopathic, refractory to standard treatment with calcitriol [49]. The continuous subcutaneous administration of an overall decreased daily dose of PTH1-34 (2.6-1.7 μg/Kg/day) with respect to the twice-daily administration, has been shown to be able to maintain serum calcium levels in the desired low-normal range in the long-term (3 years), with less fluctuations, with a decreased number of episodes of severe sintomatic hypocalcemia, avoiding hypercalciuria, with major improvements in the quality of life, without any growth abnormality. A more recent short-term (6 months) open-label, randomized, crossover trial has tested the efficacy of teriparatide multipulse pump infusion against the usual twice-daily administration in adults with postoperative HP [50]. The PTH1-34 delivered by means of pump infusion *vs* twice-daily administration has produced less variations in serum calcium, with a 50% reduction in urinary calcium excretion, normalization of markers of bone turnover, an overall decrease of 65% in the PTH daily dose to maintain normocalcemia and amelioration of magnesium metabolism.

Replacement therapy with PTH1-84

PTH1-84 has been employed in three studies as an add-on therapy to standard treatment with calcium and calcitriol. In a 2-year open-label trial, PTH1-84 (100 μg every other day by subcutaneous injection) had been added to conventional therapy in 30 adult subjects with HP [51]. PTH1-84 proved to be effective in reducing the daily requirements for calcium and calcitriol by 45 and 41%, respectively, so that calcitriol was discontinued in 7 patients. Serum calcium was maintained within the low-normal range, after an initial increase at the beginning of the PTH1-84 treatment. The treatment with PTH1-84 was safe since hypercalcemic episodes were uncommon (4% of all measurements). Urinary calcium excretion remained unchanged throughout the study with the exception at one time-point (3 months). A dual effect on BMD was observed, with an increase in BMD at the lumbar spine by 2.9 ± 4% ($p < 0.05$) and a decrease in BMD at distal 1/3 of the radius by 2.4 ± 4% ($p < 0.05$), potentially reflecting the different effects of PTH on cancellous and cortical (endosteal) bone. BMD at femoral neck remained unchanged.

A more recent histomorphometric study by the same authors has examined the direct effects of PTH1-84 (100 μg every other day for 2 years) or placebo on the skeletal tissue of hypoparathyroid subjects who underwent percutaneous iliac crest

biopsies performed at baseline and 1 year in one group, at baseline and 2 years in a second group and at 3 months (without baseline) in a subset of subjects after quadruple tetracycline labeling [52]. Analysis of structural parameters demonstrated that trabecular width was reduced at 1 year *vs* baseline in hypoparathyroid subjects then was no longer different at 2 years relative to controls, while cancellous bone volume did not change. Trabecular number was increased at 1 and 2 years as well as cortical porosity, while cortical width did not change. Analysis of dynamic parameters showed a dramatic increase in the mineralizing surface, mineral apposition rate and bone formation rate at 3 months and 1 year, returning to baseline levels in all compartments at 2 years except for mineralizing surface and mineral apposition rate that remained higher relative to baseline in cancellous bone at 2 years. These histomorphometric changes, particularly the ones at the cancellous envelope, had been predicted by changes in bone turnover markers which followed the same pattern of an early increase at 3 months and 1 year, then a slight decrease afterwards. These data show that PTH1-84 was able to restore skeletal metabolism in hypoparathyroid individuals to more physiological levels typical of euparathyroid subjects. It is likely that PTH1-84 in HP elicits osteoblast development and maturation, as demonstrated by the increase in circulating osteocalcin-positive osteogenic cells correlated to histomorphometric changes in bone formation [53].

Similar studies have been performed in 62 adult subjects with chronic HP randomized to receive a daily administration of PTH1-84 or placebo in addition to conventional therapy for 24 weeks [54]. Patients receiving PTH1-84 had their daily dose of calcium and calcitriol reduced by 75 and 73%, respectively, without developing any episode of hypocalcemia. In 15 individuals calcium supplementation was discontinued. Markers of bone turnover were markedly increased. A slight but significant decrease in BMD of the lumbar spine (1.76% ± 1.03%), hip (1.59 ± 0.57%) and total body (1.26 ± 0.49%) was observed, while BMD of distal radius remained stable. Iliac crest bone biopsies were performed at the end of the study in 23 individuals receiving PTH treatment and 21 receiving placebo, and analyzed by μCT [55]. In the biopsies of the PTH1-84 treated-group trabecular thickness and trabecular bone tissue density were reduced by 27% ($p < 0.01$) and 4% ($p < 0.01$) relative to controls, while connectivity density and cortical porosity were 34% higher (by 34%, $p < 0.05$ and 139%, $p = 0.01$, respectively). Trabecular tunneling was evident in 11 PTH1-84-treated subjects (48%) with higher levels of markers of bone turnover. In parallel, an increased cortical porosity, as evidenced by an increased number of Harversian canals (+139%, $p = 0.01$) was evidenced in the PTH1-84-treated group *vs* controls. Either aBMD or vBMD decreased at the hip by 1 and 4%, respectively, in the 6 months of the study. Conversely, at the lumbar spine while aBMD still decreased by 1.8%, vBMD increased by 12% *vs* placebo-treated subjects, reflecting diverse responsiveness to PTH1-84 at different skeletal sites differently enriched in trabecular and cortical bone.

Altogether these results indicate that PTH1-84 as add-on therapy in HP leads to a (physiological) activation of bone turnover and increased activation-frequency of new bone remodeling units, a better connection between trabecules as reflected by increased trabecular connectivity index maybe due to increased trabecular tunneling in bone of hypoparathyroid subjects.

6. CONCLUSION AND FUTURE DIRECTIONS

Insights into the different multiple pathogenetic mechanisms of the various forms of HP have helped in understanding the mechanisms of PTH action and physiology. While acquired PTH is a relatively frequent endocrine disorder, the majority of congenital hypoparathyroid states are considered rare diseases. Epidemiology of either acquired or primary HP has yet to be fully assessed in longitudinal series, hopefully taking advantage of data collections of National Registries. Genetic workup protocols to easily detect the genesis of newly diagnosed cases of idiopathic HP, a more accurate classification of congenital HP and a better clinical characterization of the different forms are needed.

Guidelines on the management of HP are still lacking. While conventional treatment regimens with calcium and calcitriol are generally accepted to control hypocalcemic symptoms, they are not

effective in restoring a physiologic calcium and phosphate homeostasis and a normal skeletal metabolism, since PTH action on kidney and bone is lost. PTH replacement therapy, with either PTH1-34 or PTH1-84, may restore a more physiological bone metabolism and dynamics, as demonstrated by bone quality studies. Whether PTH has to be administered alone or in combination with the classic therapy with calcium and calcitriol has still to be ascertained in larger and longer randomized controlled trials. Moreover, potential long-term benefits (on kidney, quality of life and cardiovascular system) and/or toxicity of PTH have to be assessed in longer intervention studies. In addition, a better characterization of the skeletal disturbances in HP will potentially serve to better identify the direct action of PTH in bone.

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