

Clinical and laboratory profile of primary hyperparathyroidism in Kashmir Valley: A single-center experience

Raiz Ahmad Misgar, Parvez Mohiuddin Dar¹, Shariq Rashid Masoodi, Munir Ahmad¹, Khursheed Alam Wani¹, Arshad Iqbal Wani, Mir Iftikhar Bashir

Departments of Endocrinology and ¹General Surgery, Sher-i-Kashmir Institute of Medical Sciences, Srinagar, Jammu and Kashmir, India

ABSTRACT

Background: Although primary hyperparathyroidism (PHPT) has become an asymptomatic disease in the West, in India, PHPT is still an uncommonly diagnosed, overtly symptomatic disease with skeletal, muscular, and renal manifestations. **Aims:** To describe the profile and surgical outcome of 78 consecutive PHPT patients over a period of two decades at a single center. **Materials and Methods:** All patients who underwent evaluation and surgery for PHPT from January 1996 to December 2015 were included. Evaluation included measurement of serum total calcium, inorganic phosphorus, alkaline phosphatase, intact parathyroid hormone, 25-hydroxy Vitamin D, 24 hour urinary calcium and radiological survey. Ultrasonography neck and technetium-99m sestamibi scan were used for preoperative localization. **Results:** A total of 78 patients were identified during the two decades of whom 29 patients were studied retrospectively and 49 patients prospectively. Mean age of patients was 44.72 ± 12.46 , and male:female ratio was 1:6. The most common presenting features were nephrolithiasis and/or nephrocalcinosis (64.10%), bone pain (44.1%), abdominal pain (39%), constipation (26%), and myopathy (14.10%). Fractures were present only in 10.25%, and brown tumors in 6.41% patients. The cure rate in our series was 96.15%. The mean parathyroid gland weight was 2.05 ± 3.03 g. None of the 41 patients in whom long-term follow-up was available, had recurrence of PHPT. **Conclusions:** The profile of PHPT is changing with older age at presentation, and emergence of renal stone disease and decline in overt skeletal disease as common presentation. The parathyroid weight in our study resembles that reported from developed countries.

Key words: Fractures, hypercalcemia, nephrolithiasis, parathyroid adenoma, primary hyperparathyroidism

INTRODUCTION

Primary hyperparathyroidism (PHPT) is a disease characterized by hypercalcemia due to autonomous production of parathyroid hormone (PTH). The classic description of PHPT was given by Albright *et al.*, about

80 years ago.^[1] PHPT is the third most common endocrine disorder in the West after diabetes mellitus and thyroid disorders.^[2] Overall, about 1% of the adults have PHPT in the West, and this figure rises to 2% in people older than 55 years.^[3] With the advent of multichannel biochemical screening in the 1970s, the incidence of PHPT increased around the world. The clinical profiles of PHPT remarkably differ with regions of the world. In developing countries, such as India, PHPT is still uncommonly diagnosed, overtly symptomatic disease with skeletal, muscular,

Corresponding Author: Dr. Shariq Rashid Masoodi, Department of Endocrinology, Sher-i-Kashmir Institute of Medical Sciences, Srinagar, Jammu and Kashmir, India. E-mail: shariq.masoodi@gmail.com

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and renal manifestations.¹⁴⁻⁷¹ In contrast, PHPT has become an asymptomatic disease in the West with classic manifestations seen only in 2% cases nowadays.⁸¹ In this study, we describe the clinical characteristics, biochemical profile, and outcome of 78 patients with PHPT seen over a period of two decades at a single center from the Kashmir valley.

MATERIALS AND METHODS

All patients who underwent evaluation and surgery for PHPT from January 1996 to December 2015 at Sher-i-Kashmir Institute of Medical Sciences were included in the study. A total of 78 patients were identified during the two decades, of whom 29 patients were studied retrospectively (1996–2012) and remaining 49 patients were studied prospectively (2012–2015). The diagnosis of PHPT was based on the following: (i) persistent elevation of serum calcium above the upper limit of normal range (10.5 mg/dl); (ii) increased intact PTH (iPTH); and (iii) histological evidence (after parathyroid surgery) of parathyroid adenoma or hyperplasia. Evaluation of the patients included the measurement of serum total calcium, inorganic phosphorus, total alkaline phosphatase (ALP), iPTH, 25-hydroxy Vitamin D (25-OHD), serum albumin, and 24 hour urinary calcium and creatinine. Serum total calcium, inorganic phosphorus, total ALP, and serum creatinine were measured by automated techniques. The normal laboratory range was 8.5–10.5 mg/dl for total serum calcium, 2.5–4.5 mg/dl for serum phosphorus, and 30–140 IU/L for serum ALP. Radiological survey of hands, skull, lumbar spine, pelvis, and any other suspected or known site of fracture was performed. Imaging studies for localization of parathyroid adenoma included ultrasonography (USG) neck and technetium-99m (^{99m}Tc) sestamibi scan. Serum iPTH was measured by chemiluminescent immunometric assay and serum 25-OHD was measured by radioimmunoassay. Vitamin D deficiency was defined as serum 25-OHD level <20 ng/ml.⁹¹

Parathyroid surgery

In patients in whom a single parathyroid adenoma was localized on ^{99m}Tc sestamibi scan, unilateral neck exploration was performed with removal of the adenoma. Patients with doubtful lesion or nonlocalized lesions underwent bilateral neck exploration, and all parathyroid glands were examined with the removal of 3½ glands.

Statistical analysis

Statistical analysis was done on PC Windows using Statistical Package for Social Sciences (SPSS), version 11.5.0, from SPSS Inc., Chicago IL. The results were expressed as percentage or mean ± standard deviation, as specified.

Pearson's Chi-square method was used for comparing proportions and percentages, whereas Student's *t*-test was used for comparing continuous variables. ANOVA was used wherever needed. Where the data were not uniformly distributed nonparametric test such as Mann–Whitney U-test, Kolmogorov–Smirnov Z-test, or Kruskal–Wallis H-test was used. A *P* < 0.05 was taken as statistically significant.

RESULTS

The clinical characteristics of patients are shown in Table 1. An overwhelming majority (67/78; 85.7%) of the patients were females giving a male: female ratio of 1:6. The mean age of patients was 44.72 ± 12.46 with a median of 45 years and a range of 16–70 years. Nephrolithiasis and/or nephrocalcinosis [Figure 1] was the most common presentation, seen in 50 (64.10%) patients followed by bone pain in 26 (44.1%), abdominal pain in 24 (39%), constipation in 16 (26%), and myopathy in 11 (14.10%). Seven (8.97%) patients manifested psychiatric abnormalities. A parathyroid nodule was

Table 1: Clinical characteristics of 78 patients with primary hyperparathyroidism

Variable	Frequency (%)
Age (years), mean (SD)	44.72 (12.46)
Male:female ratio	1:6
Clinical/radiological feature	
Nephrolithiasis	50 (64.10)
Bone pains	26 (44.10)
Abdominal pain	24 (39)
Constipation	16 (26)
Proximal muscle weakness	11 (14.10)
Polyuria and polydipsia	9 (11.54)
Fractures	8 (10.25)
Psychiatric abnormalities	7 (8.97)
Graveluria	6 (7.69)
Pancreatitis	3 (4.41)
Sub-periosteal resorption	16 (20.51)
Salt-pepper skull	15 (19.23)
Brown tumors	5 (6.41)

SD: Standard deviation

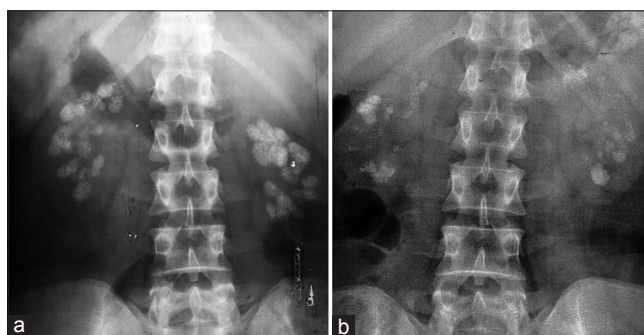


Figure 1: (a) Radiograph of abdomen showing extensive bilateral nephrolithiasis; (b) striking improvement after successful parathyroid surgery

palpable in three patients. Skeletal involvement (osteopenia, sub-periosteal resorption, pathological fractures, salt and pepper appearance of skull, brown tumors) was present in 31 (39.74%) patients; 8 (10.25%) had fractures [Figure 2]. About one-fourth (19; 24.38%) of our patients had both renal and skeletal manifestations.

Out of fifty patients with nephrolithiasis, 15 (30%) had a past history of at least one surgery for renal stones prior to the diagnosis of PHPT, and another four patients had received extracorporeal shock wave lithotripsy at least once prior to diagnosis of PHPT.

The biochemical variables of the patients are shown in Table 2. All patients had hypercalcemia. The mean serum calcium level was 12.5 ± 1.7 mg/dl, (median 12, range 10.7–19). The mean serum iPTH level was 377.6 ± 386.1 pg/ml (median 224.5, range 70–1900). Hypophosphatemia (serum inorganic phosphorus < 2.5 mg/dl) was documented in 54 (69.23%) patients. The mean serum inorganic phosphorus level was 2.2 ± 0.6 mg/dl (median 2.2). Hypercalciuria (24 h urinary calcium ≥ 4 mg/kg) was present in 41 (52.56%) patients. The serum total ALP was elevated (>140 IU/L) in 40 (51.28%) patients. The mean serum ALP was 255.1 ± 336.8 IU/L (median 154).



Figure 2: Radiograph showing advanced bone disease. (a) Fracture of femur; (b) brown tumor of tibia

Table 2: Biochemical variables of 78 patients with primary hyperparathyroidism

Variable	Mean (SD)	Median (range)
Serum calcium	12.5 (1.7)	12 (10.7-19)
Serum phosphate (mg/dl)	2.2 (0.6)	2.2 (0.8-3.5)
Serum ALP (U/L)	255.1 (336.8)	154 (45-2476)
Serum iPTH (pg/ml)	377.6 (386.1)	224.5 (70-1900)
Serum 25-OHD (ng/ml)	37.2 (58.1)	22.8 (4.3-312)

ALP: Alkaline phosphatase, 25-OHD: 25-hydroxyvitamin D, iPTH: Intact parathyroid hormone, SD: Standard deviation

Serum 25-OHD was available for 54 patients. The mean 25-OHD level was 37.2 ± 58.1 ng/ml (median 22.8, range 4.3–312). Vitamin D deficiency was present in 38% patients. We did not find any correlation between Vitamin D status and biochemical parameters (serum calcium and iPTH) or adenoma weight.

A few of our patients had rare and unusual features. There was clinical suspicion of multiple endocrine neoplasia-1 (MEN-1) in 3 patients. Two females; aged 25 and 23 years had PHPT and microprolactinoma, whereas a 58-year-old female patient had PHPT and acromegaly. Two of our patients had associated adrenal incidentalomas causing sub-clinical Cushing's syndrome in one of them. A 27-year-old female patient presented in postpartum period with nephrogenic diabetes insipidus as the sole manifestation of PHPT, which settled immediately after parathyroid surgery.

All our patients underwent USG neck and Tc-99m sestamibi scan for localization of parathyroid adenoma. In our series, the sensitivity of USG and Tc-99m sestamibi scan for the localization of adenoma was 89.8% and 95.3%, respectively.

Operative findings and pathological features

At the time of surgery, single adenoma was involved in 69 (88.46%) double adenomas in 6 (8.57%) and more than 2 gland involvement in 3 (4.28%) patients. Among the 69 patients with single adenoma, right inferior gland was involved most often (40; 57.97%), followed by left inferior (22; 31.88%) and right superior (7; 0.14%); none of the patients had involvement of left superior gland. On histopathology, adenoma was found in 75 (94.44%), hyperplasia in 3 (3.79%) patients. There was no case of parathyroid carcinoma. The mean parathyroid gland weight was 2.05 ± 3.03 g (median 1.05; range 0.1–13.8). Using Pearson's correlation coefficient, the mean parathyroid gland weight showed a strong correlation with serum calcium and iPTH.

Postoperative course

The mean postoperative serum iPTH level was 61.8 ± 43.8 pg/ml (range: 10.7–154). Postoperative hungry bone syndrome (HBS) was observed in 8 (10.12%) patients. This was managed with oral calcium and calcitriol in five patients, whereas three patients needed parenteral calcium gluconate infusion. Permanent hypoparathyroidism was observed in a single patient, and postoperative pancreatitis was documented in one patient. There was no perioperative mortality. Transient vocal cord paralysis and surgical wound hematoma were observed in one patient each. No patient sustained permanent vocal cord paralysis, wound infection, or sepsis.

The surgical success (cure) for PHPT is defined by the maintenance of eucalcemia at the arbitrarily accepted interval of 6 months after surgery.^[10] Based on this definition, the overall cure rate in our series was 96.15% (75 out of our 78 patients achieved cure). Persistent disease was seen in three patients. One of these patients had MEN-1 (PHPT and acromegaly); she underwent the removal of all four parathyroid glands. The second patient was a young male in whom preoperatively left inferior adenoma was localized but had a persistent disease; however, he achieved cure after second surgery. Out of 75 patients who achieved cure, long-term follow-up (more than one year, range 1–9 years) was available for 41 patients. During this follow-up period, none had recurrence of PHPT.

DISCUSSION

The comparison of our study with other Indian studies is shown in Table 3. The traditional age of presentation of PHPT in India is in the 4th decade.^[4,7,11] In our study, the mean age of presentation was 44 years. Another recent Indian study has reported a mean age of presentation of 48 years.^[12] Our results reflect a shift in the presentation of PHPT from fourth to fifth decade in India. However, our patients continue to be much younger than patients from the developed countries.^[13,14] One reason for early presentation in Indian patients could be associated Vitamin D deficiency.^[4,11]

Renal stone disease (50:64.10% patients) was the most common presentation in our series. Other Indian studies have reported 31–70% prevalence of renal stone disease in PHPT.^[4-7] A significant (52.56%) proportion of our patients had hypercalciuria. Most of the Indian studies have not reported data on hypercalciuria. One Indian study has reported hypercalciuria in 85% patients.^[7] The prevalence of renal stones has fallen from 57% to <5% in the West due to the detection of more and more asymptomatic cases.^[15] Thirty percent of our patients with renal stones had a past history of at least one surgery for renal stones and another four patients (8%) had received lithotripsy

prior to diagnosis of PHPT. Surprisingly, in none of these patients serum calcium estimation had been advised during previous evaluation. This significant delay in the diagnosis of PHPT reflects the lack of awareness among urologists, nephrologists, and general practitioners regarding PHPT.

Skeletal manifestations account for most of the morbidity associated with PHPT. Mishra *et al.* in 2001 in a study of 29 patients reported osteitis fibrosa cystica in all of them and fractures in 57% of the patients.^[4] Four years later, Bhansali *et al.* in a study of 52 patients reported bone disease in 67% and fractures in 48% patients.^[5] A systematic review of PHPT in India has reported fractures in 40% and brown tumors in 42% patients.^[16] A recent Indian study reported fractures in 25.8% of PHPT patients and brown tumors in none.^[12] In our study, fractures were present only in 10.25% and brown tumors in 6.41% patients. This is the lowest prevalence of fractures in a cohort of PHPT patients from India. Our results reflect a changing trend in the presentation of PHPT in India wherein the overt skeletal disease in the form of fractures and brown tumors is on the decline. The remarkably low prevalence of fractures in our series probably is due to earlier diagnosis of PHPT for last few years (more than half of our subjects were enrolled from 2013 onwards). Another reason may be the improvement in calcium and Vitamin D nutrition. The improvement in Vitamin D nutrition is reflected by the mean serum 25-OHD of 37.2 ng/ml in our patients. The frequency of specific radiological manifestations of PHPT in the United States declined from 23% in the 1960s to a remarkably low 2% in the 1990s.^[8,17] The difference in the severity of skeletal disease in PHPT between Western and Eastern populations is determined by calcium and Vitamin D nutrition, but additional factors also play a role.^[18,19]

PHPT can present as recurrent acute pancreatitis or chronic pancreatitis.^[20,21] Previous data from India report that 12–13% patients with PHPT have pancreatitis.^[6,7,22] In our series, pancreatitis was present in only 3 (4.41%) patients. The mechanisms of PHPT induced pancreatitis include hypercalcemia-induced activation of trypsinogen to trypsin,

Table 3: Comparison of present study with other Indian studies

	Present study (n=78)	Harinarayan <i>et al.</i> ^[11] (n=20)	Mishra <i>et al.</i> ^[4] (n=29)	Bhansali <i>et al.</i> ^[5] (n=52)	Gopal <i>et al.</i> ^[6] (n=79)	Priya <i>et al.</i> ^[7] (n=39)	Mithal <i>et al.</i> ^[12] (n=50)
Place	Kashmir	Delhi	Lucknow	Chandigarh	Mumbai	Delhi	Delhi
Age (years)	44.7 (12.5)	38 (15)	38	38 (13)	33.5 (8.82)	38.4 (15)	48.3 (15.8)
Serum calcium (mg/dl)	12.5 (1.7)	10.9 (0.9)	12.4 (3.1)	12.2 (1.1)	12.55 (1.77)	12.52 (1.60)	12.2 (1.9)
Serum phosphate (mg/dl)	2.2 (0.6)	3.1 (0.9)	2.2 (0.7)	2.8 (0.6)	1.81 (0.68)	2.58 (0.56)	2.3 (0.7)
Serum ALP (U/l)	255.1 (336.8)	425 (249)	1544	361 (360)	762.2	1086 (1551)	872 (1401.8)
Serum iPTH (pg/ml)	377.6 (386.1)	438 (350) pmol/L	82.7 pmol/L	809 (696)	866.6 (799)	662 (446)	573.2 (657.5)
Serum 25-OHD (ng/ml)	37.2 (58.1)	8.39 (5.09)	13.52	NR	NR	10.21 (5.82)	18.2 (15.3)
Parathyroid weight (g)	2.05 (3.03)	4.56	8.6	6.35 (4.4)	3.31	6.34 (5.87)	4.2 (5.9)

Unless otherwise stated, values are mean (SD). ALP: Alkaline phosphatase, NR: Not reported, 25-OHD: 25-hydroxy Vitamin D, iPTH: Intact parathyroid hormone, SD: Standard deviation

ductal obstruction due to pancreatic calculi, and finally genetic risk factors.

All our patients had hypercalcemia and their mean serum calcium level was 12.5 mg/dl, which is remarkably similar to that reported by other Indian studies.^[4-7] We documented hypophosphatemia in 69.23% patients, which is in agreement with Western data.^[23] A previous Indian study has reported hypophosphatemia in 65% patients with PHPT, but another Indian study has reported a normal mean serum phosphorus in PHPT patients.^[5,10] The mean serum iPTH level in our patients was 377.6 pg/ml, which is lower than that reported by previous Indian studies.^[4-7] The serum total ALP was elevated in 51.28% patients. Elevated ALP has been consistently reported by other Indian series due to high prevalence of bone disease in PHPT patients. The mean parathyroid weight (2.05 ± 3.03 g) in our study is markedly lower than that reported by other Indian studies [Table 3]. The mean parathyroid weight in our study resembles that reported from developed countries.^[15] We found a strong correlation of parathyroid gland weight with serum calcium and iPTH, as has been reported previously.^[7,24]

The mean serum 25-OHD (37.2 ± 58.1 ng/ml) in our study was higher than that reported by previous Indian studies;^[3,6,10,11] however, Vitamin D deficiency was present in 38% of our patients. An inverse correlation between serum 25-OHD concentration and parathyroid gland weight has been reported previously.^[4,24,25] We did not find any correlation between Vitamin D status and biochemical parameters (serum calcium and iPTH) or adenoma weight. These results are consistent with a recent Indian study.^[12] The likely reason is the possibility of prior Vitamin D treatment and uncertainty about its timing and amount, which could have confounded the 25-OHD measurements at the time of presentation. In addition, Vitamin D may not be the only significant factor in the development of bone disease in PHPT patients, other factors could be playing a significant role.

The preoperative localization of an abnormal parathyroid gland can reduce operative time, postoperative morbidity, and the need for repeat surgery. The imaging methods for localization include high-resolution USG, ^{99m}Tc sestamibi scan, computerized tomography, and magnetic resonance imaging. The sensitivity of USG to localize the adenoma has been reported as 65–77%,^[5,6] whereas the sensitivity of ^{99m}Tc sestamibi scan has been reported as 86.9–100%.^[6,26] In our series, the sensitivity of USG and ^{99m}Tc sestamibi scan for localization of adenoma was 89.8% and 95.3%, respectively. With a sensitivity of 89.8%, we conclude that USG is an effective localization modality as it is inexpensive and is widely available.

The overall cure rate for our series was 96.15%. Mishra *et al.*, in a study of 29 patients reported a cure rate of 100%.^[4] Another Indian study has reported a cure rate of 96%.^[5] Previous Indian studies have reported postoperative HBS in a large proportion of patients from 24% to 82%.^[5,6,11,27,28] In our study, postoperative HBS was observed in only 10.12% patients. Our results are in agreement with a recent Indian study in which postoperative HBS was seen in only four patients (8%) out of fifty.^[12] Our policy to treat all patients with preoperative serum 25-OHD level <30 ng/ml with Vitamin D is in all probability, responsible for much lower prevalence of postoperative HBS in our series.

Consistent with the data about recurrent PHPT on long-term follow-up revealing recurrence rates of zero to 41.6%,^[5,6,27,29,30] none of the 41 patients in our series on whom follow-up was available for 1–9 years, had recurrence of PHPT.

The strengths of our study include its large size and largely prospective nature with about two-thirds (62%) of the subjects evaluated prospectively. Lack of data on bone mineral density and for many patients, on Vitamin D status are the limitations of the study.

CONCLUSION

In conclusion, our study reflects a changing trend in the clinical profile of PHPT in India. There is a shift in the age of presentation of PHPT from fourth to fifth decade. Renal stone disease is emerging, the most common presentation, whereas overt skeletal disease in the form of fractures and brown tumors is on the decline. The mean parathyroid weight in our study resembles that reported from the developed countries.

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Conflicts of interest

There are no conflicts of interest.

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