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Advances in the treatment of hypoparathyroidism with PTH 1–34☆

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ABSTRACT

Hypoparathyroidism is a rare disorder of calcium metabolism which is treated with calcium and vitamin D analogs. Although conventional therapy effectively raises serum calcium, it bypasses the potent calcium reabsorption effects of PTH on the kidney which leads to hypercalciuria and an increased risk of nephrocalcinosis and renal insufficiency. Twenty-five years ago, we launched the first systematic investigation into synthetic human PTH 1–34 replacement therapy in both adults and children. These studies led to our current understanding of the complex nature of PTH 1–34 therapy and to the challenges we still face in our pursuit of a safe and effective physiologic replacement therapy for hypoparathyroidism. The normalization and minimal fluctuation of serum and urine calcium levels were the primary management goals. As the frequency of PTH 1–34 injections increased, the total daily dose required to normalize calcium homeostasis decreased and episodes of hypercalcemia and hypercalciuria diminished, producing a more physiologic biochemical profile. Twice-daily injections achieved simultaneous normalization of serum and urine calcium levels in many patients but the persistent elevation of bone markers and the difficulty in reducing urine calcium to normal levels in the more severe cases, suggested an alternative to PTH 1–34 injections was needed. The studies with PTH 1–34 delivered by insulin pump represent an important advance in the management of hypoparathyroidism. PTH 1–34 delivered by insulin pump normalized serum and urine calcium and markers of bone turnover. Additionally, pump delivery of PTH 1–34 produced stable magnesium values within the normal range and reduced magnesium excretion. Currently, PTH 1–34 delivery by pump is the only alternative to PTH injections that has been tested in both adults and children and proven to achieve a physiologic biochemical profile.

1. Introduction

Hypoparathyroidism is a rare disorder of calcium homeostasis characterized by low or undetectable levels of parathyroid hormone (PTH) with hypocalcemia and hyperphosphatemia. Over the past century, this rare disorder has been treated with active vitamin D and calcium supplements given in numerous pills throughout the day. The goal of conventional therapy is to raise serum calcium through potentiating intestinal absorption of dietary calcium in the GI tract. Therapy with active vitamin D bypasses the direct homeostatic actions of parathyroid hormone on the kidney and bone and leads to phosphate retention and elevated urinary calcium excretion. Although there are no clinically apparent adverse effects of conventional therapy on bone, it has adverse effects on the kidney including nephrocalcinosis, nephrolithiasis, and chronic renal insufficiency. Hypoparathyroidism due to autoimmune polyendocrine syndrome type 1 (APS-1) is associated with malabsorption in the majority of patients. As this and other GI diseases preclude normal absorption of oral medications, such patients may require intermittent intravenous (IV) calcium infusions to maintain normal levels of blood calcium. Twenty-five years ago, we launched the first systematic investigation into synthetic human PTH 1–34 replacement therapy in both adults and children. These studies led to our current understanding of the complex nature of PTH 1–34 therapy and to the challenges we still face in our pursuit of a safe and effective physiologic replacement therapy for hypoparathyroidism.

In 1925, JP Collip's novel use of bovine parathyroid hormone (bPTH) extract in hypocalcemic parathyroidectomized dogs was the first experiment in the field of PTH replacement of hypoparathyroidism and laid the groundwork for studies in human subjects [1,2]. Albright and Ellsworth described, in 1929, their first attempt at PTH replacement therapy in a 14-year old boy with post-surgical hypoparathyroidism [3] who received a single-daily subcutaneous PTH injection over four days (Fig. 1). PTH alleviated symptoms of neuromuscular irritability, raised serum calcium and urine phosphate excretion, and lowered serum phosphate levels. After three PTH doses, urine calcium excretion levels increased more than ten-fold. Based on these preliminary

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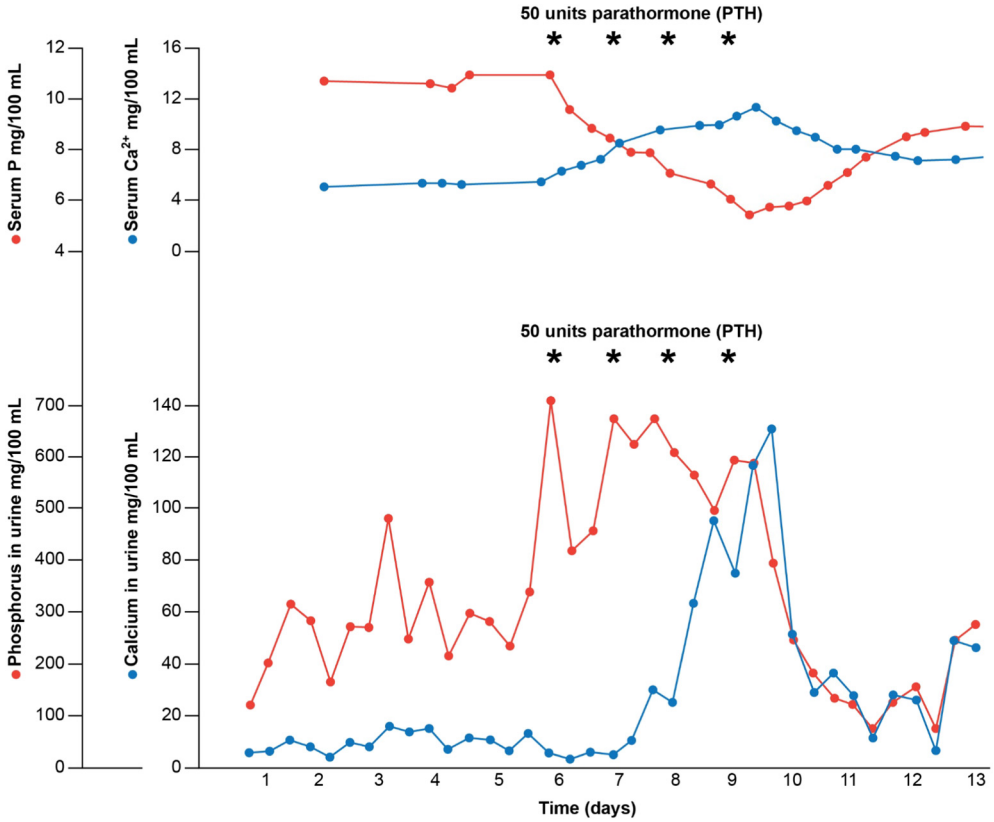

Fig. 1. First case report of once-daily PTH subcutaneous injections given over 4 days in a 14 yo boy with post-surgical hypoparathyroidism. [Adapted from: Albright F, Ellsworth R J. Clin Invest, 7 (1929) 183. [3]].

observations, Albright concluded that PTH modified urine phosphate excretion. He also incorrectly concluded that a primary action of PTH was to increase urine calcium excretion. The single-daily 50-unit bPTH dose was too high and should have been titrated down to achieve a more physiologic response, but the experiment was aborted after four doses and Albright did not further pursue studies into PTH replacement therapy for hypoparathyroidism. Vitamin D was discovered in 1924 and soon after became the treatment of choice for hypoparathyroidism [4,5].

2. Overview PTH 1–34 studies

PTH 1–34 was sequenced in 1972 [6] and developed as a potential therapy for osteoporosis [7]. Investigation into PTH1–34 replacement of hypoparathyroidism was not pursued until twenty years later. In 1992, we launched a series of randomized controlled studies in adults and children ages 4–70 years with hypoparathyroidism. We tested various dose regimens and, more recently, the novel use of an insulin pump to deliver PTH 1–34. We used synthetic human PTH 1–34, which was formulated at the NIH pharmacy [8]. The normalization and minimal fluctuation of serum and urine calcium levels were the primary goals of PTH 1–34 replacement therapy. PTH 1–34 doses were titrated to pre-dose AM serum and 24-h urine calcium excretion levels. No study participant received diuretics or phosphate binders. With the initiation of PTH therapy, treatment with calcitriol and calcium was abruptly discontinued. At the conclusion of the studies, patients resumed treatment with conventional therapy.

To determine if PTH 1–34 had a sustained calcemic effect, we initially compared subcutaneous PTH 1–34 to conventional therapy in a 20-week randomized crossover trial. During the conventional treatment arm, subjects received twice-daily oral calcitriol and 1000 mg of calcium supplementation divided into three daily doses. A single-daily PTH subcutaneous (sc) injection produced well-known pharmacodynamic effects on the kidney, including a rapid rise in cyclic AMP and phosphate excretion, and a decrease in urine calcium excretion [8]. This study also confirmed subcutaneous PTH 1–34 given once daily could control calcium concentrations in the blood and urine for periods up to 10 weeks. Subsequently, we compared twice-daily PTH 1–34 injections to once daily sc injections and later to PTH 1–34 delivered through an insulin pump in both adults and children. As the frequency of PTH injections increased, the total daily dose required to maintain normal calcium homeostasis decreased and episodes of hypercalcemia and hypercalciuria diminished, producing a more physiologic biochemical profile.

To further understand the effects of the PTH 1–34 dose size and frequency on calcium homeostasis, we studied 17 adults (ages 19–64 years) and 14 children (ages 4–17 years) comparing once-daily with twice-daily PTH 1–34 injections in a randomized crossover design over a 28-week period. The studies in adults and children yielded similar results [9,10]. All patients had low or undetectable PTH levels at baseline. Responses to PTH therapy differed based on disease etiology. This study was the first to highlight the unique physiologic responses in patients with an activating mutation in the calcium sensing receptor (CaR) compared to patients with other forms of hypoparathyroidism [9]. The calcium-sensing receptor (CaSR) is a G-protein coupled receptor activated by extracellular calcium and magnesium. Activating mutations in the CaSR shift the receptor set point to a heightened sensitivity to extracellular calcium and inhibit tubular calcium reabsorption resulting in inappropriately high levels of urine calcium excretion when serum calcium levels are in the normal or below normal range.

Single or twice-daily subcutaneous injections of PTH 1–34 restored serum and urine calcium to the normal or near-normal range in subjects with post-surgical, autoimmune or idiopathic hypoparathyroidism. Once-daily PTH 1–34 injections were not effective in managing CaR. Twice-daily PTH increased serum calcium to the near normal range in

patients with CaR (1.67 ± 0.12 vs 1.91 ± 0.15 mmol/L; once vs twice daily, $P < 0.001$), but urine calcium excretion levels remained elevated during this treatment regimen [9]. Furthermore, CaR patients required a higher mean PTH 1–34 dose compared to patients with hypoparathyroidism with other etiologies for both dose regimens (0.96 ± 56, CaR vs 0.47 ± 0.33 μg/kg/day, other etiologies for twice-daily PTH; 2.62 ± 1.58, CaR vs 1.0 ± 0.81 μg/kg/day, other etiologies for once-daily PTH; $P < 0.05$, for both). In children, twice daily PTH allowed for a > 50% reduction in total daily PTH 1–34 dose required to maintain normal calcium homeostasis. Additionally, twice-daily doses of PTH 1–34 were more effective than once-daily doses in maintaining serum calcium in the normal range in children (twice-daily 2.04 ± 0.03 mmol/L vs once-daily 1.87 ± 0.03 mmol/L; $P < 0.01$) [10].

Our studies have shown, in a randomized parallel group study, twice-daily PTH 1–34 injections, compared to conventional therapy, are safe and effective for 3 years in adults and children with hypoparathyroidism [11,12]. Furthermore, twice-daily PTH 1–34 injections maintained mean serum calcium in the low or just below the normal range with normal mean urine calcium excretion and renal function. Children had normal linear growth, renal function, and bone accrual throughout the study period during both treatment arms. Plasma phosphate decreased significantly ($P < 0.01$) from baseline (2.27 ± 0.08 mmol/L) to year three (1.67 ± 0.12 mmol/L) in response to twice daily PTH 1–34 injections [12]. Children were encouraged to maintain a normal diet including dairy products. Dietary calcium intake ranged from 700 to 1600 mg according to semiannual food frequency questionnaires.

An observational study of 14 children (ages 6–16 years) with CaR or APS-1 treated long-term, up to 10 years, with twice or three-times daily PTH1–34 injections confirmed that PTH1–34 therapy led to normal mean linear growth and bone accretion velocities [13]. Mean serum alkaline phosphatase, serum and 24-h urine calcium remained in the normal range and correlated with the PTH dose. Mean ± SD serum and 24-h urine calcium levels during treatment were 2.05 ± 0.11 mmol/L (N: 2.05–2.5 mmol/L) and 6.93 ± 1.3 mmol/24 h/1.73 M^2 (N: 1.25–7.5 mmol/d), respectively. Mean serum calcium decreased significantly from study baseline to 1 y (−0.13 mmol/L, $P < 0.04$), as did urine calcium (−1.6 mmol/d, $P < 0.03$), and did not change significantly thereafter (> 1–10 y). Serum phosphate decreased significantly during PTH therapy and levels were inversely related to PTH dose ($P < 0.01$). Average disease duration at baseline was 8.6 ± 4.5 years at study entry. Thirteen children, who had renal imaging at or just before study baseline, had evidence of nephrocalcinosis. Renal function remained normal throughout the study.

3. PTH 1–34 delivered by an insulin pump

Based on the results from our previous studies, we concluded that more frequent injections allowed a significant decrease in the total daily PTH 1–34 dose required to maintain eucalcemia. Smaller PTH doses were more effective in reducing the urine calcium excretion level and reduced or eliminated fluctuation in the serum and urine calcium levels. To further optimize the metabolic response to PTH, we initiated studies using an insulin pump (Omnipod by Insulet) to deliver PTH 1–34 [14,15]. Calcitriol and calcium supplements were discontinued at baseline and all patients received cholecalciferol 1000 IU daily to maintain adequate vitamin D levels. Initial basal rates were estimated based upon body weight (0.2 μg/kg/day) and prior calcitriol or PTH 1–34 dose requirements. Basal rates ranged from 3 to 7 pulses per hour, with each pulse delivering a 0.1 μg PTH 1–34 dose in a fixed 0.5 microliter volume. The study of children with congenital hypoparathyroidism, included a 4-h or 8-h nighttime basal rate increase of 1 pulse per hour from midnight to 0400, or from midnight to 0800, to mimic the known circadian variation in circulating PTH [16,17].

PTH delivered by insulin pump simultaneously normalized serum and urine calcium and markers of bone turnover. Children with APS-1 or CaR, who are often refractory to conventional therapy, had normal mean serum calcium (2.02 ± 0.05 mmol/L) and normal mean 24-h urine calcium excretion (5.17 ± 1.10 mmol/24 h/1.73 m^2) during pump therapy. Adults with postsurgical hypoparathyroidism who received PTH 1–34 delivered by pump also had normal mean serum calcium (2.09 ± 0.06 mmol/L) and normal mean 24-h urine calcium excretion (3.98 ± 1.90 mmol/24 h). In the same study, twice-daily PTH injections in children with APS-1 or CaR resulted in mean ± SE serum calcium below the normal range (1.88 ± 0.03 mmol/L) and elevated urine calcium excretion (6.67 ± 0.76 mmol/24 h/1.73 m^2). Twice-daily PTH injections in the adult subjects resulted in normal mean ± SE serum calcium (2.15 ± 0.04 mmol/L) and elevated mean urine calcium excretion (9.66 ± 0.44 mmol/24 h). In addition, pump delivery led to a 65% reduction in the PTH dose required to maintain eucalcemia (13 ± 4 μg/day [0.17 ± 0.03 μg/kg/day] vs. 37 ± 14 μg/day [0.47 ± 0.13 μg/kg/day], pump vs twice-daily PTH, $P < 0.001$) [14]. Children with APS-1 or CaR had a similar dose reduction when PTH 1–34 was administered through an insulin pump device (0.32 ± 0.04 vs. 0.85 ± 0.11 μg/kg/day, pump vs twice daily injections, $P < 0.001$) [15].

The circadian pattern of serum and urine calcium and magnesium were significantly different comparing twice-daily injections with PTH 1–34 administered through an insulin pump device. Serial testing over a 24-h period in adults and children [14,15] during twice-daily PTH injections revealed a biphasic pattern for both serum and urine calcium and magnesium and for urine cAMP compared to minimal fluctuation

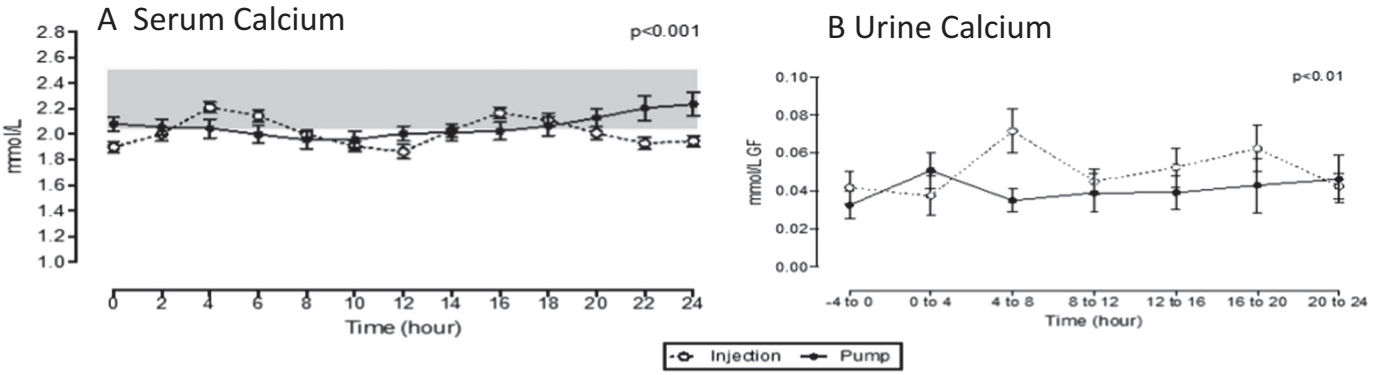

Fig. 2. A: Serial (q 2 h) serum calcium levels comparing PTH1–34 delivered by twice-daily subcutaneous injections vs pump in children with hypoparathyroidism. Fig. 2B: Serial (q 4 h) urine calcium excretion levels comparing PTH1–34 delivered by twice-daily injections vs pump in children with hypoparathyroidism. [Reproduced from: Winer KK et al. J Pediatr. 165(2014)556. [15]] Ca excretion (CaE) = $\text{calcium}_{\text{urine}} \times \text{creatinine}_{\text{serum}}/\text{creatinine}_{\text{urine}}$. Urine measures were corrected to body surface area of 1.73 m^2.

or no circadian pattern during pump delivery ($P < 0.01$, pump vs injection; 24-h serum and urine profiles for adults and children) (Fig. 2; [15]).

4. PTH 1–34 effects on magnesium

Many patients with hypoparathyroidism have hypomagnesemia which is treated with magnesium supplements. Hypomagnesemia and the requirement for magnesium supplementation is most common in patients with autoimmune hypoparathyroidism or with CaR. PTH effects on serum and urine magnesium are similar to PTH effects on calcium. The calcium sensing receptor (CaSR) regulates extracellular divalent cations, and both calcium and magnesium are its primary ligands [18]. Our studies reflect improved control of magnesium homeostasis in adults and children with increased PTH dose frequency [9,10]. Similar to the PTH effects on serum calcium, twice-daily PTH1–34 injections in children resulted in significantly higher serum magnesium compared to a single daily injection (0.71 ± 0.02 vs 0.66 ± 0.02 mmol/L; twice-daily vs once-daily PTH, $P < 0.01$) [10]. Adults receiving twice-daily PTH injections also had significantly higher mean serum magnesium levels compared to once-daily PTH injections (0.68 ± 0.08 vs. 0.64 ± 0.07 mmol/L twice-daily vs. once-daily PTH injections, $P < 0.01$) [9].

In children, 24-h repeated measures of serum magnesium were subnormal during the latter part of the day (10–24 h time points) in response to a single daily PTH injection. Twice-daily PTH produced normal mean serum magnesium levels throughout the day, which were significantly higher at 14–18 h and 24 h ($P < 0.01$ for 14–18, 24 h, twice-daily vs once daily; Fig. 3A) [10].

Compared to twice daily injections, pump delivery of PTH 1–34 produced stable magnesium values maintained within a narrow range over a 24-hour period (Fig. 3B) [15]. In children with APS-1 or CaR, pump delivery of PTH 1–34 also reduced magnesium excretion (6.06 ± 1.28 [pump] vs. 7.38 ± 1.33 mmol/24 h/1.73 m^2, $P < 0.001$, N: 3.04–4.25) and normalized mean serum magnesium (0.74 ± 0.02 [pump] vs. 0.65 ± 0.02 mmol/L, $P < 0.001$, N: 0.75–1.00). Furthermore, compared to twice daily injections, pump delivery of PTH 1–34 reduced the mean magnesium supplement dose (532 ± 105 [pump] vs. 944 ± 158 mg/d, $P < 0.001$) required to maintain normal serum magnesium [15].

5. PTH 1–34 effects on the kidney

In the normal physiologic state, serum calcium is maintained within a narrow range with minimal fluctuation. In the kidney, the combined actions of PTH and the CaSR control calcium and magnesium excretion. Our initial study comparing once-daily subcutaneous PTH 1–34 injections with conventional therapy illustrates the effects of PTH on the kidney in patients with hypoparathyroidism [8]. Repeated measures of urine calcium excretion reveal a biphasic response that reflects two apparently opposing effects occurring sequentially following a subcutaneous PTH 1–34 injection (Fig. 4). First, the immediate CaSR-mediated rise in urine calcium excretion mirrors the concurrent acute rise in serum calcium. This was followed by the PTH-mediated rise in tubular calcium reabsorption which reduces urine calcium excretion.

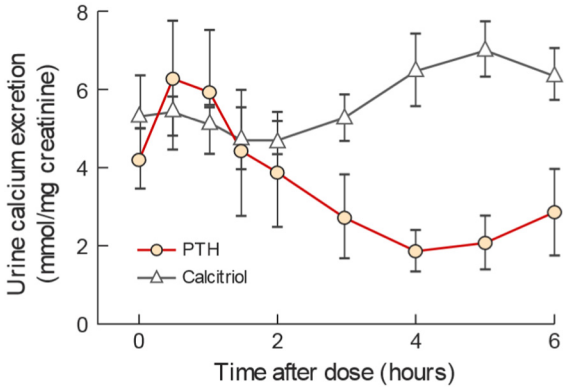

Fig. 4. Serial urine calcium levels in response to PTH1–34 vs calcitriol and calcium in adults with hypoparathyroidism. Repeated measures of urine calcium excretion after a subcutaneous PTH 1–34 injection given at time 0 reveal a biphasic response and overall decrease in calcium excretion. Calcitriol had no calcium retaining effect on the kidney and led in a rise in urine calcium excretion.
[Adapted from Winer KK et al., JAMA. 276 (1996) 631. [8]].

The transient rise in urine calcium excretion after a PTH injection is most evident in patients with a gain of function mutation of the CaSR which is characterized by disproportionate hypercalciuria associated with small increases in blood calcium. Patients with CaR have intractable hypercalciuria leading to nephrocalcinosis and renal damage which may appear, in the more severe cases, during early childhood. Patients with this disorder were referred to us because of profound hypocalcemia which was unresponsive to high doses of active vitamin D and calcium [19]. We studied 23 patients with CaR who, at their baseline evaluation, had moderate to severe nephrocalcinosis.

PTH1–34 delivered by pump avoids the calcium fluctuations in the

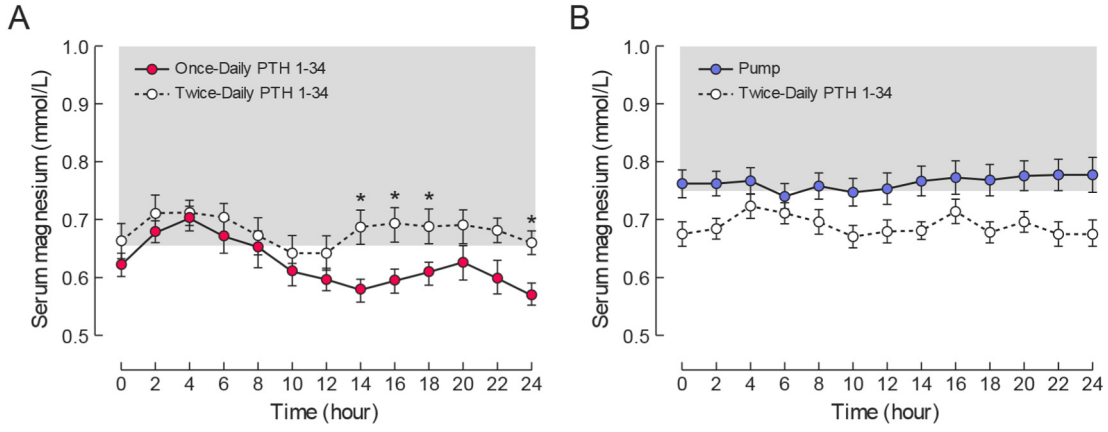

Fig. 3. Serum magnesium results from two studies in children showing (Fig. 3A) the differences between once daily PTH vs twice-daily PTH 1–34 injections in 14 children. Serum magnesium levels improved during the latter half of the day (12–24 h.) with twice-daily PTH injections. Fig. 3B shows the serum magnesium profile 12 children comparing twice-daily subcutaneous injections and PTH 1–34 delivered through an insulin pump which raised serum magnesium values into normal range throughout the 24-h period with no fluctuation (pump vs twice daily PTH injection, $P < 0.001$).
[3A: Adapted from Winer KK et al. J Clin Endocrinol Metab. 933(2008)389. [10] 3B Adapted from Winer KK et al. J Pediatr. 165(2014)556. [15]].

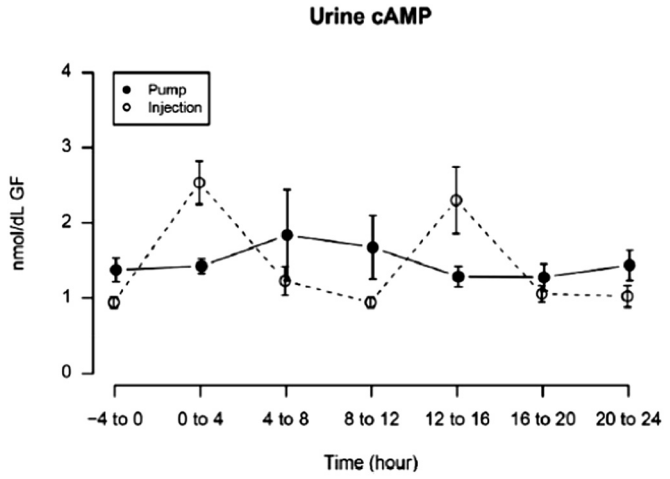

Fig. 5. Urine cyclic AMP excretion patterns are significantly different comparing PTH 1–34 delivered by pump vs twice daily injections in adults with post-surgical hypoparathyroidism ($P < 0.001$, pump vs injections).
[Reproduced from: Winer KK et al. J Clin Endocrinol Metab. 97 (2012), 391. [14]].

blood and urine associated with relatively large subcutaneous injections and led to normal urine calcium [14,15]. Patterns of urine cyclic-AMP excretion generated in response to PTH 1–34 delivered by pump compared to sc injections reflect two distinct levels of PTHR1 activation. PTH injections resulted in a rapid but transient rise in urine cyclic AMP levels which immediately returned to baseline. By contrast, PTH delivered by pump maintained a sustained level of cyclic-AMP above baseline throughout the day ($P < 0.001$, pump vs injections; Fig. 5). This cyclic AMP pattern along with the significant reduction in urinary calcium excretion during pump delivery of PTH 1–34 compared to injections, suggests that the renal tubule must be continuously exposed to PTH to sustain its calcium conserving effects [14].

In hypoparathyroidism, chronically elevated urine calcium excretion leads to interstitial calcium-phosphate deposits in the kidney with varying degrees of renal insufficiency. Levy et al. conducted a retrospective study of 29 children with congenital hypoparathyroidism (50% of the cohort had DiGeorge Syndrome) who were treated with conventional therapy up to 7 years. They found 39% of patients had nephrocalcinosis and 45% had an eGFR between 60 and 90 mL/min/1.73 m^2. Furthermore, higher calcium concentrations and greater proportion of time with hypercalcemia were associated with a lower eGFR [20]. In our studies, up to 80% of adult patients had renal insufficiency at study entry, during treatment with conventional therapy [9,11]. Large epidemiologic studies in Denmark have also found a high prevalence of renal insufficiency in adults with both surgical and non-surgical hypoparathyroidism [21,22]. Our longitudinal study of children with APS-1 or CaR had normal renal function for up to 10 years with PTH 1–34 therapy despite the high prevalence of nephrocalcinosis (100% of the 13 patients who had renal imaging) at baseline [13]. The pathophysiologic process leading to progressive renal injury associated with nephrocalcinosis needs further exploration [23]. This includes the need for a greater understanding of the factors beyond hypercalciuria that contribute to the susceptibility to ectopic mineralization and progressive renal damage.

6. PTH effects on bone

PTH regulates skeletal remodeling and potentially has both anabolic and catabolic effects on bone. The predominant effect of exogenous PTH therapy depends on the dose and method of delivery. The dual action of PTH, however, may be evident at various skeletal sites in the same individual in response to a given PTH regimen [24–27].

Adults with hypoparathyroidism have decreased bone remodeling and increased bone density. In a randomized crossover study comparing once-daily to twice daily injections, adults with hypoparathyroidism had a mean ± SD alkaline phosphatase level in the normal range (66 ± 2.1 U/L; N:37–116 ng/mL) measured at study baseline, while receiving conventional therapy. Single daily PTH 1–34 injections produced elevated mean serum alkaline phosphatase levels (243 ± 272 U/L), but twice-daily injections (146 ± 51 U/L) resulted in a significantly lower mean alkaline phosphatase level (once-daily vs twice-daily PTH injections, $P < 0.005$) [9].

In a 3-year, randomized parallel group study of 27 adults comparing twice-daily PTH 1–34 injections to conventional therapy, the average duration of hypoparathyroidism in study participants at baseline was 14 years (range 1–36 years). Thirteen adults who were randomized to receive conventional therapy with calcitriol and calcium had normal markers of bone turnover and a rise in whole body BMD and anteroposterior (AP) lumbar spine BMC (measured by DXA) over the 3-year study ($P < 0.01$ for both skeletal areas). Mean AP spine Z- and T-scores increased by 1 SD [11]. There were no significant changes in Z- or T-scores in other skeletal sites over the three-year study in response to conventional therapy.

In the same study, 14 adults who were randomized to receive twice-daily PTH 1–34 injections had no significant differences in BMC or BMD measures compared to the conventional treatment group over the 3-year duration of the study. BMD and BMC values were stable with no changes in the AP spine and whole body. There was a gradual increase over the 3 years in femoral neck BMD ($P < 0.05$). Markers of bone turnover were significantly higher throughout the 3-year period in the group treated with PTH 1–34 compared to the calcitriol-treated group (twice-daily PTH vs calcitriol, $P < 0.01$) [11].

Linear growth and bone mineral density were normal in 12 children with hypoparathyroidism treated over 3 years with either conventional therapy or PTH 1–34. Bone density over 3 years, measured by DXA, did not differ comparing the two groups: calcitriol therapy vs. twice-daily PTH 1–34 injections. Mean serum alkaline phosphatase levels were normal during conventional therapy and increased into the high normal or just above the normal range during PTH 1–34 therapy [12]. A longitudinal study, up to ten years, of PTH 1–34 therapy in 14 children with APS1 or CaR demonstrated normal mean ± SD serum alkaline phosphatase and bone accrual velocity [13].

Normalization of markers of bone turnover was achieved with pump delivery of PTH 1–34 in children and adults. Pump delivery in children reduced alkaline phosphatase, osteocalcin and NTX by 37–63%, compared to twice-daily PTH injections ($P < 0.02$). For the two markers of bone turnover with established pediatric norms, the mean values during pump delivery were in the mid-normal range, but were high normal or slightly above normal during twice-daily delivery [15]. This finding is particularly compelling in children with severe congenital hypoparathyroidism who are considered refractory to conventional therapy with activated vitamin D. Additionally, the black box warning associated with both rhPTH 1–34 and rhPTH 1–84 precludes treatment in children, leaving this group without an alternative therapy.

7. The off-label use of rhPTH 1–34 in refractory hypoparathyroidism

Recent studies from Europe demonstrated rhPTH 1–34 (teriparatide, Forteo®) delivered by insulin pump led to a sustained long-term improvement in mineral homeostasis in children with refractory hypoparathyroidism. Linglart et al. treated three hypoparathyroid children (2 with APS-1) with rhPTH 1–34 delivered by pump for three years with a reduction of symptoms and improved control of serum and urine calcium, which were maintained in the near normal range. Serum magnesium and phosphate levels were also normal [28]. Saraff et al. describe a study of four children (ages 8–13 years) with symptomatic hypocalcemia resistant to active vitamin D and calcium supplements

[29]. Three patients had APS1 due to AIRE gene mutations and all four patients had malabsorption. This case series demonstrated that rhPTH 1–34-delivered by an insulin pump (Medtronic) for up to eight years led to a substantial reduction in hypocalcemia related hospital admissions. All four patients preferred pump therapy over conventional therapy. The PTH 1–34 dose, 0.3–0.5 μg/kg/day, maintained serum calcium and phosphate and urine calcium within the normal range. Mishra et al. describe the use of rhPTH 1–34 in the management of acute hypocalcemia in two children with hypoparathyroidism. The short-term use of subcutaneous rhPTH 1–34 injections effectively replaced multiple IV calcium infusions, the conventional treatment of severe hypocalcemia, which may contribute to excessive calcium excretion and renal damage [30].

8. PTH 1–84

The full-length peptide, PTH 1–84, and its N-terminal active fragment, PTH 1–34, produce similar pharmacodynamic profiles and have identical biological effects when given to patients with hypoparathyroidism [8,31]. Therefore, the principles for effective management learned from the studies with PTH 1–34 also apply to PTH 1–84. As there are no studies comparing the two peptides, any claims that PTH 1–84 is longer-acting compared to PTH 1–34 remain unproven [32].

In 2006, rhPTH 1–84 was approved in Europe as a treatment of osteoporosis given in 100 μg daily subcutaneous injections with supplemental calcium and vitamin D. The same doses approved for treatment of osteoporosis [33] were used for treatment of hypoparathyroidism [26]. Studies with 100 μg rhPTH 1–84, given daily or every other day as an add-on to vitamin D and calcium for replacement therapy in hypoparathyroidism led to both anabolic and catabolic changes in BMD at various skeletal sites [26,27]. Management of hypoparathyroidism with PTH 1–84 primarily aims to normalize serum calcium and reduce active vitamin D and calcium supplement doses. Fixed doses of PTH 1–84, however, do not allow minor PTH dose adjustments for inevitable calcium variability in response to illness, exercise, and other environmental and lifestyle factors [34].

9. Future directions

PTH 1–34 delivered by insulin pump represents an important advance in the study of replacement therapy of hypoparathyroidism. This method of PTH delivery led to the normalization of key biochemical markers of calcium homeostasis in adults and children. Twice-daily injections achieved simultaneous normalization of mean serum and urine calcium levels in many patients and provided an effective alternative to conventional therapy but the persistent elevation of bone markers and the difficulty in reducing urine calcium to normal levels in the more severe cases, suggests an alternative to PTH 1–34 injections is needed. PTH delivery by pump is the only alternative that has been tested in both adults and children and proven to achieve a physiologic biochemical profile.

Future investigation of PTH replacement in hypoparathyroidism will likely abandon once-daily injections with short-acting PTH analogs. Long-acting PTH analogs with an improved pharmacodynamic profile [35] may be effective but have not yet been tested in patients with hypoparathyroidism. Current management of hypoparathyroidism with subcutaneous PTH injections is feasible only if PTH is available in multidose vials or a pen device with flexible dosing capability. To give patients more autonomy, a portable calcium monitoring device should be developed to become an integral part of management. Regardless of the method of PTH delivery, the principle goal of replacement therapy is to mimic normal physiology. Therefore, management should focus on maintaining serum calcium within a narrow physiologic range and avoid abnormal elevations in urine calcium and markers of bone turnover. We have shown this is possible with pump delivery of PTH 1–34. Other treatment modalities are on the horizon and further investigation may show they offer a similar benefit.

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