

Parathyroid hormone replacement in hypoparathyroidism

Hypoparathyroidism results from insufficient parathyroid hormone (PTH) to maintain normal serum levels of calcium and phosphate. Unlike most endocrine deficiency disorders, the current standard of treatment is not replacement with PTH but supplementation with calcium and vitamin D. Normal physiology cannot be fully restored with calcium and vitamin D, and long-term complications of this treatment include impaired renal function, nephrolithiasis and ectopic soft tissue calcification. In the last decade clinical studies have emerged using PTH for the treatment of hypoparathyroidism either in place of or in addition to standard treatment with calcium and vitamin D. The effects of PTH replacement on biochemical indices, bone metabolism and quality of life have been promising.

Keywords: hypocalcemia • hypoparathyroidism • parathyroid hormone replacement

Hypoparathyroidism is a rare endocrine disorder where hypocalcemia and hyperphosphatemia are due to absent or insufficient production of parathyroid hormone (PTH). PTH maintains normal serum calcium levels by increasing renal tubular reabsorption of calcium, stimulating bone turnover to allow the release of calcium from bone and stimulating the activation of vitamin D which in turn increases intestinal calcium absorption. Clinical manifestations of hypoparathyroidism are due to hypocalcemia and include increased neuromuscular irritability, muscle pain and tingling, lack of focus or ability to concentrate, anxiety and depression, and in extreme cases pseudotumor cerebri, systolic heart failure, arrhythmias and seizures. Long-term complications of hyperparathyroidism may also be due to treatment which increases serum calcium but does not correct high urinary calcium excretion or hyperphosphatemia, leading to high calcium-phosphate product and precipitation in the soft tissue. Clinical complications include nephrolithiasis, premature cataracts and ectopic soft tissue calcification, including the basal ganglia [1–7].

In adults the most common cause of hypoparathyroidism is surgical removal of or damage to the parathyroid glands, and this is estimated to occur after 1–3% of total thyroidectomies [8–10]. In children the causes are usually genetic, including 22q11.2 deletion resulting in DiGeorge syndrome, mutations in the PTH gene, mutations in transcription factors regulating the development of parathyroid glands and activating mutations in the extracellular calcium-sensing receptor [1]. Other causes include autoimmune (either isolated or part of autoimmune polyendocrine syndrome type 1), infiltrative (from hemochromatosis, transfusion-dependent thalassemia, Wilson's disease or metastatic cancer) and idiopathic.

Hypoparathyroidism is the last endocrine deficiency disorder to have therapeutic replacement with the missing hormone approved, which only occurred in January 2015. Current standard treatment is oral calcium, usually high doses and vitamin D supplementation, usually the active form of vitamin D calcitriol. Although this treatment regimen appears simple, management is difficult as it often requires multiple daily

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doses and large number of tablets that have to be taken and carried around. Vitamin D analogs and calcium can normalize serum calcium by increasing intestinal absorption but this leads to increased filtered load of calcium, which in the absence of the renal calcium reabsorbing effect of PTH leads to hypercalciuria [11]. Long term this may be associated with nephrolithiasis, nephrocalcinosis and impaired renal function [2,12]. To avoid hypercalciuria, treatment with vitamin D analogs and calcium aims to maintain serum calcium at or slightly below the lower limit of normal [1]. This proves to be difficult, and patients often experience episodes of both hypocalcemia and hypercalcemia and reduced quality of life [5]. Furthermore, phosphorus levels are high on standard treatment, and this can contribute to progression of basal ganglia calcification [6].

In the last decade clinical studies using PTH (1–34) and PTH (1–84) for the treatment of hypoparathyroidism have emerged. PTH (1–34) is a truncated analog that contains the biologically active region of PTH, while PTH (1–84) is the intact hormone. Based on molecular weight, 40 µg of PTH (1–34) is the equivalent to 100 µg of PTH (1–84) [13]. Both PTH (1–34) 20 µg daily and PTH (1–84) 100 µg daily are approved for the treatment of severe osteoporosis, while only PTH (1–34) is approved in the USA. A range of doses for both PTH (1–34) and PTH (1–84) have been studied, and treatment outcomes are summarized in this article.

Effects on biochemical levels

PTH (1–34)

Initial clinical trials were performed with PTH (1–34) and evaluated whether PTH (1–34) maintained normal levels of calcium and phosphorus in the serum and urine better than standard treatment with calcitriol and calcium [14,15]. The first trial was a randomized crossover trial that administered either once daily PTH (1–34) or calcitriol and calcium carbonate in 10 participants with hypoparathyroidism [15]. Both regimens were adjusted on a daily basis during the first 2 weeks and weekly thereafter with a primary goal of maintaining normal serum calcium levels and a secondary goal of maintaining normal urinary calcium levels. Although both treatment regimens maintained normal serum calcium over a 24 h period, PTH (1–34) significantly decreased urinary calcium excretion compared with standard calcitriol and calcium supplements. Also, PTH (1–34) resulted in lower serum phosphorus levels over a 24 h period, although not always in the normal range, and tended to increase urine phosphorus levels. Mean serum 25-hydroxyvitamin D and 1,25-dihydroxyvitamin D levels were similar for both treatment arms suggesting that PTH (1–34) was able

to stimulate activation of vitamin D. Subsequent crossover trials by the same group showed that twice daily injections of PTH (1–34) resulted in less fluctuation in serum calcium than once daily dose in adults and children, particularly those with hypoparathyroidism due to a mutation in the calcium-sensing receptor [16,17]. The total daily dose with twice a day regimen was also reduced by half compared with once a day regimen (46 ±52 vs 97 ±60 µg/day for adults) [16].

Long-term clinical trials comparing twice daily PTH (1–34) with calcitriol and calcium have been conducted in 27 adults [14] and 12 children [18]. Both trials were of 3 year duration. In adults and children, both PTH (1–34) and calcitriol with calcium maintained similar levels of serum calcium, phosphorus and magnesium, though usually just outside the normal range for calcium and phosphorus. In adults PTH (1–34) was able to normalize mean 24 h urine calcium excretion while calcitriol and calcium resulted in hypercalciuria (5.8 ±0.27 vs 8.2 ±0.51 mmol/24 h, respectively; normal range 1.25–6.25 mmol/24 hr) [14]. In children both treatments resulted in normal calcium excretion with no between-group differences [18]. Over the 3 years, there were no between group differences in creatinine clearance [14].

Finally, this group compared twice daily injections with continuous delivery by a pump that was programmed with several basal delivery rates and allowed for boluses in an effort to approach normal physiology [19]. Compared to twice daily administration of PTH (1–34), continuous delivery resulted in even less fluctuation in serum calcium, more than 50% reduction in urinary calcium, and further reduced the total daily dose of PTH (1–34) required to maintain eucalcemia.

PTH (1–84)

Later clinical trials were performed with PTH (1–84) to assess whether the addition of PTH (1–84) to standard treatment would allow for dose reductions of calcitriol and calcium supplementation. Ultimately, this would minimize therapeutic complications such as the risk of ectopic soft tissue calcification. PTH (1–84) has a longer half-life and may have a longer effect on serum calcium with serum calcium levels returning to baseline 24 h after injection [20] compared with PTH (1–34), which can result in hypocalcemia 24 h after injection [15].

The first study on the use of adjunctive PTH (1–84) was an open-labeled study of PTH (1–84) 100 µg every other day for 2 years in 30 patients [21]. Requirements for both supplemental calcitriol and calcium decreased while maintaining stable, mostly normal levels of serum calcium and 24 h urinary calcium excretion.

Serum phosphate levels did fall significantly, closer to normal range. Finally, despite decreased requirements for calcitriol, 1,25-dihydroxyvitamin D levels did not change.

This was followed by two randomized, double-blinded, placebo-controlled studies of 6 months duration [22,23]. The first study was performed in Denmark. Sixty-two patients with predominantly postsurgical hypoparathyroidism were randomized to either the addition of daily PTH (1–84) 100 µg or placebo to standard vitamin D and calcium [22]. The addition of daily PTH (1–84) allowed for maintenance of normal plasma calcium and phosphate levels while reducing the total daily doses of active vitamin D and calcium by 75%. However, daily PTH (1–84) did result in more frequent episodes of hypercalcemia, and subsequently hypercalciuria, especially during the first 5 months. Five subjects required PTH (1–84) at less frequent dosing after being discontinued from vitamin D and calcium.

The second randomized, double-blinded, placebo-controlled study was a multinational study with 134 patients randomized 2:1 to PTH (1–84) 50 µg/day starting dose or placebo [23]. Dose of PTH (1–84) was titrated up to 75 or 100 µg/day with a goal of eliminating calcitriol and reducing calcium to ≤500 mg/day. The primary end point was ≥50% reduction from baseline dose of both calcitriol and calcium while maintaining normal serum calcium levels. 53% of the patients in the PTH (1–84) group achieved this end point compared with 2% in the placebo group. No difference was noted in 24 h urinary calcium excretion rates at the end of the study, but the treatment group had overall higher levels of serum calcium levels than the placebo group. In fact, although the serum calcium levels were higher with PTH (1–84), 24 h urinary calcium excretion actually decreased slightly. Phosphate levels were lower in the treatment group, which resulted in a significant decrease in the mean calcium-phosphate product. There were fewer clinical symptoms of hypocalcemia in the treatment group.

One long-term trial on the addition of PTH (1–84) to standard therapy has been published [24]. This study used a dose of 100 µg every other day for 4 years in 27 patients. The results confirmed that the addition of PTH (1–84) decreases calcitriol and calcium requirements while maintaining eucalcemia and normalizing phosphorus levels. There was a trend toward a decline in urine calcium excretion. Changes in kidney function were not assessed.

Overall, clinical trials have consistently demonstrated that PTH replacement either in place of or in addition to vitamin D analogs and calcium can maintain stable normal levels of calcium levels, maintain or

decrease urinary calcium excretion and decrease phosphate levels compared with standard therapy alone. Longer observation in a larger number of subjects will be needed to determine whether a favorable biochemical response to PTH therapy will translate into long-term benefits, such as preservation of kidney function and prevention of basal ganglia calcification.

Effects on bone metabolism

Adults with hypoparathyroidism have been found to have increased bone mineral density (BMD), especially at sites rich in trabecular bone [2,25–27]. Furthermore, the duration of hypoparathyroidism positively correlates with lumbar spine BMD [27–29], and hypoparathyroidism has been shown to protect against bone loss during early menopause [30,31]. High BMD in hypoparathyroidism has been attributed to a state of decreased bone turnover. Hypoparathyroid patients tend to have decreased markers of bone turnover [28], and bone histomorphometry studies have confirmed reduced rates of bone resorption and formation as well as a prolonged quiescent period [29,32]. The balance between resorption and formation has been found to be slightly positive in hypoparathyroid patients compared with negative in normal individuals [32]. In addition to these dynamic changes, bone microarchitecture is also altered with greater trabecular bone volume, number and thickness; lower trabecular separation; increased connectivity and more plate-like structures that are associated with enhanced bone strength [29,33].

Despite high BMD, data on fracture risk in patients with hypoparathyroidism have been contradictory and limited due to the low prevalence of the disease. The largest study was a case-control study of 688 patients with postsurgical hypoparathyroidism of a median duration of 8 years, the total fracture risk was similar to the control group but there was a significantly lower risk of fractures at the proximal humerus and upper extremities without differences at other sites [4]. Also, despite the low bone turnover state, risk of atypical femur fractures was the same [4]. Fujiyama *et al.* also found less vertebral fractures in 13 postmenopausal women with hypoparathyroidism compared with controls [30]. In contrast, Mendonca *et al.* found that 63% (10 out of 16) of hypoparathyroid patients had prevalent vertebral fractures compared with 2 out of 16 matched controls [28]. There are a few differences between this study and the one by Fujiyama *et al.* that may explain the discrepancies. Although both studies were performed in postmenopausal women with postsurgical hypoparathyroidism, the duration of hypoparathyroidism was more consistent (mean 12.9 ±3.3 years) in the former study than the latter (mean 15.3 ±12.4 years). In the latter study this led to a notably

wider range of BMD at the lumbar spine, and BMD at this site, total hip, and femoral neck were similar to the control group. The BMD at the distal one third radius was actually lower. Mendonca *et al.* did propose that decreased bone turnover may result in inefficient repair of microdamage and that thicker trabecular bone could be at the expense of reducing resilience and the ability to absorb and dissipate energy [28–29,34].

In response to the administration of PTH, markers of bone turnover increase as early as 4 weeks [22]. In long term studies, bone turnover markers tend to start in the low- to mid-normal range at baseline, increase dramatically beyond normal ranges and decline to steady-state toward normal levels by 30 months [14,24]. In contrast, treatment with calcitriol and calcium results in steady, normal levels of bone turnover markers [14].

Although the increase in bone turnover markers with PTH (1–34) and PTH (1–84) has been consistent across studies, the effect on BMD has differed [14,21–22], possibly due to differences in the total daily dose and dosing schedule of PTH. Rubin *et al.* had chosen to use 100 µg of PTH (1–84) every other day in their trial due to increases in markers of bone turnover to levels that were within or slightly higher than the normal range [21]. Treatment with PTH (1–84) every other day for 2 years resulted in increased lumbar spine BMD of $2.9 \pm 4\%$, while femoral neck BMD did not change and the distal one third radius BMD decreased by $2.4 \pm 4\%$ [21]. Results were confirmed in their follow-up long-term trial of 4 years with continued increase in lumbar spine BMD and no change at the femoral neck [24]. The BMD at the distal one third radius had remained stable after the initial decline and was not significantly different from baseline at the end of the 4 years [24]. This pattern is similar to the effect of PTH in osteoporotic women. The intermittent administration of PTH used in the treatment of osteoporosis results in increased bone turnover and bone mineral density, particularly at sites rich in trabecular bone [35]. In contrast, the addition of daily PTH (1–84) 100 µg for 6 months resulted in significant decreases in BMD at the whole body, spine, hip and femoral neck with the greatest losses in the femoral neck [22]. The greater dose and frequency in this regimen may have overstimulated bone turnover to a state similar to hyperparathyroidism, which has greater effects on cortical bone. In a study that is harder to compare, Winer *et al.* used twice daily PTH (1–34) with a total daily dose slightly higher than the bioequivalent of 100 µg of PTH (1–84) [14]. There were no significant between-group differences in BMD or bone mineral content (BMC) of the lumbar spine, femoral neck, distal one third radius and whole body over the 3 years. However, while PTH (1–34) maintained whole body and spine BMD and BMC, treatment with calcitriol and calcium resulted in a gradual rise in whole

body BMD and lumbar spine BMC. PTH (1–34) did increase BMD at the femoral neck and no change was observed at the distal one third radius. All studies have been too small and short to assess effect on fracture risk.

Histomorphometry studies confirm that treatment with PTH (1–84) restores normal bone metabolism after an initial period of extremely rapid bone turnover [36]. In parallel with changes in bone turnover markers, mineralizing surface, mineral apposition rate and bone formation rate increased at 3 and 12 months and generally returned to baseline by 24 months. After 2 years of treatment, PTH (1–84) has been shown to reduce trabecular width, increase trabecular number and increased cortical porosity, consistent with increased bone-remodeling rate in both trabecular and cortical compartments with tunneling resorption in the trabecular compartment. On a cellular level, PTH (1–84) seems to stimulate osteoblast development and maturation [37]. Overall, there has been a consistent pattern of initial rapid increase in bone turnover from a suppressed to supranormal state, followed by a gradual return to normal but higher than baseline levels. This pattern has been suggested to be due to changes in PTH sensitivity [36]. Physiologically, an increase in hormonal sensitivity is expected after a prolonged period of hormonal deficiency and this then reacclimates to normal with time.

In children bone turnover markers were slightly elevated with PTH (1–34) treatment alone compared with calcitriol and calcium [18]. However, this did not seem to affect skeletal development as there were no between group differences in bone mineral accrual, linear growth or weight gain over 3 years [18].

Effects on quality of life

Although severe psychiatric symptoms associated with hypocalcemia have long been recognized in case reports and series [38,39], more recent data suggest that quality of life is lower in patients with hypoparathyroidism despite treatment that stabilizes their biochemical values. Compared to women with history of thyroid surgery but intact parathyroid function, women with postsurgical hypoparathyroidism report higher scores for anxiety, depression and somatization with increased exhaustion tendency, pain in limbs and heart complaints (e.g., palpitations) [5]. These scores exceeded one standard deviation from the means of the normal range and did not correlate with duration of disease or serum calcium levels; however, these patients were well-controlled with a mean serum total calcium of 8.6 ± 0.84 mg/dl. In another study with more poorly controlled (mean serum total calcium of 5.4 ± 0.94 mg/dl) and longer duration of hypoparathyroidism, cognitive impairment was positively correlated with duration of

disease and calcium phosphorus product and negatively correlated with average serum calcium [7].

Cusano *et al.* have studied the effects of PTH (1–84) on quality of life in an open-label study of 54 patients [40]. Despite well-controlled biochemical levels, the patients were confirmed to have significantly lower scores than the normal reference range in all 8 domains of the RAND 36-Item Health Survey, which measures quality of physical and mental health. While maintaining calcium levels at goal, the addition of PTH (1–84) improved the total score, including components of both mental and physical health, within 1 month [40], and improvements were sustained up to 5 years [41].

In contrast, a randomized, placebo-controlled, double-blinded trial showed that the addition of 100 µg of PTH (1–84) daily to standard treatment did not improve quality of life compared with placebo [42]. However, the study was of only 6 months duration and the higher PTH (1–84) dose resulted in more episodes of hypercalcemia than placebo. In addition, muscle strength and associated electrophysiological indices slightly but significantly deteriorated with PTH (1–84), which was also attributed to hypercalcemia. In the 3 year randomized open-labeled trial in which calcium levels were well-controlled, Winer *et al.* found no difference in 9 min walk-run test between the PTH (1–34) and placebo groups and no difference between baseline and after initiation of PTH [14].

Safety

In the two randomized controlled trials of PTH (1–84) in hypoparathyroidism, adverse events that were significantly higher in frequency with PTH over placebo were nausea and episodes of hypercalcemia, especially at higher doses or during titration when PTH is added to oral supplements [22,23]. To minimize the risk of hypercalcemia it is essential to down-titrate active vita-

min D and calcium supplements at the start of PTH therapy and to closely monitor serum calcium after each change in the dose of the supplements or PTH. Other common complaints in both PTH and placebo groups were similar to those associated with hypoparathyroidism and included infections, musculoskeletal aches/spasms, paresthesias, headache, cardiovascular complaints and hypocalcemia.

PTH (1–84) has recently been US FDA approved for hypoparathyroidism as an adjunct treatment to calcium and vitamin D. Similar to PTH(1–34) for osteoporosis, it also carries a boxed warning for a potential risk of osteosarcoma and is only recommended for patients who cannot be well-controlled on calcium and vitamin D alone. PTH (1–34) has been US FDA approved for osteoporosis since 2002. It is approved for use of no more than 2 years due to observations of osteosarcoma in rodents in this time frame, which actually represents 80–90% of their normal life span [43]. To date, no increased risk of osteosarcoma has been observed in humans treated for either osteoporosis [44] or hypoparathyroidism [14,18,24]. There is an increased concern in children or young adults who have open epiphyses. In the clinical trial with 12 children, bone mineral accrual and linear growth appeared to proceed normally with PTH (1–34) [18]. However, in these pediatric patients it may be judicious to have a more physiological regimen of PTH replacement as with a pump to avoid supranormal elevation of bone turnover [18]. The main difference in the use of PTH in hypoparathyroidism and osteoporosis is that PTH is used to replace a deficiency in the former disorder

Future perspective

Overall, the use of PTH either in place of or in addition to standard calcium and vitamin D supplements appears to be efficacious and safe in these limited

Executive summary

- Hypoparathyroidism is due to absent/insufficient production of parathyroid hormone resulting in hypocalcemia and hyperphosphatemia.
- Current standard treatment is supplementation with calcium and calcitriol, but this may be complicated by episodes of hypocalcemia, hypercalcemia and hypercalciuria, leading to nephrolithiasis, impaired renal function and ectopic soft tissue calcification.
- Replacement with parathyroid hormone analogs (with or without calcium and vitamin D) allows reduction or elimination of oral calcium and active vitamin D analogues and also maintains serum calcium closer to normal levels, decreases phosphate levels and may decrease urinary calcium excretion despite higher serum calcium.
- Parathyroid hormone analogs may restore normal bone metabolism but the effects on fracture risk are unclear.
- Parathyroid hormone analogs may improve quality of life.
- Initiation of parathyroid hormone analogs requires close monitoring of serum calcium levels and down-titration of calcium and calcitriol supplements to prevent hypercalcemia.
- Parathyroid analogs should be considered for hypoparathyroid patients who are uncontrolled on standard treatment or have poor quality of life.

clinical studies. There are biochemical benefits, such as decreasing urinary calcium excretion while maintaining serum calcium closer to normal range. However, PTH has not yet been proven to have long-term benefits in preserving renal function and limiting soft tissue calcification. The effects of hypoparathyroidism on fracture rates and the effects of PTH use in hypoparathyroidism on clinically significant bone outcomes are still unclear. Finally, the cost of PTH may also be a factor. From a clinical perspective, PTH seems to be an excellent option for hypoparathyroid patients who are not well-controlled on standard vitamin D and calcium supplements, who have poor quality of life, or who have hypercalciuria that is difficult to control. The

recent availability of PTH has the potential to improve the clinical care of most difficult cases of hypoparathyroidism and with more experience may become a useful therapeutic option in general.

Financial & competing interests disclosure

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