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PTH(1-84) replacement therapy for the treatment of hypoparathyroidism

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Abstract

Hypoparathyroidism is a rare disease characterized by hypocalcemia and insufficient circulating levels of parathyroid hormone (PTH). Conventional therapy includes calcium and active vitamin D supplementation, often in large doses. Therapy with calcium and vitamin D, however, does not address certain problematic aspects of the disease, including abnormal bone metabolism and reduced quality of life. Hypoparathyroidism is the only classic endocrine deficiency disease for which the missing hormone, PTH, is not yet an approved treatment. PTH(1-84) may soon become a therapeutic option for patients with hypoparathyroidism. PTH (1-84) has been demonstrated to maintain serum calcium while reducing or eliminating requirements for calcium and active vitamin D supplementation. Data from bone densitometry, bone turnover markers and histomorphometry of bone biopsy specimens show positive structural and dynamic effects on the skeleton. PTH replacement therapy may also be associated with improved quality of life. PTH(1-84) replacement therapy for hypoparathyroidism is promising, although further acquisition of long-term data is needed.

Keywords

hypoparathyroidism; natpara; parathyroid; parathyroid hormone; PTH(1-84)

Parathyroid hormone (PTH) is critically important for the control of calcium and phosphate homeostasis. PTH is responsible for the regulation of normal serum ionized calcium levels through effects on calcium and phosphate handling in the kidneys, mobilization of calcium from the skeleton and renal synthesis of 1,25-dihydroxyvitamin D, the active form of vitamin D. Hypoparathyroidism is a rare disorder characterized by hypocalcemia and low or insufficient PTH concentrations. The acute clinical manifestations of hypoparathyroidism are related to hypocalcemia and can include life-threatening arrhythmias, laryngospasm and

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seizures. Chronic manifestations of the disease include hyperphosphatemia, hypercalciuria, nephrolithiasis and nephrocalcinosis, abnormal skeletal remodeling, neurocognitive complaints and reduced quality of life [1–4]. The renal manifestations may be due to the treatment of hypoparathyroidism with calcium and active vitamin D but not directly a feature of the disease itself.

The most common cause of hypoparathyroidism is damage or inadvertent removal of the parathyroid glands during neck surgery. Autoimmune disease and rare genetic disorders such as DiGeorge syndrome, familial isolated hypoparathyroidism and autoimmune poly-glandular syndrome type 1 are also associated with hypoparathyroidism. Severe magnesium deficiency can result in low PTH concentrations through impairment of PTH release and PTH resistance and is the only reversible cause of the disorder [1]. With only approximately 59,000 individuals with hypoparathyroidism in the USA [5], hypoparathyroidism has received orphan drug designation in the USA and the European Union.

Hypoparathyroidism is the only classic endocrine deficiency disease for which the missing hormone, PTH, is not yet an approved therapy. There are currently no formal guidelines for the treatment of hypoparathyroidism. Conventional treatment includes calcium and active vitamin D supplementation, often in large doses. Active vitamin D therapy is usually in the form of 1,25-dihydroxyvitamin D (calcitriol), although 1-hydroxycholecalciferol (alphacalcidol) is also in use outside the USA. The goal of therapy is to maintain serum calcium in the low-normal range while reducing hypercalciuria. Adjunctive thiazide diuretic therapy is sometimes used to increase renal tubular calcium reabsorption [1]. Serum calcium is not always maintained with conventional therapy and concerns exist regarding the use of calcium and active vitamin D in large doses. Moreover, conventional therapy with calcium and active vitamin D does not alleviate quality of life complaints and does not reverse the abnormally low bone remodeling of the disease. Randomized control trial [6,7] and long-term data from a cohort of subjects treated with open-label PTH(1-84) from our group [8,9] have investigated the effects of PTH(1-84) in hypoparathyroidism. These data are discussed in further detail below and summarized in Table 1.

Chemistry, pharmacokinetics & pharmacodynamics of PTH(1-84)

PTH is produced by the parathyroid glands first as a 115-amino acid polypeptide (pre-pro-PTH). Within the parathyroid cell, pre-pro-PTH is cleaved at the amino-terminal region to a 90-amino acid peptide (pro-PTH) and then to a biologically active secretory product, the 84-amino acid peptide. The process of PTH biosynthesis takes less than 1 h [10]. Further intraglandular processing and extraglandular metabolism result in circulating PTH fragments with unclear biological activity. The first two amino acids are necessary for binding to the PTH receptor, which is expressed in various tissues including bone, cartilage, kidney and breast. PTH has both anabolic and catabolic actions on the skeleton. When present chronically in excess, as in primary hyperparathyroidism, PTH has a catabolic skeletal effect by stimulating RANKL, a potent stimulator of osteoclast-mediated bone resorption [11–13]. In lower doses, administered intermittently, PTH can be osteoanabolic, utilizing the *Wnt* signaling pathway [14–16]. Recombinant human PTH(1-34) is a fully active but truncated amino-terminal fragment of the intact 84-amino acid peptide. In a key historical landmark of

therapeutic drug development, PTH (1-34) was shown to be osteoanabolic in osteoporosis [17] and was then approved in the USA and worldwide for the treatment of osteoporosis in men and postmenopausal women at high risk for fracture. The full-length molecule, PTH(1-84), was approved by the European Union for the treatment of postmenopausal osteoporosis. Both PTH(1-84) and PTH(1-34) are administered as a subcutaneous injection.

The notion that PTH might be beneficial in hypoparathyroidism was raised by Fuller-Albright in 1929 when he experimented with parathyroid extract in hypoparathyroidism [18]. Many decades passed without further investigation until more recently when both PTH(1-34) [19–26] and PTH(1-84) [6–9] were studied in hypoparathyroidism. PTH(1-34) has a short half-life with the circulating peak concentration being reached by 30 min after injection and an exponential clearance and half-life of 75 min. Use of PTH(1-34) in hypoparathyroid subjects, therefore, requires multiple doses per day [27]. The pharmacokinetics of PTH(1-84) are slower than those for PTH (1-34) [28] and as discussed in further detail below, PTH(1-84) can be administered daily or even every other day in some hypoparathyroid subjects.

The protocols investigating PTH(1-84) therapy in hypoparathyroid subjects have advised injection into the thigh based on data from Fox *et al.* studying four different modes of administration of PTH(1-84) in healthy postmenopausal women [29]. PTH(1-84) 100 μg was administered as a 15 min intravenous infusion, subcutaneous injection into the thigh or abdomen or intradermal injection into the abdomen. Intravenous infusion resulted in an immediate and dramatic increase in PTH levels; however, rapid clearance resulted in the fastest restoration of preinfusion PTH concentrations and the smallest and shortest serum calcium response. Subcutaneous injection into the thigh compared to the abdomen resulted in a smaller but more prolonged PTH increase and a larger and longer serum calcium response, despite a 15% lower PTH exposure versus the abdomen. After subcutaneous injection into the thigh, the time to predose PTH levels was 12 h after injection. The maximum serum calcium increase was 0.82 mg/dl, occurring 6 h after injection, with a greater than 24 h time to predose calcium levels. Intradermal injection resulted in a shorter PTH and serum calcium response than with subcutaneous injection.

Sikjaer *et al.* published the results of a pharmacokinetic and pharmacodynamic study of PTH(1-84) 100 μg subcutaneous daily into the thigh in 21 well-established hypoparathyroid subjects after 24 weeks of treatment [30]. The median age was 57 years (range 37–75) and 17 were female. PTH levels increased promptly with a median peak level of 26.5 pmol/l (interquartile range 20.1–42.5 pmol/l) 15 min after injection into the thigh. A biphasic pattern was seen with two peaks in plasma PTH concentrations in most subjects. The second peak to a level of 18.4 pmol/l (15–30 pmol/l) occurred 90–120 min after injection. Thereafter, PTH levels declined with a plasma half-life of 2.2 h (1.7–2.5 h), reaching predose levels 16 h after injection. Calcium and 1,25-dihydroxyvitamin D levels increased after injection, with ionized calcium peaking after 7 h (5–10 h) and returning to baseline concentrations after approximately 24 h. Asymptomatic hypercalcemia occurred in 71% of subjects, although urinary calcium, phosphate and magnesium excretion levels were unchanged. In view of the rather high incidence of hypercalcemia, the authors noted that a

daily dose of 100 μg may be too high for some patients and suggested the need for individual adjustment in PTH dose.

Another study from Clarke and colleagues investigated the effect of a single dose of PTH(1-84) 50 or 100 μg subcutaneous into the thigh compared with oral 1,25-dihydroxyvitamin D (calcitriol) in seven hypoparathyroid subjects [31]. Each patient received a single dose of 50 μg, followed by a washout period of 7 days and then a single 100-μg dose. The median age was 51 years (range 39–69) and six were female. Subjects had a diagnosis of hypoparathyroidism for at least 12 months prior to study entry. The mean supplement doses at baseline were 1.5 g/day of calcium (range 0.8–3) and 0.5 μg/day of calcitriol (range 0.5–0.75). Plasma PTH levels increased rapidly after administration of PTH(1-84) 50 or 100 μg, with an approximate half-life of 2.5–3 h, declining to predose levels after approximately 12–24 h. Similar to the work of Sikjaer *et al.*, there was a biphasic pattern with a first peak at a median time of 10–15 min and a second peak at 1–3 h. Compared to calcitriol therapy, the median area under the curve for PTH was similar for serum calcium and 1,25-dihydroxyvitamin D concentrations; however, 1,25-dihydroxvitamin D levels with calcitriol therapy had declined to baseline levels at 24 h while remaining above baseline at 24 h with PTH therapy. Serum calcium levels peaked after 8–12 h with calcitriol and after 12 h with either dose of PTH(1-84); levels remained above baseline at 24 h with both therapies. With PTH(1-84), the median area under the curve for phosphate was strongly negative. The calcium phosphate product was lower at both doses of PTH than at baseline (3.31–3.39 $mmol^2/l^2$ at baseline to 2.82–2.91 $mmol^2/l^2$ after PTH; converted to SI units from the original text by multiplying mg^2/dl^2 by 0.0807), in contrast to an increase in the calcium-phosphate product with calcitriol therapy from baseline (3.15 $mmol^2/l^2$ at baseline to 3.55–3.71 $mmol^2/l^2$ after calcitriol). PTH reduced urinary calcium excretion with a nadir in the 3- to 6-h sample. PTH(1-84) at the 50-μg dose reduced 24-h urine calcium excretion by 12% and at the 100-μg dose by 26%. PTH at the 50-μg dose increased urinary phosphate excretion by 53% and at the 100-μg dose by 45%.

Effects of PTH(1-84) on mineral metabolism – serum & urine calcium, phosphate

Randomized control trials

Sikjaer *et al.* conducted a double-blind trial of 62 subjects randomized to PTH(1-84) 100 μg daily versus placebo over 24 weeks [6]. The mean age was 52 years (range 31–78 years) and 86% were women. The average duration of hypoparathyroidism was 9 years (range 1–37). The etiology of hypoparathyroidism was postoperative in 58 subjects and idiopathic in four. The mean supplement doses at baseline were 1.5 g/day of calcium (range 0.4–22.5) and 2 μg/day of 1-hydroxycholecalci-ferol (range 0.25–42). Subject demographics, baseline characteristics and laboratory data were similar between the groups. The authors found that serum calcium concentrations in the PTH (1-84) arm were maintained despite a 75% decline in supplemental calcium requirements and a 73% decline in active vitamin D requirements ($p < 0.05$ for both). Calcium and active vitamin D were discontinued completely in seven subjects in the PTH arm compared with none in the placebo arm ($p < 0.01$). Asymptomatic hypercalcemia occurred frequently early in the study as calcium and active vitamin D

therapy were down-titrated, with 19% of calcium measurements above the upper normal limit during the study. Serum phosphate levels decreased from 1.44 ± 0.2 to 1.29 ± 0.2 mmol/l ($p < 0.05$) in the PTH arm. However, there were no between-group differences in the calcium-phosphate product ($p = 0.55$). Urine calcium excretion was unchanged at study conclusion.

The REPLACE trial is the pivotal trial of PTH(1-84) therapy in hypoparathyroidism. It was a double-blind, multicenter randomized trial of PTH(1-84) versus placebo over 24 weeks [7]. 134 subjects were enrolled and randomized 2:1 to the PTH group. PTH was started at a dose of 50 μg daily but could be titrated to 75 or 100 μg daily as needed by the study investigators. There were three primary endpoints of the REPLACE trial. At 24 weeks, the endpoints required at least a 50% reduction in both calcium and active vitamin D supplementation from baseline and maintenance of a serum calcium value at their baseline but not higher than normal. For all subjects, the mean age was 48 ± 13 years and 78% were women. The mean duration of hypoparathyroidism was 13 ± 10 years. The etiology of hypoparathyroidism was postoperative in 99 subjects, idiopathic in 22, autoimmune in nine, known genetic disorder in three and radiation in one. Subject demographics, baseline characteristics and laboratory data were similar between the groups. The mean supplement doses at baseline were 2.1 ± 1 g/day of calcium and 0.89 ± 0.5 μg/day of 1,25-dihydroxyvitamin D. A remarkably higher proportion of subjects in the PTH(1-84) arm (48 subjects or 53%) achieved the primary outcome than in the placebo group (one subject or 2%; $p < 0.0001$). A secondary outcome of the trial was the proportion of subjects that achieved complete independence from active vitamin D and a reduction in oral calcium to less than 0.5 g/day. This secondary outcome was reached in 36 subjects or 43% of the PTH group compared to two subjects or 5% of the placebo group ($p < 0.0001$). Serum and urine calcium excretion were similar between the groups. The mean serum phosphate concentration declined significantly in the PTH group by 0.05 mmol/l as did the mean calcium-phosphate product from 3.2 to 2.8 $mmol^2/l^2$ ($p < 0.0001$).

Cohort studies

Long-term data are available from a cohort of subjects treated with open-label PTH(1-84) from investigators at Columbia University [8,9]. The first published data included 30 subjects treated with open-label PTH(1-84) 100 μg every other day for 24 months [8]. The mean age was 49 ± 12 years and 73% were women. The average duration of hypoparathyroidism was 19 ± 15 years. The etiology of hypoparathyroidism was postoperative in 15 subjects, idiopathic in 11, autoimmune in one, autosomal dominant in one and due to DiGeorge syndrome in two. The mean supplement doses at baseline were 3.0 ± 2 g/day of calcium and 0.68 ± 0.5 μg/day of 1,25-dihydroxyvitamin D. Supplemental calcium requirements fell significantly to 1.7 ± 1 g/day as did active vitamin D requirements to 0.40 ± 0.5 μg/day ($p < 0.05$ for both). There were small but significant increases in serum calcium early in the study during titration of supplemental calcium and active vitamin D; serum calcium values were unchanged thereafter. Serum phosphate decreased from 1.44 ± 0.2 to 1.29 ± 0.2 mmol/l ($p < 0.05$). Urine calcium excretion was unchanged.

The second published study from this cohort included 27 subjects treated with open-label PTH(1-84) for 4 years [9]. These data included, but were not limited to, subjects from the earlier experience who had reached the 4-year time point. The initial starting dose was 100 μg every other day but could be adjusted when alternative dosing regimens became available. The mean age was 51 ± 12 years and 74% were women. The average duration of hypoparathyroidism was 20 ± 15 years. The etiology of hypoparathyroidism was postoperative in 16 subjects, idiopathic in 10 and due to DiGeorge syndrome in one. The mean supplement doses at baseline were 2.7 ± 3 g/day of calcium and 0.65 ± 0.7 μg/day of 1,25-dihydroxyvitamin D. Supplemental calcium requirements fell significantly to 1.7 ± 3 g/day as did active vitamin D requirements to 0.36 ± 0.7 μg/day ($p < 0.01$ for both). There were small but significant increases in serum calcium early in the study during titration of supplemental calcium and active vitamin D; serum calcium values were unchanged thereafter. The trend for serum phosphate was a significant decline over the course of the study ($p = 0.006$). Urinary calcium excretion was significantly decreased over the course of 4 years ($p = 0.003$) and fell significantly below baseline during years 1, 2 and 3. Although urinary calcium excretion at year 4 was still below pretreatment values, the difference did not achieve statistical significance.

Effects of PTH(1-84) on skeletal indices

Structural and dynamic skeletal abnormalities have been noted in hypoparathyroid patients. Histomorphometric studies of bone biopsy specimens from untreated subjects show increased bone mass at both the cortical and cancellous compartments as well as markedly reduced bone turnover [32,33]. Serum bone turnover markers are suppressed or at the low end of the normal range. Despite bone density values being higher than healthy controls, hypoparathyroid subjects may have a higher incidence of vertebral fracture [34], although overall fracture risk may be similar to age-matched controls [35].

Bone turnover markers

Markers of bone formation and resorption increase in subjects treated with PTH(1-84). In the study by Sikjaer *et al.* using PTH at a dose of 100 μg daily, bone turnover markers increased up to 12-fold baseline levels by 6 months with some markers starting to level off by 20 weeks [6]. In our cohort of subjects treated with an initial PTH dose of 100 μg every other day, bone turnover markers increased up to threefold above baseline levels at 12 months [9]. This peak was followed by a gradual decline, reaching steady-state levels at approximately 30 months, which remained significantly above baseline for some of the markers through 48 months.

Bone density by dual energy x-ray absorptiometry & qualitative computed tomography

In the study of Sikjaer and colleagues through 24 weeks, bone density by dual energy x-ray absorptiometry decreased significantly at the lumbar spine by 1.8 ± 1% and the total hip by 1.6 ± 0.6% but was unchanged at the radius [6]. Lumbar spine and hip qualitative computed tomography measurements were obtained from 31 subjects at baseline and week 24 (17 on PTH treatment). In contrast to the areal bone density data, the PTH group had a median increase of 12.2% in volumetric bone mineral density at the lumbar spine while the placebo

group decreased by 0.7% ($p = 0.02$). Compared to the placebo group, the PTH group demonstrated a decrease of 2.3% in volumetric bone density at the total hip ($p < 0.05$) and a trend toward a 4.1% decrease at the femoral neck ($p = 0.06$).

In our cohort study following hypoparathyroid subjects through 2 years of PTH therapy, bone density by dual energy x-ray absorptiometry at the lumbar spine increased 2.9 ± 4% from baseline and decreased at the distal radius by 2.4 ± 4% ($p < 0.05$ for both), while bone density at the hip was unchanged [8]. After 4 years of PTH therapy, bone density at the lumbar spine by dual energy X-ray absorptiometry increased 5.5 ± 9% from baseline ($p < 0.0001$). Bone density at the distal radius decreased significantly by 2.0 ± 6% ($p = 0.02$) at 2 years without further progression at year 4. Bone density at the hip was unchanged [9].

These data are compatible with the differential effects of PTH at sites that are primarily trabecular (lumbar spine) or cortical (distal one-third radius) [17,36–39]. The results of bone density measurements from the REPLACE study have not yet been published.

Bone histomorphometry

Sikjaer *et al.* published results from 44 hypoparathyroid subjects (23 on PTH treatment) who underwent iliac crest bone biopsies after 24 weeks of therapy, further examined with micro-computed tomography [40]. Compared to placebo-treated subjects, PTH therapy was associated with decreased trabecular thickness (0.16 vs 0.22 μm [PTH vs placebo]; $p < 0.01$), decreased trabecular bone tissue density (804 vs 840 mg/cm^3; $p < 0.01$) and increased connectivity density (7.79 vs 5.78 1/mm^3; $p < 0.05$). There was a decrease in Haversian canal separation in the PTH-treated subjects (0.501 vs 0.638 μm; $p < 0.01$) associated with a trend toward increased cortical porosity (10 vs 7%; $p = 0.09$). Intratrabecular tunneling was noted in 48% of biopsies in the PTH-treated subjects and in none of the biopsies in placebo-treated subjects. Subjects with intratrabecular tunneling had significantly higher levels of markers of bone turnover.

In our study, 64 hypoparathyroid subjects treated with PTH (1-84) for 2 years underwent iliac crest bone biopsies and compared to age- and sex-matched controls [41]. Biopsies were performed at baseline and at 1 or 2 years, with another group of subjects having a biopsy at 3 months after a quadruple-label protocol (tetracycline before initiating PTH therapy and prior to biopsy). PTH therapy was associated with structural changes at 2 years, including reduced trabecular width (144 ± 34 to 128 ± 34 mm; $p = 0.03$), intratrabecular tunneling with increased trabecular number (1.74 ± 0.34 to 2.07 ± 0.50 1/mm; $p = 0.02$) and increased cortical porosity (7.4 ± 3.2% to 9.2 ± 2.4%; $p = 0.03$). After 2 years of PTH(1-84) therapy, trabecular width was no longer different in the hypoparathyroid subjects compared to controls. Dynamic parameters including mineralizing surface, mineral apposition rate and bone-formation rate increased significantly at 3 and 12 months in all three bone envelopes. Mineralizing surface peaked at 12 months from 0.7 ± 0.6% to 7.1 ± 6.0% ($p = 0.001$). By 24 months, bone-formation rate returned to baseline in all envelopes, while mineralizing surface and mineral apposition rate had reached baseline levels at the endocortical and intracortical envelopes.

Effects of PTH(1-84) on quality of life

Hypoparathyroid patients often describe neurocognitive complaints, and quality of life in hypoparathyroid subjects on conventional therapy is reduced using standardized measures [42–44]. Two groups have investigated the effect of PTH(1-84) on quality of life. Our group previously published results showing that PTH (1-84) was associated with improvement in quality of life measures through 1 year of therapy [43]. We have recently published our results through 5 years of therapy [45]. Sixty-nine hypoparathyroid subjects were treated with open-label PTH(1-84) for up to 5 years. The earliest subjects were treated with 100 μg every other day. Alternative dosage regimens of 25, 50 and 75 μg daily were made available during the study period and the dose of PTH was adjusted for subjects based on biochemical parameters. The RAND 36-Item Short Form (SF-36) Health Survey was used to measure quality of life, consisting of 36 items covering eight domains of physical and mental health [46,47]. Serum calcium was maintained in the intended low-normal range for the majority of subjects during the study period; however, the percentage of subjects with serum calcium values maintained strictly within the normal reference range was lower. At baseline, subjects scored significantly lower than the normative reference range in all eight domains of mental and physical health. PTH(1-84) therapy was associated with improvement in seven out of the eight domains, four mental health domains and three physical health domains. Beneficial effects were noted early with PTH treatment and persisted through 5 years.

Sikjaer and colleagues published their results using PTH (1-84) 100 μg daily or placebo in a double-blind fashion in 62 subjects [48]. Quality of life was assessed using the SF-36 survey and the WHO-5 Well-Being Index. They found improvement in quality of life in both the placebo and PTH groups without between-group differences. There was a high incidence of hypercalcemia during the trial, however, and the authors posited that the fluctuations in serum calcium could have negated a positive effect of PTH therapy. Given that hypoparathyroid subjects may acclimate to relatively lower serum calcium values, this data may indicate that maintaining serum calcium within the normal reference range for healthy individuals may not be appropriate for all patients with regard to their physical and mental well-being.

Further study in a randomized control manner with PTH doses titrated to patients' biochemical parameters is needed for further evaluation of the effects of PTH therapy on quality of life.

Safety & tolerability

Osteosarcoma is of concern given the noted toxicity in rats administered very high doses of PTH for a prolonged period of time [49,50]. This does not appear to be a human toxicity, however. Results from clinical trials with cumulative numbers of 16,000 subjects treated with up to 3 years of continuous therapy have not reported any skeletal malignancies [17,51–53]. With over 10 years of clinical post-approval experience with PTH(1-34) and 7 years for PTH(1-84), no adverse signal of osteosarcoma has been observed [54,55]. It is possible that in addition to dose and duration of exposure, physiology may account for the increased incidence of osteosarcoma in rats. Rats undergo skeletal modeling for virtually

their entire lives with continued skeletal growth. The rat skeleton may comprise immature and potentially tumorigenic cells that respond to PTH in an uncontrolled manner [55].

With regard to other adverse events, hypercalcemia may occur early in the treatment course and is easily remedied by reducing supplemental calcium and active vitamin D [6,9,33]. In the REPLACE trial, the incidence of adverse and serious adverse events was similar between the PTH and placebo groups. There were no differences in either group in the cardiovascular variables (blood pressure, heart rate or QTc interval) or renal variables (serum creatinine or estimated glomerular filtration rate) [7]. Data in our cohort of subjects treated through 4 years have not raised any safety concerns [9], although further long-term data are necessary.

Conclusion

Conventional therapy of hypoparathyroidism consists of large doses of calcium and active vitamin D, with attendant long-term concerns about nephrocalcinosis, nephrolithiasis and soft tissue calcifications. Conventional therapy cannot address some problematic aspects of the disease, including abnormal skeletal remodeling and reduced quality of life. PTH(1-84) is a promising therapeutic option for patients with hypoparathyroidism. PTH therapy has been shown to decrease calcium and active vitamin D requirements while maintaining serum calcium. Data from subjects treated with PTH(1-84) show a return toward more euparathyroid levels of skeletal indices. Some data suggest a reduction in the calcium-phosphate product, urine calcium and improvement in quality of life, although further information in these areas is necessary.

Expert commentary

Hypoparathyroidism is the only classic endocrine deficiency disease for which the missing hormone, PTH, is not yet an approved treatment. PTH(1-84) shows great promise in the therapy of hypoparathyroidism. If PTH(1-84) becomes a US FDA-approved therapy for hypoparathyroidism, it is likely that application to patients with hypoparathyroidism will be selective. Patients who are well controlled with reasonable amounts of calcium and vitamin D supplementation and no quality of life complaints may not need PTH therapy. These patients would appear to represent only a small fraction of those with this disease. Rather, PTH therapy is likely to be beneficial for the majority of patients who have hypoparathyroidism. PTH (1-84) has not been formally evaluated in children whose skeletons are developing. Given the chronic nature of the disease and the need for PTH therapy over years, further long-term data in adults are necessary. More data are also needed on the potential beneficial effects of PTH on urinary calcium and quality of life.

Five-year view

Other delivery systems of PTH and PTH analogs that do not require subcutaneous injection and may have increased acceptability to patients, such as a microneedle patch system, are being studied in osteoporosis [56,57] and may be applied to hypoparathyroid patients in the future. The current methods of subcutaneous PTH replacement are not physiological.

Further investigation is needed using more physiological delivery systems, such as continuous subcutaneous pump delivery.

Information resources

The proceedings from the First International Workshop on Hypoparathyroidism were published in the Journal of Bone and Mineral Research and provide an extensive review on the topic, including epidemiology, diagnosis, pathophysiology and target-organ involvement (reference [1]). The Hypoparathyroidism Association website (https://www.hypopara.org/) is a good resource for patients.

References

Papers of special note have been highlighted as:

• of interest

•• of considerable interest

1•. Bilezikian JP, Khan A, Potts JT Jr, et al. Hypoparathyroidism in the adult: epidemiology, diagnosis, pathophysiology, target-organ involvement, treatment, and challenges for future research. J Bone Miner Res. 2011; 26:2317–37. The proceedings from the First International Workshop on Hypoparathyroidism provide an extensive review on the topic, including epidemiology, diagnosis, pathophysiology and target-organ involvement. [PubMed: 21812031]

2. Cusano NE, Rubin MR, Sliney J Jr, Bilezikian JP. Mini-review: new therapeutic options in hypoparathyroidism. Endocrine. 2012; 41:410–14. [PubMed: 22311174]

3. Shoback D. Clinical practice. Hypoparathyroidism. N Engl J Med. 2008; 359:391–403. [PubMed: 18650515]

4. Mitchell DM, Regan S, Cooley MR, et al. Long-term follow-up of patients with hypoparathyroidism. J Clin Endocrinol Metab. 2012; 97:4507–14. [PubMed: 23043192]

5. Powers J, Joy K, Ruscio A, Lagast H. Prevalence and incidence of hypoparathyroidism in the United States using a large claims database. J Bone Miner Res. 2013; 28:2570–6. [PubMed: 23737456]

6••. Sikjaer T, Rejnmark L, Rolighed L, et al. The effect of adding PTH(1-84) to conventional treatment of hypoparathyroidism: a randomized, placebo-controlled study. J Bone Miner Res. 2011; 26:2358–70. Original data investigating the use of PTH(1-84) in hypoparathyroidism. [PubMed: 21773992]

7••. Mannstadt M, Clarke BL, Vokes T, et al. Efficacy and safety of recombinant human parathyroid hormone (1-84) in hypoparathyroidism (REPLACE): a double-blind, placebo-controlled, randomised, phase 3 study. Lancet Diabetes Endocrinol. 2013; 1:275–83. The pivotal trial investigating the use of PTH(1-84) in hypoparathyroidism. [PubMed: 24622413]

8••. Rubin MR, Sliney J Jr, McMahon DJ, et al. Therapy of hypoparathyroidism with intact parathyroid hormone. Osteoporos Int. 2010; 21:1927–34. Original data investigating the use of PTH(1-84) in hypoparathyroidism. [PubMed: 20094706]

9••. Cusano NE, Rubin MR, McMahon DJ, et al. Therapy of hypoparathyroidism with PTH(1-84): a prospective four-year investigation of efficacy and safety. J Clin Endocrinol Metab. 2013; 98:137–44. Original data investigating the use of PTH(1-84) in hypoparathyroidism. [PubMed: 23162103]

10. Potts JT Jr, Kronenberg HM, Habener JF, Rich A. Biosynthesis of parathyroid hormone. Ann N Y Acad Sci. 1980; 343:38–55. [PubMed: 6994557]

11. Lee SK, Lorenzo JA. Parathyroid hormone stimulates TRANCE and inhibits osteoprotegerin messenger ribonucleic acid expression in murine bone marrow cultures: correlation with osteoclast-like cell formation. Endocrinology. 1999; 140:3552–61. [PubMed: 10433211]

12. Khosla S. Minireview: the OPG/RANKL/RANK system. Endocrinology. 2001; 142:5050–5. [PubMed: 11713196]
13. Huang JC, Sakata T, Pfleger LL, et al. PTH differentially regulates expression of RANKL and OPG. J Bone Miner Res. 2004; 19:235–44. [PubMed: 14969393]
14. Locklin RM, Khosla S, Turner RT, Riggs BL. Mediators of the biphasic responses of bone to intermittent and continuously administered parathyroid hormone. J Cell Biochem. 2003; 89:180–90. [PubMed: 12682918]
15. Tobimatsu T, Kaji H, Sowa H, et al. Parathyroid hormone increases beta-catenin levels through Smad3 in mouse osteoblastic cells. Endocrinology. 2006; 147:2583–90. [PubMed: 16484320]
16. Iwaniec UT, Wronski TJ, Liu J, et al. PTH stimulates bone formation in mice deficient in Lrp5. J Bone Miner Res. 2007; 22:394–402. [PubMed: 17147489]
17. Neer RM, Arnaud CD, Zanchetta JR, et al. Effect of parathyroid hormone (1-34) on fractures and bone mineral density in postmenopausal women with osteoporosis. N Engl J Med. 2001; 344:1434–41. [PubMed: 11346808]
18. Albright F, Ellsworth R. Studies on the physiology of the parathyroid GLANDS: I. Calcium and phosphorus studies on a case of idiopathic hypoparathyroidism. J Clin Invest. 1929; 7:183–201. [PubMed: 16693857]
19. Winer KK, Ko CW, Reynolds JC, et al. Long-term treatment of hypoparathyroidism: a randomized controlled study comparing parathyroid hormone-(1-34) versus calcitriol and calcium. J Clin Endocrinol Metab. 2003; 88:4214–20. [PubMed: 12970289]
20. Winer KK, Sinaii N, Peterson D, et al. Effects of once versus twice-daily parathyroid hormone 1-34 therapy in children with hypoparathyroidism. J Clin Endocrinol Metab. 2008; 93:3389–95. [PubMed: 18492754]
21. Winer KK, Sinaii N, Reynolds J, et al. Long-term treatment of 12 children with chronic hypoparathyroidism: a randomized trial comparing synthetic human parathyroid hormone 1-34 versus calcitriol and calcium. J Clin Endocrinol Metab. 2010; 95:2680–8. [PubMed: 20392870]
22. Winer KK, Yanovski JA, Cutler GB Jr. Synthetic human parathyroid hormone 1-34 vs calcitriol and calcium in the treatment of hypoparathyroidism. JAMA. 1996; 276:631–6. [PubMed: 8773636]
23. Winer KK, Yanovski JA, Sarani B, Cutler GB Jr. A randomized, cross-over trial of once-daily versus twice-daily parathyroid hormone 1-34 in treatment of hypoparathyroidism. J Clin Endocrinol Metab. 1998; 83:3480–6. [PubMed: 9768650]
24. Winer KK, Zhang B, Shrader JA, et al. Synthetic Human Parathyroid Hormone 1-34 Replacement Therapy: a Randomized Crossover Trial Comparing Pump Versus Injections in the Treatment of Chronic Hypoparathyroidism. J Clin Endocrinol Metab. 2011; 97:391–9. [PubMed: 22090268]
25. Gafni RI, Brahim JS, Andreopoulou P, et al. Daily parathyroid hormone 1-34 replacement therapy for hypoparathyroidism induces marked changes in bone turnover and structure. J Bone Miner Res. 2012; 27:1811–20. [PubMed: 22492501]
26. Winer KK, Fulton KA, Albert PS, Cutler GB Jr. Effects of Pump versus Twice-Daily Injection Delivery of Synthetic Parathyroid Hormone 1-34 in Children with Severe Congenital Hypoparathyroidism. J Pediatr. 2014; 165:556–63. e551. [PubMed: 24948345]
27. Lindsay R, Nieves J, Henneman E, et al. Subcutaneous administration of the amino-terminal fragment of human parathyroid hormone-(1-34): kinetics and biochemical response in estrogenized osteoporotic patients. J Clin Endocrinol Metab. 1993; 77:1535–9. [PubMed: 8263137]
28. Schwietert HR, Groen EW, Sollie FA, Jonkman JH. Single-dose subcutaneous administration of recombinant human parathyroid hormone [rhPTH(1-84)] in healthy postmenopausal volunteers. Clin Pharmacol Ther. 1997; 61:360–76. [PubMed: 9084461]
29. Fox, J.; Wells, D.; Garceau, R. Relationships between pharmacokinetic profile of human pth(1-84) and serum calcium response in postmenopausal women following 4 different methods of administration [abstract MO0173]. Program of the 33rd Annual Meeting of the American Society of Bone and Mineral Research; 2011; San Diego, CA.

30. Sikjaer T, Amstrup AK, Rolighed L, et al. PTH(1-84) replacement therapy in hypoparathyroidism: a randomized controlled trial on pharmacokinetic and dynamic effects after 6 months of treatment. J Bone Miner Res. 2013; 28:2232–43. [PubMed: 23649554]
31. Clarke BL, Kay Berg J, Fox J, et al. Pharmacokinetics and pharmacodynamics of subcutaneous recombinant parathyroid hormone (1-84) in patients with hypoparathyroidism: an open-label, single-dose, phase I study. Clin Ther. 2014; 36:722–36. [PubMed: 24802860]
32. Rubin MR, Dempster DW, Zhou H, et al. Dynamic and structural properties of the skeleton in hypoparathyroidism. J Bone Miner Res. 2008; 23:2018–24. [PubMed: 18684087]
33. Rubin MR, Dempster DW, Kohler T, et al. Three dimensional cancellous bone structure in hypoparathyroidism. Bone. 2010; 46:190–5. [PubMed: 19782782]
34. Mendonca ML, Pereira FA, Nogueira-Barbosa MH, et al. Increased vertebral morphometric fracture in patients with postsurgical hypoparathyroidism despite normal bone mineral density. BMC Endocr Disord. 2013; 13:1. [PubMed: 23286605]
35. Underbjerg L, Sikjaer T, Mosekilde L, Rejnmark L. Post-Surgical Hypoparathyroidism - Risk of Fractures, Psychiatric Diseases, Cancer, Cataract, and Infections. J Bone Miner Res. 2014 [Epub ahead of print].
36. Silverberg SJ, Shane E, de la Cruz L, et al. Skeletal disease in primary hyperparathyroidism. J Bone Miner Res. 1989; 4:283–91. [PubMed: 2763869]
37. Bilezikian JP, Brandi ML, Rubin M, Silverberg SJ. Primary hyperparathyroidism: new concepts in clinical, densitometric and biochemical features. J Intern Med. 2005; 257:6–17. [PubMed: 15606372]
38. Dempster DW, Muller R, Zhou H, et al. Preserved three-dimensional cancellous bone structure in mild primary hyperparathyroidism. Bone. 2007; 41:19–24. [PubMed: 17490921]
39. Rubin MR, Cosman F, Lindsay R, Bilezikian JP. The anabolic effects of parathyroid hormone. Osteoporos Int. 2002; 13:267–77. [PubMed: 12030541]
40. Sikjaer T, Rejnmark L, Thomsen JS, et al. Changes in 3-dimensional bone structure indices in hypoparathyroid patients treated with PTH(1-84): a randomized controlled study. J Bone Miner Res. 2012; 27:781–8. [PubMed: 22161686]
41. Rubin MR, Dempster DW, Sliney J Jr, et al. PTH(1-84) administration reverses abnormal bone-remodeling dynamics and structure in hypoparathyroidism. J Bone Miner Res. 2011; 26:2727–36. [PubMed: 21735476]
42. Arlt W, Fremerey C, Callies F, et al. Well-being, mood and calcium homeostasis in patients with hypoparathyroidism receiving standard treatment with calcium and vitamin D. Eur J Endocrinol. 2002; 146:215–22. [PubMed: 11834431]
43. Cusano NE, Rubin MR, McMahon DJ, et al. The effect of PTH(1-84) on quality of life in hypoparathyroidism. J Clin Endocrinol Metab. 2013; 98:2356–61. [PubMed: 23596139]
44. Sikjaer T, Rolighed L, Hess A, et al. Effects of PTH(1-84) therapy on muscle function and quality of life in hypoparathyroidism: results from a randomized controlled trial. Osteoporos Int. 2014; 25(6):1717–26. [PubMed: 24687385]
45. Cusano NE, Rubin MR, McMahon DJ, et al. PTH(1-84) is associated with improved quality of life in hypoparathyroidism through 5 years of therapy. J Clin Endocrinol Metab. 2014; 99(10):3694–9. [PubMed: 24978675]
46. Ware JE Jr, Sherbourne CD. The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. Med Care. 1992; 30:473–83. [PubMed: 1593914]
47. RAND Health. Medical Outcomes Study. 36-Item short form survey scoring instructions. 2010. Available from: www.rand.org/health/surveys_tools/mos/mos_core_36item_scoring.html
48. Sikjaer T, Rolighed L, Hess A, et al. Effects of PTH(1-84) therapy on muscle function and quality of life in hypoparathyroidism: results from a randomized controlled trial. Osteoporos Int. 2014; 25:1717–26. [PubMed: 24687385]
49. Vahle JL, Sato M, Long GG, et al. Skeletal changes in rats given daily subcutaneous injections of recombinant human parathyroid hormone (1-34) for 2 years and relevance to human safety. Toxicol Pathol. 2002; 30:312–21. [PubMed: 12051548]

50. Jolette J, Wilker CE, Smith SY, et al. Defining a noncarcinogenic dose of recombinant human parathyroid hormone 1-84 in a 2-year study in Fischer 344 rats. Toxicol Pathol. 2006; 34:929–40. [PubMed: 17178693]

51. Orwoll ES, Scheele WH, Paul S, et al. The effect of teriparatide [human parathyroid hormone (1-34)] therapy on bone density in men with osteoporosis. J Bone Miner Res. 2003; 18:9–17. [PubMed: 12510800]

52. Saag KG, Zanchetta JR, Devogelaer JP, et al. Effects of teriparatide versus alendronate for treating glucocorticoid-induced osteoporosis: thirty-six-month results of a randomized, double-blind, controlled trial. Arthritis Rheum. 2009; 60:3346–55. [PubMed: 19877063]

53. Greenspan SL, Bone HG, Ettinger MP, et al. Effect of recombinant human parathyroid hormone (1-84) on vertebral fracture and bone mineral density in postmenopausal women with osteoporosis: a randomized trial. Ann Intern Med. 2007; 146:326–39. [PubMed: 17339618]

54. Andrews EB, Gilsenan AW, Midkiff K, et al. The US postmarketing surveillance study of adult osteosarcoma and teriparatide: study design and findings from the first 7 years. J Bone Miner Res. 2012; 27:2429–37. [PubMed: 22991313]

55. Cipriani C, Irani D, Bilezikian JP. Safety of osteoanabolic therapy: a decade of experience. J Bone Miner Res. 2012; 27:2419–28. [PubMed: 23165426]

56. Daddona PE, Matriano JA, Mandema J, Maa YF. Parathyroid hormone (1-34)-coated microneedle patch system: clinical pharmacokinetics and pharmacodynamics for treatment of osteoporosis. Pharm Res. 2011; 28:159–65. [PubMed: 20567999]

57. Hattersley, G.; Bilezikian, JP.; Guerriero, J., et al. Bone Anabolic Efficacy and Safety of BA058, a Novel Analog of hPTHrP: Results from a Phase 2 Clinical Trial in Postmenopausal Women with Osteoporosis. The Endocrine Society's 94th Annual Meeting and Expo; 2012; Houston, TX. p. OR08-1

Key issues

- Hypoparathyroidism is the only classic endocrine deficiency disease for which the missing hormone, parathyroid hormone (PTH), is not yet an approved treatment.
- PTH(1-84) is a promising therapeutic option for patients with hypoparathyroidism.
- PTH(1-84) therapy has been demonstrated to decrease calcium and active vitamin D requirements while maintaining serum calcium and to improve the abnormal bone remodeling state in subjects with hypoparathyroidism.
- Given the chronic nature of the disease and the need for ongoing PTH therapy, further long-term data are necessary.

Table 1

Trials of PTH(1-84) therapy in hypoparathyroidism.

Study (year)	Study population	Trial design	Results: calcium and active vitamin D supplementation	Results: serum and urine calcium, phosphate	Results: bone turnover markers	Results: bone density	Ref.
Rubin *et al.* (2010)	30 subjects 25–68 years	Open-label PTH(1-84) 100 μg every other day 2 years duration	PTH(1-84) reduced calcium and active vitamin D requirements by 45 and 41%, respectively	Serum calcium maintained despite lower supplement requirements Urinary calcium unchanged Serum phosphate significantly decreased	N/A	Significantly increased at the lumbar spine by 2.9% from baseline and decreased by 2.4% at the forearm; no change at hip sites	[8]
Sikjaer *et al.* (2011)	62 subjects 25–80 years	Randomized Double-blind PTH(1-84) 100 μg daily vs placebo 24 weeks duration	PTH(1-84) reduced calcium and active vitamin D requirements by 75 and 73%, respectively	Serum calcium maintained despite lower supplement requirements No between-group differences in urinary calcium at study conclusion Serum phosphate levels significantly decreased although the calcium-phosphate product was unchanged	Significantly increased up to 13-fold above baseline values at 24 weeks	Significantly decreased at the lumbar spine by 1.8% and at the hip by 1.6%; no difference at the forearm By quantitative computed tomography, volumetric bone density at the lumbar spine significantly increased by 12.2%	[6]
Cusano *et al.*† (2013)	27 subjects 25-68 years	Open-label PTH(1-84) 100 μg every other day‡ 4 years duration	PTH(1-84) reduced calcium and active vitamin D requirements by 37 and 45%, respectively	Serum calcium maintained despite lower supplement requirements Urinary calcium was significantly below baseline during years 1–3; urinary calcium was below pretreatment values at year 4 but did not achieve statistical significance Serum phosphate levels were unchanged	Significantly increased up to threefold above baseline values at 6–12 months, subsequently declining to steady-state levels at 30 months	Significantly increased at the lumbar spine by 5.5%; at the forearm there was a significance decline of 2.0% at 2 years without further decline; unchanged at the hip	[9,40]
Mannstadt *et al.* (2013) (REPLACE trial)	134 subjects 18–85 years	Randomized Double-blind Multicenter PTH(1-84) 50 μg daily‡ vs placebo 24 weeks duration	PTH(1-84) reduced calcium and active vitamin D requirements by 52 and 78%, respectively	Serum calcium maintained despite lower supplement requirements No between-group differences in urinary calcium at study conclusion Serum phosphate levels and the calcium-phosphate product significantly decreased	Not yet reported	Not yet reported	[7]

†Included some subjects from the study by Rubin *et al.* [8].

‡Dose titrated to biochemistries.