Management of Hypoparathyroidism: Summary Statement and Guidelines

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Objective: Hypoparathyroidism is a rare disorder characterized by hypocalcemia and absent or deficient PTH. This report presents a summary of current information about epidemiology, presentation, diagnosis, clinical features, and management and proposes guidelines to help clinicians diagnose, evaluate, and manage this disorder.

Participants: Participants in the First International Conference on the Management of Hypoparathyroidism represented a worldwide constituency with acknowledged interest and expertise in key basic, translational, and clinical aspects of hypoparathyroidism. Three Workshop Panels were constituted to address questions for presentation and discussion at the Conference held in Florence, Italy, May 7–9, 2015. At that time, a series of presentations were made, followed by in-depth discussions in an open forum. Each Workshop Panel also met in closed sessions to formulate the three evidence-based reports that accompany this summary statement. An Expert Panel then considered this information, developed summaries, guidelines, and a research agenda that constitutes this summary statement.

Evidence: Preceding the conference, each Workshop Panel conducted an extensive literature search as noted in the individual manuscripts accompanying this report. All presentations were based upon the best peer-reviewed information taking into account the historical and current literature.

Consensus Process: This report represents the Expert Panel's synthesis of the conference material placed in a context designed to be relevant to clinicians and those engaged in cutting-edge studies of hypoparathyroidism.

Conclusions: This document not only provides a summary of our current knowledge but also places recent advances in its management into a context that should enhance future advances in our understanding of hypoparathyroidism. **(*J Clin Endocrinol Metab* 101: 2273–2283, 2016)**

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Abbreviations: ADH, autosomal dominant hypocalcemia; BMD, bone mineral density; CaSR, calcium-sensing receptor; eGFR, estimated GFR; GFR, glomerular filtration rate; rh, recombinant human.

For related articles see pages 2284, 2300, 2313

Hypoparathyroidism is a rare disorder of mineral metabolism characterized by hypocalcemia and absent or deficient production of PTH. In contrast to primary hyperparathyroidism, a relatively common disorder of PTH overproduction, this rare counterpart has not been the subject of intense discussion and clinical attention until recently. Hence, guidelines for its clinical management have only recently been the subject of interest and concerted deliberations (1, 2). This report presents a summary of current information about epidemiology, presentation, diagnosis, clinical features, and management of hypoparathyroidism. Based upon current evidence, a set of guidelines is proposed to help clinicians diagnose, evaluate, and manage this disorder. This document should be helpful to all who are or will become interested in hypoparathyroidism. It not only provides a summary of our current knowledge of hypoparathyroidism but also places recent advances in its management into a context that should enhance future advances in our understanding of this disorder.

Parathyroid Hormone

The highly conserved structure of PTH throughout the animal kingdom illustrates well the importance of this molecule in vertebrate biology (3). PTH is the major circulating regulator of calcium homeostasis. It acts on the bone and kidney cells directly, whereas its role in calcium homeostasis of the gastrointestinal tract is secondary due to its influence on the production of active vitamin D (1,25-dihydroxyvitamin D_3). The exquisite physiological relationship between the serum calcium (Ca^{2+}) concentration and PTH secretion is described by a steep, negative sigmoidal curve. Over a very narrow concentration range, the ionized calcium is reciprocally related to the circulating PTH concentration (4). This relationship is mediated by the extracellular calcium-sensing receptor (CaSR). When PTH production is absent or deficient, the expected calcium-conserving effects of PTH on the renal tubule are lost. The phosphaturic effects of PTH are also lost. These two pathophysiological processes are responsible, in part, for the characteristic hypocalcemia and hyperphosphatemia of hypoparathyroidism. Neuromuscular irritability, one of the cardinal clinical features of hypoparathyroidism, is due to hypocalcemia. Ectopic deposition of insoluble calcium phosphate complexes in soft tissues is primarily due to hyperphosphatemia and an elevated calcium-phosphate product. Ectopic calcification can also occur in the context of chronic hyperphosphatemia, even if the calcium-phosphate product is not exceeded.

Etiologies and Epidemiology of Hypoparathyroidism

Etiologies

Hypoparathyroidism most commonly results from anterior neck surgery, constituting 75% of all cases (5). Relevant aspects of this and other etiologies of hypoparathyroidism are provided in companion papers (6, 7). Autoimmune disease causing hormonal deficiencies of parathyroid glands alone or in combination with other endocrine glands constitutes the second most common etiology (8). Disorders of magnesium metabolism can be mistaken for hypoparathyroidism. Hypermagnesemia will suppress PTH and can be associated with a functional hypoparathyroidism (9). Similarly, and clinically more relevant, severe hypomagnesemia can impair PTH secretion and action, with patients demonstrating low serum calcium and PTH levels. There are also inborn errors of magnesium metabolism that masquerade as a primary deficiency of the parathyroids (10). Rare, but important to consider are disorders in which the parathyroid glands are infiltrated and tissue is destroyed by deposits of iron or copper or by tumor metastases (11–15).

Genetic disorders can also be causative (16–18) but are infrequent from an epidemiological viewpoint. Genetic forms of hypoparathyroidism are comprised of a number of syndromic (associated with other glands and systems, including polyglandular deficiency, DiGeorge's syndrome, Bartter's syndrome) and nonsyndromic isolated forms (6). Autosomal dominant hypocalcemia (ADH) 1 and 2 are due to activating mutations in the genes encoding the CaSR and G protein α 11 subunit, respectively. These individuals may have normal levels of PTH but hypocalcemia, representing a steady state of the abnormally sensitive CaSR. When the evaluation suggests a genetic cause (see below), as for example young age, family history, candidiasis, or multiple endocrine gland failure, genetic counseling and germline mutation testing should be considered.

Epidemiology

The best prevalence estimates of hypoparathyroidism in the United States are 60 000 to 115 000 (6, 19). Using the U.S. definition of an orphan disease, less than 200 000 in the U.S. population, this disease fits that categorization. Prevalence estimates from Denmark confirm the very low prevalence of this disorder (20–22). Because the prevalence of hypoparathyroidism depends upon the incidence and the etiology of hypoparathyroidism is heavily dependent upon the sequelae of anterior neck surgery, incidence figures vary widely as a function of demographics related to numbers of anterior neck operations performed. In general, permanent hypoparathyroidism after neck surgery

occurs in between 0.12 and 4.6% of anterior neck operations (23). Not surprisingly, the lower end of this range is evident from high-volume centers with greater surgical expertise, whereas the higher end of the range occurs in patients who need more aggressive neck surgery and in centers where anterior neck surgery is not as frequently performed and experience typically is not as great.

Diagnosis

The diagnostic biochemical hallmarks of hypoparathyroidism are hypocalcemia in association with deficient production of PTH (8, 24). It is thus readily distinguished from pseudohypoparathyroidism, a genetic disorder of PTH resistance in which the circulating PTH concentration is elevated (25–28). The diagnosis of hypoparathyroidism is also readily distinguished from secondary causes of hypocalcemia (eg, vitamin D deficiency) in which the PTH level is also high. In hypoparathyroidism, circulating concentrations of active vitamin D (1,25-dihydroxyvitamin D_3) and bone turnover markers are usually in the lower normal range (16, 17, 29, 30). Urinary calcium excretion varies as a function of calcium intake, although the fractional excretion of calcium is increased in hypoparathyroidism due to the lack of PTH (16, 17).

The diagnosis of hypoparathyroidism depends, importantly, on the PTH assay. "Two-site" assays for PTH do not detect large, inactive mid- and carboxy-terminal fragments of PTH that constitute most circulating PTH in euparathyroid subjects (16, 31). Rather, capture and detection antibodies recognize together the carboxy- and amino-terminal ends of the molecule and are thus not confounded by these large, circulating inactive PTH fragments. The second- and third-generation assays differ from each other in their amino-terminal recognition sites, with the third-generation assay measuring PTH (1-84) rather exclusively (32). Theoretically, one might expect third-generation assays for PTH, generally referred to as "whole" PTH, to be more specific and therefore more useful, but there is not much difference clinically between these two types of assays. The second-generation assay for PTH is more widely used and provides excellent discrimination between hypocalcemia due to hypoparathyroidism and the hypocalcemic states of secondary hyperparathyroidism. The diagnosis of hypoparathyroidism requires either undetectable or inappropriately low PTH levels in the context of hypocalcemia.

Clinical Manifestations of Hypoparathyroidism

The hypocalcemia of hypoparathyroidism can present emergently after anterior neck surgery or in individuals with well-known hypoparathyroidism whose needs for supplemental calcium and active vitamin D change or who are noncompliant. Such acute hypocalcemic states can be a medical emergency because seizures and laryngospasm, which can occur under these circumstances, are each potentially life-threatening. More commonly, the clinical presentation of hypoparathyroidism is due to the effects of chronic hypocalcemia and hyperphosphatemia and, thus, not a medical emergency. More mild and often nonspecific neuromuscular symptoms are often the initial clinical manifestations. Alternatively, but less likely, some patients with hypoparathyroidism are discovered not so much from symptoms, but by the discovery of hypocalcemia from a biochemical screening test.

Hypocalcemia can affect the function of most organs, but in hypoparathyroidism, the most obvious organ systems that become dysfunctional are neurological, cognitive, muscular, and cardiac (5, 8, 33). The divalent cationic imbalance renders these systems subject to an irritability that can be subtle (paresthesia, brain fog, prolonged QcT on electrocardiogram) or life-threatening as described. Chronic hypocalcemia and hyperphosphatemia, with an elevated serum calcium-phosphate product, can lead over the years to soft tissue calcifications, untreated or as a function of the need for large amounts of supplemental calcium and active vitamin D. These calcifications are typically seen in the brain (basal ganglia in particular) (34) and in the kidney (stones and nephrocalcinosis) but can also be seen in joints, eyes, skin, vasculature, and other organ systems (5, 8, 33–36).

Skeletal manifestations

Bone mineral density (BMD), as determined by dual energy x-ray absorptiometry, is typically above average at all measurement sites (37–39). Imaging with peripheral quantitative computed tomography and high-resolution peripheral computed tomography, as well as direct histomorphometric analysis of bone by transiliac bone biopsy, demonstrates that both cortical and trabecular compartments of bone are affected (eg, increased cortical volumetric BMD and trabecular bone volume fraction and decreased cortical porosity) (40–42). Lower bone turnover is a characteristic of this disease, as best seen by dynamic histomorphometry of the bone biopsy.

Reduced bone remodeling (37, 43, 44) is associated with positive bone balance (45), which helps to account for the above-average features of skeletal density and microstructure. The abnormally low bone remodeling in hypoparathyroidism and dense bone suggests that hypoparathyroid bone is hypermature and, therefore, potentially more subject to fracture than euparathyroid bone. Fracture data, however, are sparse, in part because this is

a rare disease. Large cohorts to ascertain fracture incidence are virtually impossible to assess. A small cohort showed an increase in morphometric vertebral fractures in postmenopausal women with hypoparathyroidism; however, larger registry studies in Denmark did not show a difference in overall fracture rate between hypoparathyroid patients and controls (21, 22, 46).

Renal manifestations

One expects hypercalciuria and reduced urinary phosphate excretion because PTH effects on tubular functions are lacking. This is not generally seen in hypoparathyroidism because the filtered load of calcium is usually lower than normal. Similarly, hyperphosphatemia leads to a greater filtered load of phosphate. Hence, urinary calcium and phosphate excretion may be normal in untreated hypoparathyroid subjects. However, once treated, many of these individuals are hypercalciuric because they require large amounts of calcium and/or active vitamin D for control of the serum calcium concentration. They are also at risk for renal calcium deposition, either as frank stones or calcinosis, because of the elevated calcium-phosphate product often worsened by the need for large amounts of calcium and active vitamin D (47). Ectopic calcium deposition, however, does not require an elevated calcium-phosphate product. Renal function is also at risk over time. The risk to renal function in hypoparathyroidism is particularly high in those with activating CaSR mutations (8, 47).

Quality of life

One of the most frequent complaints of patients with hypoparathyroidism is that their quality of life is diminished, including the classical description of "brain fog." Assessments of quality of life such as using standardized measures have documented scores in some studies lower than expected norms (21, 48–54). The lower quality of life measures seem to be irrespective of the etiology of the hypoparathyroidism, the duration of disease, or the extent to which biochemical control is achieved with calcium and active vitamin D.

Natural history and complications

The aforementioned biochemical and target organ descriptions of patients with hypoparathyroidism represent, in part, the disease's natural history as well as complications due to the need for large amounts of calcium and active vitamin D. The pervasive aspects of these complications can be insidious, occurring over decades (20–22, 47). For example, a recent study (47) of patients who had hypoparathyroidism for well over a decade demonstrated the following complications, with percentages of subjects shown in parentheses: hypercalciuria (38%), intrarenal calcifications (31%), reduction of glomerular filtration rate (GFR) <60 mL/min/1.73 m^2 (41%), and basal ganglia calcification (52%). Although rarely seen, basal ganglia calcifications have been reported to be associated with clinical neurological findings. The neurological symptomatology is often associated with calcifications elsewhere in the brain as well (50). In other studies, patients have also been shown to be at higher risk for seizures, serious infection, depression/bipolar affective disease, cardiovascular disease, cataracts, and fractures of the upper extremities (21, 22).

Guidelines for diagnosis and evaluation (Tables 1 and 2)

The diagnosis should be established by the concurrent measurement of albumin-corrected or ionized serum calcium below the lower limits of the normal range and low or undetectable levels of PTH, as determined by either a second- or third-generation immunoassay on at least two occasions separated by at least 2 weeks. Chronic hypoparathyroidism can be diagnosed in patients after anterior neck surgery 6 months postoperatively. Total adjusted serum calcium takes into account the influence of the albumin concentration as follows: for every 1 g/dL reduction in the serum albumin, the total calcium is adjusted upward by 0.8 mg/dL. In theory, measurement of free or ionized serum calcium should be a more accurate physiological measurement than the albumin-corrected total serum calcium concentration. There are several limitations to the accurate direct measurement of ionized calcium. Measurement of ionized calcium requires a free-flowing source of venous blood, not impeded by a tourniquet. Until the blood is processed and accessed by the measuring instrument, strict anaerobic collection conditions are necessary. In addition, the measuring instrument must be properly calibrated, and samples have to be measured immediately.

Table 1. Diagnosis and Evaluation of Hypoparathyroidism

Hypocalcemia (albumin-adjusted) confirmed on at least two occasions separated by at least 2 weeks.
PTH concentration, by second- or third-generation immunoassay, that is undetectable or inappropriately low (ie, <20 pg/mL) in the presence of hypocalcemia on at least two occasions.
Phosphate levels in the upper normal or frankly elevated range (helpful but not mandatory).
After neck surgery, chronic hypoparathyroidism is established only after 6 months.

Table 2. Evaluation of Hypoparathyroidism

Family history: History of hypoparathyroidism or other endocrine deficiency disease
Personal history: Previous anterior neck surgery, other endocrine disease
Physical examination
Ectopic calcifications (eg, eyes)
Signs of previous neck surgery
Chvostek's or Trousseau's sign
Nail beds for fungal infection
Mucosal candidiasis
Range of joint motion
Skin for vitiligo
Biochemical evaluation (after the diagnosis has been made)
Phosphate
Magnesium
25-hydroxyvitamin D
1,25-dihydroxyvitamin D
BUN/creatinine
24-hour urine for creatinine clearance or eGFR, calcium excretion, and biochemical stone risk profile
Target organ imaging
X-ray (skull)
Renal ultrasound or computed tomography scanning
BMD by dual-energy x-ray absorptiometry
Genetic studies: If a genetic basis is suspected (young age, family history, multiple endocrine gland failure)

Abbreviation: BUN, blood urea nitrogen.

These technical issues somewhat limit the clinical utility of the ionized calcium measurement (55). Most clinicians will always assess the serum calcium concentration in relationship to the albumin concentration and make adjustments as noted above.

1. Historical aspects: family history; personal history of anterior neck surgery; gastrointestinal, renal, and skeletal review for gastrointestinal symptoms, renal stones, and fractures, respectively; general quality of life; medications and supplements.
2. Physical examination, key elements: eye examination for cataracts and calcifications, anterior neck for signs of previous surgery, signs of neuromuscular irritability (Chvostek's, Trousseau's sign), nail beds for fungal infection, mucosal candidiasis, range of motion of joints, skin for vitiligo.
3. Biochemical evaluation, key elements assuming the PTH has been measured and documented to be consistent with the diagnosis: chemistry panel including phosphate and magnesium, 25-hydroxyvitamin D, 1,25-dihydroxyvitamin D, 24-hour urinary calcium excretion, estimated or calculated GFR, and biochemical stone risk profile, if the clinical situation warrants.
4. Imaging studies: dual-energy x-ray absorptiometry, skull x-ray for basal ganglia and other intracerebral calcifications, abdomen for renal stones and calcifications.
5. Genetic studies: if the patient's presentation suggests a genetic basis (eg, young age, family history, multiple autoimmune features), genetic counseling and germline mutation testing should be considered.

Management of Hypoparathyroidism

Acute hypocalcemia

Although hypoparathyroidism is a chronic disorder, patients can present with acute hypocalcemia in settings that reflect the early consequences of anterior neck surgery, unanticipated changes in requirements for calcium and vitamin D, or in patients who become noncompliant or poorly compliant (5, 8, 24, 56, 57). Signs of acute hypocalcemia range from mild paresthesia to carpal or pedal spasm and, in the extreme, laryngospasm or seizures. Urgent management of symptomatic hypocalcemia requires iv Ca^{2+} salts in two steps: one or two ampules of a 10% solution of calcium gluconate, containing 90–180 mg elemental calcium in 50 mL of 5% dextrose, over 10 to 20 minutes followed by a slower infusion of calcium gluconate, 0.5 to 1.5 mg/kg/h over an 8- to 10-hour period. The experience with the use of PTH in this acute setting is too limited to make any specific recommendations (58–61).

Management of the chronic hypocalcemia of hypoparathyroidism (Table 3)

For many years, the conventional therapeutic approach to the hypocalcemia of hypoparathyroidism has been the judicious use of calcium and active vitamin D, namely calcitriol or an analog as noted below. Some experts have also regarded parent vitamin D (cholecalciferol or ergocalciferol) to be useful. In patients with hypercalciuria, thiazide diuretics can be helpful.

There are six goals of chronic management therapy: 1) to prevent signs and symptoms of hypocalcemia; 2) to maintain the serum calcium concentration slightly below normal (ie, no more than 0.5 mg/dL below normal) or in the low normal range; 3) to maintain the calcium-phos-

Table 3. Conventional Management of Chronic Hypoparathyroidism

Dietary calcium and oral calcium supplements
Active vitamin D or analogs
Magnesium
Thiazide diuretics when necessary to help manage hypercalciuria and low salt diet
Phosphate binders and low phosphate diet, if necessary to control hyperphosphatemia

phate product to below 55 mg^2/dL^2 (4.4 $mmol^2/L^2$); 4) to avoid hypercalciuria; 5) to avoid hypercalcemia; and 6) to avoid renal (nephrocalcinosis/nephrolithiasis) and other extraskeletal calcifications.

During adjustments to dosing with calcium and/or active vitamin D, the serum calcium should be measured weekly or monthly depending upon the clinical situation. In patients who have achieved a stable dosing regimen with calcium and active vitamin D, with or without parent vitamin D or thiazide diuretics, the serum calcium should be measured, on average, twice a year. In patients who have had a tendency to become hypercalciuric, 24-hour urine calcium measurements are recommended (5, 8).

Calcium supplementation

The mainstay of calcium supplementation in hypoparathyroidism is calcium carbonate. Calcium can be administered more efficiently with this calcium salt because 40% of it is elemental calcium (62). In several situations, however, calcium citrate (20% elemental calcium), the other most common form of calcium supplementation, can be helpful, such as when achlorhydria is present (63), in the setting of proton pump inhibitor therapy (64–66), or in patients who complain of constipation with calcium carbonate. The amount of calcium supplementation required varies enormously, with amounts as high as 9 g/d in some subjects (39). Many practitioners will try to limit the amount of calcium supplementation by being more proactive with the use of active vitamin D.

Active and parental vitamin D

The rationale for using active vitamin D (1,25-dihydroxyvitamin D; calcitriol) is clear in hypoparathyroidism because the lack of PTH, along with the tendency to hyperphosphatemia, impairs the renal conversion of 25-hydroyvitamim D to its activated form. Like supplemental calcium, the range of active vitamin D to manage hypoparathyroidism is enormous, but generally it is between 0.25 and 2 μg daily (67–70). Other vitamin D formulations that undergo activation in the liver are used outside the United States, such as 1α-hydroxyvitamin D (alfacalcidol) and dihydrotachysterol (67, 69, 71, 72). Titrating upward the use of active vitamin D formulations can help to reduce the amount of calcium supplementation patients require.

Patients are also typically supplemented with either of the two parental forms of vitamin D (vitamin D_2 [ergocalciferol] or vitamin D_3 [cholecalciferol]). The rationale for using these forms of vitamin D is that many tissues generate their own 1,25-dihydroxyvitamin D and other metabolites of vitamin D that may have beneficial nonskeletal effects. Additionally, in high concentrations, 25-hydroxyvitamin D, to which parent vitamin D is converted in the liver without impairment in hypoparathyroidism, has pharmacological properties that mimic the active form of vitamin D.

Thiazide diuretics

Thiazide diuretics promote renal tubular calcium retention and are used by many experts when hypercalciuria is present. It is important to monitor serum potassium and magnesium because renal losses due to thiazide use can lead to hypokalemia or hypomagnesemia (8). Thiazide diuretics should not be used in patients with autoimmune polyendocrine syndrome type 1 with adrenal insufficiency and in certain forms of autosomal dominant hypoparathyroidism type 1 that are accompanied by Bartter's syndrome.

Phosphate binders

Only in situations where hyperphosphatemia is well above normal (eg, >6.5 mg/dL) are phosphate binders or low-phosphate diets employed (5).

Monitoring conventional management with calcium and vitamin D (Table 4)

The frequency of monitoring of serum calcium, phosphate, and other analytes such as magnesium is very much a function of the extent to which a patient is stable on a given dosing regimen. Subjects who are well controlled could be monitored on a yearly or twice-yearly basis, whereas other subjects require much more frequent monitoring. As noted above, when amounts of supplemental calcium and active vitamin D are adjusted, more frequent monitoring is indicated, often several times per week until a stable serum calcium concentration is achieved. Renal function is monitored annually by a 24-hour urine collection for calcium and creatinine excretion along with a measured creatinine clearance or estimated GFR (eGFR). In some patients whose urinary calcium is within normal limits from year to year and in whom there are no overt renal complications, some clinicians will opt not to mea-

Table 4. Monitoring Guidelines on Conventional Therapy

Calcium, phosphate, magnesium, BUN/creatinine and eGFR: yearly or more frequently if the clinical situation is appropriate
24-hour urine for calcium and creatinine
As clinically indicated
Renal imaging (for nephrolithiasis/nephrocalcinosis)
Ophthalmological exam (cataracts)
Central nervous system imaging (basal ganglia and other sites of calcification)
BMD

Abbreviation: BUN, blood urea nitrogen.

sure the urinary calcium excretion annually. Urinary magnesium excretion can be helpful in certain situations. In patients who have a history of renal lithiasis or calcinosis, renal imaging is recommended every 5 years if asymptomatic or more frequently if signs or symptoms develop. It is not clear whether basal ganglia and other central nervous system calcifications require monitoring if detected upon baseline screening because it is difficult to attribute clinical features of these central nervous system calcifications (47, 73). Follow-up examination of the eyes for cortical cataracts would depend upon baseline findings and the clinical situation.

Although BMD is typically above average in hypoparathyroidism (5), standard monitoring is recommended as per recommendations of the International Society of Clinical Densitometry (74).

Advances in chronic management of hypoparathyroidism: PTH peptides

Although the conventional use of calcium and active vitamin D can control patients with hypoparathyroidism, they often require very high doses that raise concerns for unwanted complications of hypercalciuria, renal stones, renal calcinosis, impaired renal function, and ectopic calcifications (5). There are other patients who, despite very high amounts of calcium and active vitamin D, are subject to wide swings in their serum calcium with associated symptomatology. In both situations, reduced quality of life complaints tend to persist (48, 52, 53, 75). Additionally, markedly abnormal skeletal macro- and microstructure persist (37). Until recently, hypoparathyroidism was the last remaining classic endocrine deficiency disorder for which the missing hormone was not available as a U.S. Food and Drug Administration (FDA) or European Medicines Agency-approved therapy. The advent of PTH as an approved replacement therapy for hypoparathyroidism provides an additional useful therapeutic option in its management, particularly for those who require large amounts of calcium and active vitamin D for control or who, despite such large supplemental therapy, cannot be controlled. In 2015 in the United States, the FDA approved recombinant human (rh) PTH (1-84) for the management of hypoparathyroidism (76).

The experimental basis for use of PTH in hypoparathyroidism

PTH (1–34)

Winer et al (77) established the experimental basis for the use of PTH in hypoparathyroidism in her classic studies with the amino-terminal fragment of PTH known as teriparatide [PTH (1–34)]. She demonstrated beneficial control in children and in adults when teriparatide was administered daily but even better control when the peptide was administered in twice-daily dosing regimens (77–80). More recently, she and her colleagues adapted a pump delivery system by which teriparatide could be administered continuously (30, 81). Under these conditions, urinary calcium excretion fell and markers of bone turnover normalized. A smaller daily dose was required with pump delivery vs multiple daily dosing regimens. An open-label trial of PTH (1–34) in adult subjects with postsurgical hypoparathyroidism showed improvement in quality of life (54).

PTH (1-84)

Theoretically, PTH (1-84) is more attractive as a replacement hormone in hypoparathyroidism because the full-length peptide is exactly what is missing in this disease. Its longer in vivo and biological half-life makes once-daily dosing more feasible than PTH (1–34) (82–84). Several investigative groups that have studied rhPTH (1-84) over the past decade have made the following observations: a substantial reduction, often as much as 50%, in the need for calcium and active vitamin D in both short- and long-term studies (38, 39, 52); only transient reductions in urinary calcium excretion (38); a tendency for lumbar spine BMD to increase and the distal 1/3 radius site to fall (39); a rapid increase in bone turnover, as evidenced by circulating markers and dynamic histomorphometric analyses of bone that return to a new steady state that is higher than baseline values by 2–3 years (43); and improvements in quality of life as determined by the Short Form-36 scale with protocols that minimized hypercalcemia (52, 75). A study with relatively large fluctuations in serum calcium did not demonstrate improvement in quality of life (53). These observations were followed by a pivotal, multinational, randomized, double-blinded, placebo-controlled phase 3 clinical trial of rhPTH (1-84) in hypoparathyroidism (85). This 26-week study involving over 130 subjects with a randomization scheme of 2:1 (drug:placebo) had as it primary endpoint three elements: a reduction by 50% in calcium supplements and in active vitamin D along with maintenance of the serum calcium. This "triple endpoint" was met in over half of the study subjects and in virtually none of the subjects who received placebo (53 to 2%; $P < .001$). There was also a major difference in the percentage of subjects who could eliminate active vitamin D entirely while taking no more than 500 mg of oral daily calcium (43 to 5%; $P < .001$). The protocol allowed for titration of drug from 50 to 100 μg/d, with most subjects (52%) needing the highest dose. The FDA indication is for subjects with hypoparathyroidism of any etiology, except ADH, who cannot be well controlled on calcium and active vitamin D. The FDA did not restrict its approval to

surgical forms of hypoparathyroidism. The FDA approved rhPTH (1-84) with a "black box" warning because of the history of rat osteosarcoma using all forms of PTH that have been studied so far but did not limit the duration of use.

Selection of the patient for rhPTH (1-84) therapy

The decision to recommend rhPTH (1-84) depends, in part, on the definition of the extent to which the physician and the patient feel that good control is achieved by conventional therapy. In our view, the definition of good control goes beyond the mere maintenance of a serum calcium concentration within normal limits and the avoidance of symptomatic hypocalcemia. Subjects who require very large amounts of calcium and active vitamin D to maintain their serum calcium and to avoid hypocalcemia are at risk for serious long-term complications of such therapy. The following guidance (Table 5) is offered to recommend consideration of rhPTH (1-84) therapy in any patient with well-established chronic hypoparathyroidism of any etiology except for ADH: variable and inconstant control of the serum calcium with frequent episodes of hypo- and hypercalcemia; nephrolithiasis, nephrocalcinosis, or reduced creatinine clearance or eGFR to <60 mL/min; hypercalciuria and/or other biochemical indices of renal stone risk; persistently elevated serum phosphate and/or calcium-phosphate product (>55 mg^2/dL^2 or 4.4 $mmol^2/L^2$); excessive amounts of oral medications required to control symptoms such as >2.5 g of calcium or >1.5 μg of active vitamin D, or both; and a gastrointestinal tract disorder that might lead to variable calcium and vitamin D absorption. The decision to recommended rhPTH (1-84) should take into account the fact that it is currently an expensive drug.

Table 5. Indications for Considering the Use of rhPTH (1-84) in Hypoparathyroidism

1. Inadequate control of the serum calcium concentration (this could be due to intercurrent illness, compliance, absorption, or intrinsic changes in requirements that are beyond facile correction with calcium and active vitamin D)
2. Oral calcium/vitamin D medications required to control the serum calcium or symptoms that exceed 2.5 g of calcium or >1.5 μg of active vitamin D or >3.0 μg of the 1-α vitamin D analog
3. Hypercalciuria, renal stones, nephrocalcinosis, stone risk, or reduced creatinine clearance or eGFR (<60 mL/min)
4. Hyperphosphatemia and/or calcium-phosphate product that exceeds 55 mg^2/dL^2 (4.4 $mmol^2/L^2$)
5. A gastrointestinal tract disorder that is associated with malabsorption
6. Reduced quality of life

A management approach with rhPTH (1-84)

The recommendations from the labeling are as follows. The lowest dose of 50 μg is initiated once daily sc into the thigh. Simultaneously, the dose of active vitamin D is reduced by 50%. The serum calcium concentration is monitored within the first week of initiation and similarly whenever the dose of rhPTH (1-84) is changed or as often as needed. The goals of therapy with rhPTH (1-84) are to minimize or eliminate the use of active vitamin D, to reduce supplemental calcium to 500 mg daily, and to maintain the serum calcium in the lower range of normal. An alternative approach would be to start by reducing oral calcium by 50% instead of active vitamin D. The dose of rhPTH (1-84) can be increased in 25-μg steps to 100 μg daily. There are no factors that can predict what ultimate dose will work best for a given patient.

If rhPTH (1-84) is to be discontinued for any reason, due regard for acute manifestations of hypocalcemia are very important because PTH in any form has a short half-life. The 25-hydroxyvitamin D level in all patients should be within a range generally considered to be acceptable, namely 20 to 50 ng/mL, and particularly so in individuals who are discontinuing rhPTH (1-84). The dosing of calcium and active vitamin D should be increased or started with careful frequent monitoring for signs and symptoms of hypocalcemia. In view of a recent example of abrupt hypocalcemia developing in two subjects who stopped teriparatide therapy (86), a recommendation to double or triple the ambient calcium and active vitamin D regimen should be seriously considered, as well as a regimen to taper the dose of rhPTH (1-84) (85).

Safety

Since teriparatide was introduced as a treatment for osteoporosis in 2002, ongoing surveillance has not revealed any information that might suggest that human subjects are at risk for osteosarcoma, a toxicity that regularly develops in rats exposed to high doses of any form of PTH (87–90). The "black box" warning for rhPTH (1-84) thus reiterates this cautionary note, although rhPTH (1-84) has no therapeutic time limit for treatment. Hypercalcemia can occur, but the experience with rhPTH (1-84) so far does not indicate that this is likely to be an issue (39).

Research Agenda for the Future

The workshop participants identified several areas that are recommended for more research over the next 5 years. They are listed here in broad categories:

1. International epidemiology of hypoparathyroidism
2. Cellular, biochemical, molecular, and biomechanical findings responsible for increased bone mass in hypoparathyroidism
3. Fracture incidence
4. Genetics
5. Effects of replacement therapy with rhPTH (1-84) on
   a. Natural history
   b. Skeletal dynamics
   c. Renal function
   d. Quality of life
   e. Complications
6. Feasibility and application of new delivery systems and/or analogs or mimetics that bind to the PTH receptor
7. Safety

Summary

This workshop addressed key aspects of the diagnosis, etiology, epidemiology, evaluation, and treatment of hypoparathyroidism. It led to a series of guidelines for the diagnosis, evaluation, and management of this disease. A set of research questions resulting from this conference identified items that are proposed for future research.

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