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Use of parathyroid hormone in hypoparathyroidism

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Abstract

Hypoparathyroidism is a disorder characterized by hypocalcemia, deficient PTH, and abnormal bone remodeling. Standard treatment of hypoparathyroidism consists of oral calcium and vitamin D supplementation. However, maintaining serum calcium levels can be a challenge. In addition, 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 review focuses on the use of PTH in the treatment of hypoparathyroidism, in the form of teriparatide [PTH(1-34)] and the full-length molecule, PTH(1-84). Studies in hypoparathyroid subjects demonstrate that PTH(1-34) and PTH(1-84) lower or abolish supplemental calcium and vitamin D requirements as well as increase markers of bone turnover. Densitometric and histomorphometric studies in some subjects treated with PTH(1-34) and PTH(1-84) show an improvement in bone-remodeling dynamics and return of bone metabolism toward normal levels. Given the chronic nature of hypoparathyroidism, and the expectation that PTH will be used for extended periods of time in hypoparathyroidism, further studies are needed to determine the long-term safety of PTH therapy in this population.

Keywords

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

INTRODUCTION

Hypoparathyroidism is a disorder characterized by hypocalcemia and low or absent PTH. Other typical laboratory abnormalities include hyperphosphatemia, hypercalciuria, and reduced concentrations of 1,25-dihydroxyvitamin D. Hypocalcemic symptoms are the major clinical features of the disease, including perioral numbness, paresthesias, and carpal/pedal muscle spasms. Laryngeal spasm, tetany, and seizures are serious and potentially life-threatening complications (1-4).

The diagnosis of hypoparathyroidism is readily made in the setting of hypocalcemia with markedly reduced or absent PTH levels. The most common etiology of hypoparathyroidism is neck surgery, following inadvertent removal or irreversible damage to the parathyroid

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glands. Other causes of hypoparathyroidism include autoimmune destruction of the parathyroid glands and rarely, congenital syndromes of parathyroid dysgenesis such as Di-George syndrome (5, 6). Marked magnesium deficiency is the only known reversible cause of hypoparathyroidism; in this case, magnesium replacement can completely reverse the functional hypoparathyroid state.

Many patients with hypoparathyroidism complain of reduced quality of life, in particular describing symptoms of cognitive dysfunction. The term “brain fog” has often been described (1). There are limited data regarding quality of life in hypoparathyroidism or the ability of therapy to lessen or resolve these complaints. One study of women with post-surgical hypoparathyroidism treated with calcium and vitamin D supplementation *vs* healthy controls showed that despite the majority of subjects demonstrating eucalcemia, hypoparathyroid patients had significantly higher global complaint scores in various validated quality of life questionnaires, with predominant increases in the subscale scores for anxiety, phobic anxiety and their physical equivalents (7). Two recent reports of men and women with hypoparathyroidism of various etiologies have also demonstrated quality of life deficits (8, 9).

Patients with hypoparathyroidism typically have abnormal bone remodeling. Bone mineral density (BMD) measured by dual energy X-ray absorptiometry of the lumbar spine, hip, and radius sites is often above average values for a healthy population at peak bone mass (10-12). In addition, histomorphometric analysis of bone biopsy specimens of patients with hypoparathyroidism show greater cancellous bone volume, trabecular width, and cortical width compared to age- and sex-matched controls (10). Double-tetracycline labeled bone biopsy specimens demonstrate profoundly suppressed dynamic skeletal indices, including mineralizing surface and bone formation (10). Micro-computed tomography of bone biopsy specimens of hypoparathyroid patients also show greater bone surface density, trabecular thickness, trabecular number, and connectivity density in comparison to matched controls (13). Serum and urine markers of bone turnover are in the lower half of the normal range or frankly low (14, 15).

TREATMENT OF HYPOPARATHYROIDISM

There are no formal guidelines for the management of hypoparathyroidism. In the acute setting, intravenous calcium may be necessary. Standard therapy of hypoparathyroidism is oral calcium and vitamin D supplementation at varying doses, based on clinical judgment, with the goal of ameliorating symptoms of hypocalcemia, maintaining serum calcium within the low-normal range, and avoiding hypercalciuria (3). Thiazide diuretics, which enhance distal renal tubular calcium reabsorption, are sometimes used as an “adjuvant” therapy (1). Patients are typically not easily controlled with standard therapy, as maintaining normal serum calcium levels can be a challenge due to wide swings in supplementation requirements over time. Patients with hypoparathyroidism may require up to 6 g of calcium (rarely, intermittent iv administration is required) and 2 μg of 1,25-dihydroxyvitamin D daily in addition to large doses of parent vitamin D. Concerns also exist regarding hypercalciuria and nephrocalcinosis as well as ectopic soft tissue calcification that can be associated with exposure to such prolonged, high dose supplements (1).

Parathyroid hormone as a therapeutic option

Fuller-Albright first experimented with parathyroid extract in hypoparathyroid subjects in 1929 (16). Unfortunately, these early experiments were abandoned and little was done with the concept of PTH replacement in hypoparathyroidism until more recently. Hypoparathyroidism remains the only classic endocrine deficiency disease for which the missing hormone, PTH, is not yet an approved treatment (17). There are many potential advantages of PTH in the management of hypoparathyroidism, including a reduction in the amounts of calcium and vitamin D requirements; reduction in urinary calcium; reduction in ectopic soft tissue calcification; improvement in bone quality; and improvement in quality of life.

There are two formulations of PTH that have been investigated in hypoparathyroidism, namely the full-length molecule, PTH(1-84), and the fully active but truncated amino-terminal fragment, PTH(1-34) (teriparatide). Both formulations have primarily been studied as a sc injection. In the studies of PTH(1-34), the dose of PTH was titrated by investigators to achieve independence from active vitamin D therapy (18-24), while in the studies of PTH(1-84), PTH was used as an add-on to standard therapy (14, 15, 25-30). The pharmacokinetics of PTH(1-84) are slower than those for PTH(1-34) (31, 32), which may help 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. PTH(1-34) has also been studied as sc pulses administered through a pump. A summary of the major published research to date using these agents is presented in Tables 1 and 2 and in further detail below.

Studies of PTH(1-34) (teriparatide)

There are short-term dose-finding studies of PTH(1-34) as well as 3-yr randomized open-label trials in adults and children, published by Winer et al. (18-23). In addition, a recent cohort study of PTH(1-34) in 5 subjects in whom iliac-crest biopsies were obtained was recently published by Gafni et al. (24). PTH(1-34) was first investigated in 10 adult hypoparathyroid subjects in a 20-week randomized crossover study of daily PTH(1-34) *vs* calcium and 1,25-dihydroxyvitamin D supplementation (18). PTH(1-34) normalized mean serum calcium compared with standard therapy, although diminishing effects were seen 12 h after administration. PTH(1-34) also therapy significantly decreased urinary calcium and increased bone turnover markers. This study was followed by a 28-week randomized crossover dose-finding trial of once-daily *vs* twice-daily PTH(1-34) in 17 subjects (19). Subjects treated with twice-daily PTH(1-34) had reduced variation in serum calcium and normalized urine calcium at a lower daily PTH dose compared to once-daily dosing. Both regimens resulted in elevations in bone turnover markers above the normal range, although the twice-daily PTH(1-34) regimen produced lower absolute values.

The twice-daily dosing regimen was chosen for a subsequent 3-yr randomized, open-label trial of PTH(1-34) *vs* calcium and 1,25-dihydroxyvitamin D supplementation in 27 subjects (20). The subjects were aged 18-70 yr, 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

1 g of dietary calcium, and subjects randomized to 1,25-dihydroxyvitamin D additionally received 1 g of calcium carbonate 4 times daily. The dose of PTH or 1,25-dihydroxyvitamin D was adjusted by the investigators to maintain serum calcium within or just below the normal range; a mean±SD dose of PTH(1-34) of 37±2.6 μg and 1,25-dihydroxyvitamin D dose of 0.91±0.2 μg were required. Mean serum calcium levels showed no differences between treatment arms. Mean urinary calcium excretion was within the normal range from years 1-3 in subjects treated with PTH(1-34), but remained above normal in the 1,25-dihydroxyvitamin D group, although there were no statistically significant differences between the two groups. Mean serum phosphorus remained above the normal range in both arms without significant between-group differences. Serum and urine bone turnover markers increased significantly by as much as 6-fold in the PTH-treated group and peaked at 2-2.5 yr of treatment. Despite these remarkable changes in markers of bone turnover in the PTH-treated group, there were no statistically significant differences in BMD between groups. Subjects in the PTH arm maintained stable BMD and bone mineral content (BMC) at the lumbar spine, femoral neck, and whole body throughout the 3 yr, although there was a non-significant downward trend in the distal one-third radius BMD. The calcium and 1,25-dihydroxyvitamin D group, on the other hand, demonstrated a gradual rise in BMC and BMD. The investigators noted no significant difference in the incidence of adverse events between the two groups.

A dose-finding study of once-daily versus twice-daily PTH(1-34) in children (21) was followed by a 3-yr randomized trial comparing twice-daily PTH(1-34) *vs* 1,25-dihydroxyvitamin D treatment in 12 children aged 5-14 yr (22). The etiologies of hypoparathyroidism were autoimmune, sporadic calcium receptor mutations, and idiopathic. The 1,25-dihydroxyvitamin D arm was also administered combined calcium (1.2 g/d) and cholecalciferol (800 IU/d) supplementation divided into four daily doses. The dose of PTH or 1,25-dihydroxyvitamin D was adjusted by the investigators to maintain serum calcium within or just below the normal range; a mean±SD dose of PTH(1-34) of 0.6±0.5 μg/kg (approximately 27 μg/dose) and 1,25-dihydroxyvitamin D dose of 0.009±0.004 μg/kg (approximately 0.3 μg/dose) were required. Mean serum calcium levels showed no differences between treatments. At study conclusion, mean urinary calcium excretion remained within the upper half of the normal range and mean serum phosphorus remained above the normal range without significant between-group differences. BMC and BMD Z-scores increased in both groups, as expected for growing children. Neither BMC nor BMD differed across time or between treatment groups at the lumbar spine, femoral neck, total femur, or whole body, although there was a significant downward trend 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.

A 24-week, open-label crossover trial of pulsatile PTH(1-34) delivery *via* pump *vs* sc injection investigated a different mode of administration (23). Eight subjects with post-surgical hypoparathyroidism were studied, aged 36-54 yr. PTH(1-34) was delivered either sc or *via* an Omnipod insulin pump adapted for PTH delivery with seven basal rates [2, 3, 4, 5, 6, 7, or 8 micropulses per hour, with each pulse delivering 0.1 μg PTH(1-34) (daily dose range 4.8-19.2 μg/day)]. There was less fluctuation in serum calcium with the pump *vs*

twice-daily delivery of PTH(1-34), despite a 65% reduction in the PTH dose (13±4 *vs* 37±14 μg/d; $p<0.001$). Pump therapy resulted in a 59% reduction in urine calcium compared to injection. The marked reduction in urinary calcium excretion with pump therapy might be explained by the need for the renal tubules to be constantly exposed to PTH in order for its calcium conserving actions to be seen. Bone turnover markers normalized, and were consistently lower, during pump *vs* twice-daily delivery. The investigators noted no significant difference in the incidence of adverse events between the two groups. At study conclusion, seven of eight patients preferred pump to twice-daily delivery.

Gafni et al. studied 5 subjects with hypoparathyroidism, aged 15 to 49 yr (3 adolescents and 2 adults), in an open-label study of PTH(1-34) administered over 18 months (24). The etiologies of hypoparathyroidism were post-surgical, sporadic calcium receptor mutation, idiopathic, and DiGeorge syndrome. The dose of PTH was adjusted by the investigators to maintain serum calcium within or just below the normal range; a mean±SD dose of PTH(1-34) of 0.57±0.24 μg/kg/d was required. Subjects were treated with twice daily (no.=4) or thrice daily (no.=1) injections. There were no significant changes from baseline in serum calcium, 24-h urine calcium, or phosphorus. Bone turnover markers were suppressed at baseline with the exception of an adolescent male in a pubertal growth spurt, and consequently increased up to 6-fold above baseline with PTH therapy, with the majority of the markers peaking by 12 months. Consistent with the bone turnover markers, double-labeled iliac crest bone biopsies before and after 12 months of treatment demonstrated increased cancellous bone volume, trabecular number, and osteoid associated with a decrease in trabecular separation. An increase in bone volume was reflected as an increase in trabecular number, formed *via* intratrabecular tunneling. Cortical porosity was also increased without an increase in cortical thickness. Despite these significant changes in bone turnover and volume, BMD Z-scores increased significantly only at the total hip (0.66±0.8 to 1.2±1.2; $p<0.05$), but not at the lumbar spine or femoral neck. Total-body BMD initially decreased initially and subsequently stabilized, whereas Z-scores gradually declined in the distal radius (0.06±1.51 to −0.58±1.39; $p<0.05$).

Studies of PTH(1-84)

PTH(1-84) has been studied in adults in two 24 week double-blind placebo-controlled studies as well as a longer term open-label study with data now through 4 yr of treatment. Sikjaer et al. published the results of a randomized, double-blind investigation of PTH(1-84) 100 μg daily *vs* placebo over 24 weeks in 62 subjects (15). The majority of patients were women with post-surgical hypoparathyroidism, aged 25-80 yr. PTH(1-84) therapy reduced calcium and active vitamin D requirements by 75% and 73%, respectively, with 15 subjects able to discontinue calcium supplementation entirely (47%). Calcium and active vitamin D 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. Urinary calcium initially increased from weeks 2-8 of PTH, with no significant between-group differences from week 12 until study conclusion. PTH significantly decreased serum phosphate. Treatment with PTH(1-84) significantly increased bone turnover markers by 4 weeks of treatment, up to 13-fold above baseline, whereas there were small but significant decreases

in BMD of the lumbar spine (−1.76±1.0%), hip (−1.59±0.6%), and total body (−1.26±0.5%), but not the forearm. There was an increased incidence of nausea in subjects taking PTH(1-84) *vs* placebo.

As part of the study by Sikjaer et al., 31 patients underwent central quantitative computed tomography of the spine and hip at baseline and week 24 (17 on PTH treatment) (26). At the lumbar spine, despite the small decrease in areal BMD described above, volumetric BMD (vBMD) increased by 12.8% (p=0.02) in the PTH arm compared with the placebo group. In contrast, the hip region showed decreased vBMD at the total hip (−2.3%; p<0.05) and trochanteric region (−3.7%; p=0.03). Also at the hip, trabecular vBMD tended to increase and cortical vBMD tended to decrease in the PTH group compared to placebo, although these changes were statistically significant only for the intertrochanteric region. In addition, 44 subjects underwent iliac crest bone biopsies analyzed with micro-computed tomography (23 on PTH treatment). At trabecular bone, PTH decreased trabecular thickness and trabecular bone tissue density, while increasing the connectivity density and bone surface to volume ratio. Trabecular tunneling was evident in 11 (48%) of the biopsies from the PTH group and none of the placebo-treated subjects. Patients with tunneling had 2- to 5-fold higher levels of biochemical markers of bone resorption and formation (p<0.05). At cortical bone, the number of Haversian canals per area and Haversian canal separation were greater in the PTH group, resulting in a tendency toward an increased cortical porosity.

Recently, Bilezikian et al. reported the results of a double-blind study of 134 subjects randomized 2:1 to PTH(1-84) (no.=90) or placebo (no.=44) for 24 weeks (29). Subjects receiving PTH(1-84) were started at a 50 μg daily dose, which was increased to 75 or 100 μg if oral calcium and active vitamin D doses were sufficiently high to allow for reduction. A “responder” was defined as a subject able to reduce their supplementation of both calcium and active vitamin D by at least 50% by week 24 while maintaining a serum calcium level of greater than or equal to baseline. At the end of treatment, 48/90 (53.3%) subjects in the PTH(1-84) group and 1/44 (2.3%) in the placebo group were responders (p<0.001). The mean dose of oral calcium supplementation increased from baseline by 5.7% in the placebo group but decreased by 52.0% in the PTH(1-84) group (p<0.001). Active vitamin D supplementation was reduced by 30.5% in the placebo group and 78.4% in the PTH(1-84) group (p<0.001). At study conclusion, 37 (41.1%) subjects in the PTH(1-84) group and 1 (2.3%) in the placebo group achieved independence from active vitamin D and could be maintained on an oral calcium dose of ≤0.5 g/d. Preliminary analysis suggested an improved ratio of urinary calcium excretion to serum calcium level. Serum bone turnover markers increased by 8 weeks, reaching up to 10-fold above baseline at 24 weeks. There were significant declines in BMD in the hip region in the PTH(1-84) group (−2.8% at the femoral neck and −2.4% at the total hip compared to placebo; p<0.001); although no significant differences at the lumbar spine or distal radius (28). Treatment with PTH(1-84) was generally well tolerated (27).

Rubin et al. published a study of 30 subjects treated with open-label PTH(1-84) 100 μg every other day for 2 yr (33). The subjects were aged 25-68 yr and the major etiologies of hypoparathyroidism were post-operative and autoimmune. PTH(1-84) reduced calcium and active vitamin D requirements by 45% and 41%, respectively, with 7 subjects able to stop all

active vitamin D supplementation ($p<0.05$). Serum calcium levels remained stable despite the decrease in supplementation requirements, and hypercalcemia was rare. Mean urinary calcium was unchanged at 24 months. Serum phosphate was decreased. While BMD increased at the lumbar spine by 2.9±4% from baseline ($p<0.05$), femoral neck BMD remained unchanged, and distal one-third radial BMD decreased by 2.4±4% ($p<0.05$).

A histomorphometric analysis of this cohort was published by Rubin et al. including 64 subjects with hypoparathyroidism treated with PTH(1-84) 100 μg every other day for 2 yr (14). Forty-eight subjects underwent percutaneous iliac crest bone biopsies either at baseline and at 1 or 2 yr or a single biopsy at 3 months with a quadruple-label protocol, receiving tetracycline before initiation of PTH(1-84) treatment and prior to biopsy. Serum bone turnover markers were also measured. Changes in structural parameters noted after 2 yr of PTH(1-84) therapy included reduced trabecular width and increased trabecular number and cortical porosity, consistent with an increased remodeling rate in both trabecular and cortical compartments. Dynamic parameters, including mineralizing surface, mineral apposition rate, and bone-formation rate, increased significantly at 3 months, peaking at 1 yr and persisting at 2 yr. Serum bone turnover markers increased significantly, peaking at 5 to 9 months of therapy. They declined thereafter but still were greater than baseline values after 2 yr.

The prospective trial described above was extended, and the 4-year results of 27 subjects, many from the above cohort, was recently published (30). Treatment with PTH(1-84) reduced supplemental calcium requirements by 37% ($p=0.006$) and active vitamin D requirements by 45% ($p=0.008$) from baseline to 4 yr, with 7 subjects (26%) able to stop active vitamin D completely. Serum calcium concentration remained stable despite the decrease in supplement requirements. Hypercalcemia was uncommon (11 episodes in eight subjects over 4 yr; 1.9% of all values), with most episodes occurring within the first 6 months and resolving with adjustment of supplemental calcium and vitamin D. Urinary calcium excretion was significantly decreased over the course of 4 yr ($p=0.003$) and fell significantly below baseline during years 1, 2, and 3. While urinary calcium excretion at year 4 was still below pre-treatment values, the difference did not achieve statistical significance. The trend for serum phosphorus was a significant decline over the course of the study. Lumbar spine BMD increased by 5.5±9% at 4 yr ($p<0.0001$). Femoral neck and total hip BMD remained stable. At 4 yr, distal radius BMD was not different from baseline. Bone turnover markers increased significantly, reaching a 3-fold peak from baseline values at 6-12 months ($p<0.05$ for all), subsequently declining to steady-state levels at 30 months. Treatment with PTH(1-84) was generally well tolerated.

There are two recent reports of quality of life with PTH(1-84) therapy. A study of 54 subjects with hypoparathyroidism treated with open-label PTH(1-84) every other day for 1 yr showed improvement in various quality of life measures, particularly those relating to mental health (8). Sikjaer et al. did not find a benefit to PTH therapy in their trial (9). However, subjects in their study experienced large fluctuations in serum calcium, which may have deranged any potential advantage.

SAFETY

The safety of PTH has recently been reviewed with specific reference to reports of osteosarcoma in rats when administered 3-60-times the equivalent dose to human subjects for 75 yr of human equivalent time (34, 35). The 10-yr history of PTH as a treatment for osteoporosis does not provide any evidence that osteosarcoma is a risk when PTH(1-34) or PTH(1-84) is used for the treatment of osteoporosis for the approved 2-yr therapy course (36, 37). In hypoparathyroidism, we have data from relatively large cohorts of subjects treated with PTH(1-34) for 3 yr (20) and PTH(1-84) for 4 yr (30). There are case reports of use of PTH(1-34) in hypoparathyroidism for longer periods of time (38), up through 14 yr in a 20 yr-old female treated with continuous PTH(1-34) since 6 yr of age (39). In this patient, PTH therapy increased bone mass without negatively impacting mineralization and without the development of fracture or osteosarcoma. While serum calcium was adequately controlled and there was a reduction in hypercalcemic episodes, hypercalciuria persisted, and the patient developed nephrocalcinosis.

FUTURE DIRECTIONS

The results described above are promising. In hypoparathyroidism, replacement therapy with PTH reduces the need for large doses of supplemental calcium and active vitamin D. Other delivery systems of PTH and PTH analogs that may be more acceptable to patients are being studied in osteoporosis (40, 41) and may be applied to a hypoparathyroid population in the future. A comparison of PTH(1-34) *vs* PTH(1-84), particularly with respect to bone parameters, would be of interest. Further data regarding quality of life and neurocognitive testing following PTH replacement is necessary. Since therapy with PTH may well become a long-term management option in hypoparathyroidism, longer term safety data are needed. Further data in children with developing skeletons are also necessary.

SUMMARY

In hypoparathyroidism, both PTH(1-34) and PTH(1-84) lower supplemental calcium and vitamin D requirements while maintaining serum calcium, and decreasing serum phosphorus and urinary calcium excretion. Densitometric and histomorphometric studies in some subjects treated with PTH(1-34) and PTH(1-84) demonstrate that the skeletal dynamics return toward normal euparathyroid levels. So far, the cumulative experience with PTH treatment in hypoparathyroidism is encouraging. It may well become an established replacement therapy for hypoparathyroidism.

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Table 1

Summary of the major trials investigating PTH(1-34) therapy in hypoparathyroidism.

Trial	Study population	Design and intervention	Results: Urine calcium	Results: Bone turnover markers	Results: Bone density
Winer et al. (18)	10 subjects aged 18-70 yr	Randomized open-label crossover trial of daily PTH(1-34) SC (0.5-3 μg/kg/d) vs calcium and active vitamin D over 20 weeks	Mean urinary calcium excretion was decreased to within thenormal range for the PTH(1-34) arm and significantly lower at 2 and 10 weeks of therapy than the calcium and active vitamin D arm	Serum markers increased significantly at 10 weeks of treatment; urine markers increased but the difference was not statistically significant	N/A
Winer et al. (20)	27 subjects aged 18-70 yr	Randomized open-label trial of twice-daily PTH(1-34) SC (mean 37±2.6 μg) vs calciumand active vitamin D over 3 yr	No significant between-group differences; mean urinary calcium excretion was within the normal range from years 1-3 in subjects treated with PTH(1-34), but remained above normal in the active vitamin D group	Serum and urine bone turnover markers increased significantly by 2- to 3-fold in the PTH(1-34)-treated group, peaking at 2.5 yr of treatment	No significant between-group differences; the PTH-treated group maintained stable BMD and BMC at all sites, in contrast to the active vitamin D group which demonstrated a gradual rise in BMC and BMD
Winer et al. (22)	12 children aged 5-14 yr	Randomized open-label trial of twice-daily PTH(1-34) SC (mean 27 pg/dose) vs calcium and active vitamin D over 3 yr	No difference between treatments	Increased significantly in the PTH(1-34) arm at 1 year, some up to 1.5-2.5 yr	BMC and BMD increased in both groups (as expected for growing children) without between-group differences other than a significant downward trend over time in the PTH(1-34) group at the distal radius
Winer et al. (23)	10 subjects aged 36-54 yr, all postsurgical	Open-label crossover trial of pulsatile PTH(1-34) administered via pump vs SC over 24 weeks	Statistically significant 59% reduction in urine calcium inthe pump *vs* SC arm	All markers increased with PTH(1-34) regardless of mode of delivery; urine markers significantly lower during pump therapy *vs* SC	N/A
Gafni et al. (24)	5 subjects aged 15-49 yr	Open-label cohort study of PTH(1-34) SC twice or thrice daily for 18 months	Unchanged	Increased up to 6-fold above baseline with PTH therapy, with the majority of the markers peaking by 12 months	Z-scores significantly increased at the total hip (0.66±0.8 to 1.2±1.2), and gradually declined in the distal radius (0.06±1.51 to −0.58±1.39), while total-body BMD decreased initially and subsequently stabilized; no change at the lumbar spine or femoral neck

BMD: bone mineral density; BMC: bone mineral content. Studies included patients with post-surgical and intrinsic etiologies of hypoparathyroidism unless otherwise indicated. Serum calcium values were kept within normal or the low end of the normal range despite maintaining subjects off calcium and vitamin D supplementation by study design. Dose-finding studies of once daily *vs* twice daily PTH(1-34) (19, 21) are not included.

Table 2

Summary of the major trials investigating PTH(1-84) therapy in hypoparathyroidism.

Trial	Study population	Design and Intervention	Results: Calcium and active vitamin D supplement use	Results: Urine calcium	Results: Bone turnover markers	Results: Bone density
Sikjaer et al. (15)	62 subjects aged 25-80 yr	Randomized, double-blind trial of PTH(1-84) 100 μg daily *vs* calcium and active vitamin D over 24 weeks	PTH(1-84) reduced calcium and active vitamin D requirements by 75% ana 73%,respectively	Initial increase in urinary calcium from weeks 2-8 of PTH(1-84), with no significant difference from week 12 until study conclusion	Significant increase by 4 weeks of treatment, reaching up to 13-fold above baseline at 24 weeks	Small but significant decreases at the lumbar spine (−1.76±1.0%) and hip (−1.59±0.6%); no difference at the forearm
Bilezikian et al. (29, 28)	134 subjects	Randomized, double-blind trial of PTH(1-84) 50 μg daily *vs* calcium and active vitamin D over 24 weeks; patients could be increased to 75 or 100 μg daily as needed	PTH(1-84) reduced calcium and active vitamin D requirements by 52% and 78%, respectively	Preliminary analysis suggested an improved ratio of urinary calcium excretion to serum calcium level	Significant increase by 8 weeks of treatment, reaching up to 10-fold above baseline at 24 weeks	Significant declines in the hip region in the PTH(1-84) group (−2.8% at the femoral neck and −2.4% at the total hip compared to placebo; $p<0.001$); no significant differences at the lumbar spine or distal radius
Rubin et al. (25)	30 subjects aged 25-68 yr	Open-label trial of PTH(1-84) 100 μg every other day over 2 yr	PTH(1-84) reduced calcium and active vitamin D requirements by 45% and 41%, respectively	Unchanged	N/A	Significantly increased at the lumbar spine by 2.9±4% from baseline and decreased by 2.4±4% at the distal radius; no change at hip sites
Cusano et al. (30)[a]	27 subjects aged 25-68 yr	Open-label trial of PTH(1-84) 100 μg every other day over 4 yr	PTH(1-84) reduced calcium and active vitamin D requirements by 37% and 45%, respectively	Significantly below baseline during years 1, 2, and 3; below pre-treatment values during year 4 but the difference did not achieve statistical significance	Increased significantly, reaching a 3-fold peak from baseline values at 6-12 months, subsequently declining to steady-state levels at 30 months	Significantly increased at the lumbar spine by 5.5±9%; all other sites unchanged

BMD: bone mineral density. Studies included patients with post-surgical and intrinsic etiologies of hypoparathyroidism. All studies maintained serum calcium values within normal or the low end of the normal range in the setting of a reduction in supplement requirements.

[a]Included some subjects from the report of Rubin et al.