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MINI REVIEW

Mini-review: new therapeutic options in hypoparathyroidism

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Abstract Hypoparathyroidism is a disorder characterized by hypocalcemia and low or absent parathyroid hormone (PTH). While standard treatment of hypoparathyroidism consists of oral calcium and vitamin D supplementation, maintaining serum calcium levels can be a challenge, and concerns exist regarding hypercalciuria and ectopic calcifications that can be associated with such treatment. Hypoparathyroidism is the only classic endocrine deficiency disease for which the missing hormone, PTH, is not yet an approved treatment. This mini-review focuses on the use of PTH in the treatment of hypoparathyroidism. There are two available formulations of PTH: teriparatide [human PTH(1-34)] and the full-length molecule, PTH(1-84). Both PTH(1-34) and PTH(1-84) lower supplemental vitamin D requirements and increase markers of bone turnover. Densitometric and histomorphometric studies in some subjects treated with PTH(1-84) demonstrate improvement in abnormal bone-remodeling dynamics and return of bone metabolism toward normal euparathyroid levels. Further detailed examination of skeletal features following therapy with the different treatment regimens and data regarding the effect of PTH on quality of life measures are under active investigation.

Keywords Hypoparathyroidism · Parathyroid hormone · PTH(1-34) · Teriparatide · PTH(1-84)

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Diagnosis, etiologies, and clinical features

Hypoparathyroidism is a disorder characterized by hypocalcemia and deficient parathyroid hormone (PTH), typically associated with hyperphosphatemia, hypercalciuria, and reduced concentrations of 1,25-dihydroxyvitamin D. Clinical features of the disease include symptoms of hypocalcemia, such as perioral numbness, paresthesias, and carpal/pedal muscle spasms. Laryngeal spasm, tetany, and seizures are serious and potentially life-threatening complications [1]. Hypoparathyroidism is most commonly observed following neck surgery, when all parathyroid tissue is removed or irreversibly damaged. Autoimmune destruction of the parathyroid glands, and rarely, congenital syndromes of parathyroid dysgenesis such as DiGeorge syndrome, can also be causes of hypoparathyroidism [2, 3].

The diagnosis of hypoparathyroidism is readily made by the concurrence of hypocalcemia and markedly reduced or absent PTH levels. The only known reversible cause of hypoparathyroidism is associated with marked magnesium deficiency, in which magnesium replenishment can completely reverse the hypoparathyroid state.

Bone density and bone quality in hypoparathyroidism

Patients with hypoparathyroidism typically have uniformly increased bone mineral density (BMD) at lumbar spine, hip, and radius sites [4–6]. Histomorphometric analysis of bone biopsy specimens of patients with hypoparathyroidism show greater cancellous bone volume, trabecular width, and cortical width compared with age- and sex-matched controls [4]. Micro-computed tomography of bone biopsy specimens of patients with hypoparathyroidism show greater bone surface density, trabecular thickness,

trabecular number, and connectivity density in comparison with matched controls [7].

Bone turnover markers (BTM) are typically in the lower half of the normal range or frankly low [8, 9]. Double-tetracycline labeling of bone biopsy specimens demonstrates that dynamic skeletal indices, including mineralizing surface and bone formation, are profoundly suppressed in hypoparathyroid subjects [4].

Standard therapeutic approaches and challenges

Regardless of the etiology, standard treatment of hypoparathyroidism is oral calcium and vitamin D supplementation, with the aim of maintaining serum calcium within the low-normal range and avoiding hypercalciuria [10]. Thiazide diuretics are sometimes used as an "adjuvant" therapy by enhancing distal renal tubular calcium reabsorption [11]. However, with standard therapy, maintaining normal serum calcium levels can be a challenge. Concerns also exist regarding hypercalciuria and ectopic soft tissue calcification that can be associated with such treatment. In addition, patients are typically not easily controlled, with wide swings in their supplementation requirements over time. A previously sufficient regimen, therefore, may suddenly be associated with hypo- or hypercalcemia. Hypercalcemia is of particular concern in individuals treated with large doses of parent vitamin D, which can accumulate in toxic amounts in fat stores until some event (e.g., immobility) intervenes and stores are released. Prolonged hypercalcemia can result.

Patients with hypoparathyroidism may require up to 6 g of calcium (rarely, some patients will require intermittent intravenous administration), 2 μg of 1,25-dihydroxyvitamin D, and 50,000 IU of vitamin D for control. Moreover, many patients complain of reduced quality of life in ways that are hard to quantify but which are nevertheless very troubling [12]. Complaints of cognitive dysfunction are commonly reported, with the term "brain fog" typically described by hypoparathyroid patients [11].

PTH as a therapeutic option

Hypoparathyroidism is the only classic endocrine deficiency disease for which the missing hormone, PTH, is not yet an approved treatment [13]. Potential advantages of PTH in the management of hypoparathyroidism include: reduced amounts of calcium and vitamin D requirements; reduced urinary calcium; reduced ectopic soft tissue calcification; improved bone quality; and improved quality of life.

There are two formulations of PTH that have been studied in hypoparathyroidism: teriparatide [human PTH(1-34)] and the full-length molecule, PTH(1-84)—both administered by subcutaneous injection. A summary of the published research to date using these agents is presented below.

Use of teriparatide [PTH(1-34)]

PTH(1-34) was first studied in 10 adult hypoparathyroid subjects in a 20-week randomized crossover study of daily PTH(1-34) versus 1,25-dihydroxyvitamin D [14]. PTH(1-34) normalized mean serum calcium while urinary calcium was decreased compared with 1,25-dihydroxyvitamin D therapy. Diminishing effects were seen 12 h after administration, with serum calcium falling below the normal range in some subjects. PTH(1-34) therapy significantly increased BTM. This pilot study was followed by a 28-week randomized, crossover dose-finding trial of once-daily versus twice-daily PTH(1-34) in 17 subjects [15]. Calcium intake ranged from 1 to 2 g daily and subjects were maintained off 1,25-dihydroxyvitamin D supplementation. Treatment with twice-daily PTH(1-34) reduced the variation in serum calcium and normalized urine calcium at a lower daily PTH dose compared to once-daily dosing. While both treatment regimens resulted in elevations in BTM above the normal range, the twice-daily PTH(1-34) regimen produced lower absolute values.

These short-term studies were followed by a 3-year randomized, open-label trial of twice-daily PTH(1-34) versus 1,25-dihydroxyvitamin D [16]. Twenty-seven hypoparathyroid subjects were enrolled, aged 18–70 years, 14 in the PTH(1-34) arm and 13 in the 1,25-dihydroxyvitamin D arm. The major etiologies of hypoparathyroidism were post-surgical, sporadic calcium receptor mutations, and idiopathic. All subjects were instructed to maintain 2 g elemental calcium daily through diet and supplements. The dose of PTH or 1,25-dihydroxyvitamin D was adjusted by the investigators to achieve a serum calcium within or just below the normal range. Mean urinary calcium excretion was within the normal range from years 1 to 3 in subjects treated with PTH(1-34), but remained above normal in the 1,25-dihydroxyvitamin D group. Mean serum phosphorus remained above the normal range and did not differ significantly between the treatment arms. Serum and urine BTM increased significantly by 2- to 3-fold in the PTH-treated group, peaking at 2.5 years of treatment. Despite these dramatic changes in BTM, the PTH-treated group maintained stable BMD and bone mineral content (BMC) by dual energy X-ray absorptiometry (DXA) at the lumbar spine, femoral neck, and whole body throughout the 3 years, although there was a non-significant downward trend in the distal one-third radius BMD. This is in contrast

to the 1,25-dihydroxyvitamin D group, which demonstrated a gradual rise in BMC and BMD. The investigators noted no significant difference in the incidence of adverse events between the two groups. Treatment-related incidence of hypercalcemia was not reported.

PTH(1-34) was also studied in 12 children aged 5–14 years in a 3-year randomized trial comparing twice-daily PTH(1-34) versus 1,25-dihydroxyvitamin D treatment [17]. The etiologies of hypoparathyroidism were autoimmune, sporadic calcium receptor mutations, and idiopathic. The initial doses of PTH(1-34) and 1,25-dihydroxyvitamin D were 0.4 μg/kg twice daily and 0.25 μg twice daily, respectively. Both arms maintained daily calcium intake of 1.2 g daily and dose adjustments to both arms were permitted as indicated clinically to maintain urine and serum calcium within the normal range. Mean serum calcium levels remained at or just below the normal range and showed no differences between treatments. Mean urine calcium was within the upper half of the normal range and also showed no difference between treatments. Mean serum phosphorus remained above the normal range and did not differ significantly between treatment arms. As expected for growing children, BMC and BMD *Z*-scores increased in both groups. Neither BMC nor BMD differed across times or between treatment groups at the lumbar spine, femoral neck, total femur, distal one-third radius, or whole body, with the exception of a significant downward trend over time in the PTH(1-34) group at the distal radius. The investigators noted no significant difference in the incidence of adverse events between the two groups. Treatment-related hypercalcemia was not reported.

The results of a 6-month, open-label crossover trial of PTH(1-34) delivered continuously via pump versus subcutaneously were recently published [18]. Eight subjects were studied, aged 36–54, all with postsurgical hypoparathyroidism. There was less fluctuation in serum calcium with the pump versus twice-daily delivery of PTH(1-34), in the setting of a 65% reduction in the PTH dose. Pump therapy resulted in a 50% reduction in urine calcium. BTM normalized, and were consistently lower, during pump versus twice-daily delivery. The investigators noted no significant difference in the incidence of adverse events between the two groups. Treatment-related incidence of hypercalcemia was not reported.

Use of PTH(1-84)

PTH(1-84) therapy was studied in a randomized, double-blind trial of PTH(1-84) 100 μg daily versus placebo over 24 weeks [9]. Sixty-two subjects were studied, the majority of whom were women with post-surgical hypoparathyroidism, aged 25–80. PTH(1-84) reduced calcium and 1,25-dihydroxyvitamin D requirements by 75 and 73%, respectively, with 15 subjects being able to discontinue calcium supplementation entirely. Supplementation was not titrated until subjects developed hypercalcemia, and 11 subjects taking PTH(1-84) had a total of 17 episodes of symptomatic hypercalcemia, one requiring hospitalization, whereas only one episode occurred in the placebo group. PTH(1-84) significantly decreased serum phosphate. There was an initial increase in urinary calcium from weeks 2–8 of PTH(1-84), with no significant difference being noticed from week 12 until study conclusion. Treatment with PTH(1-84) significantly increased BTM, whereas there were small but significant decreases in BMD of the lumbar spine ($-1.76 \pm 1.0\%$), hip ($-1.59 \pm 0.6\%$), and total body ($-1.26 \pm 0.5\%$), but not the forearm. There was an increased incidence of nausea in subjects taking PTH(1-84) versus placebo.

Thirty subjects were treated in an open-label study of PTH(1-84) 100 μg every other day for 24 months [19]. The subjects were aged 25–68 years, and the major etiologies of hypoparathyroidism were postoperative and autoimmune. PTH(1-84) reduced calcium and 1,25-dihydroxyvitamin D requirements by 45 and 41%, respectively, with seven subjects able to stop all 1,25-dihydroxyvitamin D supplementation. Serum calcium levels remained stable despite the decrease in supplementation requirements, and hypercalcemia was rare (4% of all measurements). Mean urinary calcium was unchanged at 24 months. BMD increased at the lumbar spine by $2.9 \pm 4\%$ from baseline ($p < 0.05$). Femoral neck BMD remained unchanged, while distal one-third radial BMD decreased by $2.4 \pm 4\%$ ($p < 0.05$). PTH has known anabolic effects on cancellous bone, and these results may indicate that new, younger bone was formed at the lumbar spine as a result of PTH therapy. The results do not imply that the bone is weakened at the distal radius, with salutary effects on skeletal microarchitecture demonstrated histomorphometrically (see below).

A histomorphometric analysis was recently published of 64 subjects with hypoparathyroidism treated with PTH(1-84) 100 μg every other day for 2 years [8]. Subjects underwent percutaneous iliac crest bone biopsies either at baseline and at 1 or 2 years or a single biopsy at 3 months with a quadruple-label protocol, having received tetracycline before initiation of PTH(1-84) treatment and prior to biopsy. Serum BTM were also measured. Changes in structural parameters noted after 2 years of PTH(1-84) therapy included reduced trabecular width and increases in trabecular number. Cortical porosity increased at 2 years. Dynamic parameters, including mineralizing surface, increased significantly at 3 months, peaking at 1 year and persisting at 2 years. Serum BTM increased significantly, peaking at 5–9 months of therapy. They declined thereafter but still were greater than baseline values after 2 years.

PTH(1-84) versus PTH(1-34)

It is clear that both forms of PTH have salutary effects on the management of hypoparathyroidism. The pharmacokinetics of PTH(1-84) are substantially slower than those for PTH(1-34). This may help us to explain why dosing with PTH(1-34) has required multiple injections per day while with PTH(1-84), single daily dosing and every other day dosing appears to provide good results.

Future directions

The results with PTH are encouraging with respect to better management of hypoparathyroidism. While none of the treatment regimens with PTH are truly physiologic, they do provide a replacement hormone that reduces undue reliance on large doses of supplemental calcium and 1,25-dihydroxyvitamin D. The biopsy data indicate that the skeletal dynamics are returned toward normal. Further detailed examinations of skeletal features following therapy with the different treatment PTH regimens are ongoing. A comparison of PTH(1-34) versus PTH(1-84), particularly with respect to BMD, bone quality, and quality of life measures would be of interest. Since therapy with PTH may well become a long-term management option in hypoparathyroidism, longer-term data are needed. A recent report of PTH(1-84) for up to 4 years is promising [20]. A major area of inquiry is the extent to which PTH therapy in hypoparathyroidism improves quality of life measures. Quantitative psychometrics would provide support for the anecdotal experience that seems to indicate that patients feel much better with this therapy and that "brain fog" is lifted.

Summary

Hypoparathyroidism, although categorized as a rare disease, is nevertheless an important disorder for which much knowledge has accrued with regard to clinical and skeletal qualities. The logical use of PTH or a PTH analogue as therapy is gaining momentum and has an unequivocally important rationale. Both PTH(1-34) and PTH(1-84) lower supplemental vitamin D requirements and increase BTM. Serum calcium levels remain stable despite the decrease in supplementation requirements. Decreases in urine calcium excretion have been demonstrated with PTH(1-34), but not yet with PTH(1-84). Long-term densitometric and histomorphometric studies in subjects treated with PTH(1-84) demonstrate improvement in abnormal bone-remodeling dynamics and return of bone metabolism toward normal levels. The experience with PTH, thus, is promising and may well lead to its establishment as a standard of replacement therapy for hypoparathyroidism.

Conflict of interest Dr. Bilezikian is a consultant for Eli Lilly, NPS Pharmaceuticals, Merck, Novartis, Amgen, and receives research support from NPS Pharmaceuticals and Amgen. Dr. Rubin receives research support from NPS Pharmaceuticals. No conflicts of interest reported for the remaining authors.

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