Review Article
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Primary Hypoparathyroidism, Current Treatment, and Recent Experience with Parathormone Analogs in Adults

Primer Hipoparatiroidizm, Güncel Tedavisi ve Erişkin Hastalarda Parathormon Analoglarının Etkinliği

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Abstract

Parathormone (PTH) is a polypeptide hormone consisting of 84 amino acids. It is secreted from the parathyroid glands and functions to maintain serum calcium (Ca) and phosphate (PO4−) levels within a narrow range. Primary hypoparathyroidism (PHP) is a rare disease characterized by low PTH levels despite low serum Ca and high PO4 levels. It mostly occurs after thyroid surgery or due to autoimmunity. This review focuses primarily on hypoparathyroidism in adults, which is commonly treated with calcitriol and oral Ca. Since this treatment does not completely compensate for the physiological effects of the absent PTH, patients may still experience hypocalcemia-related symptoms. Moreover, PHP is associated with increased morbidity due to complications attributed to the disease itself and its treatment. PTH (1-34) and PTH (1-84), two analogs of PTH that have been used recently, provide better treatment outcomes. This review summarizes the etiology, current treatment modalities, and related complications, along with the recent experience of using PTH analogs.

Keywords: Hypoparathyroidism; hypocalcemia; PTH (1-34); PTH (1-84)

Özet

Parathormon (PTH), 84 amino asitten oluşan polipeptid yapıda bir hormondur. Paratiroid bezlerinden salgılanarak serum kalsiyum (Ca) ve fosfat (PO4−) seviyelerini dar bir aralıkta tutulmasını sağlar. Primer hipoparatiroidizm (PHP), düşük serum Ca ve yüksek PO4 seviyelerine rağmen düşük PTH seviyeleri ile karakterize nadir bir hastalıktır. Çoğunlukla tiroid cerrahisi sonrası veya otoimmünite nedeniyle ortaya çıkar. Bu makalede esas olarak erişkinlerde saptanan primer hipoparatiroidizm üzerinde durulacaktır. Tedavide çoğunlukla kalsitriol ve oral kullanılmakta ancak PTH'nin fizyolojik etkilerini tamam olarak karşılanmadığından, hastalar hipokalsemi ile ilişkili semptomlar yaşayabilmektedirler. Ayrıca PHP, hastalığın kendisine ve tedavisi ile ilişkili komplikasyonlara bağlı olarak artan morbidite ile ilişkilidir. Son zamanlarda PHP tedavisine 2 PTH analoğu olan PTH (1-34) ve PTH (1-84) tedavisi kullanımı sunulmuştur. Bu derleme, etiyolojiyi, güncel tedavi yöntemlerini ve ilgili komplikasyonları, PTH analoglarının kullanımıyla ilgili son deneyimler özetlenecektir.

Anahtar kelimeler: Hipoparatiroidizm; hipokalsemi; PTH (1-34); PTH (1-84)

Introduction

Parathormone (PTH), a polypeptide hormone, is secreted from the parathyroid (PT) glands. Its secretion is regulated by serum calcium (Ca) and phosphate (PO_4^-) levels and Ca-sensing receptors (CasR) located in the PT glands. PTH maintains serum Ca and PO_4^- levels within a narrow range via direct involvement of kidneys, bones, and indirectly through the intestines. PTH promotes PO_4^- excretion from the renal tubules and increases Ca and magnesium (Mg) reabsorption by distal tubules. Moreover, it increases the levels of serum Ca and PO_4^- by

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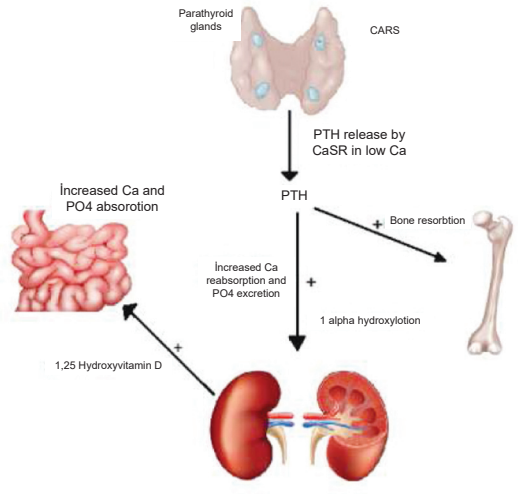

Figure 1. Regulation of Ca and PO4−homeostasis in humans.
Ca: Calcium; PO4−: phosphorus;
CaSR: Calcium-sensing receptor; PTH: Parathormone.

stimulating osteoclasts and increasing bone resorption. Osteoblasts, which are activated by PTH stimulation, increase bone formation and signal the pre-osteoclasts to differentiate into mature osteoclasts. Mature osteoclasts, in turn, increase bone resorption. Thus, PTH participates in normal dynamic bone turnover through an indirect mechanism. In addition, stimulation of 1-α-hydroxylase in the renal cells promotes PTH-induced formation of the active form 1-25$(OH)_2$ vitamin D from 25(OH)vitamin D, which in turn increases the intestinal Ca and PO_4^- reabsorption. 1-25$(OH)_2$ vitamin D and PTH work simultaneously to maintain serum Ca, PO_4^-, and Mg levels within a narrow range (8.5-10.5 mg/dL, 2.5-4.5 mg/dL, and 2.0-4.0 mg/dL, respectively) (Figure 1) (1).

Primary hypoparathyroidism (PHP) is characterized by the presence of low or normal PTH serum levels despite hypocalcemia and hyperphosphatemia. In addition, it is associated with a low bone turnover with increased bone mineral density (BMD). Although its incidence varies among different individuals, PHP is observed with a frequency of 10 to 40 cases per 100,000 individuals and surgical PHP with a frequency of 6.4 to 29 cases per 100,000 individuals. The incidence of non-surgical PHP is considerably lower, i.e., 2.3 to 17 cases per 100,000 individuals (2-6). Thus, neck surgery accounts for approximately 75% of PHP cases (5,7).

Relevant symptoms and findings of PHP include severe hypocalcemia as well as weakness; muscle cramps; numbness in the lips, fingertips, and toes; depressive symptoms; basal ganglia calcification; seizures; cataract; hypotension; laryngospasm; and cardiac arrhythmias (prolonged QT). Moreover, PHP may be present as a laboratory finding alone.

Approximately 75% of PHP cases develop after total thyroidectomy (TTx) (8). Hypocalcemia lasting longer than six months after thyroidectomy is defined as permanent PHP and should not exceed 1 to 2% in specialized centers. In other words, the risk of permanent PHP is less than 2% in the hands of surgeons performing more than 100 thyroidectomies annually (9,10). Female gender, recurrent neck surgery, the addition of central and lateral lymph node dissection (LND) to TTx, not considering PT glands during surgery, and Graves' thyroidectomies are associated with an increased risk of developing permanent PHP (11).

The second most common cause of PHP is autoimmunity (10). PHP either occurs in isolation or presents itself as a part of autoimmune polyendocrine syndrome type 1 (APS-1) associated with other autoimmune endocrinopathies such as Addison's disease and Hashimoto's disease. Autoimmune PHP is associated with varying rates of anti-CaSR antibody positivity; however, whether the antibody is functionally active or causes tissue damage is unknown (10).

The contribution of genetic causes to PHP is less than 10% (12). One of the genetic causes of PHP is APS-1, which occurs due to a mutation in the *AIRE* gene, in which other endocrine glands (i.e., Addison's disease, autoimmune thyroid disease) are also affected. APS-1 is characterized by candidiasis, alopecia, pernicious anemia, and hepatitis. DiGeorge syndrome is associated with 22q11 deletion, in which congenital heart defects, immunodeficiency, and pharyngeal and laryngeal abnormalities are observed owing to the abnormal development of the third and fourth pharyngeal pouches. Most cases are sporadic and can be detected at a rate of 1 in 4,000 to

5,000 births (13). Autosomal dominant hypocalcemia type 1 is characterized as activated CasR receptors due to mutations in the *CasR* gene. Autosomal dominant hypocalcemia type 2 is characterized by the activated alpha subunit of the G protein-a key mediator in the CasR signaling pathway due to an activating mutation of guanine nucleotide-binding protein alpha 11 (*GNA11*) gene, which suppresses PTH secretion and causes hypercalciuria and hypomagnesemia (14,15). The HRD syndrome consisting of hypoparathyroidism, sensorineural deafness, and renal dysplasia syndrome results from mutations in the GATA-binding protein 3 gene (*GATA3*) and is inherited either as an autosomal dominant or recessive disorder. Kenny Caffey type 1 disorder is caused by mutations in the tubulin-specific chaperone E (*TBCE*) gene and has clinical features such as congenital hypoparathyroidism, severely delayed growth, mental retardation, microcephaly, and facial dysmorphism (15).

Other causes of PHP are hypomagnesemia, ionizing radiations, infiltrative diseases such as hemochromatosis/hemosiderosis, Wilson's disease, and osteoblastic metastases (i.e., breast and prostate). In cases where the cause of hypoparathyroidism is not identified, following a careful clinical and laboratory evaluation and no family history can be considered idiopathic. Idiopathic cases may have *de novo* activating mutations in the *CASR* gene. Idiopathic cases have also been reported in North America with a 6% frequency (5,8,11,12,16).

PHP should be considered when there is a history of neck surgery, exposure to radiation, and the presence of autoimmune diseases.

Renal complications: Because the tubular reabsorption of Ca and excretion of PO_4^- cannot be achieved in PHP, the extent of calciuria is associated with the levels of serum Ca. Thus, high serum Ca levels (>9.5 mg/dL) due to overtreatment, hypercalciuria, decreased glomerular filtration rate (GFR), and nephrolithiasis have been reported in patients with PHP (4). It is recommended to keep the serum Ca levels in the low normal range (7.5-8.5 mg/dL) to prevent complications. Mitchell et al. showed that although serum Ca levels were within the targeted low normal range, nephrolithiasis was detected in 31% of patients, and stage 3 or more advanced chronic renal failure (CRF) in 41% of patients (4). These patients were 2 to 17 times more likely to develop CRF than their age-matched controls. GFR loss was inversely related to age, duration of disease, Ca levels above >9.5 mg/dL, high calcium levels for prolonged durations, and high $CaxPO_4$ products (4, 17). Moreover, patients with four or more episodes of hypercalcemia had a three-fold risk of developing renal diseases (17). The use of alfacalcidol above the median dose was associated with a reduced risk of renal complications (17).

In a study conducted by Undenbjerg et al., 688 patients having surgical PHP for 8.4 years were at a 4.02-fold (1.64-9.90), and 3.10 fold (1.73-5.55) increased risk of developing nephrolithiasis and CRF, respectively, as compared with healthy controls (2). In patients with non-surgical PHP, the risk of any renal disease increased three-fold, and the risk of CRF increased six-fold, compared with the controls [3.39 (1.67-6.88) and 6.01 (2.45-14.75), respectively] (3). In contrast, there was no increase in the risk of developing nephrolithiasis in patients with non-surgical PHP (3).

Cardiovascular complications: Underbjerg et al. did not detect an increase in cardiovascular disease (CVD), ischemic heart disease and arrhythmia, CVD-related hospitalization, or overall mortality in patients with surgical PHP and with a disease duration of eight years (2). In contrast, patients with non-surgical PHP had an approximately two-fold increase in ischemic heart disease, arrhythmia, and any CVD over an average follow-up of 49.7 years that was equal to the median age of patients (most since birth) (3). Patients with PHP for more than 20 years had a four-fold increased risk of developing CVD, compared with patients having a disease duration of less than 7.2 years. Patients with four or more hypercalcemic attacks had the highest risk of developing CVD (i.e., nine-fold) compared with those without these attacks (17). Unlike patients with non-surgical PHP, the minimal risk of CVD in patients with surgical PHP may be associated with shorter disease duration (11 vs. 47 years). In a population-based study,

Vadiveloo et al. suggested that PHP and non-surgical PHP were associated with 2.24-fold and 2.10-fold increased risk of developing a CVD, respectively (3,18).

Other complications: Mitchell et al. found other complications in 120 patients with mostly postsurgical PHP and a mean disease duration of 17 years. Thirty-three percent of patients were admitted to the hospital at least once due to complications related to PHP. Sixty-two percent of the admissions were due to hypocalcemia, 12% due to symptomatic hypercalcemia, and 26% due to other reasons. Basal ganglia calcification was detected in approximately half of the patients (4).

The frequency of hospitalization due to seizures in patients with surgical PHP increased (H: 3.82; 95% CI: 2.15-6.79) compared with the control group, and a 10-fold increase was observed in patients with non-surgical PHP (H: 10.05; 95% CI: 5.39-18.72) (2,3).

The risk of developing a cataract was the same as that in patients with surgical PHP as compared with the control group. The risk increased in patients with non-surgical PHP as compared with the control group (H: 4.21; 95% CI: 2.13-8.34) (3,19).

There was a 1.42-fold increase in the risk of infections requiring hospitalization in patients with surgical PHP and a 1.9-fold increase in patients with non-surgical PHP (3,19). A three-fold increase in hospitalization due to upper respiratory tract infections and a four-fold increase in urinary tract infections were reported. A significant risk continued to be present even when patients with DiGeorge and autoimmune polyglandular syndrome type 1, who had an immune deficiency, were excluded (3). Increased risk of infection was associated with disease duration, presence of more than three hypercalcemic episodes, and high serum PO_4^- levels. However, a calcitriol dose of more than 1 µg/d is known to be associated with a decrease in the infection risk (17).

Psychiatric diseases such as depression and bipolar disease were found to be increased by two-fold in patients with surgical PHP, and by 2.7-fold in patients with non-surgical PHP (3,19). Disease duration (above 20.2 years), high PO_4^- levels, and Ca and PO_4^- products ≥2.93 $mmol^2/L^2$ were found to be associated with 4.72-fold, 8.43-fold, and 6.85-fold increased mortality, respectively (17).

Effects on bone: In a retrospective study conducted on 42 patients with PHP, Mitchell et al.. reported high total hip (0.9±1.4) and spine (2.4±1.4) (p<0.001) Z scores (4). A total of 44 fractures developed in 21 patients, although 10 of them were traumatic (4). Another retrospective study performed by Underbjerg et al., in patients with surgical PHP, reported no increase in fracture risk (FR) when compared with the control group (H: 1.03; 95% CI: 0.83-1.29) (19). In contrast, proximal humerus and upper extremity were found to have a significantly lower FR, whereas other regions showed no difference (H: 0.24; 95% CI: 0.09-0.68 and H: 0.69; 95% CI: 0.49-0.97, respectively) (19). Another study from the same group on patients with non-surgical PHP reported no increase in the general FR as compared with the control group (H: 1.40; 95% CI: 0.93-2.11). However, an increased FR was detected in the forearm (p=0.003). The same study reported a significantly increased FR in patients under 18 years (18-fold) (3). The authors associate the increased risk of fractures in the upper limb with an enhanced risk of cataracts and seizures due to falls (3).

Quality of life (QoL): Disease-related symptoms, such as weakness, muscle spasm, pain, paraesthesia, muscle weakness, difficulty in concentrating, forgetfulness, sleep disturbances, and disease- and treatment-related complications, showed significantly lower QoL even in treatment-compliant patients. Personal social relationships and the professional lives of patients were significantly affected (20).

A study in Denmark with 22 surgical PHP and hypothyroidism, 22 surgical hypothyroidism alone, and 22 healthy controls found that patients with surgical hypothyroidism and PHP had significantly lower physical component scores compared with patients with surgical hypothyroidism alone and those in the control group (21). The presence of PHP exerted a negative effect on the QoL.

Astor et al. compared SF-36 scores of 283 patients with PHP (70% postsurgical) with normal population data. All domains of SF-

36 were significantly lower in patients with PHP. Moreover, scores of female patients were lower than those of male patients (p=0.03, both). The number of surgical patients was lower than non-surgical patients for physical (p=0.002), body pain (p=0.03), and vitality (p=0.04) domains (22). Hospital Anxiety and Depression Scale anxiety and depression scores were significantly higher in patients with PHP compared with the normal population. Moreover, surgical PHP patients had higher depression scores than non-surgical PHP patients (22). This decrease in QoL was not associated with serum Ca levels (22), indicating that it could be related to the direct effects of PTH, other than Ca regulation in tissues or thyroid malignancy, or Graves' disease, which could be the reason for the surgery (22). Interestingly, the study conducted by Tabacco et al., in which the effect of eight years of PTH (1-84) treatment on QoL was investigated with 20 patients (60% surgical) with an average disease duration of 25 years, reported significant improvement in 5 of 8 domains of SF-36, compared with the baseline scores. The worse the baseline scores, the more the treatment outcomes. Conventional treatment dose and physical and mental component summary scores were found to be inversely correlated (23). Similarly, another study conducted with PTH (1-84) reported a negative correlation between baseline SF-36 scores and improvement in QoL after treatment (24).

Even in patients whose serum Ca and vitamin D levels are stable, the lower SF-36 scores, compared with the normal population, could be explained by the direct effect of PTH on the central nervous system and muscle tissue. In addition, the effect of PTH treatment on the QoL could be explained by reducing conventional treatment, thereby decreasing the number of tablets taken daily (23).

Treatment

Acute treatment

Hypocalcemia is a medical urgency. Intravenous therapy should be applied in case of significantly prolonged QT, change in consciousness, tetany, seizures, laryngospasm, rapidly developing hypocalcemia after neck surgery, and corrected serum Ca level below 7 to 7.5 mg/dL even if the patient is asymptomatic. After intravenous administration of two ampules of 10% Ca gluconate (90 mg Ca^{2+} in 10 mL) in 50 mL of 5% dextrose infused in 10 to 15 min, a continuous infusion should be initiated. Electrocardiography (ECG) should be performed simultaneously to monitor the development of arrhythmias and QT duration, with a rate of 50 mL/h and an IV infusion prepared by adding ten ampules of 10% Ca gluconate in 1000 mL of 5% dextrose. In addition, oral Ca and calcitriol treatment should be started simultaneously. The infusion is discontinued after the symptoms, and ECG findings improve, and serum Ca levels reach a range of 8 to 9 mg/dL (25).

Chronic conventional treatment

Chronic treatment aims to improve the QoL by reducing the symptoms of the patient, ensuring the patient's well-being, and preventing the development of complications.

Agents used in the conventional treatment are oral Ca salts, 25(OH) vitamin D, calcitriol, thiazide diuretics, PO_4 binders, and/or recently, two new peptide analogs PTH (1-34) and PTH (1-84). The primary aim is to maintain the serum Ca levels as low as possible, and within a range where the patient does not experience hypocalcemia-related symptoms, hyperphosphatemia is prevented, and Mg levels are within the normal range.

The secondary aim is to maintain the serum Ca and PO_4^- products below 55 mg^2/dL^2 and prevent hypercalciuria after the target Ca and PO_4 levels are achieved and ultimately prevent treatment-related complications such as nephrocalcinosis, nephrolithiasis, renal insufficiency, calciphylaxis, and augmented atherosclerosis.

The frequency of follow-up visits varies from individual to individual and according to the treatment received. After the initial visit, 6-month or annual follow-up may be recommended in patients who are asymptomatic with biochemical parameters at the targeted levels. However, the majority of the patients require 3 to 6 months of follow-up. Patients who have changed their current treatment should be evaluated within two weeks. Twenty-four hours of urine Ca levels should be monitored annually.

Carbonate and citrate salts of Ca can be used. Although 1 to 2 g/day of elemental Ca is sufficient in divided doses, patients may

occasionally require up to 10 to 12 g/day Ca to achieve the targeted serum Ca levels. Ca carbonate ($CaCO_4$), which contains 40% elemental Ca and an acidic environment for absorption, is generally preferred. Ingestion of $CaCO_4$ with meals increases the absorption and binds to PO_4^- in the food. However, gastrointestinal side effects are high and adequate absorption may not be achieved in some cases using proton pump inhibitors and with achlorhydria. In such cases, Ca citrate, which contains 21% elemental Ca and does not need an acidic environment, could be preferred. Patients should be advised to take oral Ca salts 4 h after the levothyroxine treatment to enable adequate thyroid hormone absorption.

Because α-hydroxylation does not occur and is associated with impaired activation of vitamin D in PHP, calcitriol [1.25 $(OH)_2$ vitamin D] or alfacalcidol [1α(OH) vitamin D] is recommended. Calcitriol can be initiated at a dose of 0.25 μg/d and increased up to 2 μg/d. Alfacalcidol can be started at a dose of 0.5 μg and increased up to 4 μg/d. Unfortunately, conventional treatment does not completely meet the physiological effects of PTH; thus, renal excretion is directly related to serum Ca levels. In addition, hypercalcemia, hypercalciuria, hyperphosphatemia, and PO_4^- precipitation contribute to ectopic calcification and nephrocalcinosis with conventional therapy. Conventional treatment could also lead to hypercalciuria in 38% of patients, nephrolithiasis or nephrocalcinosis in 31% of patients, and stage 2 and 3 CFR in 31% and 45% of patients, respectively (17). To counter hypercalciuria, reduced oral Ca intake, sodium-restricted diet, and 25 to 100 mg/d thiazide diuretics, in divided doses, are recommended. Patients receiving thiazides should be monitored for hyponatremia and hypopotassemia. If necessary, potassium replacement or potassium-sparing diuretics can be added.

In the presence of hyperphosphatemia, PO_4^- restricted diet and PO_4-binding agents are recommended. Furthermore, reducing the dose of calcitriol treatment may also be helpful. Because Mg has an important role in PTH secretion and bioactivity, functional PHP can result in Mg deficiency; thus, hypomagnesemia should be treated when detected in patients with PHP.

Parathormone Analogs

Despite the conventional therapy, PHP-associated morbidity is high, and some patients still experience hypocalcemic episodes depending on the severity and disease duration. Thus, recently human PTH analogs PTH (1-84) and N-terminal PTH (1-34) have been developed and used in clinical trials.

Winer et al., in a 3-year randomized controlled trial, comparing PTH (1-34) (mean±SD: 37±2.6 μg/d, twice daily) with conventional treatment (mean±SD:. 0.91±0.2 μg/d calcitriol), in 27 patients, found that although serum Ca levels were within the low normal range in both arms, the 24-h urine Ca excretion remained significantly lower and in the normal ranges in the PTH arm but above the normal range in the conventional treatment arm (5.8±0.27 vs. 8.2±0.51 mmol/d, normal, 1.25-6.25 mmol/24, and 24-h urine PO_4^- and Mg were similar in both arms. Nevertheless, no positive effect of controlling hypercalciuria by PTH (1-34) has been detected on creatinine clearance after three years, probably due to relatively short follow-ups (26). In the same study, serum and urine bone turnover markers were significantly increased in the PTH (1-34) arm compared to the calcitriol arm and reached the highest level in 2.5 years of PTH (1-34) treatment (26). No significant difference was found between the two treatment arms in BMD of the whole body, lumbar spine, distal radius, and femoral neck. However, while BMD and bone mineral content (BMC) of the lumbar spine and the whole body remained stable in the PTH (1-34) arm for three years, a significant increase was achieved at the same regions in the calcitriol arm. Increased femoral neck BMD values were detected in both treatment arms (26). The increase in the calcitriol arm could be associated with a low bone turnover due to PHP, whereas the increase in serum and urine markers indicated an increased turnover with PTH (1-34). Until now, the effect of rhPTH (1-84) therapy on FR in PHP has remained unknown (27).

The same group compared PTH (1-34) treatment with twice-daily injection against the pump delivery in eight patients who had surgical PHP. The daily dose of PTH decreased by 65% to provide low normal serum Ca levels with pump delivery [13±4

(0.17±0.03) vs. 37±14 µg/d (0.47±0.13 µg/kg•d), $p<0.001$]. In addition, urinary Ca excretion reduced, serum Mg level was higher, and the need for Mg replacement decreased with pump delivery (28). Furthermore, bone turnover markers increased significantly in both groups to the physiological range; however, the values were lower in the pump delivery group. The authors concluded that PTH (1-34) treatment with pump delivery provided less frequent intervals and smaller doses, thereby causing fewer fluctuations in serum Ca levels, which is more physiological (28).

Mannstadt et al. conducted a 24-week, double-blind, placebo-controlled "REPLACE" study using PTH (1-84). They recruited 134 patients ($n=90$ in the study arm) with 76% surgical and 16% idiopathic PHP. At the beginning of the study, 68% of patients were taking high-dose calcitriol, and 32% of the patients were receiving more than 2,000 mg/day of Ca therapy. A 50% reduction in conventional treatment doses, when serum Ca levels were within the normal range, was established as the primary endpoint. The initial dose with PTH (1-84) was 50 µg/d. After dose titration, 52%, 27%, and 21% of patients received PTH (1-84) treatment doses of 100 µg/d, 75 µg/d, and 50 µg/d, respectively, at the end of the study. Finally, 53% of patients in the PTH arm and 2% in the placebo arm reached the primary endpoint. The calcitriol treatment was stopped in 43% of patients in the PTH arm and 5% of patients in the placebo arm. In addition, the need for oral Ca decreased (<500 mg/d). Similar mild side effects were detected in both arms (29).

Effects of PTH (1-84) on serum PO_4^- levels were investigated in a follow-up study of the REPLACE study, with 120 patients ($n=84$ patients in the PTH arm). The mean serum PO_4^- levels decreased and remained stable in the PTH arm. Urine PO_4^- excretion varied during the study. The levels of $CaPO_4$ products were still lower in the PTH arm than in the placebo arm (30). It was reported that $1.25(OH)_2$ vitamin D levels of patients with PTH (1-84) treatment continued in normal levels, although oral calcitriol treatment was discontinued in 62% of patients of PTH (1-84) group. Thus, PTH (1-84) resulted in a physiological transformation. In contrast, serum 25(OH)D levels declined steadily between the baseline and week 12 and subsequently stabilized. However, these remained below the baseline until week 24 in the PTH (1-84) arm. They suggested that a higher dose of 25-OH vitamin D treatment was required and the serum vitamin D levels should be monitored and replaced appropriately during PTH (1-84) use (30).

In another study conducted by Rubin et al., 33 patients were followed for six years under PTH (1-84) treatment. The PTH treatment was started with a dose of 100 µg every other day, and the dose was titrated according to the serum Ca levels and was increased up to 100 µg/d. The majority of the patients achieved a low-normal serum Ca level with a dose of 50 µg/d of PTH. At the end of the study, the need for an oral Ca replacement reduced by 53% in the first year and decreased from 2,657±190 mg/d to 1,236±190 mg/d at the end of the study ($p=0.001$). Similarly, the need for calcitriol replacement decreased by 67%, from 0.72±0.1 µg/d to 0.23±0.1 µg/d at the end of the study ($p<0.0001$) (31). Diuretics were discontinued in 16 (48%) of the patients who received calcitriol replacement and 5 (45%) of the 11 patients who received thiazide. The urine Ca excretion decreased significantly in the first, third, and sixth years of treatment, from 275±24 mg/day to 186±25 mg/day in the sixth year of treatment ($p=0.07$) (31). The serum PO_4^- levels decreased significantly in the fourth and fifth years of treatment; the significance disappeared in the sixth year. The renal function remained stable during six years of follow-up. The levels of bone turnover markers increased, starting from the first year, and remained significantly high at the end of six years. The activity of alkaline phosphatase also increased significantly at the end of the sixth year as compared to the baseline ($p<0.01$). The BMD scores of the lumbar spine and total hip increased significantly at the end of the sixth year compared to the baseline (3.8±1%, 2.4±1%, respectively). Although the femoral neck score remained similar to the baseline values at the end of the study, an average of 4.4±1% loss in the BMD score was detected in the distal radius ($p<0.0001$). Twelve hypercalcemic events that did not require hospitalization occurred

in nine patients, and hypocalcemia developed in three patients five times. In addition, a total of eight minor fractures developed in six patients at different times of the treatment in cortical bone-rich regions, and three patients developed nephrolithiasis (31).

Tay et al. conducted a study with 24 patients; at the end of 8 years of PTH (1-84) treatment, the requirement for oral Ca replacement decreased by 57% from 3,000±300 mg/d to 1,300±300 mg/d (32). The number of patients who required more than 1500 mg/day of oral Ca treatment decreased from 19 (79%) to 8 (33%) (p<0.01). The need for calcitriol treatment decreased by 76% and disappeared in half of the patients. The thiazide diuretic dose was reduced by 50% and was completely discontinued in two patients. Calcium excretion in 24-h urine decreased from 254±29 mg/d to 157±37 mg/d (p<0.01). The change in urine Ca excretion was not associated with the change in oral Ca replacement and PTH (1-84) dose (r=-0.29, p=0.26, and r=0.3, p=0.25, respectively). The renal function remained stable for eight years. The lumbar spine and total hip BMD scores increased, the femoral neck remained stable, and the distal radius score decreased (32). Throughout the study, three hypercalcemic events, which did not require hospitalization, and three hypocalcemic events developed in three patients. Eight fractures developed in six patients in the cortical bone-rich regions (32).

PHP increased the BMD score due to low bone turnover. The PTH treatment stimulated and normalized bone turnover, as evident from increased bone turnover markers (26,31). In two studies evaluating the effects of PTH (1-84) treatment on bone, bone biopsy performed 3 to 24 months after PTH (1-84) treatment showed increased new bone formation and intratrabecular tunneling in cortical and trabecular bone (33,34). In the group with a higher number of tunneling, bone turnover markers were higher, and PTH (1-84) effect on biochemical markers continued for 24 months. The increase in the "Haversian canals" in the cortical bone has been shown to cause an increase in porosity (33,34). Although PTH is anabolic for both cortical and trabecular bone, PTH (1-84) decreased the BMD score in the cortical bone-rich regions whereas increased the scores in the trabecular bone-rich regions. Because there is no control group in the 6 and 8 years of follow-up studies, it is not possible to answer the question of the developing fractures are a complication of PTH (1-84) treatment or related to PHP itself.

Thus, PTH (1-84) treatment in 6-and 8-year follow-up studies was found to be reliable; it provided stable serum Ca levels, reduced the need for conventional treatments, hypercalciuria, and ensured the normal cycle of the bone without any obvious side effects. Moreover, observing similar findings after eight years of follow-up showed that the effectiveness of the treatment probably continued.

Conclusion

Although hypoparathyroidism is a lifelong disease with high morbidity, it is preventable in most patients. Thyroid and PT surgeries with or without neck dissection are less morbid in the hands of endocrine surgeons or ENT surgeons specialized for head and neck surgeries. Each patient should be referred to experienced hands because this lifelong disease not only has severe treatment-related complications but also affects the QoL significantly. In addition, neck surgeries should be avoided because even at the hands of experienced surgeons, PHP, although much less likely, can occur (<1%). Conventional treatment with calcitriol and calcium salts is effective for the majority of patients. However, treatment-related complications could be present. The recent introduction of PTH analogs has led to more effective treatment of patients and probably less morbidity. Treatment of PTH (1-84) was approved by the Food and Drug Administration (FDA) in January 2015 for the treatment of PHP with a "black box" warning about an increased risk of osteosarcoma in rats. Fortunately, none has been observed in human studies, with 6-and 8-year follow-ups.

Although PTH (1-34) has been studied on patients with PHP, it has not been approved by the FDA or European Medicines Agency. Treatment with PTH analogs can be considered in patients with the below issues despite conventional therapy (8):

a. Inadequate control of serum Ca and PO_4^- levels.
b. High CaPO4 products and/or urinary Ca excretion.
c. Symptoms related to hypocalcemia through conventional treatment.
d. Requiring a higher dose of Ca (i.e., >2.5 g/d) or calcitriol >1.5 µg/d.
e. Evidence of nephrocalcinosis, nephrolithiasis, reduced renal functions on conventional treatment.

Hypocalcemia may be a more common adverse event with PTH (1-84) treatment than with conventional treatment. Although studies conducted to date have shown PTH (1-84) treatment to be effective, its efficacy is continuous and safe. There is a need for longer-term efficacy and safety studies, considering the lifetime necessity of the treatment.

Because of the lack of a study comparing the effectiveness of PTH (1-34) and PTH (1-84) treatments, it is not possible to comment on the effectiveness of the two molecules. However, applying two injections per day of PTH (1-34) may be a disadvantage. In addition, PTH (1-34) treatment was approved by the FDA for the treatment of osteoporosis in adults in 2002, but not for the treatment of PHP and restricted for three years (35). It is not licensed for use in long-term therapy. Science and industries are working on different formulations such as PEGylated PTH [PTH (1-34)], long-acting PTH, and TransCon PTH (36) for longer time effectiveness of PTH treatment. The cost-effectiveness of these analogs is another issue to be considered.

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Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Authorship Contributions

Control/Supervision: Murat Faik Erdoğan; Literature Review: Fatma Nur Korkmaz; Writing the Article: Fatma Nur Korkmaz; Critical Review: Murat Faik Erdoğan.

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