Hypoparathyroidism: Replacement Therapy with Parathyroid Hormone

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Hypoparathyroidism (HypoPT) is characterized by low serum calcium levels caused by an insufficient secretion of parathyroid hormone (PTH). Despite normalization of serum calcium levels by treatment with activated vitamin D analogues and calcium supplementation, patients are suffering from impaired quality of life (QoL) and are at increased risk of a number of comorbidities. Thus, despite normalization of calcium levels in response to conventional therapy, this should only be considered as an apparent normalization, as patients are suffering from a number of complications and calcium-phosphate homeostasis is not normalized in a physiological manner. In a number of recent studies, replacement therapy with recombinant human PTH (rhPTH(1-84)) as well as therapy with the N-terminal PTH fragment (rhPTH(1-34)) have been investigated. Both drugs have been shown to normalize serum calcium while reducing needs for activated vitamin D and calcium supplements. However, once a day injections cause large fluctuations in serum calcium. Twice a day injections diminish fluctuations, but don’t restore the normal physiology of calcium homeostasis. Recent studies using pump-delivery have shown promising results on maintaining normocalcemia with minimal fluctuations in calcium levels. Further studies are needed to determine whether this may improve QoL and lower risk of complications. Such data are needed before replacement with the missing hormone can be recommended as standard therapy.

Keywords: Hypoparathyroidism; Calcium; Vitamin D; Parathyroid hormone treatment

INTRODUCTION

Hypoparathyroidism (HypoPT) is rare disease characterized by hypocalcemia with inappropriate low serum levels of parathyroid hormone (PTH) [1]. Recent studies from Europe and the USA have estimated that the prevalence of HypoPT is 25 per 100,000 individuals [2-4]. Most cases occur as a complication to thyroid or parathyroid surgery, during which the parathyroid glands are accidentally damaged [5,6]. Only a minority of patients has nonsurgical HypoPT (2 to 3/100,000 individuals).

Nonsurgical HypoPT may be due to autoimmune diseases with autoantibodies directed towards the parathyroid glands, destruction of the glands (i.e., infiltrative diseases such as metastasis) or genetic mutations, including the CATCH-22 (Di-George) syndrome, HypoPT-deafness-renal dysplasia syndrome, and mutation in the auto-immune regulator (AIRE) gene [1,7]. Autosomal dominant hypocalcemia (ADH) shares biochemical similarities with HypoPT, as this disease is characterized by a state of hypoparathyroid hypocalcemia. ADH is caused by a gain-of-function mutation in the gene encoding the
calcium sensing receptor (CaSR). Due to the activating mutation, the CaSR senses the serum calcium level as being higher than it actually is resulting in a suppression of PTH secretion and a state of hypocalcemia. As parathyroid glands are actually well-functioning, although at a set-point lower than normal, this disease is not a real state of HypoPT [8]. Recent data have suggested that ADH may be present in two forms. In addition to the classical ADH type 1, caused by a mutation in the CASR gene, a mutations in the GNA11 gene has been shown to cause ADH type 2 [9,10]. Special attention should be paid to patients with ADH as they have an abnormal high renal calcium excretion in response to treatment with calcium supplements causing them to be at specific high risk of developing renal calcification as a complication to their disease [11,12].

CONVENTIONAL TREATMENT OF HYPOPARATHYROIDISM

Serum calcium levels are of major importance to a large number of physiological processes. As even small deviations impair a variety of cellular functions, serum calcium levels are normally maintained within a very narrow range [13]. In hypocalcemia, neuromuscular irritability is increased causing symptoms such as paresthesia of the distal extremities and circumoral area, muscle cramps, laryngospasm, tetany, and seizures. Chvostek and Trousseau signs may be positive. Hypocalcemia may also affect cardiac function with a prolonged QT interval which may progress to tachycardia and ventricular fibrillation, as well as hypocalcemia may cause cardiomyopathy [14,15]. The severity of symptoms generally correlates with the rapidity and magnitude and of the fall in serum calcium levels, i.e., patients developing hypocalcemia due to damage of the parathyroid glands during surgery often develop marked symptoms whereas patients with inherited causes of HypoPT such as the CATCH 22 syndrome may be relative free of symptoms despite very low calcium levels [15].

Traditionally, HypoPT is treated with calcium supplements and activated vitamin D analogues. Different traditions seem to exist at different institutions on how to titrate dose of calcium supplements and activated vitamin D. At some institutions, a relatively high daily dose of calcium (e.g., 3 to 4 g/day) is combined with a relatively low dose of active vitamin D, whereas other institutions prefer to keep dose of calcium supplements low (e.g., 800 to 1,000 mg/day) while using relatively higher doses of active vitamin D. As PTH normally stimulates the renal 1α-hydroxylase to synthesize active vitamin D (1,25-dihydroxyvitamin D [1,25(OH)2D]), HypoPT may be considered as a two-hormone deficiency state, i.e., in addition to PTH patients also have a deficiency of 1,25(OH)2D. Thus, it seems somehow reasonable to treat the disease by substituting the 1,25(OH)2D deficiency while keeping calcium intake at a normal level. However, no studies are available comparing the two treatment regimens head-to-head. As activated vitamin D analogues, alfalcacidol (1α-hydroxyvitamin D) as well as calcitriol (1,25(OH)2D) may be used. In terms of calcemic potency, calcitriol is twice as potent as alfalcacidol [16-18].

### COMORBIDITIES IN HYPOPARATHYROIDISM

Several recent studies have shown that patients with HypoPT are at increased risk of a number of comorbidities and have a variety of symptoms, as well as biochemical abnormalities despite normalization of serum calcium levels in response to conventional treatment. Taking advantages or the Danish National Hospital Register, recent cohort studies have documented that patients with HypoPT are at increased risk of a number of comorbidities [2,4,19]. As shown in Table 1, patients with HypoPT are at increased risk of getting hospitalized due to several nonskeletal diseases compared with the general background population.

| Variable                  | Postsurgical | Nonsurgical |
|---------------------------|--------------|-------------|
| Mortality                 | 0.98 (0.76–1.26) | 1.25 (0.90–1.73) |
| Renal insufficiency       | 3.10 (1.73–5.55)  | 6.01 (2.45–14.75) |
| Nephrolithiasis           | 4.02 (1.64–9.90)  | 0.80 (0.17–3.85)  |
| Ischemic heart disease    | 1.09 (0.83–1.45)  | 2.01 (1.31–3.09)  |
| Stroke                    | 1.09 (0.73–1.64)  | 1.84 (0.95–3.54)  |
| Arrhythmia                | 1.11 (0.79–1.57)  | 1.78 (0.96–3.30)  |
| Seizures                  | 3.82 (2.15–6.79)  | 10.05 (5.39–18.72) |
| Cataract                  | 1.17 (0.66–2.09)  | 4.21 (2.13–8.34)  |
| Neuropsychiatric disorders| 2.01 (1.16–3.50)  | 2.45 (1.78–3.35)  |
| Infections                | 1.42 (1.20–1.67)  | 1.94 (1.55–2.44)  |
| Fractures                 | 1.03 (0.83–1.29)  | 1.40 (0.93–2.11)  |
| Upper extremities Fx      | 0.69 (0.49–0.97)  | 1.93 (1.31–2.85)  |
| Cancer                    | 0.83 (0.61–1.13)  | 0.44 (0.24–0.82)  |
| Gastrointestinal cancer   | 0.62 (0.42–0.92)  | 0.29 (0.07–1.25)  |

Values are expressed as hazard ratio (95% confidence interval). *P<0.05.
In addition to regulating calcium homeostasis, PTH is also of importance to phosphate and magnesium homeostasis. Normally, PTH increases renal phosphate excretion by inhibiting the renal phosphate-sodium cotransporter in the proximal renal tubule [20]. Thereby, lack of PTH causes inappropriate high serum phosphate levels with an increased calcium-phosphate product. This is most likely the explanation for the increased risk of cataract, nephrolithiasis, and intracerebral calcifications observed in patients with HypoPT (Table 1). Moreover, PTH normally stimulates the renal tubular reabsorption of calcium. Thus, in HypoPT urinary calcium is increased which may contribute to the increased risk of renal stone diseases in patients with HypoPT [2]. Additional studies have suggested that intermittently elevated serum calcium levels (due to overtreatment) also may contribute to the increased risk of renal insufficiency in HypoPT [21].

Due to the very low bone turnover in HypoPT [18,22,23], bone mineral density is most often relatively high (positive Z-scores) and risk of fracture is, in general, not increased. Actually, patients with postsurgical HypoPT may have a decreased risk of fractures at the upper arm [19]. However, in nonsurgical HypoPT, risk of fractures of the upper arm seems to be significantly increased, which may be attributable to a significantly 10-fold increased risk of seizures which may cause falls and thereby fractures [4].

Often, patients with HypoPT also have a number of nonspecific complains including muscle weakness, pain/aches in muscles and bones as well as reduced cognitive skills. Risk of neuropsychiatric diseases is increased and patients have an impaired quality of life (QoL) [24,25]. PTH receptors are expressed in a variety of cells in different tissues, including the central nervous system (CNS) [26]. Whether the symptoms are due to lack of PTH in itself or attributable to disturbances in calcium-phosphate homeostasis has not yet been clarified.

Apparently, normalization of serum calcium levels in response to conventional therapy does not restore the normal physiology of calcium homeostasis. Thus, there is a need for improvement of the treatment of the disease. Remarkably, HypoPT is one of the last endocrine deficiency states which are not treated by substitution with the missing hormone. Within the last decade, several studies have investigated replacement therapy with recombinant human PTH (rhPTH) as an alternative to conventional treatment. These studies have investigated effects of subcutaneous injections with either the N-terminal fragment (rhPTH(1-34)) as well as the intact hormone (rhPTH(1-84)). Most recently, therapy with rhPTH(1-84) (Natpara, Shire, Lexington, MA, USA) has been approved by the U.S. Federal Drug Administration for treatment of HypoPT. In Europe, PTH therapy, as an approved treatment of HypoPT, is currently being evaluated by the European Medicine Agency.

**RESULTS ON SERUM CALCIUM LEVELS FROM STUDIES ON rhPTH(1-34) THERAPY IN HYPOPARATHYROIDISM**

A number of studies on effects of treatment of HypoPT with rhPTH(1-34) have been performed by a research group led by Dr. Karen Winer in the USA. In their first study, once daily injections with PTH(1-34) were compared with conventional therapy, showing that normocalcemia can be maintained by PTH therapy [27]. However, as PTH has a relatively short serum half-life (5 to 10 minutes), a rather high dose is needed to maintain normocalcemia throughout the day, if injected only once a day. On averages, the dose needed with once a day injections was 80±41 μg/day to maintain normocalcemia. In comparison, a fixed dose of 20 μg/day of PTH(1-34) is used in the treatment of osteoporosis (teriparatide). In response to injection with such a high dose, large fluctuations occur in serum calcium levels, causing manifest (or relative) hypercalcemia in the hours following an injection [27]. Accordingly, in subsequent studies effects of twice a day injections were compared with once a day injections in adults and children [28-30]. These studies showed a significant reduction in dose needed to maintain normocalcemia (on averages 22 μg/day injected twice a day) causing less pronounced fluctuations in serum calcium levels. Most recently, Winer et al. [31,32] have published data from studies in which PTH(1-34) was administered as a continuously infusion by the use of an insulin pump. Using such an infusion technique, unphysiological diurnal variations in serum calcium levels were almost eliminated. The studies by Winer et al. [31,32] have been performed in adults as well as in children.

**RESULTS ON SERUM CALCIUM LEVELS FROM STUDIES ON rhPTH(1-84) THERAPY IN HYPOPARATHYROIDISM**

So far, data from two randomized controlled trials and one large cohort study have been published on effects of replacement therapy with rhPTH(1-84) in HypoPT [22,33,34]. In contrast to the studies by Dr. Winers group, in which dose of rhPTH(1-34) was carefully titrated thereby abolishing the need for concomitant treatment with activated vitamin D analogues,
the studies on rhPTH(1-84) have been performed using fixed doses administrated only once a day. In a Danish, investigator initiated, randomized controlled double-blind study, rhPTH(1-84) was administrated once a day in a fixed dose of 100 μg/day for 6 months [22]. The study showed a marked effect on serum calcium levels with a significant reduction in needs for additional treatment with calcium supplements and activated vitamin D analogues. However, similar to the findings in the study on injections once a day by Winer et al. [27], this study showed marked diurnal variations in response to therapy with biochemical hypercalcemia in 71% of the participants in the hours following an injection [35].

In the Randomized Evaluation of Fibrinogen Versus Placebo in Complex Cardiovascular Surgery (REPLACE) study, 134 patients with chronic HypoPT were randomized to 24 weeks of treatment with rhPTH(1-84) (n = 90) or placebo (n = 44). In the study, starting dose of rhPTH(1-84) was 50 μg/day which could be up-titrated to 75 or 100 μg/day while reducing daily dose of calcium supplements and activated vitamin D analogues [34]. The primary endpoint of the study was the proportion of patients at week 24 who achieved a 50% or greater reduction from baseline in their daily dose of oral calcium and active vitamin D while maintaining a serum calcium concentration greater than or the same as baseline concentrations and less than or equal to the upper limit of normal. This primary endpoint was archived by a significantly higher proportion of participants randomized to active treatment compared with placebo (53% vs. 2%, respectively).

Similarly, in a cohort study by Columbia University in the USA, treatment with PTH(1-84) for up to 4 years have been shown to maintain normocalcemia while reducing needs for calcium supplements and activated vitamin D analogues [33].

**ADDITIONAL EFFECTS OF THERAPY WITH rhPTH IN HYPOPARATHYROIDISM**

Except for documenting the ability of maintaining normocalcemia in response to therapy with rhPTH, replacement therapy has so far not been documented to lower risk of comorbidities in HypoPT.

As PTH normally increases the renal tubular reabsorption of calcium, patients with HypoPT are prone to develop hypercalciuria. Although urinary calcium has been shown to be reduced in the hours following an injection, the hypocalciuric effect is not sustained throughout the day if rhPTH is injected only once or twice a day. The only studies demonstrating a consistently reduced renal calcium excretion in response to rhPTH therapy was the studies by Winer et al. [31,32] on pump therapy with PTH(1-34). This is somehow in accordance with the pharmacokinetic characteristics of rhPTH. Due to the short serum half-life, injections once or twice a day does not cause a sustained presence of PTH in the circulation. On the other hand, if rhPTH is delivered continuously by infusion (using an insulin pump), PTH is present in the circulation throughout the day which, apparently, is needed to lower urinary calcium.

None of the available studies have demonstrated an effect on “hard”-endpoints such as a reduced risk of extra-skeletal calcifications in response to therapy. However, none of the published studies have had a sample size or duration of treatment that allows for such measurements. Moreover, due to the rarity of the disease it is questionable whether it ever will be possible to document such effects in a randomized placebo-controlled design. In the studies by Winer et al. [28], it was reported that several of the participants preferred rhPTH(1-34) therapy compared with conventional treatment, but the studies did not show effects on measures of QoL. Similarly, in the Danish randomized controlled trial by Sikjaer et al. [36], no beneficial effects were found on QoL in response to 6 months of treatment. The lack of beneficial effects may, however, in part be attributable to the high proportion of participants experiencing hypercalcemia during the trial, i.e., the use of a fixed dose of 100 μg/day was clearly too high a dose for several of the patients. In contrast to the lack of beneficial findings on QoL in the randomized controlled trials, the cohort study by Columbia University did show an improved QoL in response to treatment compared with baseline scores [37]. As QoL, however, is a soft endpoint, a causal effect on QoL in response to replacement therapy with rhPTH needs to be documented in a placebo controlled design, as subjects initiating a new treatment are prone to favor this compared with conventional therapy.

**FURTHER DIRECTION ON THE TREATMENT OF HYPOPARATHYROIDISM**

HypoPT is a disease defined by lack of PTH resulting in hypocalcemia. However, the consequences of the diseases are not limited to symptoms of changes in serum calcium levels. Despite normalization of calcium levels in response to conventional treatment with calcium supplements and activated vitamin D analogues, a number of studies have shown that patients’ well-being remains impaired as well as patients are at increased risk of a number of complications including renal impairment, cataract and infections. Thus, the normalization of serum calci-
um levels should not be considered as a true normalization of calcium homeostasis, as conventional treatment does leave the patients with a number of complications and deficits. It is imperative to find out how to improve the treatment and prognosis of patients with HypoPT. PTH replacement therapy seems like an obvious solution, but administration of rhPTH is not straightforward. Most studies performed so far have adopted the treatment strategy used in osteoporosis, i.e., rhPTH has been injected subcutaneously on a daily basis using a fixed dose. Although the REPLACE study allowed for different fixed doses of rhPTH a precise dose titration was not an option. In the studies by Dr. Winers group, in which precise dose titrations have been performed, the dose needed to maintain normocalcemia has been shown to vary markedly between patients. Accordingly, similar to the treatment of diabetes with insulin, rhPTH probably needs to be dosed individually according to the needs of the individual patients. Moreover, several daily injections or delivery by (an insulin) pump is probably most suitable in order to provide the patients with a sustained presence of PTH in their circulation. If so, rhPTH replacement therapy may be the solution to relieve patients from symptoms and to lower risk of complications. Further studies are definitely needed to test whether such treatment regimens are of benefit.

CONCLUSIONS

Despite normalization of plasma calcium levels in response to conventional therapy with calcium supplements and vitamin D analogues, the normal physiology of calcium homeostasis is not restored in patients with HypoPT. Patients have an impaired quality of life and are at high risk of developing a number of comorbidities. Replacement therapy with PTH has recently been introduced and may help to improve the treatment of HypoPT, although further studies are needed to determine the best way of administering the drug.

CONFLICTS OF INTEREST

LR participated in an advisory board meeting for NPS pharma (Bedminster Township, NJ, USA). TS functioned as a consultant for NPS Pharma. Bedminster Township, NJ, no potential conflict of interest relevant to this article was reported.

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