Original Article

DOI: 10.7860/JCDR/2021/46621.14423

Postoperative Hypoparathyroidism: Presentation, Clinical Features and Long-term Follow-up from Tertiary Care Hospital

Internal Medicine Section

SHRIKRISHNA V ACHARYA

ABSTRACT

Introduction: Hypoparathyroidism is commonly seen after total thyroidectomy. Though most of the time it is transient in nature but permanent decrease in function of the parathyroid function is also possible.

Aim: A retrospective analysis of clinical presentation, treatment, prevalence of complications of hypoparathyroidism and its treatment with active vitamin D analogues was conducted.

Materials and Methods: A retrospective cohort study followed by location and duration of study of all patients who developed Permanent Hypoparathyroidism (PH) and who were regular in follow-up for at least three years. Any patient with intact Parathyroid Hormone (iPTH) levels <13 pg/mL and was on replacement therapy with calcium and/or vitamin D for at least one year after surgery is labelled as PH. Data of their treatment, serum calcium, phosphorous, creatinine, urine calcium/creatinine ratio and renal ultrasound was recorded. Data was represented as percentage, mean and standard deviation. Statistical analysis was conducted using SPSS version 19.

Results: Out of the 23 patients enrolled, three were male and 20 were female with a mean age of 41.2±15.2 years. The mean duration of follow-up was 48±28 months. Clinical complications in 12 patients were observed. Two patients developed renal colic due to renal stone on follow-up. None of the patients developed renal failure.

Conclusion: PH causes considerable morbidity and economic burden to family due to its lifelong treatment and monitoring. It requires regular follow-up and monitoring to prevent complications of disease as well as its treatment with active calcium salts. Around 50% of the patients suffered few relevant clinical events requiring hospitalisation.

Keywords: Parathyroid hormone, Permanent hypoparathyroidism, Vitamin D

INTRODUCTION

The prevalence of postoperative Permanent Hypoparathyroidism (PH) may vary in different studies, although literature study reveals it to be around 0-3 % [1]. But according to some multicentre studies it was 6 to 12%. It may vary from study to study depending on criteria used by different authors. This varied prevalence may be due to different criteria used for definition, inadequate follow-up. There are no clear guidelines regarding definition of PH [2]. According to European association of clinical endocrinologists, presence of low levels of PTH and treatment with calcium and calcitriol for atleast six months postsurgery is required to diagnose PH [3] whereas according to other reports it is one year after thyroidectomy [2,4]. Once patient develops PH, lifelong medical treatment along with frequent follow-up to monitor calcium levels to prevent hypercalcaemia and hypocalcaemia is required. According to most of the endocrine societies guidelines we need to monitor serum calcium, phosphate, alkaline phosphatase, magnesium, creatinine and estimated Glomerular Filtration Rate (GFR) every 3-6 months, and 24-hour urinary calcium excretion once a year. Some guidelines also recommend renal ultra sound once a year to detect nephrocalcinosis [4,5].

The most preferred treatment PH involves use of calcium salts associated with active vitamin D analogues. The aim of treatment is to prevent development of hypocalcaemic symptoms with lowest possible serum levels of calcium. Usually, serum calcium concentrations are maintained in the range between 8 to 8.5 mg/dL. There are no clear cut guidelines about the most preferred vitamin D analogue, it varies in different countries [4,5]. Some authors used thiazide diuretics, whenever there is hypercalciuria with hypocalcaemia [4,5]. Recently, there are many studies involving use of recombinant human PTH as treatment of PH [5,6]. REPLACE trial showed that patients treated with recombinant PTH require half the dose of calcium and vitamin D analogues to control their symptoms [7]. It has been postulated that that recombinant PTH is reduces the excretion of calcium in urine and also stabilises the microarchitecture of bone [6,8]. However, recombinant PTH not routinely recommended as treatment for hypoparathyroidism and it is used only in some patients who are not controlled by routine treatment. Some patients have disturbed quality of life in spite of normalisation of serum calcium and other biochemical parameters [9,10]. Underbjerg L et al., in his study found that patients with PH are more prone for renal stones, renal failure and seizures. They also showed that these patients didn't have higher risk of cardiac arrhythmias or cardiovascular mortality [11]. It has been noticed that, on long-term follow-up the risk of fractures at the upper extremities are significantly decreased in PH [12]. The main objective of this retrospective case control study is to find out the prevalence of complications of hypoparathyroidism, adverse effects of treatment in the present cohort of patients.

MATERIALS AND METHODS

This is a retrospective cohort study conducted at KS Hegde Medical Academy, Mangalore, India, from January 2019 to December 2019. Study was done on all PH patients attending endocrinology Outpatients Department during last 10 years. The informed patient consent was waived by obtaining approval from Institutional/National Review Board Committee due to the retrospective nature of study (EC/NEW/INST/2020/834).

Inclusion criteria: All patients irrespective of age and duration of disease were included in the study. All patients who were regular in follow-up for at least three years.

Exclusion criteria: Patients with irregular follow-up with insufficient clinical and biochemical data were excluded.

The data was collected regarding their original diagnosis prior to surgery, type of thyroid surgery, hypocalcaemic symptoms, hypercalcaemic symptoms, ureteric colic, ultrasonographic findings, dose of calcium and calcitriol.

Patients are diagnosed to have PH when their intact PTH concentration was less than 13 pg/mL in presence of hypocalcaemia and requirement of replacement with calcium with or without calcitriol for more than one year after surgery [9].

Criteria used for Different Clinical Complications

Hypocalcaemia was defined as a serum calcium less than 8.5 mg/dL in presence of normal albumin levels and or presence of carpopedal spasm and paraesthesias. When serum calcium is more than 10.5 mg/dL with normal serum albumin, patient is diagnosed as having hypercalcaemia. Renal failure was diagnosed, whenever creatinine value raised above 1.4 mg/dL and/ or an estimated GFR less than 60 mL/min/1.73 m^2 [5].

STATISTICAL ANALYSIS

Statistical analysis was conducted using SPSS version 19. Mean and standard deviation was calculated. Categorical variables were presented as percentage while mean and standard deviation were used to document quantitative variables.

RESULTS

In this study, a total of 23 patients were included, out of which 20 patients were females and three males. Their mean age of presentation was 41.2±15.2 years. Majority of patients had malignant disease (18 patients). In these 18 patients, 14 had thyroid malignancy and four had laryngeal malignancy. In all these patients total thyroidectomy was done along with laryngectomy in four patients with laryngial malignancy. The remaining five patients had benign disease i.e., large multi nodular goitre in three patients and resistant graves' disease with huge goitre in two patients. Out of these patients, two patients underwent total thyroidectomy and three patients had near total thyroidectomy. Thirteen patients underwent total thyroidectomy with lymphnode dissection due to suspicion of underlying malignancy. Demographic data of 23 patients with postoperative Permanent Hypoparathyroidism (PH) has been represented in [Table/Fig-1].

Variables	Values
Gender (M/F)	3/20
Age, mean±SD (years)	41.2±15.2
Benign/malignant, (n)	5/18
Total or near total thyroidectomy n (mean)	10 (43.5)
Total thyroidectomy with central neck dissection n (mean)	13 (56.5)
Follow-up, mean±SD (months)	48±28 months
Calcium dosage, mean±SD (g/day)	1.5 gm±0.7 gm
Calcitriol, mean±SD (µg/day) (n=11)	0.7 mcg±0.3 mcg

[Table/Fig-1]: Demographic data of 23 patients with postoperative Permanent Hypoparathyroidism (PH).

Most common clinical event recorded by us was carpopedal spasm. Around 35% of patients experienced tingling, paraesthesia and carpopedal spasm at least once in their follow-up period. This is mainly due to compliance with medication than as patient used to stop calcitriol after sometime. Documented hypocalcaemia observed in 21.7% patients, with their corrected calcium less than 8 mg%. Three patients developed drug induced hypercalcaemia which was corrected by reducing the dose of calcitriol. Two patients got admitted with renal colic and found to have ureteric stones. Both of them were managed conservatively. Ultrasound diagnosed nephrolithiasis in two patients, in whom we reduced the dose of calcitriol and followed-up every six months for disappearance of nephrolithiasis. Calcium and phosphorous levels in all patients were assessed. Two patients who had ureteric stones had their calcium phosphorous ratio more than 55, which became normal after reducing the dose of calcitriol [Table/Fig-2]. Authors have measured calcium creatinine ratio yearly in all patients, but none of them had hypercalciuria. All patients in present cohort had their calcium creatinine ratio less than 0.2 mg/dL. None of the patients progressed to renal failure.

Clinical events	n (%)
Paraesthesia, tingling, carpopedal spasm	8 (34.8)
Hypocalcaemia	5 (21.7)
Hypercalcaemia	3 (13)
Renal colic	2 (8.7)
Nephrolithiasis (USG)	2 (8.7)
Fractures	0

[Table/Fig-2]: Clinical complications of 23 patients.

DISCUSSION

This is one of the studies on postoperative hypoparathyroidism in which long term follow-up of patients was done both clinically and biochemically. Authors have also recorded the possible complications of both the disease and adverse effects of drugs given. Present study is unique because of regular follow-up of majority of patients and fewer complications than the studies published previously. Previously conducted studies reported higher risk of renal failure in patients with hypoparathyroidism on treatment. This is primarily due to development of hypercalcaemia and hypercalciuria arising due to treatment with calcium and calcitriol. This hypercalcaemia will lead to nephrocalcinosis or nephrolithiasis, finally resulting in renal failure. Mitchell DM et al., in his article on hypoparathyroidism reported that up to 41% of patients developed renal failure with their GFR dropping to less than 60% [13]. His study also showed that elderly patients with long standing disease and prolonged hypercalcaemia had direct correlation with impaired renal function. Decreased GFR was also observed in patients enrolled by national institute of health study [14]. None of present recorded patient developed renal failure. This may be due to smaller number of patients and may be due to frequent follow-up and monitoring of patients.

The present study also shows fluctuations of serum calcium concentrations either in the form of acute episodes of hypocalcaemia and hypercalcaemia requiring hospital admission. Most of the times, these are due to stopping of medication or excessive intake of medications. That is why frequent follow-up and monitoring of biochemical levels of calcium is of paramount important.

Authors know that nephrolithiasis and renal colic are very common in patients with hypoparathyroidism. This is mainly due precipitation of calcium salts in renal tissue due to change in ratio of calcium and phosphorous. Absence renal PTH action leads to hypercalciuria due to inefficient reabsorption of calcium and decreased secretion of phosphorous, thus facilitating nephrocalcinosis [9]. The prevalence in present cohort of patients was 8.7 percent which was comparable to 10% seen in study by Levy I et al., [14]. In another study by Mitchell DM et al., showed that in their cohort of 54 patients 31% presented either nephrolithiasis or nephrocalcinosis [13]. Surprisingly, all the patients in present cohort had their calcium creatinine ratio less than 0.2. All patients with long-term hypoparathyroidism have significant reduction in their bone remodelling. That is why patients with hypoparathyroidism have higher Bone Mineral Density (BMD) at most of the sites with highest at lumbar spine. It is also shown that hypoparathyroid patients have higher cortical and cancellous bone volumetric BMD [15]. Therefore, we rarely see bone fractures and osteoporosis in these group of patients. In present group of patients none of them had fracture till last follow-up. BMD was not

measured in present study patients. A study by Underbjerg L et al., reported higher incidence of upper extremity fractures in his cohort of hypoparathyroid patients [12]. But some time overuse of calcitriol may lower bone leading to bone resorption and thus osteoporosis [12].

A similar study done by Lorente-Poch L et al., with 32 patients with hypoparathyroidism showed that 15% patients had reduced renal function and 56% patients had clinical symptom in the form of hypocalcaemia, paraesthesia, tingling and numbness [16]. They also demonstrated that there was some reduction in quality of life.

Limitation(s)

Main drawback of this study was small sample size.

CONCLUSION(S)

Permanent Hypoparathyroidism (PH) patients on long term follow-up can present with various signs and symptoms of both hypocalcaemia and hypercalcaemia. This will lead to considerable morbidity and economic burden to the family since it is chronic disease.

REFERENCES

[1] Edafe O, Antakia R, Laskar N, Uttley L, Balakrishnan SP. Systematic review and meta-analysis of predictors of post-thyroidectomy hypocalcaemia. Br J Surg. 2014;101:307-20. PMID:24402815.

[2] Lorente-Poch L, Sancho JJ, Muñoz-Nova JL, Sánchez-Velázquez P, Serra AS. Defining the syndromes of parathyroid failure after total thyroidectomy. Gland Surg. 2015;4:82-90. PMID: 25713783 PMCID: PMC4321048.

[3] Bollerslev J, Rejnmark L, Marcocci CM, Shoback DM, Sitges-Serra A, Biesen Wv. European Society of Endocrinology clinical guideline: Treatment of chronic hypoparathyroidism in adults. Eur J Endocrinol. 2015;173:G1-20. PMID:26160136.

[4] Stack Jr BC, Bimston DN, Bodenner DL, Brett EM, Dralle H, Orloff LA, et al. American Association of Clinical Endocrinologists and American College of Endocrinology Disease State Clinical Review: Postoperative Hypoparathyroidism-Definitions and Management. Endocr Pract. 2015;21:674-85. PMID: 26135962.

[5] Brandi ML, Bilezikian JP, Shoback D, Bouillon R, Clarke BL, Thakker RV, et al. Management of hypoparathyroidism: Summary statement and guidelines. J Clin Endocrinol Metab. 2016;101:2273-83. PMID:26943719.

[6] Cusano NE, Rubin MR, McMahon DJ, Irani D, Anderson L, Levy E, et al. PTH (1-84) is associated with improved quality of life in hypoparathyroidism through 5 years of therapy. J Clin Endocrinol Metab. 2014;99:3694-99. PMID: 24978675.

[7] Mannstadt M, Clarke BL, Vokes T, Brandi ML, Ranganath L, Fraser WD, et al. Efficacy and safety of recombinant human parathyroid hormone (1-84) in hypoparathyroidism (REPLACE): A doubleblind, placebo-controlled, randomised, phase 3 study. Lancet Diabetes Endocrinol. 2013;1:275-83. PMID:24622413.

[8] Rubin MR, Cusano NE, Fan WW, Delgado Y, Zhang C, Costa AG, et al. Therapy of hypoparathyroidism with PTH(1-84): A prospective six year investigation of efficacy and safety. J Clin Endocrinol Metab. 2016;101:2742-50. PMID: 27144931.

[9] Shoback D. Hypoparathyroidism. N Engl J Med. 2008;359:391-403. PMID:18650515.

[10] Bilezikian JP, Khan A, Potts JT Jr, Brandi ML, Clarke BL, Shoback D, et al. Hypoparathyroidism in the adult: Epidemiology, diagnosis, Journal of Clinical and Diagnostic Research pathophysiology, target-organ involvement, treatment, and challenges for future research. J Bone Miner Res. 2011;26:2317-37. PMID: 21812031.

[11] Underbjerg L, Sikjaer T, Mosekilde L, Las rejnmark. Cardiovascular and renal complications to postsurgical hypoparathyroidism: A Danish nationwide controlled historic follow-up study. J Bone Miner Res. 2013;28:2277-85. PMID: 23661265.

[12] Underbjerg L, Sikjaer T, Mosekilde L, Las rejnmark. Postsurgical hypoparathyroidism-risk of fractures, psychiatric diseases, cancer, cataract, and infections. J Bone Miner Res. 2014;29:2504-10. PMID: 24806578.

[13] Mitchell DM, Regan S, Cooley MR, Lauter KB, MC Vrla, Carolyn B Becker et al. Long-term follow-up of patients with hypoparathyroidism. J Clin Endocrinol Metab. 2012;97:4507-14. PMID:23043192.

[14] Levy I, Licht C, Daneman A, Sochett E, Harrington J. The impact of hypoparathyroidism treatment on the kidney in children: Long-term retrospective follow-up study. J Clin Endocrinol Metab. 2015;100:4106-13. PMID:26323021.

[15] Silva BC, Rubin MR, Cusano NE, Bilezikian JP. Bone imaging in hypoparathyroidism. Osteoporos Int. 2017;28:463-71. PMID:27577725.

[16] Lorente-Poch L, Sancho JJ, Carballo L, Sitges-Serra A. Clinical profile and long-term follow-up of 32 patients with postoperative permanent hypoparathyroidism. Gland Surg. 2017;6(Suppl 1):S03-10. PMID: 29322017.

PARTICULARS OF CONTRIBUTORS:
1. Associate Professor, Department of Endocrinology, K S Hegde Medical Academy, Mangalore, Karnataka, India.

NAME, ADDRESS, E-MAIL ID OF THE CORRESPONDING AUTHOR:
Shrikrishna V Acharya,
Associate Professor, Department of Endocrinology, K S Hegde Medical Academy,
Deralakatte, Mangalore, Karnataka, India.
E-mail: shrikrishnaacharya@gmail.com

PLAGIARISM CHECKING METHODS: [Jain H et al.]
- Plagiarism X-checker: Sep 11, 2020
- Manual Googling: Nov 17, 2020
- iThenticate Software: Dec 14, 2020 (10%)

ETYMOLOGY: Author Origin

AUTHOR DECLARATION:
- Financial or Other Competing Interests: None
- Was Ethics Committee Approval obtained for this study? Yes
- Was informed consent obtained from the subjects involved in the study? NA
- For any images presented appropriate consent has been obtained from the subjects. NA

Date of Submission: **Sep 05, 2020**
Date of Peer Review: **Oct 17, 2020**
Date of Acceptance: **Nov 18, 2020**
Date of Publishing: **Jan 01, 2021**