Management of Hypoparathyroidism: Present and Future

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Context: Conventional management of hypoparathyroidism has focused upon maintaining the serum calcium with oral calcium and active vitamin D, often requiring high doses and giving rise to concerns about long-term consequences including renal and brain calcifications. Replacement therapy with PTH has recently become available. This paper summarizes the results of the findings and recommendations of the Working Group on Management of Hypoparathyroidism.

Evidence Acquisition: Contributing authors reviewed the literature regarding physiology, pathophysiology, and nutritional aspects of hypoparathyroidism, management of acute hypocalcemia, clinical aspects of chronic management, and replacement therapy of hypoparathyroidism with PTH peptides. PubMed and other literature search engines were utilized.

Evidence synthesis: Under normal circumstances, interactions between PTH and active vitamin D along with the dynamics of calcium and phosphorus absorption, renal tubular handing of those ions, and skeletal responsiveness help to maintain calcium homeostasis and skeletal health. In the absence of PTH, the gastrointestinal tract, kidneys, and skeleton are all affected, leading to hypocalcemia, hyperphosphatemia, reduced bone remodeling, and an inability to conserve filtered calcium. Acute hypocalcemia can be a medical emergency presenting with neuromuscular irritability. The recent availability of recombinant human PTH (1–84) has given hope that management of hypoparathyroidism with the missing hormone in this disorder will provide better control and reduced needs for calcium and vitamin D.

Conclusions: Hypoparathyroidism is associated with abnormal calcium and skeletal homeostasis. Control with calcium and active vitamin D can be a challenge. The availability of PTH (1–84) replacement therapy may usher new opportunities for better control with reduced supplementation requirements. **(*J Clin Endocrinol Metab* 101: 2313–2324, 2016)**

Physiology, Pathophysiology, and Nutritional Aspects of Hypoparathyroidism

To protect the organism against overload or deficiency of calcium, phosphate, and other ions, homeostasis is aimed at maintaining extracellular concentrations as constant and minimally variant as possible (1). It is particularly important to maintain extracellular calcium concentration as stable as possible because of the high sensitivity of a variety of cell systems or organs, including the central nervous system, muscle, and exo-/endocrine glands, to small variations in this divalent cation. Extracellular cal-

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Abbreviations: BMD, bone mineral density; DXA, dual-energy x-ray absorptiometry; QoL, quality of life; rh, recombinant human.

cium is maintained within a narrow range by bidirectional calcium fluxes taking place at the level of the intestine, bone, and kidney. In the absence of PTH or in states of resistance to its action, however, extracellular calcium concentration is much more likely to fall because homeostatic mechanisms in all three target organs are impaired.

Intestinal Calcium Absorption

Under normal conditions, intestinal absorption of calcium represents approximately 20–30% of ingested calcium (2, 3). The latter could be decreased in pathological conditions such as celiac disease, in which net calcium absorption is reduced. Except in the elderly with achlorhydria, in whom calcium carbonate absorption may be impaired (4), the different forms of calcium including dairy products are similarly absorbed (5). Dairy products are an important dietary source of calcium because of their high calcium content and absorbability (6). They provide more calcium, protein, magnesium, potassium, zinc, and phosphorus per calorie than any other usual food found in the adult diet (7). Furthermore, dairy products are rich in aromatic amino acids, which stimulate hepatic production of IGF-1 (8). Intestinal absorption of calcium is enhanced by IGF-1 by virtue of its effect to stimulate renal calcitriol. When ingested during a protein-containing meal, calcium is better absorbed with less variability (9). Recommended dietary allowance for protein is 0.8 g/kg body weight. However, in older people, it appears that higher intakes are necessary, approximately 1.1–1.2 g/kg body weight.

Intestinal calcium absorptive capacity is mainly controlled by calcitriol, which stimulates calcium transport through both genomic and nongenomic mechanisms (2). The normal daily production rate of calcitriol is 0.5–1 μg/d (10). In hypoparathyroidism, the lack of PTH is associated with lower calcitriol levels, hence reduced intestinal absorption of calcium. The hyperphosphatemia of hypoparathyroidism also limits the production of calcitriol. Under these conditions, plasma calcium homeostasis is dependent on higher intestinal cation influx. Increasing dietary intake of calcium, calcium supplements, and active vitamin D metabolites can all facilitate calcium absorption. To avoid substantial increases in postprandial urinary calcium excretion, calcium intake should be evenly distributed during the day. In many instances, increasing the amount of calcitriol can reduce the amount of supplemental calcium required.

Prebiotics such as galacto-oligosaccharides are fermented by microflora in the large intestine, lowering pH and thereby enhancing calcium absorption (11). The large intestine contains a potent vitamin D-dependent calcium transport system, which under normal conditions, contributes little to calcium homeostasis because calcium reaching the large intestine is complexed to various anions and is thereby poorly bioavailable.

When hypocalcemia occurs and its etiology is not known, magnesium deficiency should be suspected (12). Magnesium deficiency is associated with impaired secretion and action of PTH. Magnesium is present in all nutrients from cellular origin. Dietary sources of magnesium include almonds, soybean, seeds, wheat germ, wheat bran, millet, dark green vegetables, fruit, and seafood. Recommended daily allowance of magnesium is 420 and 320 mg/d for men and women, respectively. Dietary inadequacy of magnesium is most unusual under normal circumstances. But if magnesium is being persistently lost from the intestine or kidney, dietary intake may become insufficient. Net intestinal absorption of magnesium is proportional to intake, but usually averages 35 to 40%. Phosphate and cellulose phosphate form a complex with magnesium, thereby impairing its absorption. A low pH is important to displace magnesium bound to dietary fibers and to make it available to absorptive processes. Thus, prolonged nasogastric suction or chronic diarrhea, particularly when due to laxative abuse, are risk factors for magnesium depletion. Upper gastrointestinal tract fluid contains 2 mmol/L of magnesium, whereas in diarrheal fluid magnesium concentration may be as high as 30 mmol/L.

Role of the Kidney

PTH increases renal tubular calcium reabsorption. In chronic hypoparathyroidism, relative renal calcium clearance is higher than normal despite reduced glomerular filtration of calcium. There is some correlation between the renal clearances of calcium and sodium. High sodium intakes may be associated with hypercalciuria. A sound measure in the management of patients with hypoparathyroidism is to limit sodium intake, a step that may reduce hypercalciuria. Loop diuretics increase urinary calcium excretion and are contraindicated in patients with hypoparathyroidism.

Role of Bone Resorption

About 1% of total bone calcium exchanges every month, through bidirectional fluxes, under the influence of PTH and/or calcitriol. Besides calcitriol's main action to enhance dietary calcium absorption, an additional effect is to stimulate bone resorption, shown best in animal models (13). In the absence of PTH, calcium efflux from bone is more dependent upon calcitriol. A large variety of substances either circulating or produced locally, or present in the bone matrix, are also capable of influencing these fluxes (1), but they are not available pharmacologically. Many nutrients have been shown, primarily in animal studies, to influence bone resorption, such as dried plum,

blueberries, fish oil, zinc, grapes, and the phytoestrogen genistein (14–19). However, these nutrients appear to reduce bone turnover, instead of stimulating bone resorption, and cannot therefore be considered useful as therapeutic adjuncts in hypoparathyroidism.

Management of Acute Hypocalcemia

In hypoparathyroidism, hypocalcemia can occur acutely and become a true medical emergency. Hypocalcemia is defined as an ionized serum calcium (Ca^{2+}) concentration that falls below the lower limit of the normal range. Approximately 50% of the total serum Ca is in the ionized fraction, with the remainder being protein-bound (predominantly to albumin) or complexed to anions such as phosphate. Estimation of the corrected serum total Ca can be obtained with the following formula: corrected serum total Ca = measured total Ca + [0.8 × (4.0-measured serum albumin)]. In assessing the degree of hypocalcemia, the corrected serum calcium should be used. In settings where an accurate, direct ionized serum calcium can be obtained, this measurement can also be useful in guiding the acute therapeutic approach. Several recent reviews present detailed information on this topic (20–24).

The treatment of hypocalcemia in hypoparathyroidism is influenced not only by the actual calcium concentration but also by any associated symptoms. In hypoparathyroidism, many subjects chronically demonstrate calcium levels in the low-normal or mild-hypocalcemic range. The symptoms of hypocalcemia do not always follow strictly the extent to which the calcium is low. The severity of symptoms (paresthesias, carpopedal spasm, broncho- or laryngospasm, tetany, seizures, or mental status changes) and signs (Chvostek's or Trousseau's signs, bradycardia, impaired cardiac contractility, and prolongation of the QT interval) all depends upon the absolute level of calcium, the rate of decrease, and individual variability. No two subjects appear to be alike in these respects. Some patients with marked hypocalcemia will appear to be asymptomatic whereas others with what appears to be mild hypocalcemia may be symptomatic.

Clinical features of hypocalcemia for which iv calcium administration should be considered are indicated above. In addition, although some patients with marked hypocalcemia [ie, corrected calcium (7.0 mg/dL [<1.75 mmol/L]) may not be symptomatic, iv therapy may be indicated because at those levels, life-threatening features can appear rather suddenly, such as laryngeal spasm and seizures. Patients who become unable to take or absorb oral supplements can quickly become symptomatic, although the serum calcium may not have fallen dramatically at the time they present with symptoms. Finally, there are some women who typically become symptomatic during the luteal phase of their menstrual cycle. In these situations, clinical judgment and prompt decision-making to opt for iv calcium are required.

When clinical circumstances dictate urgent treatment, iv Ca^{2+} salts are used. The goals of iv calcium therapy are to control symptoms, reverse signs (eg, prolonged QT interval), and restore the serum calcium level to the lower end of the normal range. Initially, iv calcium (1 to 2 g of calcium gluconate, equivalent to 90–180 mg elemental calcium, in 50 mL of 5% dextrose) can be infused over 10 to 20 minutes. As is true for the iv administration of any electrolyte solution, calcium should not be given more rapidly because of the serious risk of cardiac dysfunction, including systolic arrest. This dose of calcium gluconate will typically increase the serum Ca^{2+} concentration for only several hours. Therefore, the acute iv administration of calcium gluconate should be followed by a slower infusion of calcium.

Ten percent calcium gluconate (90 mg of elemental calcium per 10 mL) is used. Calcium gluconate is preferred because it is less likely than calcium chloride to cause tissue necrosis if extravasated into the contiguous sc space. An iv solution containing 1 mg/mL of elemental calcium is prepared by adding 11 g of calcium gluconate (equivalent to 990 mg elemental calcium) to normal saline or 5% dextrose water to provide a final volume of 1000 mL. The calcium should be diluted in dextrose and water or saline because concentrated calcium solutions are irritating to veins. The iv solution should not contain bicarbonate or phosphate, either one of which can form insoluble calcium salts. The solution is administered at an initial infusion rate of 50–100 mL/h (equivalent to 50–100 mg/h). The dose can be adjusted to maintain the corrected serum calcium concentration at the lower end of the normal range. A typical infusion rate is 0.5 to 1.5 mg/kg of elemental calcium per hour. Over 8–10 hours, this infusion protocol will deliver as much as 15 mg/kg body weight, raising the serum calcium levels by approximately 2 mg/dL (0.5 mmol/L). The electrocardiogram can be monitored if it is warranted by the situation, such as in the setting of digoxin therapy.

Active vitamin D metabolites can be additionally administered. Because PTH is an important facilitator of the renal conversion of 25-hydroxyvitmain D to 1,25-dihydroxyvitamin D (calcitriol), this active form of vitamin D is preferred for treatment of patients with hypoparathyroidism. The initial dose of calcitriol is typically 0.25 to 0.5 μg twice daily. Its rapid onset of action (hours) and biological half-life of 4–6 hours make it a useful adjunct in the management of acute hypocalcemia. Moreover, the calcemic response to calcitriol can persist for more than 24 hours after a single oral dose (25).

In patients who present with symptomatic hypocalcemia requiring urgent iv calcium replacement therapy, the possible coexistence of hypomagnesemia should always be considered. This is particularly true in patients who are not known to have hypoparathyroidism. Their acute hypocalcemia could be explained by the reversible hypoparathyroidism of hypomagnesemia. In this setting, PTH secretion is blocked, as is the activation of vitamin D. In addition, there is a reversible resistance to PTH that is evident when magnesium is administered and circulating PTH rapidly rises. Although iv calcium is a key element of acute therapy, the hypocalcemia will be difficult to correct without first normalizing the serum magnesium concentration. If the serum magnesium concentration is low, 2 g (16 mEq) of magnesium sulfate should be infused as a 10% solution over 10 to 20 minutes, followed by 1 g (8 mEq) in 100 mL of infusate per hour. If magnesium administration is too rapid, excessive urinary losses of both magnesium and calcium can ensue. The iv route is generally preferred, although 90% is cleared by the kidney in the setting of normal renal function. Magnesium can be administered by the im route if necessary, but this is generally avoided because of the relatively high volume that is required to inject, the pain, and the "sterile" abscesses that can form. Of note, if a hypoparathyroid patient is acutely symptomatic in the setting of hypocalcemia and hypomagnesemia (eg, with seizures), iv calcium should be administered acutely before parenteral administration of magnesium.

The serum calcium level should be measured frequently in the acute setting. The recurrence of symptoms caused by hypocalcemia may indicate the need to increase the infusion rate and should be correlated with a simultaneous serum calcium value to assess the progress of treatment. Intravenous calcium should be continued until the patient is receiving an effective regimen of oral calcium and vitamin D. Intravenous infusions are generally tapered slowly (over a period of 24 to 48 hours or longer) while oral therapy is adjusted. Oral calcium and parent vitamin D therapy, in addition to calcitriol, should be initiated as soon as is practical.

There are limited data on the use of PTH in human subjects who are acutely hypocalcemic. A few cases have been reported in patients in the postoperative period status after parathyroidectomy, thyroidectomy, and renal transplant, and one hypoparathyroid individual with hypocalcemic cardiomyopathy (26–29). There is a single case report describing the use of PTH in acute neonatal hypocalcemia (30). There are no systematic data available on the use of PTH (1–34) or PTH (1–84) in the more common setting of acute hypocalcemia against a backdrop of chronic hypoparathyroidism.

In summary, because a normal level of ionized calcium is critical for many vital cellular functions, acute hypocalcemia in patients with hypoparathyroidism can be a life-threatening emergency. Urgent management should be guided by the level of serum calcium, and most importantly, by the nature and severity of the symptoms. With the administration of iv calcium therapy, serum calcium levels can be safely increased, and patients typically experience immediate and substantial relief of symptoms.

Conventional Therapy of Hypoparathyroidism

Standard therapy of hypoparathyroidism is oral calcium and vitamin D supplementation (both active and parent forms) at varying doses, based on clinical judgment. The goals of therapy are to: 1) ameliorate symptoms of hypocalcemia; 2) maintain fasting serum calcium within or slightly below to the low-normal range; 3) maintain fasting serum phosphorus within the high normal range or only slightly elevated; 4) avoid or minimize hypercalciuria; 5) maintain a calcium-phosphate product at levels well below the upper limit of normal (<55 mg^2/dL^2 or 4.4 $mmol^2/L^2$); and 6) avoid ectopic calcification of the kidney (stones and nephrocalcinosis) and other soft tissues. Serum calcium (corrected for albumin), phosphorus, and creatinine concentrations should be measured weekly to monthly during dose adjustments, and twice annually once a stable regimen has been reached. Urinary calcium and creatinine should be considered during dose adjustments and should be measured twice annually on a stable regimen to evaluate for renal toxicity (21, 22).

Calcium

Calcium carbonate and calcium citrate are the most common forms of oral calcium supplementation. Calcium carbonate contains 40% elemental calcium, and calcium citrate contains 21% elemental calcium. Calcium carbonate typically requires fewer pills per day and is less expensive and therefore more cost effective (31). Absorption of calcium carbonate is best if taken with meals and with acid present in the stomach, whereas calcium citrate is well absorbed without regard to meals and does not require gastric acid (32). Calcium citrate, therefore, may be more effective in patients with achlorhydria or in the presence of proton pump inhibitors. Illustrating this point, there are case reports of hypoparathyroid patients presenting with tetany after initiating therapy with proton pump inhibitors (33–35). Calcium citrate may also be preferred over calcium carbonate in those who complain of worsening constipation. Certain "natural" forms of calcium such as dolomite may contain significant amounts of lead or other heavy metals and are not recommended (36, 37). Coral

calcium, while touted for unsubstantiated health benefits, is essentially an expensive source of calcium carbonate (38). Calcium glubionate, gluconate, and lactate contain lower amounts of elemental calcium (6.6, 9, and 13%, respectively) and are generally not used for chronic supplemental calcium therapy. The amorphous polymorph of calcium carbonate was recently stabilized, and the results of a phase I trial in healthy postmenopausal women showed increased fractional calcium absorption compared to crystallized calcium carbonate (39). Results of phase I and II trials in hypoparathyroid subjects have not yet been published. The amount of elemental calcium supplementation required by patients with hypoparathyroidism varies greatly, typically 500–1000 mg two to three times daily, although more frequent dosing may be necessary.

Vitamin D Metabolites

Active vitamin D (1,25-dihydroxyvitamin D; calcitriol) stimulates intestinal calcium transport and absorption and promotes bone remodeling (40). Because PTH stimulates the renal 1α-hydroxylation of 25-hydroxyvitamin D, its absence, as in hypoparathyroidism, is associated with impaired activation of vitamin D. Thus, along with calcium, supplemental active vitamin D is integral to the chronic management of hypoparathyroidism. Peak serum concentrations of calcitriol are reached within 3 to 6 hours of administration, and the increase in serum calcium concentration typically follows 1–3 days later. The elimination half-life is 5–8 hours in adults. In hypoparathyroidism, the typical dose for calcitriol is 0.25 to 2 μg daily, which includes the normal daily production rate of calcitriol (10, 41–44), although higher levels are sometimes necessary. When amounts greater than 0.75 μg are required, calcitriol is typically administered in divided doses. Measurement of 1,25-dihydroxyvitamin D can be employed in special situations where compliance and/or absorption might be a concern and parenteral administration of calcitriol is considered.

1α-Hydroxyvitamin D (alfacalcidol) and dihydrotachysterol are vitamin D analogs in use for hypoparathyroidism outside the United States. They are rapidly activated by the liver to 1,25-dihydroxyvitamin D_3 and 25-hydroxydihydrotachysterol, respectively. The time to onset of action of alfacalcidol is similar to calcitriol at 1–3 days, with a longer offset of 5–7 days (41, 43, 45, 46). The time to onset of action of dihydrotachysterol is 4–7 days, with a time to offset of action of 7–21 days (47, 48). The typical dose for alfacalcidol is 0.5–3.0 μg daily and for dihydrotachysterol, 0.2–1.0 mg daily. Dihydrotachysterol is used less often now due to the development of the more specific vitamin D analogs. Although toxicity with calcitriol is easily managed due to the short half-life, severe hypercalcemia complicated by renal failure has been described with dihydrotachysterol therapy (48).

Patients are also typically supplemented with parent vitamin D (vitamin D_2 [ergocalciferol] or vitamin D_3 [cholecalciferol]). Vitamin D_3 may be more potent than D_2, although this has not been firmly established (49, 50). The half-life of the parent vitamin is 2 to 3 weeks, which some experts feel can help provide smoother control given the short half-life of calcitriol. There is also the possibility that providing the parent vitamin D compound may lead to heretofore unidentified vitamin D analogs that are beneficial with regard to "off target" effects. 25-Hydroxyvitamin D might be able in high concentrations to occupy vitamin D receptors and thereby have activity. Nonrenal expression of 1α-hydroxylase, not regulated by PTH, is another potential source of 1,25-dihydroxyvitamin D (40).

Hypercalcemia is of particular concern in individuals treated with large doses of parent vitamin D (ergo- or cholecalciferol) which can accumulate in large amounts in fat stores and, when released, can result in prolonged hypercalcemia (51). In settings where calcitriol is not readily available and/or is too expensive, parent vitamin D can be used with due regard to the cautionary note regarding vitamin D toxicity. We recommend maintaining serum levels of 25-hydroxyvitamin D to within the normal range. In this disorder, as in other metabolic bone diseases, levels of >30 ng/mL (80 nmol/L) are desirable (52).

Adjunctive Treatments

Thiazide diuretic therapy can be used to increase distal renal tubular calcium reabsorption, usually in conjunction with a low-salt diet to promote calcium retention. Effects on calcium excretion can be noted within 3 to 4 days of starting treatment (53, 54). The dose of hydrochlorothiazide is 25 to 100 mg daily. Due to the short plasma half-life of hydrochlorothiazide, twice daily dosing is most often needed (ie, 25–50 mg twice daily). Chlorthalidone is another thiazide diuretic that can be used. Doses at the higher end of the range are usually necessary to significantly lower urinary calcium with thiazide therapy, but these higher doses can be associated with hypokalemia, hypomagnesemia, and hyponatremia. Potassium supplementation or a potassium- and magnesium-sparing diuretic (eg, amiloride 2.5 to 5 mg twice a day) may be used in conjunction with hydrochlorothiazide to prevent hypokalemia and hypomagnesemia (21). The use of thiazide diuretics varies among experts, with some feeling that they are very helpful whereas others opining that they are not particularly helpful. Thiazide diuretics are not advised in congenital hypoparathyroidism due to autoimmune poly-

endocrine syndrome type 1 in patients who have concurrent Addison's disease or in autosomal dominant hypocalcemia. In situations where a diuretic is needed for other reasons, such as congestive heart disease, a thiazide diuretic should be considered, and loop diuretics should be avoided.

Phosphate binders or low-phosphate diets are generally not used unless hyperphosphatemia is particularly troublesome (22). Patients with activating calcium sensor receptor mutations may require substantial magnesium supplementation due to urinary magnesium losses (55). A small study in hypoparathyroid subjects demonstrated that magnesium supplementation does not alter plasma calcium concentrations in individuals with normal serum magnesium (56).

Clinical Aspects of Chronic Management

Treatment goals for patients with chronic hypoparathyroidism are noted in the previous section (21). One of the keys to management is to individualize therapy with particular reference to the serum calcium level. The generally accepted target serum calcium concentration for these patients is in the low-normal range, a state in which symptoms of hypocalcemia are generally uncommon. Higher serum levels of calcium, even within the normal range, are to be avoided because they can increase the risk of complications. In addition, in some patients, enhanced sensitivity to the serum calcium concentration may lead to symptoms of hypercalcemia although serum calcium is only in the high-normal range. Conversely, some patients whose serum calcium is in the low-normal range may experience symptoms of hypocalcemia. Individualized management, therefore, is necessary to optimize patient care.

Patients with hypoparathyroidism are at risk for many complications, from the disease itself as well as from adverse effects of conventional treatment regimens with oral calcium and active vitamin D (57–59). It is not possible to determine with certainty whether some of the complications of hypoparathyroidism such as ectopic calcifications and kidney stones are due to the disease, to treatment with calcium and vitamin D, often requiring very high doses, or to both.

There are no data from clinical trials that give guidance to the optimal follow-up intervals or the optimal frequency of laboratory and imaging tests. As a result, guidelines for the management of the disease have only recently been offered (60, 61). This section deals only with the use of conventional approaches to management. Replacement therapy with recombinant human (rh) PTH (1–84) is covered in the next section.

The frequency with which biochemical parameters (serum calcium, potassium, magnesium, phosphate, albumin, and creatinine) should be monitored varies with the success of controlling those biochemical parameters. In very well controlled patients, yearly or semiannual measurements might be sufficient. More often, though, more frequent monitoring is needed such as every 3 or 6 months. Twenty-four-hour urinary calcium and creatinine excretion should be measured at least once yearly because hypercalciuria is a common concern in this disease. Some experts also recommend urinary magnesium measurement. There are situations in which more frequent measurement of urinary calcium and a more complete urinary profile for stone risk factors may be needed. At the initial evaluation, baseline imaging of the kidneys with ultrasound or computed tomography is recommended (62). Surveillance for the appearance of nephrolithiasis or nephrocalcinosis may require repeat ultrasound or other imaging modality every 5 years, or earlier if signs or symptoms of kidney stones develop. Central nervous system calcifications, especially in the basal ganglia, are a well-known complication of hypoparathyroidism (57, 63). However, the clinical significance of these calcifications is unclear. In patients with long-standing hypoparathyroidism, imaging of the brain for basal ganglia and other sites of ectopic calcification is reasonable.

Patients suffering from hypoparathyroidism are at risk for cataracts (64). Although the standard senile cataract is characterized by nuclear opacities, cataracts associated with hypoparathyroidism show predominantly cortical involvement. Slit-lamp and ophthalmoscopic examinations are recommended in all patients who develop symptoms such as blurred vision or sensitivity to light. Surgical treatment of cataracts is typically a decision made by the ophthalmologist.

Children with hypoparathyroidism can have a wide variety of dental manifestations and abnormalities such as hypoplastic teeth that might require special care.

In adults with hypoparathyroidism, bone microarchitecture is abnormal, and bone mineral density (BMD), as measured by dual-energy x-ray absorptiometry (DXA), is often above that of age- and sex-matched controls (22). The clinical significance of these abnormalities is unclear. Guidelines for when repeat measurements should be made should follow recommendations of the International Society of Clinical Densitometry (65).

A key aspect of ongoing follow-up is engaging the patient as a partner in his or her medical care. Patient organizations that have formed in many countries, as well as rare disease organizations, offer a variety of resources for patients and their families, as well as health care providers (66–69). It is highly desirable for patients with hypoparathyroidism to have a basic understanding of the underlying pathophysiology, the rationale for treatment, and

signs and symptoms indicative of complications of the disorder. This is particularly important due to the fact that hypoparathyroidism is a rare disorder, and medical providers may not be familiar with the potential manifestations of the disease. In addition, the patient who understands the importance of preventing kidney damage due to excessive urinary calcium excretion might be more accepting of the 24-hour urine collections, as well as other monitoring approaches that might otherwise be seen as an inconvenience. Ongoing care with a provider familiar with the treatment of this disorder is critical for meeting the complex needs of patients and optimizing their outcomes.

Replacement Therapy of Hypoparathyroidism With PTH Peptides

Hypoparathyroidism is typically managed with calcium, active vitamin D, and at times, thiazide diuretics. With sufficient expertise, the serum calcium can be maintained, although often requiring the use of very high doses of calcium and active vitamin D. However, despite valiant efforts, some individuals continue to be difficult to control on conventional therapy, even when high doses are employed. Moreover, there are concerns with prolonged use of calcium and active vitamin D in large doses, particularly with regard to hypercalciuria, nephrolithiasis, nephrocalcinosis, and ectopic soft tissue calcification (22). In addition, conventional therapy with calcium and active vitamin D does not alleviate quality of life (QoL) complaints (64, 70, 71), nor does it reverse abnormalities in bone remodeling characteristic of the disease (72). In short, conventional therapy does not provide a physiological replacement remedy for the lack of PTH in hypoparathyroidism.

Until recently, hypoparathyroidism was the last remaining classic endocrine deficiency disease for which the missing hormone was not an approved therapy. Over the past two decades, studies of teriparatide [PTH (1–34)] and the full-length natural secretory product of the parathyroid glands, PTH (1–84), have ushered a new era in the management of this disease. In January 2015, the U.S. Food and Drug Administration (FDA) approved the use of rhPTH (1–84) for the management of hypoparathyroidism (73).

Use of PTH (1–34) in Hypoparathyroidism

In a series of classic studies, Winer et al (74) evaluated varying dose regimens of the biologically active amino-terminal fragment, PTH (1–34), including once-daily and twice-daily injections in adults and children of all etiologies. Early studies showed that PTH (1–34) achieved superior results by maintaining normal serum calcium and urinary calcium excretion levels when compared to conventional therapy. Patients who received PTH (1–34) did not concurrently receive calcitriol supplements. Thiazides and phosphate binders were not used in any of the studies. A 28-week study by the same group comparing daily with twice daily injections showed that twice-daily dosing with PTH (1–34) produced significantly higher serum calcium levels with less fluctuation throughout the day while simultaneously normalizing urine calcium levels in patients of all etiologies except those with a calcium receptor mutation (74). A longer 3-year study by Winer et al showed PTH (1–34) superior to active vitamin D by maintaining urinary calcium excretion in the normal range along with stable bone density Z-scores in adults and children (75–78). Children receiving PTH (1–34) over 3 years had stable renal function and normal linear growth and bone accrual (76).

To further refine replacement therapy with PTH (1–34), Winer recently utilized a pump delivery system and compared it with twice daily injections (77, 78). In this 6-month study, pump delivery produced normal, steady-state calcium levels with minimal fluctuation and avoided the rise in serum and urine calcium levels that are evident soon after PTH (1–34) injection. The marked reduction in urinary calcium excretion when PTH (1–34) is administered by pump would appear to emphasize a physiological point that PTH has to be continuously exposed to the renal tubule in order for the renal calcium-conserving effects to be realized. Pump delivery of PTH (1–34) achieved simultaneous normalization of markers of bone turnover, serum calcium, and urine calcium excretion. These results were achieved with a smaller daily PTH (1–34) dose and a reduced need for magnesium supplementation compared with the twice daily PTH (1–34) injection regimen.

Use of rhPTH (1–84) in Hypoparathyroidism

The rationale for using rhPTH (1–84) for hypoparathyroidism is that, in contrast to PTH (1–34), it is the native hormone and, thus, would replace what is truly missing in this disease. For reasons that have not been fully elucidated, the effective half-life of PTH (1–84) is longer than PTH (1–34), resulting in protocols that have been able to utilize effectively once-daily dosing (25, 79, 80). Initial studies demonstrated proof of concept with daily or every other day dosing by showing maintenance of serum calcium while significantly reducing the need for oral calcium and vitamin D (81, 82).

Sikjaer et al (82) studied 62 patients who were randomized in a double-blind protocol comparing a fixed dose of

rhPTH (1–84) 100 μg daily or placebo for 6 months. Over this rather short period of time, the need for active vitamin D and calcium supplements to maintain normal calcium levels fell significantly by 50 and 11%, respectively, in the group that received the drug. Following a time course in which serum calcium was monitored after injection, 71% of patients treated with rhPTH (1–84) developed hypercalcemia at one or more measurements during a 24-hour period (80). rhPTH (1–84) reduced urinary calcium excretion 2–8 hours after injection, but over the 24-hour period, urinary calcium excretion did not change (80). Similarly, urinary phosphate excretion increased only during the first 8 hours after rhPTH (1–84) injection (80).

In longer studies, rhPTH (1–84) replacement therapy continued to demonstrate these advantages (83, 84). In the work of Cusano et al (83), reductions in oral calcium and vitamin D requirements were significant and maintained over a 4-year period along with serum calcium levels that were maintained. Reductions in urinary calcium excretion were more variable and not constant over time but did achieve significance at 3 years. BMD of the lumbar spine by DXA increased, whereas hip density was stable and the distal 1/3 radius site fell. The work of Sikjaer et al (82) showed small but significant declines at the spine and hip, but not the 1/3 radius, by DXA. However, in contrast to areal BMD measurements by DXA, trabecular volumetric BMD as assessed by quantitative computed tomography scans at the lumbar spine actually increased significantly in response to therapy.

Newer imaging modalities are being assessed to determine other aspects of rhPTH (1–84) therapy in hypoparathyroidism. Trabecular bone score, a textural analysis of the lumbar spine DXA image, shows values that are within the normal range in patients who have not been treated with PTH. After rhPTH (1–84) for up to 4 years, trabecular bone score values increase in both premenopausal and postmenopausal women. By quantitative computed tomography, Sikjaer et al (85) have shown that the cortical, but not the trabecular, compartment of the hip, is reduced with rhPTH (1–84) therapy.

Bone turnover markers increase quickly and markedly with the administration of rhPTH (1–84). Both bone formation and bone resorption markers reach a peak within approximately 1 year and then decline to levels that represent a new baseline that is higher than pretreatment baseline values. These results are confirmed at the tissue level by histomorphometric analysis of bone biopsies from patients with hypoparathyroidism. As shown by Rubin et al (86), transiliac crest bone biopsies using a quadruple label technique demonstrate a marked increase in tetracycline-labeled surfaces, representing bone formation, within 3 months of rhPTH (1–84) administration. By more standard conventional bone biopsy techniques, marked changes in both trabecular and cortical compartments are seen. Within 1 year, trabecular width is reduced, and trabecular number is increased. In the work of Sikjaer et al (85), intratrabecular tunneling could be demonstrated in approximately half of the biopsied subjects treated with rhPTH (1–84), whereas none of the placebo-treated patients showed signs of intratrabecular tunneling.

In addition to these biochemical and densitometric changes with the administration of rhPTH (1–84) in hypoparathyroidism, changes in QoL metrics are also noteworthy. In the short-term study of Sikjaer et al (71), QoL as assessed by the 36-item Short Form Health Survey (SF-36) was significantly reduced in hypoparathyroid patients compared with norm-based scores. Compared with placebo, rhPTH (1–84) did not improve QoL (71). The work of Cusano et al also confirmed the reduction in QoL measures in hypoparathyroid subjects by the SF-36 scale (70). In contrast to the work of Sikjaer et al, however, the work of Cusano et al, which extended over a longer period of time, demonstrated a significant increase in virtually all eight QoL measures at 1 year (70). These improvements were sustained over a period of 5 years (84).

Phase III Study of rhPTH (1–84) in Hypoparathyroidism

The pivotal phase III trial of rhPTH (1–84) in hypoparathyroidism was reported by Mannstadt et al (87). This multicenter, multinational, placebo-controlled, double-blinded trial compared rhPTH (1–84) administered with a titration algorithm (50 μg could be increased to 75 μg or to 100 μg). The trial's triple primary end point was: 1) reduction of calcium supplementation by 50% or more; 2) reduction of active vitamin D supplementation by 50% or more; and 3) maintenance of stable serum calcium levels within the normal range. The results of the study showed that 53% of study subjects receiving rhPTH (1–84) met this triple primary end point, whereas only 2% of study subjects receiving placebo did so ($P < .001$). The secondary endpoint, the proportion of subjects who were able to eliminate all active vitamin D supplementation while reducing the dose of oral calcium to no more than 500 mg/d was also highly significant in favor of the study subjects who received rhPTH (1–84): 43 vs. 5% ($P < .001$). In most study subjects (52%), rhPTH (1–84) was titrated up to a dose of 100 μg/d. Adverse events were similar, with the most common reports related to signs of hypocalcemia, namely, muscle spasms, paresthesias, headache, and nausea.

Two other studies with rhPTH (1–84) have been reported recently. RELAY is a short, 8-week, double-

blinded, multinational, randomized trial that tested whether doses as low as 25 μg/d could be efficacious in hypoparathyroidism (88, 89). Although some study subjects were able to meet the primary end point (oral calcium not more than 500 mg/d and active vitamin D not more than 0.25 μg/d), most patients did not, confirming the results of the REPLACE trial that most patients require an amount of rhPTH (1–84) more than 50 μg/d.

The other study of recent note is called RACE. This trial is an open-label extension of the REPLACE and RELAY trials conducted in the United States only (88–90). The initial results at 1 year provide confirmatory evidence of the primary end points of the REPLACE trial, carried out for 1 year.

Management Guidelines

With the recent approval of rhPTH (1–84) by the FDA, replacement therapy is now available and is expected to contribute to improved management of hypoparathyroidism. Approved as an adjunct to calcium and vitamin D, rhPTH (1–84) is recommended for patients who cannot be well controlled on conventional therapy alone. This directive leaves room for interpretation of what constitutes a well-controlled individual. The physician should consider the following questions when assessing whether the patient is or is not well controlled.

1. Does the patient's serum calcium exhibit large swings with frequent episodes of significant hypo- and/or hypercalcemia?

2. Can the serum phosphate and/or calcium-phosphate product be maintained within an acceptable range?

3. Is the risk for renal complications high due to hypercalciuria or an unfavorable urinary biochemical stone risk profile despite optimization of conventional therapy?

4. Does the patient show evidence for renal complications such as nephrocalcinosis, nephrolithiasis, or chronic renal kidney disease?

5. Is the amount of oral medications required to control symptoms of hypocalcemia excessive?

6. Does the patient have a condition that might render calcium and vitamin D absorption from the gastrointestinal tract variable (eg, malabsorption, inflammatory bowel disease, or celiac disease)?

7. Does the patient have an autosomal dominant form of hypocalcemia due to an activating mutation in the calcium-sensing receptor? These patients are at great risk of renal damage.

The decision to recommend the use of rhPTH (1–84) in hypoparathyroidism should also take into account the fact that it is at this time a very expensive therapy. The points made above with regard to considering rhPTH (1–84) as a therapy for hypoparathyroidism should, therefore, also include the cost of the product.

An Approach to Management With rhPTH (1–84)

The official recommendations are stated in the package insert to initiate rhPTH (1–84) at 50 μg once daily as a sc injection into the thigh and to concomitantly decrease the dose of active vitamin D by 50%. Serum calcium (and albumin) concentrations are to be monitored every 3–7 days after initiation of therapy and after each dose change. The dose of rhPTH (1–84) is to be titrated every 4 weeks with the goal to discontinue active vitamin D and to reduce oral calcium supplements to an amount as low as 500 mg/d while keeping serum calcium within the low-normal range. As an alternative to the recommended reduction of active vitamin D first (as was done in the REPLACE trial), reducing oral calcium first (also by 50%), especially if the calcium supplement use is high, should also be possible. The final dosage requirement of rhPTH (1–84) required for each patient to achieve optimized management cannot be predicted by parameters such as weight or previous amounts of calcium and active vitamin D via conventional treatment. After the initial titration phase when a stable regimen is achieved, serum calcium and phosphate should be monitored every 3–6 months and urinary calcium excretion at least yearly.

It is possible that some patients who have been started on rhPTH (1–84) will be advised, or may decide on their own, to stop therapy. Before discontinuing rhPTH (1–84), serum 25-hydroxyvitamin D levels should be in the normal range. For patients receiving rhPTH (1–84) alone without any calcium and vitamin D analogs, a brief period of therapy with concomitant rhPTH (1–84), calcitriol, ergo- or cholecalciferol (parent vitamin D), and calcium may be necessary to allow the usual 3- to 4-day onset of conventional therapy to become fully effective. Furthermore, before discontinuing chronic rhPTH (1–84) therapy, one should consider potential factors that may lead to a heightened risk for sudden hypocalcemia such as malabsorption, illness, and menses in premenopausal women. A recent case series described acute hypocalcemia in two patients after the abrupt discontinuation of chronic PTH (1–34) therapy. To avoid this, subsequent patients received 2- to 3-fold the baseline requirements of standard therapy during their transition from PTH (1–34) (91).

Safety

Similar to rhPTH (1–34) for the treatment of osteoporosis, rhPTH (1–84) was approved by the FDA with a "black

box" warning due to the evidence that both PTH molecules cause osteosarcoma in rats (92, 93). Approval of teriparatide for osteoporosis is limited to 2 years at a 20-μg daily dose, but no limit has been imposed on the duration of rhPTH (1–84) therapy for hypoparathyroidism. With extensive clinical human experience with PTH (1–34) since its approval 13 years ago and with rhPTH (1–84) for a shorter period of time, no signals with either peptide have emerged to suggest that human subjects treated with either form of PTH are at increased risk for the development of osteosarcoma (94–96). Only a handful of cases of osteosarcoma have appeared in human subjects exposed to teriparatide, a number that is below what would be expected on the basis of epidemiological considerations of the background incidence of osteosarcoma in human subjects (96). In the ongoing surveillance registry of osteosarcoma, there is no evidence that any subject with osteosarcoma had ever been exposed to teriparatide (95). Hypercalcemia is another safety issue, but this concern can be mitigated by careful patient monitoring and titration protocols for calcium, active vitamin D, and rhPTH (1–84) (73). In the experience of Cusano et al (83), hypercalcemia was seen only rarely.

rhPTH (1–84) is available to patients with hypoparathyroidism only through a registry known as Risk Evaluation and Mitigation Strategies (REMS). Physicians who intend to prescribe rhPTH (1–84) must be registered in this system.

Summary

Over the past two decades, patients treated with PTH (1–34) or rhPTH (1–84) for hypoparathyroidism have shown improved calcium homeostasis. The recent FDA approval of rhPTH (1–84) represents an important advance in the management of hypoparathyroidism. It provides the natural hormone that these subjects are lacking and permits major reductions in the need for supplemental calcium and active vitamin D while maintaining normal calcium levels. Evidence also suggests that QoL is improved. Questions remain regarding ideal dosing and administration regimens for rhPTH (1–84) and its long-term effects on calcium homeostasis, bone, kidney, and other organs.

Acknowledgments

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