CASE REPORT

Two-Year Follow-Up of Parathyroid Hormone, Calcium, and Vitamin D Serum Levels in a Patient after Parathyroidectomy

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ABSTRACT

Parathyroidectomy is the definitive treatment for primary hyperparathyroidism. Because of the hungry bone syndrome and prolonged hypocalcemia risk, we must follow up on a patient's parathyroid hormone, calcium, and vitamin D serum after parathyroidectomy. In this case report, we reported on a parathyroidectomy patient whom we followed for two years and who, interestingly, had elevated parathyroid hormone levels. A 35-year-old male patient diagnosed with a left parathyroid tumor underwent parathyroidectomy and isthmolobectomy. The patient was treated with calcium, vitamin D, and levothyroxine supplementation. We diagnosed the patient with hungry bone syndrome on the fourth day of post-parathyroidectomy. Then, we documented calcium, vitamin D, and PTH levels in the next two years. The calcium levels are 7.2 (June 2022), 8.2 (July 2022), 8.5 (September 2022), 7.8 (October 2022), 8.1 (June 2023), 9.7 (June 2024). The PTH levels are 244.2 (June 2022), 328.3 (July 2022), 306.5 (September 2022), 457.2 (October 2022), 163.3 (June 2023), 34.4 (June 2024). The Vitamin D levels are 34.4 (July 2022), 13.4 (March 2023), 35.2 (September 2023), 50.4 (April 2024). We increased the dose of calcium and vitamin D supplementation. The patient is in good condition and has reached a normal level of these laboratory parameters in the second year post-parathyroidectomy. PTH, calcium, and vitamin D serum are needed for follow-up in patients after parathyroidectomy. Normalizing calcium and vitamin D serum is essential to maintaining a normal PTH level. Normal PTH, calcium, and vitamin D serum are the cure indications in this patient.

Keywords: Parathyroidectomy, parathyroid hormone, calcium, vitamin D

INTRODUCTION

Parathyroidectomy is the definitive treatment for primary hyperparathyroidism. Parathyroidectomy is the preferred choice of treatment and indicated for all patients with symptomatic primary hyperparathyroidism, along with recommendations with other considerations. However, parathyroidectomy is not without possible flaws. Hungry bone syndrome may occur postoperatively. This condition is most defined as a profound hypocalcemia of less than 8,4 mg/dL which persists for more than four days postoperatively, presenting along with hypophosphatemia, hypomagnesemia, and normal parathyroid hormone (PTH) levels.[1-7] Because of the hungry bone syndrome and prolonged hypocalcemia risk, we need to follow up on a patient's parathyroid hormone, calcium, and vitamin D serum after parathyroidectomy. PTH is integral in the regulation and homeostasis of serum calcium and phosphate. A reduction in serum calcium levels stimulates the release of PTH from the parathyroid glands which subsequently enhances calcium reabsorption through the kidney, inhibits phosphate reabsorption, and induces phosphaturia. PTH also stimulates conversion of the inactive 25-hydroxyvitamin D (25[OH]D) to the active metabolite 1,25(OH)2D through transcriptional activation of the gene which codes for the 25-hydroxyvitamin D-1a hydroxylase (CYP27B1) enzyme. This active metabolite could increase intestinal absorption of calcium and, less significantly, phosphate. These PTH responses to hypocalcemia aim to restore serum calcium levels towards the normal range.[8]

In this case, parathyroidectomy patient that we followed for two years and interestingly had elevated parathyroid hormone levels. Postoperative increase of PTH may be associated with persistent or recurrent hyperparathyroidism, vitamin D insufficiency, mild renal failure, hyperfunction of previously suppressed parathyroid glands, unrecognized familial hypercalciuric hypocalcemia, and increased bone redistribution of calcium.[9-11]

CASE ILLUSTRATION

A 35-year-old male patient diagnosed with left parathyroid tumor by laboratory and radiologic examination underwent parathyroidectomy and isthmolobectomy. The patient was treated with calcium, vitamin D, and levothyroxine supplementation. We diagnosed the patient with hungry bone syndrome on 4th day of post parathyroidectomy.

Then, we documented calcium, vitamin D, and PTH levels in the next two years. The calcium levels are 7.2 mg/dl (June 2022), 8.2 mg/dl (July 2022), 8.5 mg/dl (September 2022), 7.8 mg/dl (October 2022), 8.1 mg/dl (June 2023), 9.7 mg/dl (June 2024). The PTH levels are 244.2 pg/ml (June 2022), 328.3 pg/ml (July 2022), 306.5 pg/ml (September 2022), 457.2 pg/ml (October 2022), 163.3 pg/ml (June 2023), 34.4 pg/ml (June 2024). The Vitamin D levels are 34.4 ng/ml (July 2022), 13.4 ng/ml (March 2023), 35.2 ng/ml (September 2023), 50.4 ng/ml (April 2024). We found an increase in PTH levels in the six months; then, we increased the dose of calcium supplementation and vitamin D. The patient is now in good condition and has reached a normal level of these laboratory parameters in the second year post-parathyroidectomy. We suggested an increased PTH level in this patient because of vitamin D deficiency.

DISCUSSION

Parathyroid hormone (PTH) is secreted by the chief cells of the parathyroid glands. Calcium, ionized in the extracellular fluid as Ca^{++}, acts as a predominant regulator of PTH production. Ca^{++} which binds to the calcium sensing receptor (CaSR) results in signaling in the parathyroid gland, which inhibits PTH gene expression and PTH secretion or even enhance PTH degradation. On the contrary, lower Ca^{++} may increase PTH gene expression, promoting synthesis of PreproPTH which is then converted to ProPTH and to PTH to be secreted. Vitamin D in the active form of 1,25(OH)2D could bind to the vitamin D receptor (VDR) and also inhibit PTH gene transcription and subsequent expression.[8]

Parathyroid hormone (PTH) enhances calcium reabsorption and inhibits phosphate

reabsorption through the renal tubules, promotes renal synthesis of 1,25-dihydroxyvitamin D which subsequently increases intestinal calcium absorption, and may also increase bone resorption through stimulation of osteoclasts and release of Ca^{++} and Pi from the skeleton. Pathological overproduction of PTH may cause inappropriate increases of calcium and decrease of phosphate, with hypercalcemia cited as a complication to incorrectly treated parathyroid adenoma, possibly aggravating into a clinical phenomenon of parathyroid crisis which is characterized by extremely high calcium levels of more than 15 mg/dL.[8,12] The American Association of Endocrine Surgeons have established guidelines for definitive management of hyperparathyroidism which includes recommendations on the indications of parathyroidectomy. Parathyroidectomy is indicated for all patients with symptomatic primary hyperparathyroidism.[1]

Postoperative failure to reestablish normal calcium homeostasis within 6 months remains the most common complication of parathyroidectomy. This may be associated with persistent primary hyperthyroidism with failure to achieve normocalcemia within 6 months of surgery or recurrent primary hyperthyroidism with recurrence of hypercalcemia after a normocalcemic interval at more than 6 months after surgery. Several studies have found the incidence of permanent postoperative hypocalcemia in 0.5% to 3.8% cases, and persistent/recurrent hyperparathyroidism in 2% to 5% cases.[1,13–17]

Hungry bone syndrome is defined by profound hypocalcemia of less than 8,4 mg/dL which persists beyond four days postoperatively and often presents with hypophosphatemia, hypomagnesemia, and normal PTH level. It often occurs in the post-operative period in patients who have undergone parathyroidectomy or thyroidectomy, or even in patients with osteoblastic metastases. Several risk factors postulated to be correlated with hungry bone syndrome are elevated PTH, elevated alkaline phosphatase, radiological evidence of bone disease, higher BMI, higher blood urea nitrogen levels, larger volume of gland removal, and higher number of osteoclasts found through biopsy. Hungry bone syndrome in primary hyperparathyroidism is found to be associated with older age and higher preoperative calcium levels; meanwhile, it is found to be associated with younger age and lower preoperative calcium levels in secondary hyperparathyroidism.[5-8]

Hungry bone syndrome is treated with calcium supplementation, intravenous and oral or oral alone, vitamin D supplementation, possible magnesium supplementation to prevent calcium replacement hindrance due to hypomagnesemia and its alteration of PTH's ability to exert its effects, with monitoring to these associated levels.[5–8,18–22] Previous studies have cited causes of postsurgical persistent or recurrent hyperparathyroidism to be adenoma (68%), parathyroid hyperplasia (28%), parathyroid carcinoma (3%), and other causes such as parathyromatosis and autograft relapse (1%). Double adenomas or four-gland hyperplasia increases the likelihood of persistent or recurrent hyperparathyroidism. Other states associated with postsurgical increase in PTH include vitamin D insufficiency, mild renal failure, parathyroid hyperfunction, unrecognized familial hypercalciuric hypocalcemia, and increased bone redistribution of calcium.[9,11]

Vitamin D has specific receptors at the level of PTH production in parathyroid cells and displays direct inhibitory effect towards the hormone secretion. Through the feedback mechanism, vitamin D deficiency stimulates the cells to secrete PTH. Thus, elevated PTH value may be found following surgery and may not necessarily indicate surgical failure but instead may point to an uncorrected vitamin D deficiency. Lower levels of vitamin D before surgery has also been associated with larger parathyroid adenomas with more severe phenotype of hyperparathyroidism. PTH kinetics after parathyroidectomy have been found to remain unchanged due to lack of vitamin D deficiency correction, even as PTH is displayed

at higher values. On the contrary, achieving and maintaining normal vitamin D levels postoperatively will help absorption of calcium, normalization of PTH levels, and may improve bone mineral density.[1,20]

Short term vitamin D and calcium supplementation should be considered to prevent hypocalcemia following parathyroidectomy. Patients known to be vitamin D deficient are also strongly recommended to receive vitamin D supplementation after parathyroidectomy. Intravenous calcium administration with either calcium chloride or calcium gluconate is indicated for treatment of hungry bone syndrome in cases with serum calcium level of less than 7.6 mg/dl, symptomatic cases, or cases with ECG changes such as QTc prolongation. The recommended regimen begins with a bolus of 10% calcium gluconate 10 to 20 mL in 50 to 100 mL of D5%, given over 5 to 10 minutes, which provides an equivalent to approximately 100 to 200 mg of elemental calcium. It is followed by a continuous infusion with a dose of 100 mL 10% calcium gluconate in 1 L of D5%, equivalent to approximately 1 mg/mL elemental calcium, starting at 50 mL/hour and titrated every 4 to 6 hours according to calcium, phosphorus, and magnesium levels. The aim of administration is a rate of 0.5 to 1.5 mg elemental calcium/kg/hour. Oral supplementation of calcium using calcium citrate (211 mg elemental calcium per 1g) or calcium carbonate (400 mg elemental calcium per 1g) should also be given with vastly varying recommendations of dosage among different underlying etiologies, with case reports citing doses as low as 800 mg of elemental calcium in cases with parathyroid adenoma to doses of 36 g elemental calcium per day in cases with hungry bone syndrome after parathyroidectomy for secondary hyperparathyroidism. Vitamin D supplementation is also recommended using calcitriol 0.25 to 1 mcg per day, with consideration that the effects of vitamin D may take days to manifest in correlation to calcium levels.[1,20–23]

Several complications may occur after parathyroidectomy for parathyroid hormone, calcium, and vitamin D. Permanent hypoparathyroidism may occur after parathyroidectomy (0%-3.6%). Assessment of prolonged hypoparathyroidism requires evaluation for at least 6 months. Assessment should include calcium, PTH, and 25-hydroxyvitamin D levels. Intraoperative parathyroid hormone (PTH) monitoring can predict outcomes. PTH ≤40 pg/mL or a decrease of ≥50% from baseline minimizes the possibility of persistence. Intraoperative PTH measurement can reduce the risk of recurrence rate to 2.5%-5%. Risk factors for persistence are hyperplasia and normal parathyroid tissue on histopathology. Risk factors for recurrence are cardiac history, obesity, endoscopic approach, and low-volume center (minimum 31 cases/year). Cases with multiple adenomas or quadruple hyperplasia have a greater chance of persistence/recurrence.[1,10,24]

Surgery is considered successful if postoperative eucalcemia persists beyond the first six months. Hypercalcemia that persists during this period is defined as persistence, and recurrence is defined as hypercalcemia after 6 months of normocalcemia. Moderate postoperative hypocalcemia has been reported in 5% to 47%. Patients may experience transient paresthesias after surgery related to low or normal calcium levels, but hypocalcemia can also be asymptomatic. Calcium levels > 9.7 mg/dL for 6 months and eucalcemic parathyroid hormone elevations at 6 months may be associated with recurrence requiring long-term follow-up. Serum calcium ≥ 9.8 mg/dL for 6 months and parathyroid hormone ≥ 80 pg/mL indicate a risk of recurrence. Prophylaxis of hypocalcemia after parathyroidectomy should be considered with short-term calcium and/or vitamin D supplementation. Supplementation may be based on parameters such as preoperative calcium levels, adenoma weight, rate of HDI decline, or immediate or 24-hour calcium levels. Severe and prolonged postoperative hypocalcemia may occur and require intravenous calcium administration after parathyroidectomy, which may complicate

reoperation.[1,10]

Vitamin D is an important factor for good outcomes. Normal postoperative vitamin D levels facilitate calcium absorption and normalization of PTH levels and may increase BMD. Vitamin D deficiency can worsen a variety of medical problems, ranging from decreased BMD to cardiovascular disease. Up to 40% of patients after parathyroidectomy may have elevated postoperative PTH levels, which have been associated with vitamin D deficiency. The combination of elevated PTH levels and low 25-OH vitamin D levels has been associated with higher fracture rates in normocalcemic postmenopausal women. Normal postoperative vitamin D levels may help increase BMD, calcium absorption, and normalize PTH levels. In patients undergoing surgery for calcium absorption and maintenance of skeletal health, patients with 25-OH vitamin D deficiency should ideally receive vitamin D supplementation until adequate 25-OH vitamin D levels are achieved (>30 ng/mL). Once patients achieve normal 25-OH vitamin D levels, they should receive the recommended daily intake of vitamin D. [1,10,24]

In this case report, laboratory parameters of parathyroid hormone, calcium, and vitamin D were monitored, aiming to prevent persistence or recurrence hyperparathyroidism. The patient was also given calcium and vitamin D supplements, to maintain eucalcemia as a therapeutic goal in the patient.

CONCLUSION

The PTH, calcium, and vitamin D serum are needed for follow-up in patients after parathyroidectomy. Normalizing calcium and vitamin D serum are essential to maintain normal PTH levels. Normal PTH, calcium, and vitamin D serum are the cure indications in this patient.

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