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# **Is Parathyroid Hormone (PTH) replacement therapy effective in treating patients with hypoparathyroidism?**

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A SELECTIVE EVIDENCE BASED MEDICINE REVIEW

In Partial Fulfillment of the Requirements For

The Degree of Master of Science

In

Health Sciences – Physician Assistant

Department of Physician Assistant Studies  
Philadelphia College of Osteopathic Medicine  
Philadelphia, Pennsylvania

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## ABSTRACT

OBJECTIVE: The objective of this selective EBM review is to determine whether or not “Is Parathyroid Hormone (PTH) replacement therapy an effective treatment for patients with hypoparathyroidism?”

STUDY DESIGN: Review of a randomized control trial published in 2011, a prospective cohort study published in 2013, and a randomized crossover study published in 2012.

DATA SOURCES: All articles used were published in English, and were found in peer-reviewed journals using PubMed.

OUTCOMES MEASURED: The need to remove supplemental calcium from the diet, the amount PTH was used to maintain a normal range, and the method of PTH delivery (daily injections vs. subcutaneous pump).

RESULTS: Sikjaer et al found that patients were able to completely eliminate their daily dose of calcium and active vitamin D supplements without developing hypocalcemia compared to a placebo group. Cusano et al found that patients were able to reduce supplemental calcium and vitamin D significantly for up to four years as compared to a placebo group. Winer et al found that patients were able to use less PTH hormone to reduce supplemental calcium and magnesium supplementation from the diet.

CONCLUSIONS: The results of the three studies demonstrate that PTH replacement therapy is an adequate therapy for managing patients with hypoparathyroidism. In all three studies, PTH replacement therapy proved the maintenance of calcium levels in the blood, without hypocalcemia or hypercalcemia effects. This ultimately allowed patients to remove the need for supplemental calcium from the diet, or significantly reduce the amount of calcium and vitamin D supplements from the diet.

KEY WORDS: PTH replacement, hypoparathyroidism

## INTRODUCTION

Hypoparathyroidism is a chronic endocrine disorder that occurs when there is progressive destruction of the parathyroid glands, abnormal development, altered parathyroid hormone (PTH) production, or impaired PTH action<sup>4</sup>. This results in hypocalcemia which has a range of clinical manifestations ranging from fatigue, irritability, paresthesias to refractory heart failure, laryngeal spasms, and death<sup>4</sup>.

The incidence of hypoparathyroidism most commonly occurs in about 18% of patients after undergoing a thyroidectomy, with about 9.5% of those patients becoming symptomatic. The risk of developing hypoparathyroidism increases with age, especially for those who undergo a total thyroidectomy over the age of 50<sup>2</sup>. A rare cause of hypoparathyroidism is autoimmune, which can be isolated or combined with polyglandular autoimmunity type I (PGA-1). Congenital causes of hypoparathyroidism include DiGeorge's Syndrome where the parathyroid glands are absent or atrophied<sup>5</sup>. Transient hypoparathyroidism can be caused by manipulation of the blood supply or removal of one or more parathyroid glands during surgery<sup>2</sup>. Intermittent hypoparathyroidism can be a result of parathyroid insufficiency<sup>4</sup>.

A good history and physical exam, along with adequate laboratory testing is necessary to make the proper diagnosis of hypoparathyroidism. When serum calcium levels are decreased (less than 8.5 mg/dL) and serum phosphorous levels are elevated (>5.4 mg/dL), patients will start to become symptomatic, which includes fatigue, irritability, restless, and may include paresthesias<sup>4</sup>. If picked up early enough, a PTH immunometric assay can be ordered which will reveal a low serum PTH level. Once hypoparathyroidism is diagnosed, they are either treated as an acute or chronic patient, depending on severity of symptoms. If the patient is acute, he or she

is treated with IV calcium with calcitrol supplementation. If the patient is chronic, he or she will require lifelong oral calcium with vitamin D supplementation<sup>4</sup>.

In the United States, the surgical cause of hypoparathyroidism resulted in 8,901 cases over a 12-month period from 2007 – 2008, with 75% being transient and 25% being chronic<sup>5</sup>. Currently, the prevalence of hypoparathyroidism in the U.S. is estimated at 60-80,000 patients<sup>5</sup>. While there is no direct measurement of how much money is spent on managing patients with hypoparathyroidism, the surgical cause of the disease is measured at approximately \$4,642<sup>3</sup>.

Currently, PTH replacement therapy is not approved as monotherapy by the Food and Drug Administration in the United States. Calcium and vitamin D supplementation for hypoparathyroidism has proven to be effective but require lifelong monitoring and carry a great number of adverse reactions not limited to hypercalcemia and kidney stones<sup>4</sup>. PTH replacement therapy may be used as a treatment for patients with hypoparathyroidism<sup>4</sup>. Hypoparathyroidism is the only endocrine disorder in the United States without a single hormone replacement therapy as a treatment option<sup>4</sup>.

## OBJECTIVE

The objective of this selective EBM review is to determine whether or not, “Parathyroid Hormone (PTH) replacement therapy is an effective treatment for patients with hypoparathyroidism?”

## METHODS

The population for this study included all patients with hypoparathyroidism. The intervention studied was PTH (1-34) or PTH (1-84) replacement therapy. The treatment groups of PTH replacement therapy delivered via subcutaneous injections and continuous pump therapy were compared with placebo groups or twice daily subcutaneous injections of PTH. The

outcomes measured were patient oriented evidence. They included the number of patients who were able to remove supplemental calcium from their diet, the lowest amount of PTH necessary for subcutaneous pump therapy to maintain normal levels of calcium in the blood, and serum calcium and vitamin D levels in the blood. This systematic review includes a randomized control trial, a randomized crossover study, and a prospective cohort study.

The three studies included in this review were found using PubMed database by the author. Keywords included in the search were “PTH replacement therapy” and “hypoparathyroidism.” All articles were published in English in peer-reviewed journals. The three studies selected were chosen based on their relevance to my clinical question and whether or not they included patient oriented outcomes. One article was published in 2012 and the other two articles were published in 2011. All studies selected had very similar inclusion and exclusion criteria. Inclusion criteria included that the study was randomized, controlled, double blind and peer reviewed. Patients had to have had the diagnosis of hypoparathyroidism for at least a year and were currently on stable calcium and vitamin D supplements. Exclusion criteria included patients who had certain medication use within the timeframe of the diagnosis of hypoparathyroidism. The summary of the statistics that were utilized and reported were the mean change from baseline, relative benefit increase (RBI), absolute benefit increase (ABI), and the numbers needed to treat (NNT). Table 1 displays the demographics and characteristics of the included studies in this systematic review.

Table 1: Demographics &amp; Characteristics of Included Studies.

| Study                          | Type                       | # Pts | Age (yrs) | Inclusion Criteria  | Exclusion Criteria  | W/D | Interventions   |
|--------------------------------|----------------------------|-------|-----------|---|---|-----|---|
| Cusano <sup>1</sup><br>(2013)  | Prospective cohort         | 82    | 25 - 68   | 2 yrs hypoparathyroidism diagnosis<br>Stable regimens of supplemental Ca and vitamin D for at least 6 mo.   | Bisphosphonate use w/in 5 years or more than 6 months at a time<br>Women w/ 5 years' menopause<br>Pts who were on HRT, SERMs, corticosteroids, fluoride, Li, statin, loops, or MTX.   | 55  | PTH (I-84) subcutaneous injections every day for 2 years  |
| Sikjaer <sup>6</sup><br>(2011) | Randomized control trial   | 62    | 31 - 78   | Plasma ionized Ca and Mg levels w/in normal ranges<br>Pts with regular use of vit. D supplements for a minimum of 3 months prior to the study<br>Women on child-bearing age if they did not plan pregnancy and/or report use of contraception | Severely impaired renal patients<br>Impaired hepatic function<br>Pts dx with alcoholism or chronic drug use, malignant disease, sarcoidosis, Paget disease.<br>SERM use, corticosteroids, fluoride, Li, and anticonvulsants | 5   | PTH (I-84) subcutaneous injections every day for 6 months |
| Winer <sup>7</sup><br>(2012)   | Randomized crossover trial | 8     | 36 - 54   | Diagnosis of postsurgical hypoparathyroidism x 12 months<br>Received calcitrol and Ca supplements   | Not included in study   | 0   | PTH (I-34) delivered by insulin pump for 6 months         |

## OUTCOMES MEASURED

The outcomes measured in this study were based on the number of patients who were able to eliminate supplemental calcium from the diet. Other outcomes included were the least amount of PTH required to maintain therapeutic serum calcium levels, the method of PTH delivery (subcutaneous injections vs continuous infusion pump), and the number of patients who were able to reduce the amount of supplemental calcium from their diet. These outcomes were measured using serum calcium and vitamin D levels, urine calcium levels, and the amount of PTH necessary for delivery.

## RESULTS

In the prospective cohort study Cusano et al. 82 patients were treated with PTH (1-84) for four years, with continuous monitoring of calcium and vitamin D requirements, serum urinary calcium, serum phosphorus, bone turnover markers, and bone mineral density (BMD)<sup>1</sup>. The patients selected were based on the set of inclusion and exclusion criteria as provided in **Table 1**. Of the 82 patients who provided written informed consent to participate in the study, only 27 patients were followed for the duration of the study and were included in the analysis of data<sup>1</sup>. The most common reason for loss to follow up was logistics of travel and loss to follow up. The demographics of the study included patients between the ages of 25 – 68 years with a mean age of 51 years, and 74% were women. The two major etiologies of hypoparathyroidism were postsurgical and autoimmune disease<sup>1</sup>. Patients were administered PTH (1-84) at a starting dose of 100 mcg subcutaneously every other day. Monitoring was accomplished by a review of symptomatology and regular measurements of serum and urine calcium levels<sup>1</sup>. The levels were monitored at baseline three times before treatment and at months 1, 2, 3, 4, 5, 6, 9, 12, 18, 24, 30,

36, 42, and 48<sup>1</sup>. The primary outcome measured was if whether or not patients could have their dose of supplemental calcium and vitamin D requirements reduced or completely eliminated from their diet. The data reported was continuous and could not be converted into dichotomous data. Table 2 summarizes the data presented in the Cusano et al. study.

Table 2: Median change of supplemental calcium from baseline

|                                   | Baseline                | 4 years of PTH therapy  |
|-----------------------------------|-------------------------|-------------------------|
| Supplemental Calcium Requirements | 2.7 +/- 3 grams per day | 1.7 +/- 3 grams per day |

P = 0.006

This study demonstrates that after four years, the patients who received the PTH replacement therapy were able to significantly reduce or completely eliminate their daily calcium and vitamin D supplements from their diet. The p value is reported at 0.006 which is statistically significant, meaning that the intervention of PTH replacement therapy was proven to be effective in this study. Throughout the study, there were 11 episodes of mild hypercalcemia in eight subjects with the majority of episodes occurring within the first 6 months and resolving with adjustment of supplemental calcium and vitamin D. No episodes required hospitalizations. The most common adverse reactions reported from patients were musculoskeletal, gastrointestinal, and mental and mood.

In the randomized crossover trial Sikjaer et al. 62 patients with the diagnosis of hypoparathyroidism were randomized to daily treatment with PTH (1-84) or similar placebo for 24 weeks as add-on therapy to conventional treatment<sup>6</sup>. The patients were selected based on a set of inclusion and exclusion criteria as outlined in **Table 1**. A total of 5 patients did not complete the trial – one patient never started the treatment, two patients dropped out for personal reasons, and two patients dropped out as a result of side effects (one reporting nausea and one reporting dizziness)<sup>6</sup>. The only statistically significant adverse reaction of PTH replacement therapy

compared with the placebo group was reported to be nausea ( $p < 0.001$ )<sup>6</sup>. The demographics of the study included patients between the ages of 31 and 78 years of age with a mean age of 52 years, and 86% were females. The major etiology of hypoparathyroidism was postsurgical (94% of patients in the study). Patients were randomly assigned to receive a daily self-administered subcutaneous injection of either 100 mcg of PTH (1-84) or placebo. According to a predefined schedule, daily doses of vitamin D and calcium supplements were titrated down if patients developed hypercalcemia (plasma  $ca^{+2} > 1.40$  mmol/L). Patients were monitored with office visits, fasting blood samples, and 24-hour urine samples at weeks 1, 2, 3, 4, 6, 8, 12, 16, 20, and 24. The primary outcome measured was whether or not patients could completely eliminate the need for supplemental calcium and vitamin D from their diet. The data was reported in dichotomous form. The data was analyzed in the groups to which they were randomized (intention to treat analysis), with less than 5% of the data missing. Tables 3, 4, and 5 summarize the results of the Sikjaer et al. study.

Table 3: Number of patients able to discontinue supplemental calcium intake

|                    | PTH (n = 32) | Placebo (n=30) |
|--------------------|--------------|----------------|
| Number of patients | 15           | 0              |

Table 4: Efficacy of PTH replacement therapy in eliminating supplemental calcium from diet

| Proportion of patients eliminating supplemental calcium on placebo (CER) | Proportion of patients eliminating supplemental calcium on PTH (EER) | Relative benefit increase (RBI) | Absolute benefit increase (ABI) | Number needed to treat (NNT) |
|--|--|---------------------------------|---------------------------------|------------------------------|
|  |  | $\frac{EER - CER}{CER}$         | EER - CER                       | 1/ABI                        |
| 0  | 0.469  | 0                               | 0.469                           | 3                            |

P < 0.001

Table 5: Efficacy of PTH replacement therapy on development of adverse events

| Proportion of patients experiencing nausea on placebo (CER) | Proportion of patients experiencing nausea on PTH (EER) | Relative risk increase (RRI) | Absolute risk increase (ARI) | Number needed to harm (NNH) |
|---|---|------------------------------|------------------------------|-----------------------------|
|   |   | $\frac{EER - CER}{CER}$      | EER - CER                    | 1/ARI                       |
| 0   | 0.25  | 0                            | 0.25                         | 4                           |

P <0.001

This study demonstrates that PTH replacement therapy may eliminate the need for supplemental calcium and could be a cost-effective treatment option for patients with hypoparathyroidism. The ABI displays an increase in treatment effect with the PTH group compared with the placebo group. The RBI displays the effectiveness of PTH replacement therapy compared with the probability of eliminating supplemental calcium from the diet without the therapy. The NNT is calculated to determine the number of patients that need to receive PTH replacement therapy in order to reduce the need of supplemental calcium from the diet. In the Sikjaer et al. study, only three patients require treatment to have one completely eliminate supplemental calcium from the diet. The NNH was calculated to determine the number of patients that need PTH replacement therapy in order to experience nausea. Four patients require treatment to have one experience nausea as a side effect of PTH replacement therapy compared to the control group.

In the randomized crossover trial conducted by Winer et al. 8 patients with the diagnosis of hypoparathyroidism were used to compare continuous PTH (1-34) delivery, by insulin pump, with twice-daily subcutaneous injections. They compared the amount necessary to ensure safe and effective management of calcium levels in the serum, and whether or not subcutaneous delivery of PTH could be used as an alternative to twice-daily injections. The patients were

selected based on a set of inclusion and exclusion criteria as stated in **Table 1**. All patients selected completed the trial. The demographics of the patients selected to participate had received a diagnosis of postsurgical hypoparathyroidism for at least 12 months. The mean age was 46 years, with a range of 36 – 54 years of age. Patients were randomly assigned, at study entry in blocks of four to receive PTH (1-34) initially either by insulin pump or by twice-daily injection and were crossed over to the alternate delivery method after the initial 3-month treatment evaluation<sup>7</sup>. Patients were monitored at 0, 3, and 6 months throughout the study via four-day inpatient admissions. During these admissions, PTH therapy by pump or injections was initiated and dose adjusted before discharge. Subjects were instructed not to alter activity level throughout the study, and completed weekly questionnaires, via the study website, that screen for symptoms of hypoparathyroidism or adverse events. The primary outcome measured was the amount of PTH (1-34) required for adequate management of patients with hypoparathyroidism. The data was presented in dichotomous form. The data was analyzed in the groups to which they were randomized (intention to treat analysis), and then crossed over. Table 6 summarizes the results of the Winer et al. study.

Table 6: Median change of PTH (1-34) required from baseline

|               | Twice-daily injections | Insulin pump delivery |
|---------------|------------------------|-----------------------|
| Amount of PTH | 37 +/- 14 mcg per day  | 13 +/- 4 mcg per day  |

P < 0.001

Winer et al. demonstrates that if pump therapy is used to manage PTH delivery in patients with hypoparathyroidism, then the amount of PTH required to minimize the complications of hypoparathyroidism is less than using the subcutaneous injections of PTH. This ultimately results in reducing the cost disparity with PTH replacement therapy<sup>7</sup>. No serious adverse reactions occurred throughout the study. Two patients experiencing transient injection

site erythema. At the end of the study, seven of the either patients preferred pump therapy over twice-daily delivery due to greater convenience of use.

## DISCUSSION

These three studies support the use of PTH replacement therapy as effective in the management of patients with hypoparathyroidism. PTH replacement therapy is currently approved as an adjunct treatment for management of patients with hypoparathyroidism. The only condition in which PTH mono therapy is currently approved by the FDA is osteoporosis<sup>2</sup>. Contraindications for PTH replacement therapy include the diagnosis of hyperparathyroidism, hypercalcemia, or patients at a higher baseline risk for osteosarcoma<sup>2</sup>. Another absolute contraindication for therapy also includes Paget disease of the bone, or any type of malignancy as hypercalcemia may be a result of the natural course of the disease. Problems with PTH therapy in the past include the development of osteosarcomas. PTH replacement therapy has been studied in osteoporosis treatment and is proven to produce an accumulation of longer lived, apoptosis-resistant osteoblasts on bone surfaces that result in the risk of an osteosarcoma<sup>2</sup>.

Limitations of searching for studies were due to the fact that PTH replacement therapy is still new and not very well studied for the treatment of patients with hypoparathyroidism. Another major limitation of these three studies were the small study size. In each study, the vast majority of patients' etiology of hypoparathyroidism was due to surgical resection of the thyroid gland, therefore limiting data on those with autoimmune or genetic causes of hypoparathyroidism. Also, the only study that proved to successfully proved to safely eliminate the need of supplemental calcium and vitamin D from the diet was Sikjaer et al. Cusano et al. proved that the amount of supplemental calcium and vitamin D can be significantly reduced

while on PTH replacement therapy, while Winer et al proved that the delivery method can play a role on cost of therapy and amount of PTH necessary for successful treatment.

### CONCLUSION

Although further studies are warranted, the three studies strongly suggest that PTH replacement therapy can be used as treatment for patients with hypoparathyroidism<sup>1,6,7</sup>. Each of the studies followed the patients for an adequate amount of time although the sample sizes were relatively small in each study. However, the results still strongly supported the notion of PTH replacement therapy as being effective. Future study is warranted to determine whether or not PTH replacement therapy can be used for patients with multiple etiologies (autoimmune, genetic) of hypoparathyroidism. Study design could also be manipulated to determine whether or not PTH replacement therapy could be used for patients who had a diagnosis of acute hypoparathyroidism, as these studies only used patients who had a diagnosis of chronic hypoparathyroidism. It would also be beneficial to know the long term side effects of PTH replacement therapy as all three studies could not make a comment.

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