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REVIEW

Hypoparathyroidism and treatment with recombinant human PTH

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ABSTRACT

Introduction: Hypoparathyroidism is a rare endocrine disease, most frequently due to surgical damage to the parathyroids. Hypocalcemia, caused by this disease, can affect the function of most organs, but in particular neurological, cognitive, muscular, and cardiac functions. The long term consequences of hypoparathyroidism can include ectopic calcifications, renal complications and impaired quality of life. At last, in hypoparathyroidism higher bone mineral density and lower bone turnover markers are described, and these factors could have an impact on the risk of fracture, but still it is unclear.

Areas covered: This disease is usually treated with calcium, calcitriol, or an active vitamin D analog. Although the standard therapy can adequately control patients, sometimes very high doses are required to maintain serum calcium levels in the normal range, with poor compliance and risk of long term complications. This article analyzes the recent therapeutic approach with the use of recombinant human PTH (rhPTH), through a systematic review of English articles regarding the use of rhPTH (1–84) and (1–34).

Expert opinion: The possibility of having a therapeutic alternative, such as the rhPTH could represent a great opportunity. However, further studies are necessary to clarify several aspects especially regarding long term effects of rhPTH.

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1. Introduction

Hypoparathyroidism is a rare metabolic disease caused either by deficient or absent production of the parathyroid hormone (PTH) by the parathyroid glands or by resistance to PTH in its target tissues, called pseudohypoparathyroidism [1]. The most common form of hypoparathyroidism is postsurgical hypoparathyroidism, followed by autoimmune, genetic, infiltrative, or irradiative causes. Hypoparathyroidism is one of the few endocrine diseases characterized by hyposecretion, whose treatment, except in the United States, does not consist of administration of the defective hormone. The conventional treatment consists of supplementations with calcium and calcitriol or other active vitamin D analogs, and although many patients are adequately controlled, sometimes high doses are necessary to control serum calcium concentration [1]. Large doses of these supplements can cause long-term complications, such as renal impairment and extraskeletal calcifications [2]. Moreover, conventional therapy with calcium and active vitamin D has not proved to be capable to reverse abnormalities in bone remodeling, typical of the disease, not providing a physiological replacement remedy for the lack of PTH in hypoparathyroidism. At last, many patients with chronic hypoparathyroidism report symptoms that suggest impaired quality of life [3], and current standard treatment in hypoparathyroidism has not been demonstrated to be capable to restore well-being in these patients [4].

Recently, several studies have investigated hormone replacement therapy with recombinant human PTH (rhPTH) (1–84) and with the N-terminal PTH fragment (rhPTH (1–34)) administered by subcutaneous injection in hypoparathyroid patients, not adequately controlled with conventional therapy. In January 2015, the Food and Drug Administration (FDA) approved, only in the USA, the use of rhPTH (1–84) for the management of chronic hypoparathyroidism, not adequately controlled with standard treatment, with a 'black box' warning because of the potential risk of osteosarcoma, but without limit of the duration of use [5,6].

The main clinical features of chronic hypoparathyroidism are analyzed, in the following sections, in order to highlight the issues that chronic treatment of this disease should face, and subsequently, a systematic review of English articles, regarding the use of rhPTH (1–84) and (1–34) in hypoparathyroid patients, is conducted.

1.1. Hypocalcemia

Physiologically, PTH is secreted by the parathyroid glands as an 84-amino acid peptide, and serum calcium is the major regulatory signal for secretion of PTH. Serum calcium concentration has a very important role for several physiological processes, and small deviations of serum calcium levels impair a variety of cellular functions. Its concentration, indeed, is normally maintained within a very narrow range [7]. Low

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Article highlights

- Hypoparathyroidism is an endocrine disease characterized by hypocalcemia and hyperphosphatemia in presence of undetectable or inappropriately low levels of parathyroid hormone (PTH).
- Conventional treatment of chronic hypoparathyroidism consists mainly of calcium supplements and calcitriol, whose chronic use at high dose can lead to long-term complications, particularly renal impairment and ectopic calcifications.
- Several studies have recently investigated hormone replacement therapy with rhPTH (1-34) and rhPTH (1-84), as treatment for patients with chronic hypoparathyroidism not adequately controlled with standard treatment.
- Some studies demonstrated that injections twice-a-day of rhPTH (1-34) showed a good control of mean serum calcium levels, a reduction in the need for calcium and active vitamin D supplements, but did not obtain a significant reduction in 24-hour urinary calcium excretion compared to standard therapy. Moreover, the studies with rhPTH (1-34) therapy delivered by an infusion pump showed, instead, a near normalization of the diurnal rhythm of serum calcium, and a significant reduction of 24-hour urinary calcium excretion, compared with twice-a-day injections subcutaneous of rhPTH (1-34).
- rhPTH (1-84) provides the natural hormone, lacking in this disorder, and has an effective half-life longer than rhPTH (1-34). The studies showed that this drug permits a reduction in the need for calcium and active vitamin D supplements, maintaining normal mean serum calcium levels compared to conventional therapy, a reduction in 24-hour urinary calcium excretion at 24 weeks compared to baseline ('REPLACE' trial), and showed significant transient reductions of 24-hour urinary calcium excretion in long term study (6 years) compared to baseline.
- Several future investigations are necessary regarding evaluation of long-term efficacy and safety of rhPTH treatment.

This box summarizes key points contained in the article.

extracellular ionized calcium level causes typical signs and symptoms involving a large number of tissues and organ systems, such as brain, muscles, and heart [8]. Signs and symptoms of hypocalcemia in hypoparathyroidism are summarized in Table 1 [1,3,9]. In addition to hypocalcemia, hyperphosphatemia is another consequence of hypoparathyroidism. High phosphate levels are asymptomatic but can cause long term complications such as ectopic mineralization in soft tissues of the vascular, nervous, renal, and other organs, impairing their function [2,7]. These ectopic calcifications can be caused by the chronically elevated phosphate concentrations and high calcium–phosphate product, due to the disease itself and long-term treatments with calcium and calcitriol or other active vitamin D analogs [2,3].

Table 1. Clinical manifestations of hypocalcemia in patients affected by hypoparathyroidism.

Organ/system target	Clinical manifestations
Neuromuscular	Fatigue, muscle weakness, muscle cramping (carpopedal spasms), neuromuscular irritability, tetany, spams/twitches, cramps, laryngospasm, stridor, bronchospasm and wheezing, and Trousseau and Chvostek signs.
Neurological, psychiatric	Paresthesia and numbness (especially around mouth, fingers, and toes), seizures, poor memory and concentration, confusion or disorientation, irritability, depression, and anxiety.
Cardiovascular	Congestive heart failure, arrhythmias, fast, slow, or uneven heart rate, heart block, and ECG: prolonged QTc interval.
Bone	Fragility fractures
Gastrointestinal	Constipation, abdominal cramps, and steatorrhea.
Respiratory	Shortness of breath, wheezing, and throat tightness.
Ophthalmologic	Papilledema, posterior subcapsular cataract, and corneal calcifications.
Dental	Hypoplastic teeth, enamel hypoplasia, delayed tooth eruption, shortened premolar roots, and increased dental caries.
Dermatologic	Alopecia, dry skin, atopic eczema, and brittle nails.

1.2. Bone manifestations in chronic hypoparathyroidism

One of the key regulators of the rate of bone remodeling is PTH, and a reduction or absence of this hormone leads to a decrease in bone resorption and then to a coupled reduction in bone formation. Over time, the balance between resorption and formation favors the latter because bone mass increases in both cancellous and cortical bone compartments [1]. Indeed, bone mineral density (BMD), measured by dual-energy x-ray absorptiometry (DXA), is usually above average in these patients [10–13]. Studies performed with imaging with peripheral quantitative computed tomography (pQCT) and high-resolution pQCT, as well as direct histomorphometric analysis of bone by transiliac bone biopsy, showed that both cortical and trabecular bone are impaired. Increased cortical volumetric BMD (vBMD), decreased cortical porosity, and trabecular bone volume fraction associated to low bone turnover were described [14–16]. Higher BMD in hypoparathyroidism is due in large part to the increase in bone tissue volume rather than an increase in the amount of mineral within the tissue [10,17].

The abnormally low bone remodeling and dense bone could suggest that hypoparathyroid bone is hypermature, with an impaired bone quality, and potentially more subject to fracture than euparathyroid bone [2,18]. In this regard, some studies evaluated the fracture risk in these patients, but there are conflicting results. Recently, Underbjerg et al. conducted a nationwide Danish survey, identifying 688 patients with postsurgical hypoparathyroidism due to nonmalignant causes, treated with standard treatment (calcium and vitamin D metabolites) for more than 6 months. Each case was matched for age and sex with three controls from the general population. The long-term overall fracture risk was not different from controls, whereas the risk of fractures in the upper extremities was significantly decreased in patients with chronic hypoparathyroidism [19]. In another Danish study, Underbjerg et al. identified 180 subjects diagnosed with nonsurgical hypoparathyroidism between 1997 and 2012. Patients were compared with an age- and gender-matched control group from the general population. Although the overall fracture risk was similar between cases and controls, patients with chronic hypoparathyroidism had a greater risk of fractures in the upper extremities [20]. Therefore, further data on bone strength and the risk of fractures are sorely needed, considering that the long-term effects of increased bone mass could be beneficial, but low bone turnover could be possibly deleterious to bone quality [3].

1.3. Renal complications in chronic hypoparathyroidism

Decreased PTH secretion or action on tubular functions should cause hypercalciuria and reduced urinary phosphate excretion, but this is not generally described in chronic hypoparathyroidism because the filtered load of

calcium is usually lower than normal, and hyperphosphatemia leads to a greater filtered load of phosphate [2]. However, large amounts of calcium and calcitriol, or other active vitamin D analogs, required for maintaining normal serum calcium levels, can cause hypercalciuria and long-term complications such as renal calcium deposition (stones or calcinosis) and renal function impairment [7,18], especially in those with episodes of treatment-induced hypercalcemia [21].

1.4. Impairment of quality of life in hypoparathyroidism

Many patients affected by chronic hypoparathyroidism describe symptoms that suggest impaired quality of life [1,2]. The symptoms include physical complaints such as fatigue, muscle spasms, pain, and paresthesia; cognitive symptoms such as 'brain fog' and inability to concentrate; and emotional difficulties including depression and/or anxiety [7,18]. Some studies showed that quality of life was lower than expected norms independently by the etiology of the hypoparathyroidism, the duration of disease, or the extent to which biochemical control is achieved with calcium and active vitamin D [4,17]. It is clear that chronic hypoparathyroidism can be associated with impaired quality of life, but the nature of this impairment and its relationship to biochemical control are not well characterized.

Table 2 summarizes the main complications/comorbidities of chronic hypoparathyroidism in adults.

2. Materials and methods

A systematic review of English articles, regarding the use of rhPTH (1–84) and (1–34) in patients affected by chronic hypoparathyroidism, using MEDLINE (1996–2016) was conducted. Search terms included hypoparathyroidism, therapy, parathyroid hormone, rhPTH (1–84), PTH (1–84), rhPTH (1–34), and PTH (1–34). Randomized, open-label crossover trials; double-blind (or not), randomized open-label studies; and open-label studies, conducted in subjects affected by chronic hypoparathyroidism, treated with rhPTH, were included. All included studies had to quantitatively report the outcomes of interest, such as effects of rhPTH on bone metabolism, and/or BMD, and/or bone quality, and/or quality of life. Retrospective studies, letters, comments, editorials, case report, review, expert opinion, and personal communications were excluded. The following data were extracted from studies that met the inclusion criteria: study design, number of participants in each group, participants' age, intervention, and outcomes (serum and urine calcium, serum phosphorous, and bone markers levels; BMD; calcium and calcitriol doses; and/or evaluation of quality of life).

Due to heterogeneity in study design, different blinding methods, and variable control arms, a meta-analysis was not possible to compare the advantage of rhPTH over standard treatment (vitamin D and calcium).

3. Results

Studies selected and analyzed were 23, including 9 studies regarding rhPTH (1–34) treatment and 14 studies regarding rhPTH (1–84) in patients affected by chronic hypoparathyroidism. Studies on rhPTH (1–34) therapy included: one pivotal, randomized crossover trial [22]; six randomized, two-arm, open-label crossover studies [23–28]; and two open-label studies [29,30]. Studies on rhPTH (1–84) therapy, instead, included: one open-label, single-dose phase I study [31]; four double-blind, randomized placebo-controlled studies [12,32–34]; three randomized open-label study [35–37]; and six open-label studies [10,13,38–41]. There were no studies comparing the effects of rhPTH (1–34) and rhPTH (1–84). Moreover, the administration way was different; rhPTH (1–84) was administered as a single dose, whereas rhPTH (1–34) was administered in variable dosing regimens, such as once- or twice-daily or through pump delivery. Due to the different study designs, the results are not directly comparable.

Figure 1 shows flowchart for study selection.

3.1. Hormone replacement therapy with rhPTH (1–34) for chronic hypoparathyroidism

rhPTH (1–34) has an identical sequence to the 34 N-terminal amino acids, the biologically active region, of the human PTH [42]. rhPTH (1–34) affects calcium and phosphate metabolism in a pattern consistent with the known actions of endogenous PTH. When rhPTH (1–34) 20 µg is administered once daily, the serum calcium concentration increases transiently, beginning approximately 2 h after dosing and reaching a maximum concentration

Table 2. Complications/comorbidities of chronic hypoparathyroidism in adults.

Organ/system target	Principal mechanisms involved	Clinical manifestations/instrumental alterations
Renal	Extraskeletal calcifications related to elevated calcium–phosphate product and hypercalciuria	Renal stones, renal calcifications, and impaired renal function
Bone	Reduction in bone remodeling due to lack of PTH	Increased bone mineral density measured by DEXA
Cardiovascular	Calcium salt precipitation in vascular tissues	Ischemic heart disease[a]
CNS	Extraskeletal calcifications related to elevated calcium–phosphate product	Movement disorders, chorea, and parkinsonism
Neuropsychiatric	Lack of PTH/disturbances in calcium–phosphate homeostasis	Depression, bipolar disorders, and anxiety
Eyes	Extraskeletal calcifications related to elevated calcium–phosphate product	Cataracts[a]
Immunological	Hypocalcemia can reduce activation of second messengers in neutrophils	Infections
Musculoskeletal	Disturbances in calcium–phosphate homeostasis	Muscle weakness, pain/aches in muscles and bones, and upper extremities fractures[a]

PTH: parathormone; DEXA: dual energy x-ray absorptiometry; CNS: central nervous system.
[a]Observed in nonsurgical hypoparathyroidism.

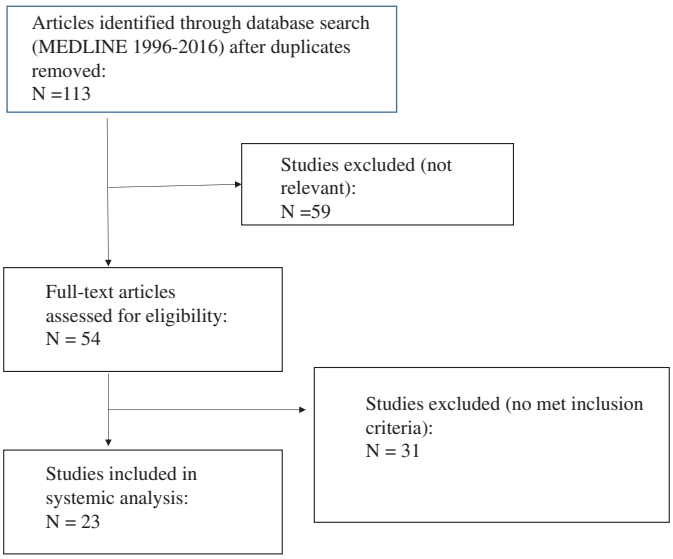

Figure 1. Flow chart for study selection.

between 4 and 6 h. The serum calcium concentration begins to decline approximately 6 h after dosing and returns to baseline by 16–24 h after each dose. The absolute bioavailability of rhPTH (1–34) is approximately 95% based on pooled data from 20, 40, and 80 µg doses. The half-life of rhPTH (1–34) in serum is about 1 h. Systemic clearance of rhPTH (1–34) exceeds the rate of normal liver plasma flow, consistent with both hepatic and extrahepatic clearance. Peripheral metabolism of PTH occurs by nonspecific enzymatic mechanisms in the liver followed by excretion via the kidneys [42].

Varying dose regimens of rhPTH (1–34) have been analyzed for the treatment of chronic hypoparathyroidism, including once-daily and twice-daily subcutaneous injections and administration pump delivery system in adults and children. The studies conducted with rhPTH (1–34) described effects including on bone metabolism, BMD, bone architecture, and quality of life.

3.1.1. Studies with rhPTH (1–34) and effects on biochemical exams, BMD, and bone tissue

The first study on effects of rhPTH (1–34) on chronic hypoparathyroidism was a pivotal randomized crossover trial lasting 20 weeks. This study showed that once-daily injection with rhPTH (1–34) maintained serum calcium in the normal range with decreased urine calcium excretion compared with calcium and calcitriol treatment in 10 adult subjects. Markers of bone turnover levels increased significantly during treatment with rhPTH (1–34) [22].

Subsequently, a 28-week, randomized crossover trial comparing once-daily and twice-daily rhPTH (1–34) regimens was conducted in 17 adult patients affected by hypoparathyroidism.

During the second half of the day, twice-daily injections of rhPTH (1–34) increased serum calcium more effectively compared with once-daily rhPTH (1–34). The total daily rhPTH (1–34) dose was markedly reduced with the twice-daily regimen and reduces the variation in serum calcium levels [23]. These results were then reconfirmed in the randomized crossover trial lasting 28 weeks, which compared two dose regimens, once daily versus twice-daily rhPTH (1–34), conducted in 14 children with chronic hypoparathyroidism [25].

After these short term trials, Winer et al. conducted two 3-year, randomized open-label studies to establish the long-term efficacy of twice-daily PTH compared with conventional treatment in 27 adults and 12 children with hypoparathyroidism [24,26]. In adults, 27 patients with hypoparathyroidism were randomized to either twice daily subcutaneously rhPTH (1–34) or oral conventional therapy with calcitriol and calcium. Serum calcium concentrations were similar in both treatment groups, and mean urinary calcium excretion was within the normal range in rhPTH (1–34)-treated patients, but remained above normal in the group treated with conventional treatment. Serum and urine bone turnover markers increased significantly in rhPTH (1–34) group and peaked at 2–2.5 years. Over the 3-year study period, bone mineral content and BMD did not show significant between-group differences. There was no significant difference in the incidence of adverse events [24]. Subsequently, a 3-year randomized parallel trial comparing twice-daily calcitriol plus calcium and cholecalciferol in four daily doses versus twice-daily subcutaneous injections rhPTH (1–34) treatment was conducted in 12 children with chronic hypoparathyroidism. In children, mean pre-dose serum calcium levels were maintained at, or just below, the normal range, and urine calcium levels remained in the normal range, with no significant differences between treatment groups. Markers of bone turnover were mildly elevated during rhPTH (1–34) therapy and remained within the normal range during calcitriol therapy. Mean BMD *Z*-scores at the anterior–posterior lumbar spine, femoral neck, distal radius, and whole body remained within the normal range and did not differ between groups throughout the study. Analysis of symptom occurrence at any time during the follow-up showed no significant differences between groups [26].

Gafni et al. treated five subjects (two adults and three adolescents) with chronic hypoparathyroidism with rhPTH (1–34) by injecting two (four patients) to three (one patient) times daily for 18 months, with doses individualized to maintain serum calcium at, or just below, the normal range [29]. Biochemical markers and BMD were assessed every 6 months, and iliac crest biopsies were performed before and after 1 year of treatment. rhPTH (1–34) treatment significantly increased bone markers, and histomorphometry showed that treatment increased cancellous bone volume and trabecular number and decreased trabecular separation. Cortical width remained unchanged; however, rhPTH (1–34) treatment increased cortical porosity. BMD *Z*-scores were unchanged at the spine and femoral neck, and total hip *Z*-scores increased, but total body BMD *Z*-scores decreased during the first 6 months of treatment and then stabilized, remaining significantly decreased compared to baseline. Radial *Z*-scores also decreased with treatment [29].

Recently, rhPTH (1–34) was administered as a continuous infusion by the use of an insulin pump with multi-micropulse release of the peptide. This particular administration of the drug allows to mimic the physiologic PTH secretion, which is about six to seven burst per hour superimposed on an

underlying circadian rhythm [43]. A pump delivery system was compared with twice-daily injections, in order to refine replacement therapy with PTH (1–34) in adults and children [27,28].

The first investigation analyzed eight adult patients with postsurgical hypoparathyroidism, in a 6-month, open-label, randomized crossover trial. The use of pump versus twice-daily delivery of rhPTH (1–34) produced normal and stable calcium concentrations with minimal fluctuation, without the rise in serum and urine calcium levels, evident, instead, soon after rhPTH (1–34) injection. Furthermore, pump delivery normalized bone turnover markers compared with twice-daily injections. Through 6 months of study, no serious adverse events occurred. Mean frequency and severity of hypocalcemic symptoms did not differ significantly between two groups. At the end of study, seven of eight patients preferred pump to twice-daily delivery [27]. Similar results were found in a study conducted on 12 children and young adults, aged 7–20 years, with congenital hypoparathyroidism, randomized to receive rhPTH (1–34), delivered either by twice-daily subcutaneous injection or insulin pump for 13 weeks [28]. In conclusion, the marked reduction in urinary calcium excretion, using rhPTH (1–34) administered by pump, suggests that PTH has to be continuously exposed to the renal tubule in order for the renal calcium-conserving effects to be realized. Pump delivery of rhPTH (1–34) achieved serum calcium, and urine calcium excretion, and normalization of markers of bone turnover. These findings were achieved with a smaller daily rhPTH (1–34) dose compared with the twice daily subcutaneous injections rhPTH (1–34).

3.1.2. Studies with rhPTH (1–34) and effects on quality of life

Recently, a 2-year, prospective open-label study showed a significant improvement in the mean scores of all eight domains of the Rand 36-Item Short Form Health Survey (SF-36) in 42 subjects with post surgical hypoparathyroidism treated with a twice-daily rhPTH (1–34) 20 μg [30]. The main limit of this study was the absence of control group, and such results should be reconfirmed.

3.2. Hormone replacement therapy with rhPTH (1–84) for chronic hypoparathyroidism

rhPTH (1–84) is identical to the full-length human 84-amino acid protein, and it increases serum calcium concentrations in a dose proportional manner. The peak plasma concentration after single subcutaneous injections of rhPTH (1–84) at 50 and 100 μg in subjects affected by hypoparathyroidism occurs within 5–30 min, followed by a second usually smaller peak at 1 to 2 h. PTH levels become undetectable by 12 or 24 h [31]. The apparent terminal half-life is 3.02 and 2.83 h for the 50 and 100 μg dose, respectively. The absolute bioavailability is 53%. Currently, no dose adjustment for rhPTH (1–84) is required for patients with mild-to-moderate renal or hepatic impairment. The recommended starting dose is 50 μg and, based on calcemic response, can be titrated at 2- to 4-week intervals upward to doses of 75 μg and then 100 μg [6].

The studies conducted with rhPTH (1–84) in patients affected by chronic hypoparathyroidism described effects on bone metabolism, BMD, bone architecture, bone fractures, and quality of life.

3.2.1. Studies with rhPTH (1–84) and effects on biochemical exams, BMD, and bone tissue

Rubin et al. investigated, in an open-label study lasting 24 months, the use of the rhPTH (1–84) in a fixed dose of 100 μg every other day by subcutaneous injection in 30 adult subjects with chronic hypoparathyroidism. Requirements for calcium and calcitriol supplements decreased significantly, respectively, by 45% and 41%. Serum calcium levels and 24-h urinary calcium excretion were mostly unchanged at 24 months. BMD increased at the lumbar spine by 2.9 ± 4% from baseline, while femoral neck BMD remained unchanged and distal one third radial BMD decreased by 2.4 ± 4%. Transient, mild hypercalcemia occurred sporadically and not time dependent or dose dependent, although it must be considered that blood sampling was performed 48 h after the last PTH injection, and therefore, there might have been missed a substantial numbers of episodes with hypercalcemia [10].

Sikjaer et al. conducted a randomized double-blind study, in which 62 patients with chronic hypoparathyroidism were treated with rhPTH (1–84) 100 μg daily or similar placebo for 24 weeks as add-on therapy to conventional treatment. Compared with placebo, patients with rhPTH (1–84) reduced their daily dose of calcium and active vitamin D significantly by 75% and 73%, respectively, without developing hypocalcemia. However, hypercalcemia occurred frequently during the downtitration of calcium and active vitamin D. Compared with placebo, rhPTH (1–84) treatment reduced significantly the need for calcium and active vitamin D, whereas plasma calcium and phosphate levels are maintained within the physiologic range. rhPTH (1–84) decreased BMD at the hip, lumbar spine, and whole body but not at the forearm, due, most likely, to the markedly increased bone turnover [12].

Cusano et al. studied the effect of 4 years of rhPTH (1–84) treatment (administered at a starting dose of 100 μg subcutaneous every other day) in 27 adults with chronic hypoparathyroidism [13], through an open-label study without control group. rhPTH (1–84) reduced the dose of calcium and calcitriol supplements, respectively, by 37% and 45%, and seven subjects were able to stop totally calcitriol. Serum calcium levels remained stable, and reductions in urinary calcium excretion were more variable and not constant over time and fell significantly below baseline during years 1, 2, and 3. Lumbar spine BMD increased by 5.5 ± 9% at year 4, and femoral neck and total hip BMD remained stable, whereas at year 4, distal radius BMD was not different from baseline. Bone turnover markers increased significantly from baseline values at 6–12 months, subsequently declining to steady-state levels at 30 months. During the study period, 11 episodes of mild hypercalcemia in eight subjects (1.9% of all values) were described, most were resolved with adjustment of calcium and vitamin D supplements [13].

In a double-blind, placebo-controlled, randomized phase III study, lasting 24 weeks named 'REPLACE,' 134 patients with hypoparathyroidism were randomly assigned to 50 μg/day of rhPTH (1–84) or placebo [32]. The dose of rhPTH (1–84) could

be titrated up from 50 to 75 μg and then to 100 μg. Compliance with injection was excellent for both groups. The 53% of patients treated with rhPTH (1–84), compared with 2% in the placebo group, achieved the 50% or greater reduction from baseline in their daily dose of oral calcium and active vitamin D, maintaining a normal serum calcium concentration. In rhPTH (1–84) group, the mean dose of oral calcium supplement and active vitamin D decreased, respectively, by 52% and 78%, and albumin-corrected serum calcium concentrations increased at the start of treatment, whereas urinary calcium excretion showed a slight decrease. On the other hand, in placebo group, total serum calcium concentrations fell rapidly and remained close to the lower end of the target range, and mean urinary calcium excretion rate also decreased. Mean serum phosphate levels were similar, at the upper limit of normal, in both groups at baseline, but decreased in the group treated with rhPTH (1–84) and remained lower than in the placebo group. The overall incidence of adverse events was similar in both groups, treated with rhPTH (1–84) and placebo group. In the rhPTH (1–84) group, only one serious adverse event, characterized by hypercalcemia, was regarded as treatment related. During the treatment period, hypocalcemia was reported as an adverse event in 23 (26%) patients in the rhPTH (1–84) group (43 events) compared with 9 (21%) patients in the placebo group (9 events) [32].

Subsequently, a 24-week, open-label, flexible-dose extension study of REPLACE, named 'REPEAT,' has been conducted [40]. Patients, who previously completed or enrolled in REPLACE, received rhPTH (1–84), 50 μg/day, escalated to 75 and then to 100 μg/day, if necessary. The primary end point was ≥50% reduction in oral calcium (or ≤500 mg/day) and active vitamin D (or calcitriol ≤0.25 μg/day or alfacalcidol ≤0.50 μg/day), maintaining normal calcium levels. Twenty-four patients were enrolled and completed the study. At study end, 75% of patients achieved the study end point, and 58% eliminated oral calcium and active vitamin D. Urinary calcium, serum phosphate, and calcium–phosphate product decreased by the study end, and mean serum bone turnover markers increased with rhPTH (1–84). During this study, any serious adverse events were described [40].

Two other studies with rhPTH (1–84) have been conducted. RELAY is a short, 8-week, double-blind, multinational randomized trial that tested whether doses as low as 25 μg/day could be efficacious in patients affected by hypoparathyroidism [18,44]. Although some subjects were able to meet the primary end point (oral calcium not more than 500 mg/day and active vitamin D not more than 0.25 μg/day), most patients did not, confirming the results of the REPLACE trial that most patients require an amount of rhPTH (1–84) more than 50 μg/day. The other recent study, called RACE, is an open-label extension of the REPLACE and RELAY trials conducted in the USA [18]. The initial results at 1 year provide confirmatory evidence of the primary end points of the REPLACE trial, carried out for 1 year [18].

Recently, 124 adult patients belonging to the study REPLACE were analyzed to determine the effect of rhPTH (1–84) (50 μg/day, titrated to 75 and then to 100 μg/day, to permit reductions in oral calcium and active vitamin D doses while maintaining serum calcium within 2.0–2.2 mmol/L) on phosphate and vitamin D metabolite levels [33]. Serum phosphate levels decreased rapidly from the upper normal range and remained lower with rhPTH (1–84). At week 24, serum calcium–phosphate product was lower with rhPTH (1–84) versus placebo. After 24 weeks, 1,25(OH)$_2$D$_3$ levels were unchanged in both treatment groups, despite significantly greater reductions in active vitamin D dose in the rhPTH (1–84) group [33].

At last, Rubin et al. has published an interesting prospective open-label study of 33 patients with hypoparathyroidism, treated with rhPTH (1–84) subcutaneous injections, with a starting dose of 100 μg every other day, lasting 6 years, without control group [41]. This study is the longest clinical experience with PTH treatment available so far in the management of hypoparathyroidism. The use of a long-term, continuous therapy with rhPTH (1–84), in this population, described a significant reduction of calcium and calcitriol requirements, maintaining stable and normal serum calcium levels and reducing urinary calcium excretion (urinary calcium excretion fell significantly below pretreatment levels at years 1, 3, and 6). Serum phosphate decreased significantly from baseline at years 4 and 5, but year-6 levels were similar to baseline values. Lumbar spine and total hip BMD increased, whereas femoral neck BMD remained stable and the distal one-third radius decreased. Bone turnover markers increased significantly and subsequently declining but remaining higher than pretreatment values [41]. Histomorphometric studies of bone biopsies, performed after 2 years, showed that trabeculae were thinner and more numerous, and there was an increase in cortical porosity [36]. The salutary effects on microarchitecture and bone size could provide biochemical advantages at cortical bone despite a decrease in BMD. This study has demonstrated, although in a small sample, a good safety regarding the control of calcium homeostasis (12 hypercalcemic events in 9 subjects; 2.5% of all values), without hypercalcemic events requiring hospitalization. The most common serious adverse event was hypocalcemia (five times in three patients), and other adverse events included eight fractures in six patients [41].

Regarding effect of rhPTH (1–84) on bone tissue, Sikjaer et al. assessed effects of rhPTH (1–84) on 3D bone structure [34]. The study involved randomized 62 patients with chronic hypoparathyroidism into 24 weeks of treatment with either rhPTH (1–84) 100 μg/day subcutaneously or similar placebo as an add-on therapy. Micro-computed tomography (μCT) was performed on 44 iliac crest bone biopsies (23 on PTH treatment) obtained after 24 weeks of treatment. Compared with placebo, PTH caused a 27% lower trabecular thickness ($p < 0.01$) and 4% lower trabecular bone tissue density ($p < 0.01$), whereas connectivity density was 34% higher ($p < 0.05$). Trabecular tunneling was evident in 11 (48%) of the biopsies from the PTH group. At cortical bone, the number of Haversian canals per area was 139% higher ($p = 0.01$) in the PTH group, causing a tendency toward an increased cortical porosity ($p = 0.09$). At different subregions of the hip, areal BMD (aBMD) and vBMD, as assessed by DXA and QCT, decreased significantly by 1–4% in the PTH group. However,

at the lumbar spine, aBMD decreased by 1.8% ($p < 0.05$), whereas vBMD increased by 12.8% ($p = 0.02$) in the PTH compared with the placebo group [34].

Recently, an interesting study has been conducted on restoration of the euparathyroid state associated with improvement of bone dynamics both in hypoparathyroidism and in primary hyperparathyroidism [45]. The study investigated changes in BMD and trabecular bone score with restoration of the euparathyroid state by parathyroidectomy in primary hyperparathyroidism or rhPTH (1–84) in hypoparathyroidism. This was a 2-year prospective intervention study in which the authors evaluated aBMD by DXA and trabecular bone score in 52 hypoparathyroid patients treated with rhPTH (1–84) and 27 patients with primary hyperparathyroidism who underwent parathyroidectomy. Treatment with rhPTH (1–84) was associated with significant increases of aBMD in lumbar spine and decreases in distal one-third radius by 18 months in hypoparathyroid patients. At this time point, hypoparathyroid subjects demonstrated a significant increase in trabecular bone score from baseline, while there were no significant changes in trabecular bone score following parathyroidectomy. BMD increases with both administration of PTH in a state of PTH deficiency or removal of PTH in a state of PTH excess, but only hypoparathyroid patients treated with rhPTH (1–84) appeared to have improvements in microarchitectural pattern as assessed by trabecular bone score [45].

At last, recently, Rubin et al. utilized direct 3D microstructural analysis to determine the extent to which bone changes such as reduced trabecular thickness and an increase in trabecular number may be related to bone strength [37]. Iliac crest bone biopsies from 58 hypoparathyroid subjects were analyzed by μCT and by microfinite element analysis. Biopsies were performed at baseline and at 1 or 2 years of rhPTH (1–84). After 1 year of treatment with rhPTH (1–84), force (the maximum load sustained, in the long axis of the biopsies) and Young's modulus (an index of resistance to compressive forces) tended to increase. The 1-year change in cancellous mineralizing surface predicted 1-year changes in μCT variables. The biopsies obtained after 2 years of rhPTH (1–84) showed no change from baseline. The results indicated that rhPTH (1–84) improved skeletal quality in hypoparathyroid early in treatment [37].

3.2.2. Studies with rhPTH (1–84) and effects on quality of life

Cusano et al. tested the improvement in quality of life measures through 5 years with rhPTH (1–84) therapy in 69 hypoparathyroid patients, receiving open-label rhPTH (1–84). Before and during therapy, subjects completed the SF-36. rhPTH (1–84) therapy was associated with improvement in mental and physical health as determined by the SF-36 metric [38], confirming the results obtained in the previous study conducted on 54 hypoparathyroid subjects receiving open-label rhPTH (1–84) for 12 months [39]. However, both studies did not have control group. On the other hand, a placebo-controlled study conducted on 62 patients with chronic hypoparathyroidism [randomized to 6 months of treatment with either rhPTH (1–84) 100 μg/day or placebo, given as add-on therapy to conventional treatment] did not demonstrate improvement in quality of life in rhPTH-treated group, evaluated with SF-36 and WHO-5 Well Being Index [35].

3.3. Risk of osteosarcoma, potential adverse events, and the use of rhPTH

Osteosarcoma is a rare bone cancer, which mainly affects adolescents and young adults. Though lower-grade variants exist, most are high-grade malignancies with a high propensity for lung metastases [46]. The occurrence of osteosarcoma was described in a study conducted on rats treated with PTH. The increased incidence of osteosarcoma in rats could be justified by the use of the doses of PTH much higher than systemic exposure described in humans and by the different bone homeostasis and physiology in rats [47,48]. No signals have emerged to suggest that human subjects treated with either forms of PTH are at increased risk for the development of osteosarcoma, during the clinical human experience with rhPTH (1–34) and with rhPTH (1–84, 49). Only a handful of cases of osteosarcoma have appeared in patients exposed to rhPTH (1–34), a number that is below what would be expected on the basis of epidemiological considerations of the background incidence of osteosarcoma in human subjects. In the ongoing surveillance registry of osteosarcoma, there is no evidence that any subject with osteosarcoma had ever been exposed to rhPTH (1–34) [49].

Up to now, regarding the main adverse events during treatment with rhPTH, the controlled and cohort studies have reported hypercalcemia episodes, although less pronounced and of shorter duration compared with conventional treatment [10,12,22,26]; hypocalcemia episodes, including only three cases of severe hypocalcemia [13]; bone pain [12,23,24]; and nephrolithiasis, reported only in one case, developed despite normal serum calcium concentrations [13].

4. Conclusions

Summarizing, the studies conducted on rhPTH (1–34) were the first to use the rhPTH to treat hypoparathyroidism. Randomized, open-label crossover trials demonstrated that injections of rhPTH (1–34) twice-a-day showed a good control of serum calcium levels compared with conventional therapy, but did not show a significant reduction in 24-h urinary calcium excretion compared to standard therapy with calcium and calcitriol supplements, in patients affected by chronic hypoparathyroidism [24,26]. On the other hand, the studies with rhPTH (1–34) therapy, delivered by an infusion pump, showed a near normalization of the diurnal rhythm of serum calcium and phosphate levels, a significant reduction of 24-h urinary calcium excretion, and markers of bone turnover normalized, compared with twice-a-day injections subcutaneous of rhPTH (1–34). Moreover, the total daily rhPTH (1–34) dose required to maintain normocalcemia was reduced [27,28]. Compared with twice-daily administration, pump delivery of rhPTH (1–34) provided more physiologic calcium homeostasis and bone turnover. BMD measurements remained stable over the 3-year study period [27,28]. Regarding the effect on quality of life, recently, an open-label trial of rhPTH (1–34) in 42 adult patients with

postsurgical hypoparathyroidism showed improvement regarding this aspect, but there was not a control group [30]. The limits of these studies were as follows: no longer duration than 3 years, small patient samples, and lack of double-blind randomized trials. Moreover, the trials conducted by Winer et al. originated from a single-center, posing a sampling bias.

On the other hand, rhPTH (1–84) provides the natural hormone, lacking in this disorder, and has an effective half-life longer than rhPTH (1–34). The studies showed that this drug permits an important reduction in the need for calcium and active vitamin D supplements, maintaining normal mean calcium levels compared to conventional therapy, but only transient reductions in urinary calcium excretion [32,41]. Regarding the effects on BMD, a tendency of increase on lumbar spine and total hip BMD, whereas femoral neck BMD remained stable and the distal one-third radius decreased, together with an increase of bone turnover markers [41]. A beneficial effect of rhPTH (1–84) in terms of quality of life was described, as showed by the evaluation of SF-36 scale in hypoparathyroid patients [38]; on the other hand, another protocol did not demonstrate the same improvement in quality of life [35].

5. Expert opinion

The studies, conducted up to now, have shown that rhPTH can be an attractive treatment option for subjects affected by chronic hypoparathyroidism, which are unable to control stably serum calcium concentrations, requiring very large amounts of calcium and active vitamin D with the associated risks of serious long-term complications. However, currently, only the use of rhPTH (1–84) was approved by the FDA, in the USA, with a 'black box' warning because of the potential risk of osteosarcoma [5,6], and further investigations, especially randomized controlled trials, should be conducted with large samples of patients and for a long period in order to evaluate long-term efficacy and safety of rhPTH treatment.

rhPTH (1–84) and rhPTH (1–34), the latter especially delivered by an infusion pump, are able to reduce the dosage of supplements with calcium and vitamin D maintaining normal mean serum calcium levels. However, rhPTH is not capable to mimic exactly the physiological PTH levels and the physiological regulation of calcium–phosphate homeostasis during 24 h. Probably, in the future, other dosages and mode of administration could be studied. Moreover, in the coming years, further long-term investigations are necessary to evaluate the effects of rhPTH therapy on urine calcium excretion in order to clarify its effect, since, up to now, it has shown only transient reduction. Moreover, rhPTH treatment, because of its mechanism of action, has also a potential preventive role for other complications, such as renal complications, extraskeletal calcifications, or regarding other organs involved in the disease, but long term studies should be conducted to evaluate the real effects of rhPTH on these complications, comparing conventional treatment.

Both the real risk of fracture due to chronic hypoparathyroidism disease and the impact of rhPTH treatment should be clarified. In this regard, it should be properly deepened and clarified the long term effect of rhPTH on BMD changes, bone strength, and bone quality.

The treatment with rhPTH tends to increase both bone formation markers, and as suggested by Rubin et al. [50], this may indirectly reflect a recovery of osteoblast function by means of both increased cell differentiation and decreased preosteoblast and osteoblast apoptosis, but also bone resorption markers, resulting in an overall increase in bone turnover compared to conventional therapy. The marked increase in bone turnover may induce a 'renewal' of the overmineralized bone that is typically observed in a state of chronic hypoparathyroidism, inducing a more physiological bone metabolism [36]; however, these aspects should be clarified.

Regarding the effects on BMD, contrasting data are reported in literature. Indeed, studies with rhPTH (1–34) showed that BMD levels maintained stable over 3 years [24,26] and with rhPTH (1–84) showed a tendency for lumbar spine and total hip BMD to increase, whereas femoral neck BMD remained stable and the distal one-third radius decreased over 6 years, in addition to an increase of bone turnover markers [41,45]. On the other hand, Sikjaer et al. described decreased BMD at the hip, lumbar spine, and whole body but not at the forearm after 24 weeks of treatment with rhPTH (1–84) compared with placebo [12]. These results could be explained by differential effects of rhPTH on bone metabolism according to different doses and number of daily administration because PTH is more catabolic compared to the intermittent dosing. Moreover, regarding the effect on bone microarchitecture by rhPTH (1–84), the study by Sikjaer et al. assessed this aspect using μCT on iliac crest bone biopsies [34]. This analysis showed that rhPTH (1–84), compared with placebo, caused a lower trabecular thickness and lower trabecular bone tissue density, whereas connectivity density was higher, indicating a better connected trabecular network in the PTH-treated patients and a tendency toward an increased cortical porosity. However, because the trabecular separation did not differ between the two groups, the higher connectivity density was probably caused by the trabecular tunneling in the rhPTH-treated patients [34]. These microarchitectural changes could improve bone quality [37]; however, further long-term investigations should be performed.

rhPTH treatment has also a potential role on improvement of quality of life, but, up to now, only three open-label studies, without control group (two with rhPTH (1–84) and one with rhPTH (1–34)) showed an improvement regarding this issue [30,38,39]. On the other hand, a placebo-controlled study conducted on 62 hypoparathyroid patients did not show improvement of quality of life parameters [35]. Therefore, long-term effects regarding quality of life and neurocognitive function require further studies. It is clear that impaired quality of life can be associated with chronic hypoparathyroidism, but it must still be clarified whether impairment of well-being results directly from only PTH deficiency without or with the involvement of changes in calcium homeostasis and the role of PTH in the central nervous system. Moreover, further studies are necessary to create adequate methods for assessing quality of life in these particular patients in order to monitor this parameter over time and demonstrate the effect of treatment on this aspect.

Concerning safety profile of rhPTH data derived by randomized, open-label crossover studies with rhPTH (1–34) [23–26], randomized, double-blind placebo-controlled study with rhPTH (1–84) [32] and data in cohorts of subjects treated with rhPTH (1–84) for 4–6 years [13,41] have not raised any safety concerns. Episodes of hypercalcemia can occur during the first few months of treatment with rhPTH, but usually it is readily corrected with titration of the patient's supplementation regimen. The prospective 6-year investigation on efficacy and safety of rhPTH (1–84) showed that many adverse events, such as nausea; headache; musculoskeletal disorders; fatigue; dizziness; neurological, mental, and mood alterations; paresthesia; and increased urination, tended to decrease during treatment with rhPTH (1–84) [41]. However, further investigations are necessary. Currently, safety and efficacy of rhPTH (1–84) have not been described in patients <18 years of age. This drug is avoided in case of pediatric and young adult hypoparathyroid subjects with open epiphyses, considering the increased baseline risk for osteosarcoma [6]. Regarding patients aged 65 and over, there are no sufficient clinical studies that describe the response to this drug in these subjects compared to younger subjects. Therefore, caution is recommended in increasing the dosage in elderly patients [6]. For both drugs, the studies have shown a good compliance and a high tolerance.

There are no studies that directly compare rhPTH (1–84) and rhPTH (1–34). The studies conducted had variable subjects and methods, and this heterogeneity makes difficult the comparison. However, rhPTH (1–84) could be considered more attractive than rhPTH (1–34), as replacement hormone therapy, because the full-length peptide is exactly what is missing in this disease and its effective half-life longer than rhPTH (1–34). Moreover, the results derived by studies with rhPTH (1–84) for treatment of chronic hypoparathyroidism have been conducted with a longer duration and with more patients compared with studies conducted with rhPTH (1–34).

At last, deciding on the target patient group for rhPTH is essential, considering also the cost of this treatment. In this regard, a recent guideline recommends taking into consideration rhPTH (1–84) therapy in any patient with well-established chronic hypoparathyroidism of any etiology, in particular, in case of variable and inconstant control of the serum calcium with frequent episodes of hypo- and hypercalcemia; oral calcium/vitamin D medications required to control the serum calcium or symptoms that exceed 2.5 g calcium or >1.5 µg active vitamin D; hypercalciuria; renal stones; nephrocalcinosis; stone risk; or reduced creatinine clearance or eGFR (estimated glomerular filtration rate) (<60 mL/min); hyperphosphatemia and/or calcium–phosphate product that exceeds 55 mg^2dL^2 (4.4 $mmol^2L^2$); gastrointestinal tract disorder that is associated with malabsorption; and, finally, reduced quality of life [2].

In the future, new possible therapeutic approaches could be studied; in this regard, recently, a study has described the pharmacological properties of PCO371, a novel orally active small molecule that acts as a full agonist of PTH type 1 receptor (PTHR1), a class B G-protein-coupled receptor. In hypocalcemic rats, PCO371 restores serum calcium levels without increasing urinary calcium and with stronger and longer-lasting effects than PTH injections. These results can suggest that PCO371 can provide a new treatment option for PTH-related disorders, including hypoparathyroidism, but of course, more studies need to be performed [51].

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