

Persistently Elevated Parathyroid Hormone Level after Curative Parathyroidectomy in Patients with Primary Hyperparathyroidism

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ABSTRACT

Background: Persistent elevation of parathyroid hormone (PTH) levels following curative parathyroidectomy is a dynamic & multifactorial process. This study was designed to study the frequency of persistent hyperparathyroidism in our patients and to identify the potential causal factors for persistent PTH elevation following parathyroidectomy.

Methodology: The study included prospectively collected data on post-operative patients of primary hyperparathyroidism who underwent parathyroidectomy from 2004-2018. Data was analyzed by SPSS version-21. For descriptive statistics, frequency and percentages were calculated, while mean \pm standard deviation were calculated for age, duration of disease, pre-operative and post-operative biochemical parameters, like serum PTH, calcium and vitamin D levels.

Results: A total of 11 (39.3%) patients, were diagnosed as persistent hyperparathyroidism, out of the 30 patients, who underwent parathyroidectomy. All patients were female with a mean age of 45.27 \pm 17.2 years and a mean duration of symptoms of 21.3 months. The mean post-operative PTH level, vitamin D and calcium were 154.04 \pm 78.64 pg/ml, 22.28 \pm 13.79 ng/ml 9.46 \pm 0.79 mg/dl, respectively. Fluctuation of PTH hormone in relation to erratic vitamin D intake was reported in 8 patients, and recurrent parathyroid adenoma was reported in three patients, which was subsequently re-operated.

Conclusion: Adequate vitamin D supplementation is essential in the pre and post-operative period to prevent persistent parathyroid stimulation and possible dysregulation. Surveillance for recurrence of hyperparathyroidism should be maintained long term.

Keywords: Hyperparathyroidism, Parathyroidectomy, Parathyroid adenoma

INTRODUCTION

Despite apparently curative parathyroid adenectomy, the parathyroid hormone (PTH) remains persistently elevated in 8% to 40% of patients.¹⁻² Persistently elevated PTH (PPTH) is defined as sustained hypercalcemia and elevated PTH detected within six months of parathyroid adenectomy.³ Other studies have defined PPTH as PTH level > 65 μ g/ml with a normal calcium level (< 10.2 mg/dl) at the first post-operative visit, within weeks of surgery.⁴⁻⁵ A study from India reported PPTH elevation 30% of patients for several years post parathyroid adenectomy.⁶ Several factors have been implicated for this persistent elevation of PTH, including low vitamin D (vit-D) levels, impaired renal function, a secondary response to bone re-mineralization, ectopic gland location, errors in frozen section, in-experienced surgeon, presence of persistent disease and development of another autonomous

adenoma in the remaining parathyroid glands.⁴ An understanding of the factors that commonly contribute to the treatment failure can help prevent persistence and recurrence of the disease after successful curative parathyroidectomy.

The purpose of this study was to estimate the frequency of PPTH at our tertiary care endocrine center and to ascertain the potential casual factors that predispose an individual to remain pathologically active in terms of secreting the PTH hormone after curative parathyroidectomy. This would help in identifying patients who would be more likely to have post-surgical PTH elevation despite surgical removal of adenoma and need regular surveillance.

SUBJECTS AND METHODS

A prospectively collected data on post-operative patients of Primary Hyperparathyroidism, registered at the Endocrine Unit of Jinnah Postgraduate Medical Centre and Medical Institute of Diabetes Endocrinology & Metabolism, Karachi; from 2004 to 2018 was analyzed. The study was approved by the Institutional Review Board (IRB) of Jinnah

Conflict of Interest: The authors declared no conflict of interest exists.

Citation: Ahsan T, Ghaus S, Pal KMI, Erum U, Jabeen R. Persistently elevated parathyroid hormone level after curative parathyroidectomy in patients with primary hyperparathyroidism. J Fatima Jinnah Med Univ. 2022; 16(4):180-184.

DOI: <https://doi.org/10.37018/QWUZ3082>

Postgraduate Medical Centre, as well as the IRB of Medical Institute of Diabetes Endocrinology & Metabolism. Informed oral consent was taken from the patients for including their demographic and biochemical data in the study. Vitamin D, serum intact PTH, calcium, creatinine and alkaline phosphate were analyzed for all the patients at regular intervals over an extended period of time. Intact PTH and vitamin D levels were measured using the Chemiluminescence Immunoassay. Clinical presentation and laboratory parameters were studied. The adenomas were localized with a combination of ultrasound, Sestamibi and MRI scans pre-operatively. Although intra-operative PTH was not available, complete excision was judged by the operating surgeon and confirmed by the subsequent histopathology showing an intact capsule of the gland. All patients with persistently raised PTH levels were re-evaluated for adenoma recurrence by hormonal analysis and imaging modalities.

All patients who underwent parathyroidectomy during the study period were assessed and a total of 11 patients, with PPTH after parathyroid adenectomy, were included in the study as per-protocol analysis. PPTH was diagnosed on the basis of raised PTH with either raised or normal calcium (Ca) despite complete surgical removal of the parathyroid adenoma.

Data was analyzed by SPSS version-21. For descriptive statistics, like gender and clinical features, frequency and percentages were calculated, while mean \pm standard deviation were calculated for age, duration of disease, pre-operative and post-operative biochemical parameters, like serum PTH, calcium and vitamin D levels.

RESULTS

A total of 11 (39.3%) patients, were diagnosed as persistent hyperparathyroidism, out of the 30 patients who underwent parathyroidectomy, during the study duration. The complete adenoma excision was confirmed on histopathology showing intact capsule. All 11 patients were female with a mean age of 45.27 \pm 17.2 years and a mean duration of symptoms of 21.3 months, prior to diagnosis of primary hyperparathyroidism. Of these 11 patients, 1 (9%) patient was entirely asymptomatic, 6 (54.5%) patients had musculoskeletal symptoms of generalized body aches and myalgia, 2 (18.1%) patients had recurrent pathological fractures, 1 (9.0%) had a jaw mass and 1 (9.0%) patient had symptoms pertaining to hypercalcemia including recurrent renal stones and pancreatitis. There were no clinical or hormonal indicators of MEN syndrome in

these 11 patients and all the patients had normal renal function with a mean Creatinine level of 0.74 \pm 0.2 mg/dl.

The mean pre-operative PTH level was 673.35pg/ml and the median was 518 μ g/ml while the mean pre-operative vitamin D level was 19.4 \pm 15.7 ng/ml and mean serum Ca was 11.65 \pm 1.3 mg/dl. The mean post-operative PTH level was 154.04 \pm 78.64 μ g/ml and median was 136 μ g/ml while the mean post-operative vitamin D level was 22.28 \pm 13.79 ng/ml and mean serum Ca was 9.46 \pm 0.79 mg/dl, which was measured within two weeks postoperatively in all the patients, as shown in Fig-1. All patients were advised for daily supplementation with vitamin D 2000 IU. Elevated levels of PTH were reported in 8 of these patients, which were seen to correlate with erratic vitamin D intake and improved compliance led to normalization of PTH levels (Figures 2 and 3). However, in three patients repeat imaging studies showed recurrent parathyroid adenoma evidenced by positive Sestamibi scan. These recurrent adenomas were detected over a period of 4-8.5 years after initial parathyroid adenectomy. All three patients underwent successful repeat parathyroid adenectomy, following which two of them had normal PTH level post - surgery. However, one patient continues to have raised PTH levels with low vitamin D, fluctuating repeatedly. Her repeat Sestamibi and PET/CT scans were negative for a recurrent adenoma. She remains on subsequent follow-up. One of the patients had parathyroid carcinoma and her PTH levels normalized on subsequent follow-up.

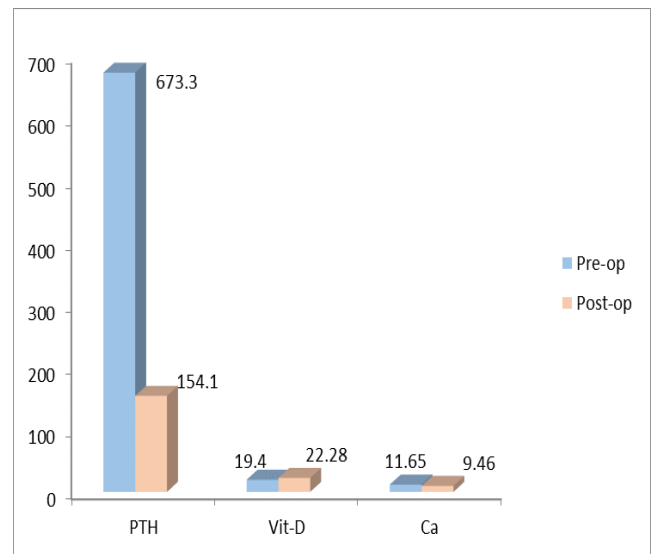


Fig 1: Mean pre- and post-operative biochemical parameters.

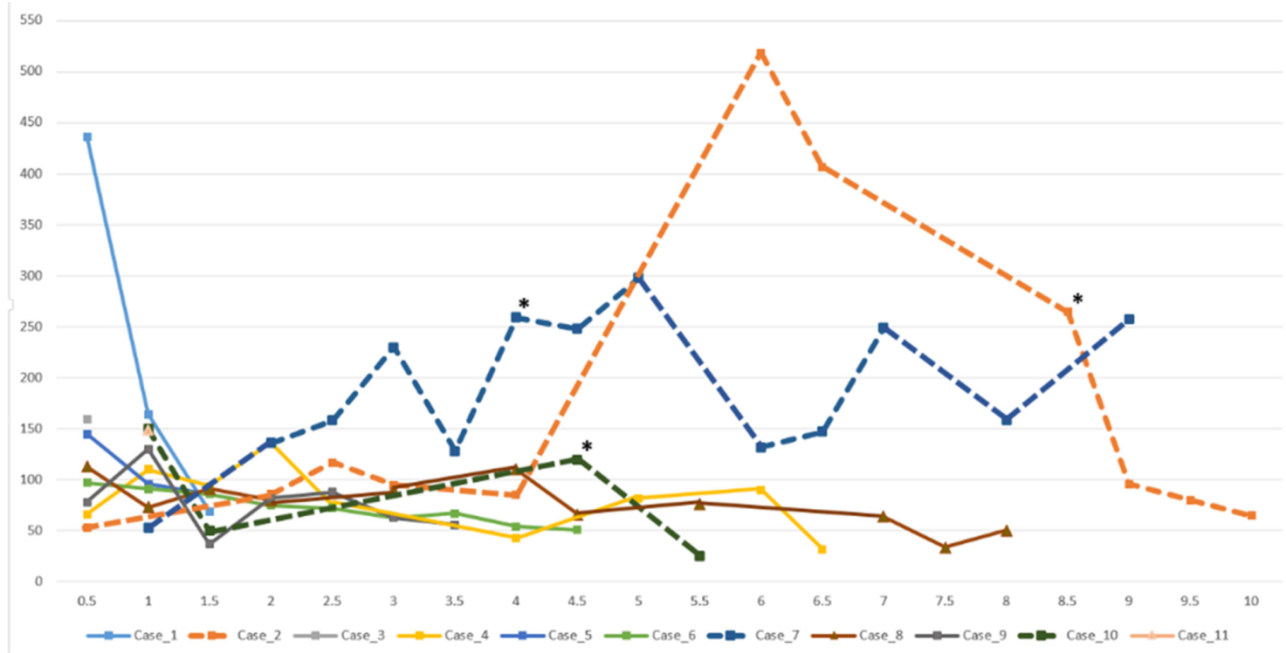


Figure 2: PTH Levels over years Post-Parathyroidectomy. Patients with recurrent adenomas are depicted by a dashed line, with repeat parathyroidectomies indicated by *. Normal level of PTH was 16-87 pg/ml.

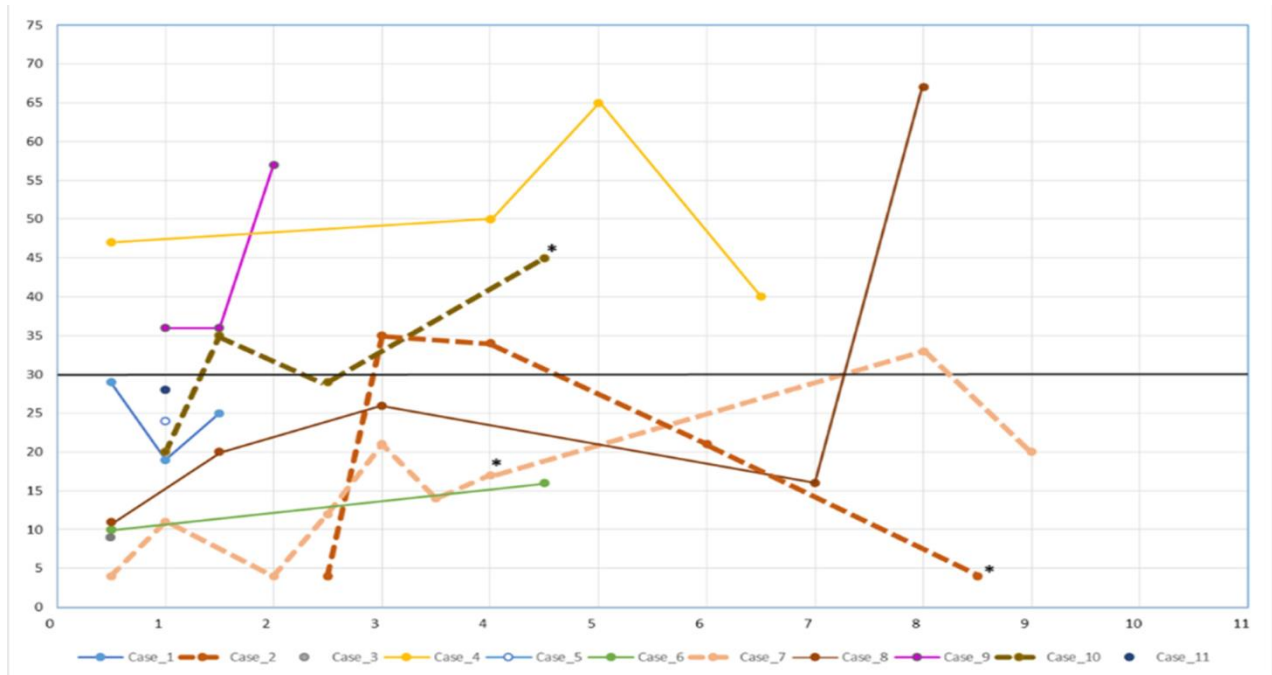


Figure 3: Vitamin D Levels over years Post-Parathyroidectomy. Patients with recurrent adenomas are depicted by a dashed line, with repeat parathyroidectomies indicated by *. Vitamin D Sufficiency was defined as > 30 ng/ml, as indicated by a horizontal black line.

DISCUSSION

In spite of a notable progress in the armamentarium for the management of primary hyperparathyroidism, persistence or recurrence of hyperparathyroidism still accounts for 2.5-5% of cases of PPTH.⁷⁻⁹ Classically

with the short half-life of PTH in the plasma, the successful removal of an adenoma, either through conventional techniques or through laparoscopic removal, is gauged by immediate intra-operative PTH levels. Persistence of PTH elevation after successful

removal of parathyroid adenectomy can be perplexing.¹⁰⁻¹¹ In some cases, this normalization or even sub-optimal PTH is short lived. A modest elevation of calcium and PTH may re-surface in a matter of weeks and months, as described in this small study. However, many patients remain normocalcemic despite surge in PTH levels. A mean prevalence of 23.5% has been reported as normocalcemic PPTH.¹² This transient surge in the PTH can be attributed to the increased bone re-mineralization (bone hunger) during initial post-operative period.¹³ Nonetheless, the continuum of biochemical abnormalities over a prolonged period of time, needs further evaluation. Another possibility of recurrence of PTH elevation could be due to a functional overshoot of the remaining parathyroid glands, which had been relatively dormant during the course of hypersecretion from the parathyroid adenoma.

In addition, our study represents that patients with PPTH had lower post-operative vitamin D and normal to low Ca⁺⁺ levels than those with normal post-operative PTH levels. A Brazilian study reported an inverse relationship between vit-D and PTH.¹⁴ Another study reported that biochemical responses with either increased serum calcium or increased parathyroid hormone levels were the strongest predictors for the risk of recurrent primary hyperparathyroidism and subsequent hypercalcemia.¹⁵ Moreover, the majority of the patients with hyperparathormonemia normalized their PTH levels with regular daily oral calcium and vit-D supplementation, suggesting that vit-D deficiency has strong implication in regulation of Ca and PTH. Hence, supports the hypothesis that low vit-D levels with isolated hyperparathormonemia, is the most crucial contributing element for PPTH elevation, despite efficacious parathyroidectomy. An Indian study reported vitamin D level of 16 ng/ml as the inflection point, below which a steady accrual in intact PTH (iPTH) levels commence.¹⁶

Contrary to that, we also identified that few patients, despite erroneously raised preoperative Ca and PTH never went on to develop persistence PTH elevation. This nullifies the hypothesis that pre-surgical values of PTH and Ca can potentially identify every patient who would be likely to have PPTH elevation, hence we propose the notion that this group of patients might have an altered set point for PTH regulation, involving either resistance to PTH or a reduced sensitivity of Ca sensing receptors. Though other causal factors contributing to the resurgence of PTH have not been elucidated yet, it has been reported that the most

frequent cause of PPTH is in-adequate localization, previously unnoticed multi-glandular disease or ectopic location.¹⁷⁻¹⁸ However, in our study participants, the adequacy of surgery was already established by evidence of intact capsule of the excised gland, in all the cases. In this small series, 3 patients went on to develop another parathyroid adenoma in one of the remaining glands, after a considerable period of time from the removal of the first adenoma. A late recurrence rate of 10.7% was reported up to 17 years later after apparent curative surgery for primary hyperthyroidism.¹⁹ It is therefore important that patients, in whom a parathyroid adenoma has been removed, must be under regular surveillance to ensure continued normal PTH, vit-D and Ca homeostasis. There is no overt clinical finding for PPTH during the immediate postoperative phase, hence these patients requires laboratory analysis at regular intervals. Moreover, the clinical implication of PTH is uncertain for years, but the persistence of elevated PTH has pathological consequences affecting different organs, in the long-run.

The small sample size of this study makes the generalization of these findings difficult. Whether or not this finding would serve to identify patients at risk for PPTH, it signifies the importance of early recognition of patients that need prompt and regular surveillance for disease recurrence. Moreover, we recommend that all patients who undergo parathyroid adenectomy for parathyroid adenoma, carcinoma, or multiple gland removal for hyperplasia, must be supplemented with regular vit-D to ward off the persistent parathyroid stimulation caused by hypovitaminosis D and its consequences, which is rampant in our population. Also, appropriate localization of adenoma at normal location and ectopic glands with meticulous search results in cure of disease for most of the patients.

Furthermore, as there is little consensus regarding the management of PPTH, larger multicenter studies are needed to identify causal factors for recurrence or persistence of PTH elevation to delineate an optimal surveillance strategy for disease recurrence with timely laboratory evaluation.

CONCLUSION

Persistent PTH elevation is frequently seen in post-operative patients, of primary hyperparathyroidism, despite curative parathyroidectomy and closely related to fluctuations in vitamin D levels. Adequate vitamin D supplementation is essential in the pre and post-operative period to prevent persistent parathyroid

stimulation and possible dysregulation. Surveillance for recurrence of hyperparathyroidism should be maintained long term.

Acknowledgements: We would like to thank Dr. Erum Sohail for proof-reading this article.

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