

Laboratory and Imaging Profile of Primary Hyperparathyroidism: A Record Based Retrospective Study

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ABSTRACT

Introduction: Primary Hyperparathyroidism (PHPT) is an uncommonly diagnosed symptomatic disease that occurs in India. Unlike Western countries, where the disease is asymptomatic, various manifestations occur in India that are skeletal, muscular, and renal. Studies on PHPT from developing countries like India have shown that symptomatic PHPT is still common compared to developed countries. Data on PHPT from Kerala (a state with health indices comparable to the Western world) are lacking.

Aim: To compare the preoperative and postoperative calcium and Parathyroid Hormone (PTH) levels among the participants.

Materials and Methods: A record-based retrospective study was conducted at Amrita Institute of Medical Sciences, Cochin, in the Department of Endocrinology. All 116 patients who had PHPT from January 2013 to December 2019 were included in the study. The data available in the hospital records were

analysed for various laboratory values and imaging diagnoses. The preoperative and postoperative calcium and PTH levels were compared. Data were analysed by paired sample t-test (Wilcoxon sign-rank test). The data analysis was done using coGuide.

Results: The mean age was 53.42±14.89 years in the study population. Among the 116 subjects, 46 (39.66%) were males and 70 (60.34%) were females; 83 (71.55%) had the symptomatic disease. The majority, 80 (68.97%) participants underwent single parathyroidectomy. The difference between preoperative and postoperative calcium and PTH was statistically significant (p-value <0.001).

Conclusion: PHPT largely occurs in the fifth decade of life, and the majority were symptomatic. Females were more affected compared to males in the present study. Preoperative imaging is recommended in routine practice.

INTRODUCTION

PHPT is a condition characterised by the autonomous production of PTH, leading to the development of hypercalcaemia. The classical features of PHPT were described by Albright F et al., about eight decades ago [1]. PHPT is one of the most common endocrine disorders in developed countries [2]. The prevalence of PHPT varies among different regions of the world. In developing countries like India, PHPT remains underdiagnosed, and patients often have overt symptoms involving the skeletal, muscular, and renal systems by the time they are diagnosed [3-6].

In contrast to developing countries, the disease manifests as asymptomatic in most developed countries [7]. The reason for the varied geographic presentation of the disease remains unclear. One factor for early recognition of asymptomatic or early PHPT in developed countries is better biochemical screening [8]. Vitamin D deficiency may lead to severe forms of PHPT. This severity can be further aggravated by a predominantly vegetarian diet, which acts as an important risk factor for vitamin D deficiency [9]. A study was conducted by Misgar RA et al., among PHPT patients in the Kashmir Valley, which showed that the most common presenting features were nephrolithiasis, bone pain, abdominal pain, constipation, and myopathy [10]. Another study from western India showed that clinical manifestations in Indian patients were primarily renal and skeletal [5]. However, there is a lack of evidence on the clinical and imaging profile of PHPT patients in South India.

Hence, this study was planned to describe the laboratory and imaging profiles of patients with PHPT in Kerala and to compare pre- and post-operative hormonal levels in these patients.

Keywords: Adenoma, Calcium, Hyperplasia, Parathormone level

MATERIALS AND METHODS

The present study was a record-based retrospective study conducted at the Department of Endocrinology, Amrita Institute of Medical Sciences, Kochi, Kerala, India. Retrospective analysis of data of all patients with biochemically confirmed PHPT between January 2013 and December 2019 was analysed from May 2022 to November 2022, from the hospital information system. The Institutional Ethics Committee approved the study of Amrita Institute of Medical Sciences (IEC Reference number: ECASM-AIMS-2023-041), Cochin, Department of Endocrinology. A consent waiver was obtained as it was a record-based study. However, procedural consent and consent for blood draws were obtained during the treatment in the hospital.

Inclusion criteria: Confirmed cases of PHPT with elevated calcium levels and raised PTH levels above the assay-specific range were included.

Clinical presentation was broadly divided into three forms: mild symptomatic (body ache and joint pain), symptomatic (pancreatitis, renal calculus, fractures), and incidental finding (when evaluated for unrelated complaints).

Exclusion criteria: Patients with secondary/tertiary hyperparathyroidism, incomplete data, and non-PTH-mediated hypercalcaemia were excluded from the study.

Procedure

A total of 116 patient data was retrieved from the hospital information system in the Department of Endocrinology from the year 2013 to 2019 who underwent Tc MIBI scanning. Details like the age of the patient, symptoms, biochemical parameters, and imaging features were analysed. Calcium levels and PTH levels were measured in all patients. Biochemically confirmed patients with PHPT after ruling

out Familial Hypocalcaemic Hypercalcaemia (FHH) with urine calcium creatinine ratio were subjected to imaging like ultrasound neck and Technetium 99 m sestamibi (MIBI)- 99 m Tc-methoxy isobutyl isonitrile Tc MIBI scanning. A 15 mCi of 99 m Tc-MIBI is injected intravenously and dynamic and static images of the anterior neck, and mediastinum were obtained at 20 minutes, two hours, and three hours post-injection using a dual head variable angle Gamma camera. Dynamic and static images of the anterior neck and mediastinum were obtained at 20 minutes, two hours, and three hours post-inject using a dual head variable angle Gamma camera. Single-Photon Emission Computerised Tomography (SPECT) scan of the neck was also performed (GE Optima NM/CT 640). Patients who had localised lesions or were suspected lesions on imaging were posted for parathyroid surgery. In those patients with negative imaging, medical management was done in the form of diuretics and calcimimetics; 15 mCi of 99 m Tc-MIBI was injected intravenously. Normal calcium levels were considered when they ranged from 8.6-10.0 (mg/dL), hypercalcaemia was considered when it was serum calcium levels >10 mg/dL, and PTH levels were considered normal between 15.0-65.0 pg/mL [6].

STATISTICAL ANALYSIS

Pre-operative and post-operative laboratory parameters were considered the primary outcome variable: Imaging profile was considered the primary explanatory variable. Descriptive analysis was carried out by mean and standard deviation for quantitative variables, and frequency and proportion for categorical variables. For normally distributed quantitative parameters, the mean values were compared between preoperative and postoperative using paired sample t-test. (Wilcoxon sign-rank test). The p-value <0.05 was considered statistically significant. Data were analysed by using coGuide software, V.1.0 [11].

RESULTS

A total of 116 subjects were included in the final analysis. The mean age of the study samples was 53.42±14.89 (range 15 to 79) years where the majority were female with 70 (60.34%). Among the patients with PHPT, 83 (71.55%) participants were symptomatic, and 33 (28.45%) were asymptomatic. Among patients who were symptomatic pancreatitis was seen in 6 (5.17%) patients, renal stones in 40 (34.48%) patients and bony pains in 52 (44.8%) patients. Around nine (7.76%) patients had a palpable neck mass on examination out of which six patients had adenoma, two patients had hyperplasia and one patient had malignancy.

Family history was present in 4 (3.45%) patients out of which two patients were Multiple Endocrine Neoplasia (MEN) suspects, hypertension was seen in 49 (42.24%) patients and type 2 diabetes was present in 33 (28.45%) patients. The most common site of adenoma was right inferior in 44 (37.93%) patients. Out of 116 participants, 11 (9.48%) participants had hyperplasia [Table/Fig-1].

The pre-operative mean calcium levels were 11.76 mg/dL, mean phosphorous levels were 2.51 mg/dL, the mean calcium creatinine ratio was 0.29±0.25 in the study population [Table/Fig-2].

For localisation of the lesion, patients underwent imaging like an ultrasound of the neck, Tc sestamibi. Around 76 patients had data on ultrasound neck, 51 (43.97%) patients had a single adenoma, 2 (1.72%) patients had two adenomas, and 1 (0.86%) patient had hyperplasia. Among the people with MIBI, 107 (92.24%) participants had adenomas, 4 (3.45%) participants had two adenomas, and one (0.86%) participant had hyperplasia. Once the lesion was localised, patient underwent parathyroidectomy. Single gland parathyroidectomy was done in 80 patients (68.97%), followed by hemithyroidectomy in 10 patients (8.62%) who had associated thyroid nodules, two gland excision or parathyroidectomy was done in four patients (3.45%), two patients (1.72%) underwent subtotal thyroidectomy, and one patient (0.86%) had total parathyroidectomy

Parameters	n (%)
Age (in years) (Mean±SD)	53.42±14.89 (range 15 to 79)
Gender	
Male	46 (39.66%)
Female	70 (60.34%)
Presentation	
Symptomatic	83 (71.55%)
Asymptomatic	33 (28.45%)
Adenoma	
Right superior	6 (5.17%)
Right inferior	44 (37.93%)
Left superior	9 (7.76%)
Left inferior	37 (31.90%)
Both lobes	6 (5.17%)
Ectopic	9 (7.76%)
Not localised	5 (4.31%)
Hyperplasia	11 (9.48%)
Pancreatitis	6 (5.17%)
Renal Stones	40 (34.48%)
Fractures	15 (12.93%)
Bony pains	52 (44.82%)
Neck mass	
Palpable	9 (7.76%)
Non-palpable	107 (92.24%)
Family history	4 (3.45%)
Blood pressure	49 (42.24%)
Type 2 Diabetes Mellitus	33 (28.45%)

[Table/Fig-1]: Summary of baseline and laboratory parameter (N=116).

Preoperative laboratory parameter	Mean±SD (Range)
Calcium (mg/dL)	11.76±1.48 (range 7.5 to 18)
Phosphorous (mg/dL)	2.51±0.65 (range 1.40 to 5.01)
ALP (IU/L)	355.73±911.98 (range 56 to 6485)
PTH (pg/mL)	626.73±687.05 (range 77 to 2893)
Vitamin D (ng/mL)	22.5±14.23 (range 3 to 64.60)
Creatinine (mg/dL)	1.02±0.52 (range 0.27 to 3.79)
Calcium creatinine ratio	0.29±0.25 (range 0 to 1.70)

[Table/Fig-2]: Summary of pre-operative laboratory parameter (N=116).

ALP: Alanine Phosphatase; PTH: Parathormone

and 17 patients (14.66%) did not undergo parathyroidectomy out of which 12 patients underwent medical management, remaining five patients wanted to get operated locally for social reasons [Table/Fig-3]. The sensitivity and comparison between imaging modalities could not be assessed because not all patients had both investigations done as this is a retrospective data analysis. Surgical exploration was done in four patients out of which one patient was Multiple Endocrine Neoplasia (MEN) suspect, one patient had hyperparathyroidism jaw tumor syndrome (HRPT2), genetically proven, and the other two patients had hyperplasia in histopathology.

The post-operative mean PTH levels were 96.05 pg/mL; the mean calcium levels were 9.53 mg/dL in the study group. Histopathology of the patients who underwent surgery had benign adenoma in 75 (64.66%) patients, 3 (2.59%) patients had malignancy, 19 (16.37%) patients had atypical adenoma/atypical hyperplasia [Table/Fig-4].

Genetic studies were done on two patients, one patient was a young male who presented with a jaw tumour and hypercalcaemia. The other patient was a young female who had persistent hypercalcaemia. Both of these patients had HRPT2 mutation

Clinical and treatment details	Percentages
USG Neck (76 underwent)	
Single adenoma	51 (43.97%)
2 adenomas	2 (1.72%)
Hyperplasia	1 (0.86%)
Not localised	22 (18.97%)
Not applicable	40 (34.48%)
MIBI	
Adenoma	107 (92.24%)
2 adenomas	4 (3.45%)
Hyperplasia	1 (0.86%)
Not localised	4 (3.45%)
Parathyroidectomy (99 underwent)	
Single parathyroidectomy	80 (68.97%)
Hemithyroidectomy	10 (8.62%)
Two glands	4 (3.45%)
Subtotal	2 (1.72%)
Total parathyroidectomy	1 (0.86%)
Total thyroidectomy+single parathyroidectomy	1 (0.86%)
Radiofrequency ablation	1 (0.86%)
Not done	17 (14.66%)
Medical management	12 (10.34%)

[Table/Fig-3]: Summary of imaging profile and parathyroidectomy of the study population (N=116).
USG: Ultrasonography; Note: Out of 17 patients who did not undergo parathyroidectomy 12 underwent medical management in the same center but the remaining five patients had gone to other centers and hence no further information was available

Reports	Percentages
Post PTH (pg/mL) (N=111)	96.05±119.62 (range 5.9 to 832.0)
Post Calcium (mg/dL) (N=111)	9.53±0.77 (range 6.4 to 12.2)
Histopathology report	
Benign	75 (64.66%)
Malignant	3 (2.59%)
Atypical adenoma/Atypical hyperplasia	19 (16.37%)
Not available	19 (16.38%)

[Table/Fig-4]: Summary of other parameters (N=116).
PTH: Parathyroid Hormone

positive which causes hyperparathyroidism-jaw tumour syndrome. Both patients underwent a single parathyroidectomy and followed-up. Among the rest of the patients, five patients were MEN suspects (MEN1/4) but genetic studies were not done on these patients.

Among the study population, the difference between pre-operative and post-operative calcium and PTH was statistically significant (p -value <0.001) [Table/Fig-5].

Parameter	Pre- and postoperative		Wilcoxon sign-rank test
	Preoperative median (IQR)	Postoperative median (IQR)	
Calcium (mg/dL)	11.40 (10.83 to 12.30)	9.60 (9 to 9.90)	<0.001
PTH (pg/dL)	289 (162.98 to 811)	56 (25.50 to 130.50)	<0.001

[Table/Fig-5]: Comparison of pre-and post-operative calcium and Parathyroid Hormone (N=116).

DISCUSSION

This study was conducted to assess the laboratory and imaging profile of patients with PHPT. The majority were females in the present study. PHPT was symptomatic in 71.55% of the participants. The pre-operative calcium levels among the participants were 11.76±1.48, and PTH was 626.73±687.05. The USG neck showed 43.97% had a single adenoma, and MIBI showed 92.24% had an adenoma among the participants.

In this current study, the mean age of the participants was 53.42 years, which was similar to the findings of the study by Misgar RA et al., [10]. Few other studies have shown that the mean age was forty years [4-6,12]. Thus, the current study shows a shift in the age of PHPT patients. Studies in Western countries, however, show the presentation in the fifth decade of life [13,14]. This shift in age among the Indian population may be caused due to the associated vitamin D deficiency [3,12]. The preoperative calcium levels among the study participants were 11.76±1.48 mg/dL. This was similar to most of the Indian studies [3,4,5,12]. The mean PTH was 626.73, which is similar to other studies [3,5,6,12].

The preoperative diagnosis, location of the parathyroid gland, and tumour size can contribute important information during the surgery [15]. Preoperative imaging ensures the availability of this information and also reduces the need for repeat surgery. The available imaging for parathyroid glands includes USG neck and Tc^{99m} sestamibi scan. Histopathological examination can be done postoperatively to confirm the diagnosis. In this current study, USG neck showed 43.97% had a single adenoma, and MIBI showed 92.24% had an adenoma among the participants. Misgar RA et al., in their study observed that a single adenoma was seen in 88.46%, double adenomas in 8.57%, and more than two gland involvement in 4.28%, at the time of surgery [10]. In their study, all patients underwent USG neck and Tc-99 m sestamibi scan. They observed the sensitivity of the Tc-99 m sestamibi scan (89.8%) was greater than USG (95.3%) for localising adenoma. As the authors took those patients who underwent Tc MIBI for hypercalcaemia patients and analysed them, they could not assess the superiority of imaging between Ultrasound neck and TC MIBI.

In the present study, histopathological examination revealed that 64.66% of the study participants had benign lesions in the parathyroid gland. Single parathyroidectomy was performed for 68.97% of the participants. Misgar RA et al., in their study observed that on Histopathological Examination (HPE), adenoma was found in 94.44% and hyperplasia in 3.79%, there was no case of parathyroid carcinoma [10].

The post-operative calcium and PTH levels were compared to assess the effect of surgery. The difference between pre-operative and post-operative calcium and PTH was statistically significant. This indicates that the surgery has a clinical impact on calcium and PTH levels. Comparative evaluation of previously published studies has been done in [Table/Fig-6] [3,10,16].

Serial number	Author's name and year	Place of study	Number of subjects	Parameters compared	Values/ importance
1.	Amir A et al., in 2010 [16]	Montreal	1000	Pre-operative serum calcium levels and post-thyroidectomy hypocalcaemia rate	patients with a preoperative corrected calcium level below 2.27 mmol/L had a post-thyroidectomy hypocalcaemia rate of 63%, whereas those with a calcium level above 2.27 mmol/L experienced hypocalcaemia 24% of the time (p <0.001)
2.	Misgar RA et al., in 2016 [10]	Kashmir, India	78	Mean Pre-operative serum calcium levels	12.5 mg/dL
3.	Mishra SK et al., in 2001 [3]	India	28	Mean Pre-operative serum calcium levels	3.1 mmol/L
4.	Present study	India	116	Mean Pre-operative serum calcium levels	11.76±1.48 (range 7.5 to 18)

[Table/Fig-6]: Comparative evaluation of previously published study [3,10,19].

Limitation(s)

The strength of this study was that pre-operative and post-operative comparisons were made for the study participants. The limitation was the study's retrospective nature, which limits the chance for clinical assessment of the patient.

CONCLUSION(S)

The present study findings reveal that parathyroidectomy has a significant impact on serum calcium and PTH levels. There was a shift in the mean age of occurrence of PHPT among the Indian population. The presentation is symptomatic and occurs commonly in the fifth decade of life. Preoperative imaging is recommended in routine practice to decide on the type of surgery needed and minimise the need for repeat surgery. A long-term prospective study involving a large sample size is recommended in the future.

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